The Chemistry of Functional Groups, Supplement D
Edited by S. Patai and Z. Rappoport

Supplement D

The chemistry of **halides, pseudo-halides and azides** Part 2

Edited by

SAUL PATAI

and

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Foreword

This Supplement D contains material on halides, pseudo-halides and azides. The same functional groups have been treated previously in the following main volumes of the Chemistry of the Functional Groups series:

The Chemistry of the Azido Group (1971)
The Chemistry of the Carbon–Halogen Bond (2 parts, 1973)
The Chemistry of Cyanates and their Thio Derivatives (2 parts, 1977)

Chapters which were also intended to appear in this volume, but did not materialize were the following: "Advances in the preparation and uses of azides"; "Recent advances in biological reactions involving halides and pseudo-halides"; and "Syntheses and uses of isotopically labelled halides and azides". We hope that these chapters will be included in a future supplementary volume, which should be published in several years' time when the amount of new and unreviewed material justifies this.

The present volume concludes the first set of supplementary volumes (Supplements A, B, C, D, E and F) which cover among themselves all the subjects treated in the Functional Groups series.

We will be very grateful to readers who would call our attention to omissions or mistakes in this and other volumes in the series.

SAUL PATAI
ZVI RAPPOPORT

Jerusalem, October 1982

The Chemistry of Functional Groups
Preface to the series

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

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

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

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

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

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

(c) Chapters describing the characterization and characteristics of the functional groups, i.e. a chapter dealing with qualitative and quantitative methods of deter-

mination including chemical and physical methods, ultraviolet, infrared, nuclear magnetic resonance and mass spectra: a chapter dealing with activating and directive effects exerted by the group and/or a chapter on the basicity, acidity or complex-forming ability of the group (if applicable).

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

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

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

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

The Chemistry of Alkenes (*two volumes*)
The Chemistry of the Carbonyl Group (*two volumes*)
The Chemistry of the Ether Linkage
The Chemistry of the Amino Group
The Chemistry of the Nitro and Nitroso Groups (*two parts*)
The Chemistry of Carboxylic Acids and Esters
The Chemistry of the Carbon–Nitrogen Double Bond
The Chemistry of the Cyano Group
The Chemistry of Amides
The Chemistry of the Hydroxyl Group (*two parts*)
The Chemistry of the Azido Group
The Chemistry of Acyl Halides
The Chemistry of the Carbon–Halogen Bond (*two parts*)
The Chemistry of Quinonoid Compounds (*two parts*)
The Chemistry of the Thiol Group (*two parts*)
The Chemistry of Amidines and Imidates
The Chemistry of the Hydrazo, Azo and Azoxy Groups (*two parts*)
The Chemistry of Cyanates and their Thio Derivatives (*two parts*)
The Chemistry of Diazonium and Diazo Groups (*two parts*)
The Chemistry of the Carbon–Carbon Triple Bond (*two parts*)
Supplement A: The Chemistry of Double-bonded Functional Groups (*two parts*)

The Chemistry of Ketenes, Allenes and Related Compounds (two parts)
Supplement B: The Chemistry of Acid Derivatives (two parts)
Supplement C: The Chemistry of Triple-Bonded Groups (two parts)
Supplement D: The Chemistry of Halides, Pseudo-halides and Azides (two parts)
Supplement E: The Chemistry of Ethers, Crown Ethers, Hydroxyl Groups and their Sulphur Analogues (two parts)
The Chemistry of the Sulphonium Group (two parts)
Supplement F: The Chemistry of Amino, Nitroso and Nitro Groups and their Derivatives (two parts)

Titles in press:

The Chemistry of Peroxides
The Chemistry of Organometallic Compounds
The Chemistry of Organic Se and Te Compounds

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

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

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Contents

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CHAPTER **20**

Electrophilic assistance to reactions at a C—X bond

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I. INTRODUCTION

Electrophilic assistance, other than the general assistance by solvent molecules, is a common phenomenon in nucleophilic substitution and elimination reactions at appropriate C—X bonds. It is especially important when X is a halogen, and many reactions can be appreciably accelerated by the addition of a suitable Lewis acid. For chlorides, bromides and iodides, silver ion is frequently used. Since the silver halide is insoluble in most solvents, reactions which otherwise would be thermodynamically unfavourable can proceed to completion in the presence of silver ion. When there are several possible pathways to products, it is found that the product ratios in the presence of silver ion frequently differ from those in its absence.

There have been several reviews of electrophilic assistance to reactions of alkyl halides[1–4].

One would expect the principle of hard and soft acids and bases[5–8] to govern the type of Lewis acid required for catalysis at a given C—X bond[3,9,10].

Using terminology more common to inorganic chemistry, one can consider reactions at C—X bonds assisted by Lewis acids to be reactions of coordinated ligands. The acceleration observed can frequently be correlated with the energy of the formation of a linkage between X^- and the Lewis acid, as measured by equilibrium constants[3,11]. However, when a metallic ion is present as an unreactive complex with the solvent, the slow rate at which coordination sites become available for inner-sphere coordination of the X of the C—X bond reduces the catalytic activity to below that expected on thermodynamic grounds. Fox example, although CrF^{2+} has considerable stability, Cr^{3+} (present as the relatively stable $[Cr(H_2O)_6]^{3+}$) is inert in the hydrolysis of *t*-butyl fluoride[12].

Electrophilic assistance at a C—X bond is an extremely important component of Friedel–Crafts reactions. There is an enormous volume of literature dealing with both the mechanism and the synthetic utility of these reactions, which one cannot hope to cover as only one of many components to a short chapter, and these reactions have been excluded from consideration[13,14]. After a general consideration of the efficiencies of various Lewis acids in assisting reaction at a carbon–halogen bond, a detailed treatment will be given of mechanistic aspects of silver ion assistance. Attention will then be given to mechanistic aspects of various other types of electrophilic assistance. Finally, a brief survey, mainly with the aim of presenting leading references, will be given of some of the important synthetic applications.

II. RELATIONSHIP BETWEEN EXTENT OF ASSISTANCE AND LEWIS ACIDITY

A. Alkyl Fluorides

When the X of the C—X bond is the hard fluorine, one would expect 'hard' acids to serve as effective catalysts, and it has long been known that hydronium ion catalyses the solvolyses in hydroxylic solvents of alkyl[15], benzyl[16,17] and acyl[18] fluorides. Similarly, metal ions considered as 'hard' form stable monofluoride complexes and these can also act as catalysts towards C—F heterolysis.

For the hydrolysis of benzyl fluoride in 2 M perchloric or hydrochloric acid, Clark and Jones[10] found Th(IV) and Zr(IV) to be powerful catalysts and Al(III) to be a milder, but effective, catalyst. Subsequently, they reported[19] that Mg(II) functions as an even milder catalyst. While they had no direct evidence upon which to make a choice, they expressed a preference for a metal ion-assisted S_N2 pathway. Swain and Spalding[17], while recognising that both S_N1 and S_N2 routes were consistent with their finding that the specific rates of acid-catalysed solvolysis follow the Hammett h_0 function, had previously expressed a preference for the S_N1 route:

$$PhCH_2F + H_3O^+ \rightleftharpoons (PhCH_2FH)^+ + H_2O$$

followed by

$$(PhCH_2FH)^+ \xrightarrow{Slow} PhCH_2^+ + HF \quad (S_N1)$$

as opposed to

$$H_2O + (PhCH_2FH)^+ \xrightarrow{Slow} PhCH_2\overset{+}{O}H_2 + HF \quad (S_N2).$$

Recent analyses[20,21] of the data available for the solvolyses of benzyl *p*-toluenesulphonate and benzyl chloride in terms of the extended Grunwald–Winstein equation[22] have indicated marked dependencies of the reaction rates upon both solvent nucleophilicity and solvent ionizing power, suggesting (for these substrates at least) a bimolecular mechanism.

A similar, but more comprehensive, study by Rudakov and coworkers[12,23–25] used *t*-butyl fluoride as the organic substrate and added metal ions as their nitrate salts. Since *t*-butyl derivatives are considered to be standard S_N1-type substrates, the hydrolysis is not mechanistically ambiguous[26]. Since fluorine does not have low-lying vacant d orbitals, the interaction with Lewis acids was assumed to be of pure donor–acceptor character ('hard'–'hard' interactions favoured). They found that the activities of the metal ions decreased in the order of the stability constants for monofluoride complex formation[27]: Zr(IV), Th(IV), Sc(III), Al(III), Fe(III), Be(II), Ga(III), Mg(II), Zn(II), Cd(II). The proton fell between Ga(III) and Mg(II), in terms of both catalytic activity and magnitude of the stability constant. The stability constant (K) for the complex is defined by the relationship: $K = [MF^{(n-1)+}]/[M^{n+}][F^-]$. Other metals, known to bind only weakly with fluoride ion, were found to be inactive: K(I), Ag(I), Cu(II), Zn(II), Cd(II), Hg(II), La(III). It is particularly noteworthy that this list includes Ag(I), Zn(II) and Hg(II), reagents commonly used for rendering electrophilic assistance towards C—Cl, C—Br and C—I bond heterolysis. For the proton-catalysed hydrolysis it was shown[23] that in nitric and sulphuric acid solutions the logarithms of the specific rate had a linear relationship with the Hammett H_0 values, with a slope of close to unity. This suggests that specific (rather than general) acid catalysis was involved. An identical conclusion had previously been reached[28] for the acid-catalysed S_N1 hydrolysis of triphenylmethyl fluoride in 50% acetone, based on the order of catalytic efficiency $HClO_4 > HCl \gg CH_3COOH$.

B. Assistance to Unimolecular Solvolyses of Alkyl Chlorides and Bromides

Rudakov and coworkers have also carried out an extensive study of the relative catalytic efficiencies of various Lewis acids towards *t*-butyl chloride solvolysis in aqueous ethanol. A study with Cd(II) showed only a mild catalysis[29,30], consistent with the *t*-BuCl–Cd^{2+} complex being of low stability, and it was concluded that coordination energy was important only in the transition state and not in the ground state[30]. A study[31,32] with a range of metal ions added as their nitrates showed those

from subgroups Ia[33], IIa and IIIb of the periodic table to be inactive and those from Ib, IIb, IIIa, IVa, Va and VIIb to be active. The hydronium ion was found to be inactive. In particular, appreciable activity was found for Ag(I), Cd(II), Hg(II), In(III), Tl(III), Pb(II), Bi(III) and Pd(II). Strong dative bonding was proposed within the $MX^{(n-1)+}$ complex, with the metal giving up d electrons to the vacant 3d orbitals on chlorine. It was also shown that Cd(II) and Pb(II) were effective in assisting the solvolysis of *t*-butyl bromide in aqueous ethanol[34]. In 32 wt% ethanol–water at 25°C, Tl(III), Hg(II) and Pd(II) had activities, towards *t*-butyl chloride, too high to measure by the technique employed and the following order was then observed[31,32]: Ag(I), Bi(III), Cd(II) and Pb(II); it was subsequently reported[12] that these were followed in turn by Tl(I), Co(II), Mn(II), Cu(II), Ga(III) and Zn(II).

C. Brønsted-type Relationship

Bringing together the results for *t*-butyl halide solvolysis under the action of Lewis acids, a relationship of the Brønsted type[35,36] was developed[12,34].

The interaction mechanism was considered to be of the form

$$t\text{-BuX} + M^{n+} \longrightarrow [t\text{-Bu}^{\delta+}\cdots X^{\delta-}\cdots M^{n+}] \longrightarrow t\text{-Bu}^{+} + MX^{(n-1)+}$$

and the kinetics were found to follow an equation with terms corresponding to unassisted and assisted reaction:

$$-d[RX]/dt = k_0[RX] + k_1[M^{n+}][RX].$$

The stability constant(K)[27] for complexing of M^{n+} with X^- was defined as $K = [MX^{(n-1)+}]/[M^{n+}][X^-]$. If, instead of rate, the rate relative to the appropriate unassisted rate was used, a very general relationship of the Brønsted type was found to accommodate virtually all of the available data:

$$\log(k_1/k_0) = -0.7 + 0.84 \log K.$$

This relationship could be applied when X was F, Cl or Br and for measurements in aqueous ethanol as well as in water. It accommodates H_3O^+ catalysis of the *t*-butyl fluoride reactions, as well as the catalysis by metal ions of differing charge, electronic structure and solvation energy. The slope of 0.84 can be considered to imply a product-like transition state on the assisted heterolysis of the C—X bond. In the original Brønsted relationship[35,36], values close to zero were considered to reflect a reactant-like transition state and values close to unity a product-like transition state.

It was suggested[34] that the equation might be applicable to situations within which the $MX^{(n-1)+}$ complex is of high stability, but its formation is hindered by high stability for the M^{n+} aquo-complex, if it was possible to determine the relative concentration of ions with aqua-vacancies. However, the required information is either not available or not of sufficient accuracy.

For the study of *t*-butyl chloride solvolysis in aqueous ethanol, assisted by Cd(II), three different solvent compositions were employed, for each of which K values were available[37]. A Brønsted relationship with the same slope accommodated the data but the line was displaced slightly[12,34]. This suggests that solvent variation can also be accommodated by a Brønsted relationship, but clearly more work needs to be done in this area. This type of analysis also suggests that Lewis acid species which are inactive in water or which do not exist in water may be active in non-aqueous solvents provided that the appropriate $MX^{(n-1)+}$ complex is of reasonable stability in that solvent.

In nitromethane, *t*-BuCl undergoes isotopic exchange with $H^{36}Cl$ and both unassisted and assisted terms are present in the rate equation[38]. It was also shown that the HCl_2^- complex is formed in appreciable concentrations when chloride ion is present:

$$HCl + Cl^- \overset{K}{\rightleftharpoons} HCl_2^-$$

The values for this compound[38] place it on the previously described Brønsted plot. Similarly, hydrogen chloride catalyses both radiochloride exchange and racemization of arylalkyl chlorides in nitromethane[39], the rearrangement of camphene hydrochloride to isobornyl chloride in nitrobenzene[40] and the methanolysis of triphenylmethyl chloride in benzene[41] (HCl_2^- was shown to be stable in benzene[42]).

Using various models for the transition state, and based upon ion pair and ion triplet models for the transition states for assisted and unassisted solvolyses, Rudakov and Kozhevnikov have attempted to develop a thermodynamic theory of the rates of the S_N1 hydrolyses of halogen compounds under the influence of metal ions[3,43].

D. Electrostatic Catalysis

The ionization of triphenylmethyl chloride in diethyl ether is considerably accelerated by lithium perchlorate, and this has been interpreted as electrostatic catalysis by lithium perchlorate ion pairs. The coulombic fields associated with the lithium and perchlorate ions are considered to be the influences pulling the triphenylmethyl chloride molecule apart[44]. In low polarity solvents it will be difficult to distinguish between ionization stabilized by electrostatic aggregation and ionization assisted by prior complex formation with cations, such as lithium, which are inert in the more usually employed hydroxylic solvents. Similarly, lithium perchlorate has been shown[45] to be catalytically active in the allylic rearrangement of 1-phenylallyl chloride to cinnamyl chloride in ether, tetrahydrofuran, propylene oxide, diethyl carbonate and (to a lesser extent) in dimethylformamide.

E. Assistance to Bimolecular Solvolyses of Alkyl Halides

Rudakov[46] developed techniques for determining the order of reaction with respect to the reacting ion, and ways of detecting an intermediate, by a combined measurement of reaction rate and solubility of the alkyl halide. Preliminary experiments[47] showed that the hydrolyses of methyl iodide, ethyl bromide, *n*-butyl chloride and *n*-butyl bromide were all accelerated strongly by Hg(II) and Ag(I) (stability constants for $MX^{(n-1)+}$ formation 10^7–10^9) and weakly by Bi(III) and Cd(II) (stability constants for $MX^{(n-1)+}$ formation 10^2–10^3).

Ethyl bromide was found to be the most convenient substrate and a detailed study[47] was made with $Cd(NO_3)_2$ at 95°C and with $Hg(NO_3)_2$ at 25°C. Second-order kinetics, first order in ethyl bromide and in metal ion, were observed. It was possible to evaluate the stability constant for EtBr···Hg(II) formation, $K = 0.3 \pm 0.1$ M^{-1}. When the rate for Cd(II) reaction was used to estimate the corresponding rate at 25°C, a difference in activities of about 10^5-fold between Hg(II) and Cd(II) was indicated, comparable with a $10^{7.5}$-fold difference in stability constants for MBr^+ formation[27]. The Hg(II)-assisted solvolysis was subsequently extended[48] to ethyl chloride and iodide, to methyl chloride, bromide and iodide, and to isopropyl chloride and bromide, with observation of the same second-order kinetic pattern.

The EtBr···Ag(I) complex had a stability constant of 1.6 M^{-1} but a rate coefficient for the silver ion-assisted reaction could be obtained only for a dominant route involving two silver ions[49], consistent with a known high stability for Ag_2Br^+[27b]. However,

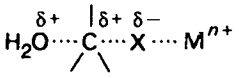
silver ion-assisted solvolyses of methyl iodide[50], ethyl iodide[51], and isopropyl bromide[51] could be analysed so as to give appropriate rate coefficients for simultaneous processes involving catalysis by one or two silver ions.

With Tl(III) added as the perchlorate in aqueous perchloric acid, only a term of first-order in substrate and of first-order in Tl(III) was observed for interaction at 25°C with ethyl bromide, isopropyl chloride and isopropyl bromide[52]. The Tl(III) was found to be about 100 times less effective than Hg(II) in promoting the solvolysis of ethyl bromide, despite having a slightly greater affinity for Br^-. The relatively slow reaction of ethyl bromide with Pb(II) was investigated by a potentiometric technique and the similar-speed reaction with Cd(II) was reinvestigated by this technique. For these slower reactions, both catalysed and uncatalysed terms were obtained in the rate equation:

$$-\mathrm{d[EtBr]}/\mathrm{d}t = k_0[\mathrm{EtBr}] + k_1[\mathrm{EtBr}][\mathrm{M}^{2+}]$$

Both the nitrate and perchlorate salts were investigated and for $Cd(NO_3)_2$ evidence was obtained for an additional route involving nucleophilic nitrate ion participation[53].

The above results[47–53] were considered together[3,54] and a superficial resemblance to the previously discussed metal ion-assisted S_N1 reactions of *t*-butyl halides could be seen. The ions M^{n+} forming the more stable $MX^{(n-1)+}$ complexes again tend to be the more active ones, and when the C_2H_5X–M^{n+} system was considered, the hydrolyses of ethyl bromide catalysed by the divalent ions Pb^{2+}, Cd^{2+} and Hg^{2+} and the Hg^{2+}-assisted hydrolyses of ethyl chloride and ethyl iodide gave a good Brønsted-type plot when $\log(k_1/k_0)$ was plotted[55] against log *K*. However, the plot lay below that for the *t*-butyl halide solvolyses and it was of shallower slope. Also, for ethyl bromide hydrolysis, the Ag(I)-assisted rate was much faster and the Tl(III)-assisted rate was much slower than one would predict from the plot and the appropriate stability constants for formation of AgBr and $TlBr^{2+}$. These deviations were increased when methyl halides were considered and reduced when isopropyl halides were considered. A broad spectrum of S_N2-type transition states was proposed, depending upon the extent of orbital overlap between the nucleophile and the alkyl group:



It was assumed that this was largely determined by the nucleophilic character of the medium and the alkyl group. Only a secondary dependence on the electrophile was proposed and the electrophilic assistance was considered to involve a reduction in the amount of S_N2 character. This, in turn, was considered to bring about an 'inductive retardation'[54], which was proposed to be at a maximum when methyl halides and multicharged ions possessing high electron affinity (such as Tl^{3+}) were involved. An equation was proposed of the form

$$\log(k_1/k_0) = \log K - P_R P_X P_{M^{n+}}$$

where P_R, P_X and $P_{M^{n+}}$ are constants depending on the properties of the alkyl group, the halogen and the Lewis acid, and the second term represents the 'inductive retardation'. With a suitable choice of standard conditions, these three terms can be evaluated[54].

One possibility, which apparently has not yet been unambiguously documented but which should be kept in mind, is that an unassisted S_N2 reaction could in the presence of powerful electrophilic assistance be converted to an S_N1-type reaction. This type of behaviour may be relevant to a recent study of the hydrolysis of isobutyl iodide

catalysed by Hg(II), Th(II) and Ag(I) ions. Kinetic studies suggested an assisted S_N2-type process with water as the attacking nucleophile, but product studies indicated that rearrangements consistent with formation of an intermediate *t*-butyl carbocation had occurred[56]. This type of borderline behaviour is not uncommon, and Bunton[57] pointed out several years ago that the description of the borderline region depends to some extent upon the mechanistic tests applied.

The interactions between alkyl halides and aluminium, boron and gallium halides appears to involve predominant formation of 1:1 complexes. These investigations have been closely related to studies of Friedel–Crafts reactions[58].

III. SILVER ION ASSISTANCE TO REACTIONS OF ALKYL HALIDES

A. General Considerations

The interaction of a suspension of silver oxide in water with α-chloroacids was an important step in many of the schemes used to establish the occurrence of a Walden inversion[59]. Some of the earliest kinetic studies of organic reactions involved interaction of silver salts with alkyl halides[60–65]. Indeed, some of this accumulated information has been used in the development of modern theories for the mechanisms of these reactions. Silver salts were in use for development of synthetic techniques during the nineteenth century. The Gautier synthesis of alkyl isocyanides involves alkyl halides interacting with silver cyanide[66], but when sodium or potassium cyanide is employed the major product is the nitrile with only small amounts of isocyanide[66]. The Victor Meyer synthesis of nitroalkanes similarly employed silver nitrite, which was believed, until recently, to give a higher nitroalkane/alkyl nitrite ratio than the sodium or potassium salt[66].

B. Mechanism Studies with Silver Nitrate

Burke and Donnan[60] investigated the kinetics of reactions of alkyl iodides with a solution of silver nitrate in methanol or ethanol. Although approximately constant second-order rate coefficients were found throughout each run, the values increased as the initial silver nitrate concentration was increased. A more recent analysis[67] shows that, in the initial stages of reaction, the true kinetic order is close to 2.5, which can be subdivided into unity for the alkyl iodide and 1.5 for silver nitrate. The second-order rate coefficients remain approximately constant throughout each run because the expected fall off is counterbalanced by an autocatalysis by precipitated silver halide[64,68]. Added calcium nitrate or nitric acid had only slight accelerative effects but appreciable acceleration of the reaction of ethyl iodide with silver nitrate in ethanol at 24.5°C was achieved through ammonium nitrate addition[63]; the acceleration was assumed to require free nitrate ions. The reaction produces both diethyl ether and ethyl nitrate, and little (if any) ethylene is produced:

$$EtI + AgNO_3 \xrightarrow{EtOH} \begin{cases} EtONO_2 + AgI \\ Et_2O + HNO_3 + AgI \end{cases}$$

It was found[63] that, *irrespective of the silver nitrate concentration*, 70% of the overall reaction was with acid formation.

In ethanol, for reaction of 0.025 M alkyl iodides with 0.25 M silver nitrate at 24.5°C, a rate sequence Me, 0.43; Et, 1.00; *n*-Pr, 0.45; *n*-Bu, 0.32; iso-Bu, 0.063; iso-Pent, 0.27 was observed[60]. A very similar sequence, Me, 0.81; Et, 1.00; *n*-Pr, 0.51; iso-Bu, 0.084; neo-Pent, 0.013 was subsequently observed by Dostrovsky and Hughes[69] for the reaction of 0.10 M alkyl bromides with 0.14 M silver nitrate in 70% aqueous ethanol at 64°C. These sequences are intermediate between those that one would predict for unimolecular and bimolecular silver ion-assisted pathways. Pearce and Weigle[65] obtained similar results in a study of the reaction of ethyl iodide with silver nitrate in ethanol, methanol and ethanol–methanol mixtures at 25.0°C and their data can also be interpreted in terms of an overall 2.5 order.

Donnan and Potts[62] found that silver nitrate reacted considerably slower with ethyl iodide in acetonitrile than in ethanol but the kinetic pattern was very similar. The kinetics have also been reinterpreted in terms of 2.5-order rate coefficients[67]; the values are 0.0085 $M^{-3/2}$ s^{-1} at 25.0°C in acetonitrile and 0.136 $M^{-3/2}$ s^{-1} in ethanol. This is consistent with the formation of a relatively stable silver complex, $Ag(CH_3CN)_2^+$, in acetonitrile[70].

Baker[71] studied the unassisted and silver nitrate-assisted solvolyses of benzyl bromide and its *p*-methyl and *p*-nitro derivatives in 90% ethanol. At 30°C, the relative unassisted solvolysis rates were: *p*-Me, 4.1; H, 1.0; *p*-NO_2, 0.1. In the presence of 0.0125 M silver nitrate, the background solvolysis was swamped out and, at 0°C, the *p*-Me to H ratio was 65, and at 30°C, the H to *p*-NO_2 ratio was 50. The larger spread of values is consistent with an increased contribution within the transition state of ionization relative to nucleophilic attack. The product from the silver nitrate-assisted reaction contained about 24% nitrate ester accompanying the ether and alcohol solvolysis products.

Prévost and Boyer[72] studied the reactions of tertiary alkyl chlorides of type RMe_2CCl and R_3CCl with silver nitrate in aqueous acetone and in ethanol. In relatively highly aqueous acetone or in ethanol the reactions were of second order but at low concentrations of water the order rose to 2.4 for RMe_2CCl substrates and 3.5 for R_3CCl substrates. In 95% acetone the orders were two for RMe_2CCl substrates and three for R_3CCl substrates. For the third-order reaction, they showed that the order could be subdivided into unity in R_3CCl and two for silver ion. They considered, but rejected, the following pathway:

$$R_3CCl + 2\,Ag^+ \longrightarrow R_3C^+ + AgCl + Ag^+$$

Strong evidence for pathways of this type, but with preassociation, have since been obtained for reaction with *t*-butyl chloride in aqueous ethanol[73].

Prévost and Singer[74] extended the above study to a consideration of the effect of alkyl chain length in the reaction of silver nitrate with $Me_2CCl(CH_2)_{n-1}CH_3$ in ethanol. It was found that second-order behaviour applied only as far as $n = 4$ and, for $n > 9$, the order fell to unity. The rates under identical conditions oscillated and then levelled off for $n > 10$.

In the early 1950s, the mechanism of the substitution reaction of a silver salt (AgY), such as the nitrate, with an alkyl halide (RX) in aqueous ethanol was given the notation S_N1 Ag^+ and formulated as follows[75]:

$$RX + Ag^+ \xrightarrow[\text{surface}]{AgX} R^+ + AgX$$

$$R^+ \xrightarrow{H_2O} ROH + H^+$$

$$R^+ \xrightarrow{R'OH} ROR' + H^+$$

$$R^+ \xrightarrow{Y^-} RY$$

This designation was largely based on the relative rates with different alkyl groups lying closer to a S_N1 than a S_N2 sequence, the observation of extensive racemization when reaction was at a chiral centre, and the frequent observation of rearranged products[69]. Indeed, Ingold stated[75] that while metal ion-catalysed, S_N2-like reactions may exist, no strong evidence for them had been forthcoming up until that time. Dewar proposed an essential identical reaction path[76]. Evidence for bimolecular (S_N2 Ag^+) silver ion-assisted reactions was, however, soon to be forthcoming.

Vona and Steigman[77] studied the solvolysis reactions of primary and secondary alkyl chlorides and bromides in pyridine, both in the presence and absence of silver nitrate. The high solubility of silver chloride and bromide in pyridine allowed homogeneous conditions to be maintained during reaction. The silver ion assistance was milder than in hydroxylic solvents, presumably due to the high stability of the $Ag(Pyr)_2^+$ complex. The products were the quaternary pyridinium salts plus, for secondary alkyl halides, alkene; for alkene-producing reactions the product ratio was unchanged by the presence of silver nitrate. The kinetics could be expressed in the form

$$-d[RX]/dt = k_1[RX] + k_2[RX][AgNO_3]$$

Replacement of silver nitrate by other nitrate salts showed that positive salt effects were not sufficient to account for the second term of the rate expression and, in the presence of silver nitrate, added tetra-*n*-butylammonium nitrate did not change the k_2 value.

Primary alkyl halides reacted in the silver ion-assisted reaction five times as rapidly as secondary alkyl halides. Although reduced from a value of about 20 for the unassisted reaction, this was the sequence expected for bimolecular reaction (S_N2 Ag^+). It was concluded that both electrophilic assistance by silver ions and nucleophilic attack by pyridine molecules were involved and the greater reactivity of the primaries plus the unchanged product ratios in the presence of silver ion assistance were interpreted in terms of the nucleophilic attack being the dominant driving force.

There has been a considerable amount of subsequent work, both in hydroxylic solvents and also in the dipolar aprotic solvent, acetonitrile. Acetonitrile is of relatively low nucleophilicity and, while it can act as a nucleophile towards powerful alkylating agents, 0.01 M concentrations of an only moderately nucleophilic arenesulphonate ion can swamp out the background solvolysis[78,79]. Accordingly, in the presence of nitrate ions, competitive formation of nitrilium ions is not to be expected. The degree of dissociation of silver nitrate as a function of concentration in acetonitrile has been established both by conductivity[80] and Raman studies[81]. As in pyridine, one would expect electrophilic assistance to be weakened by solvent complexation and nucleophilic assistance to be maximized due to the poor solvation of anions in dipolar aprotic solvents; these factors make acetonitrile an excellent solvent within which to search for S_N2 Ag^+ reactions.

Hammond and coworkers[82] investigated the reactions of methyl, ethyl, isopropyl and neopentyl iodides with silver nitrate and perchlorate in acetonitrile. The *t*-butyl iodide reacted too fast for measurements to be possible. Participation by nitrate ion was indicated by the nitrate salt reacting considerably faster than the perchlorate salt. A low reactivity for neopentyl iodide, backside attack severely hindered, was also taken as evidence for anion participation. The order in silver nitrate was between one and two, approaching two at the higher concentrations. Similar characteristics were observed in benzonitrile. Lithium perchlorate accelerated the reaction with silver perchlorate but no perchlorate ester was detected. On the mistaken assumption[78,83] that covalent perchlorate esters would not solvolyse in acetonitrile, this was interpreted as assistance by perchlorate, leading to a carbenium–perchlorate ion pair which then always underwent reaction with the solvent (route *b* of Scheme 1).

$$X^- + R{-}I + Ag^+ \xrightarrow{\text{Slow}} X^-R^+ + AgI$$

$$X^-R^+ \xrightarrow{(a)} R{-}X$$

$$X^-R^+ \xrightarrow{(b)} HX + \text{olefin or solvent alkylates.}$$

SCHEME 1

The finding by Burke and Donnan[63] that, in ethanol, the product ratio from the silver ion-assisted reaction of ethyl iodide was independent of the nitrate ion concentration gave indirect support to this mechanism. If preassociation of the alkyl iodide and silver ion prior to attack by nitrate ion[67] is incorporated, the mechanism is not unreasonable, and with minor amplification (Scheme 2), it can be seen to resemble the Sneen ion-pair (S_N2 C^+) mechanism[84] for bimolecular nucleophilic substitution reactions.

$$R{-}I + Ag^+ \rightleftharpoons (R{-}I{-}Ag)^+$$

$$(R{-}I{-}Ag)^+ \rightleftharpoons R^+I^-Ag^+$$

$$X^- + R^+I^-Ag^+ \xrightarrow{\text{Slow}} X^-R^+ + AgI$$

$$X^-R^+ \longrightarrow R{-}X$$

$$X^-R^+ \longrightarrow HX + \text{olefin or solvent alkylates}$$

SCHEME 2

Formulated either as in Scheme 1 or as in Scheme 2, the mechanism requires that the product ratio (from X^-R^+) be independent of the identity of the halogen previously removed by the silver ion. It was subsequently reported that in its reaction with silver nitrate in acetonitrile 2-octyl bromide gives substantially more olefin than 2-octyl chloride, showing that the identity of the halogen does influence the product ratio, and the mechanism was modified to one in which product formation was from a $NO_3^-R^+X^-Ag^+$ ion quartet[67]; the kinetic evidence for nitrate ion participation in this system follows.

Pocker and Kevill further showed[67] that, for 2-octyl bromide, 2-octyl chloride and 1-octyl bromide, the kinetics were of very close to 2.5 in order:

$$\text{Rate} = k_{2.5}[RX][AgNO_3]^{1.5}$$

In the case of 2-octyl bromide, the reaction was shown to be accelerated by added tetraethylammonium nitrate, and decelerated by added tetraethylammonium perchlorate. Unlike in pyridine, where primary alkyl halides reacted faster than secondary, the 2-octyl bromide was found to be about three times more reactive than the 1-octyl bromide, suggesting more S_N1 character in acetonitrile.

$$\text{Rate} = k_{2.5}[RX][AgNO_3]([AgNO_3] + [Et_4NNO_3])^{1/2}$$

Optically active 2-octyl bromide was shown to react with silver nitrate in acetonitrile at 100.1 °C to give, in addition to a mixture of alkenes (16.4%), 2-octyl nitrate (83.6%)

of predominantly inverted configuration (87(±3)% maintenance of optical purity). Kornblum and Hardies[86], using much more concentrated solutions at room temperature, isolated an 81% yield of 2-octyl nitrate which also had a high net inversion (87% maintenance of optical purity). Heterogeneous reaction in diethyl ether or petroleum ether also gave mainly inverted nitrate ester, with slightly reduced optical purity in diethyl ether and considerable loss of optical purity in petroleum ether. It was suggested[86] that the substitution reaction probably proceeds stereospecifically, but loss of optical purity results from racemization of 2-octyl bromide during reaction. The results were considered[85] to be consistent with the quadrupole ion intermediates, $NO_3^- R^+Br^-Ag^+$, proposed on the basis of kinetic and product studies[67].

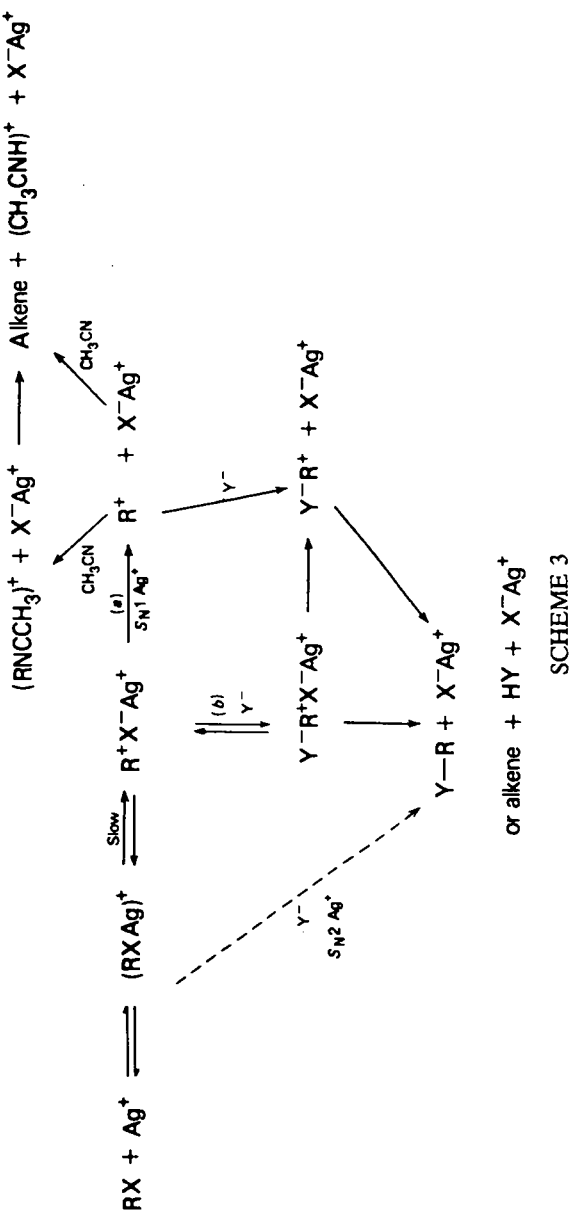
Kornblum and Hardies also investigated[86] the stereochemistry of the reaction of α-phenylethyl chloride with silver nitrate. The α-phenylethyl chloride is particularly susceptible to racemization induced by silver chloride[87] and considerable loss of optical purity was observed. For homogeneous reaction in acetonitrile and heterogeneous reaction in petroleum ether a net inversion of configuration was observed, and for heterogeneous reaction in ethyl ether or benzene a net retention of configuration was observed. Presumably, in the second pair of solvents, the initial nucleophilic attack is by the solvent to give an intermediate oxonium ion or π complex with inversion and then a second inversion occurs when these are attacked by nitrate ion. The intermediate in benzene was designated as a π complex (rather than a σ complex) since little or no alkylation of the solvent was observed.

Pocker and Wong[88] investigated the reaction of neopentyl iodide with silver nitrate in acetonitrile. They found, at temperatures in the range 25–75°C, over 65% of the products to be alkenes, suggesting that a substantial portion of the reaction must be going through a *t*-pentyl carbocation and probably also through *t*-pentyl nitrate, since *t*-alkyl nitrates would decompose[89] during the duration of these slow reactions. Although 2.5-order kinetics gave reasonably good correlations, they proposed that the kinetics of attack on the alkyl halide–silver ion complex were best explained by assuming concurrent second- (unassisted or solvent-assisted) and third-order (anion-assisted) processes of the type

$$\text{Rate} = k_2[\text{RI}][\text{Ag}^+] + k_3^{\text{Y}^-}[\text{RI}][\text{Ag}^+][\text{Y}^-]$$

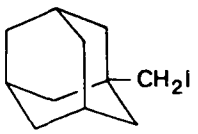
with the assumption that only free silver and nitrate ions[80,81] are active as electrophiles and nucleophiles. The rates were enhanced by added nitrate ions but remained essentially unchanged when perchlorate ions were added. The equation was found to hold over a 25-fold variation in silver nitrate concentration. The increase in rate with increasing silver nitrate concentration was not much greater than for silver perchlorate; the $k_3^{NO_3^-}$ value is only about twice the $k_3^{ClO_4^-}$ value. Indeed, for reaction with both silver nitrate and silver perchlorate, the kinetic pattern observed parallels that for *t*-pentyl iodide or chloride[90] and *t*-butyl chloride[91].

For the reaction of *t*-butyl chloride with silver nitrate, it was proposed[91] that the effect of the nitrate ion was not in attacking the $(t\text{-BuCl}\cdots\text{Ag})^+$ complex but in attacking the $(t\text{-Bu}^+\text{Cl}^-\text{Ag}^+)$ ion triplet formed upon ionization, so as to prevent internal return of chloride ion (Scheme 3). At low salt concentrations, reaction (*a*) will be dominant, but, as $[Y^-]$ increases, path (*b*) will become significant, and this is believed to be the major pathway leading to substitution. At temperatures of 45°C or less, the *t*-alkyl nitrate is the dominant product, from *t*-pentyl chloride or iodide[90] as well as from *t*-butyl chloride, provided that the silver nitrate concentration is at least 0.04 M. This expanded scheme was put forward because the *t*-butyl carbocation formed in conventional S_N1 reactions in aprotic solvents gives very low yields of substitution products, even in the presence of more powerful nucleophiles[92]. With neopentyl iodide, it is


RX + Ag+
(RXAg)+
Slow
R+X−Ag+
(a)
SN1 Ag+
R+ + X−Ag+
CH3CN
(RNCCH3)+ + X−Ag+
Alkene + (CH3CNH)+ + X−Ag+
CH3CN
(b)
Y−
Y−R+X−Ag+
Y−R+ + X−Ag+
Y−
SN2 Ag+
Y−R + X−Ag+
or alkene + HY + X−Ag+

SCHEME 3

possible that the bimolecular (S_N2 Ag^+) reaction usually expected for a primary alkyl halide is sufficiently sterically retarded that an S_N1 Ag^+-type mechanism dominates the course of the reaction. If the mechanism proposed for *t*-butyl chloride is applied, there is the interesting requirement that the internal return which is circumvented must return to the original neopentyl iodide and not to the *t*-pentyl iodide which would be obtained after rearrangement. The *t*-pentyl iodide would react extremely fast under the experimental conditions and return to this species would be kinetically equivalent to product formation. Rearrangement would then occur within the ion quartet (or the ion pair formed after silver iodide loss). Support for this viewpoint comes from the observation that 1-adamantylcarbinyl iodide (**1**) reacts twice as fast as neopentyl iodide (**2**) towards either silver nitrate or silver perchlorate even though **1** lacks the ability to rearrange because of steric bias[90].



(1)

$(CH_3)_3CCH_2I$

(2)

A comparison[91] of *t*-butyl chloride and *t*-butyl chloride-d_9 in their reactions with either silver nitrate or silver perchlorate leads to a k_H/k_D value which within experimental error is identical to that observed (2.62 ± 0.02) in the unassisted dehydrochlorination[92]. In contrast, bimolecular chloride ion-promoted dehydrochlorination[93] exhibited a value of 3.81 ± 0.21. These deuterium isotope effects are consistent with the view that the silver ion assists an ionization of the C—X bond, with nitrate ion sometimes having the secondary role of circumventing internal return.

Pocker and Wong claimed that the reaction of 2-octyl bromide with silver nitrate, previously analysed in terms of 2.5-order rate coefficients[67], could also be analysed in terms of the two-term equation (rate = $k_2[RBr][Ag^+] + k_3[RBr][Ag^+][NO_3^-]$) for salt concentrations of 0.01–0.07 M. However, the k_2 value of 4.4×10^{-6} M^{-1} s^{-1} and the k_3 value of 3.71×10^{-2} M^{-2} s^{-1}, coupled with a degree of dissociation for the salt of about 0.8 at 0.01 M and 0.6 at 0.07 M, show that the component from the second-order process to the overall rate is in the range 0.3–1.5%. Accordingly, this reaction could be viewed as proceeding only by the pathway governed by the third-order term. Indeed, this can be seen from the fact that, at 0.03 M silver salt concentration, silver nitrate reacts 80 times faster than silver perchlorate[67,94,95]; the rate with silver perchlorate represents an upper limit to that for the non-anionically assisted process.

For reaction with *tert*-pentyl chloride and iodide, Pocker and Wong[90] found the ratio of elimination to substitution to be, at a given temperature, independent of the concentration of silver nitrate or added tetraethylammonium nitrate and, in contrast to the results for 2-octyl halides, also independent of the identity of the displaced halogen. This indicates a much weaker leaving-group effect in the product-forming step for reaction of a tertiary alkyl halide relative to that for reaction of a secondary alkyl halide and it suggests a major difference in mechanism for reaction with two classes of alkyl halides.

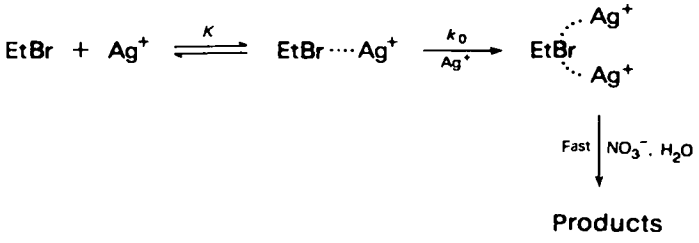
Colcleugh and Moelwyn-Hughes[96] and Huq[97] have investigated the reaction of methyl iodide with silver nitrate in water. Both investigations showed that the experimental second-order rate coefficients were constant throughout any given run but the values increased as the concentration of silver nitrate increased. When the ionic strength was kept constant at 0.05 M by addition of potassium nitrate, an increase in

the silver nitrate concentration caused a modest *decrease* in the experimental second-order rate coefficient (k_2). Both investigations led to the expression

$$k_2 = k_2^\circ + k_3[NO_3^-]\gamma^2,$$

where γ is the mean activity coefficient of the ions and k_2° is the second-order rate coefficient at very low salt concentration. One of the few differences between the two studies was the acceptance of literature values for γ in the earlier work[96] and calculation in the subsequent work[97]. When silver perchlorate was substituted for silver nitrate, the rate increased with salt concentration but the effect was not as marked. While the rate increases with increasing nitrate ion concentration, very little (if any) nitrate ester is produced; methyl nitrate would solvolyse extremely slowly under the reaction conditions[98]. It was proposed[96,97] that two intermediates are involved, of composition $(RIAg)^+$ and $(NO_3RIAg)^0$. In the latter, it was suggested that the anion approaches the methyl end of the molecule (without reaction) and gives coulombic assistance to drawing in the silver ion as it is approaching the halide end of the molecule. However, since nitrate ion has a Swain–Scott n value of 1.03 ($n(H_2O) = 0$ by definition[99]), it is difficult to see why such an ideally situated nitrate ion would give way to water molecules in the completion of the overall substitution process. One possibility is that the species should be considered as a solvent-separated ion pair, $NO_3^-\|(RBrAg)^+$, rather than an intimately assembled aggregate. Indeed, within such a solvent-separated species, the nitrate ion could exert general base catalysis towards the hydrolysis reaction. One of the few instances where general base catalysis has been proposed for reactions at sp^3-hybridized carbon in aqueous solution is for the intramolecular cyclizations of δ-hydroxysulphonium ions[100], an internal S_N2-type reaction which also involves a RX^+-type substrate.

As briefly discussed in Section II.E, Rudakov and coworkers have shown that aqueous solutions of silver nitrate can interact with alkyl halides through two distinct complexes, involving one or two silver ions. For ethyl bromide[49], with silver nitrate concentrations in the range 0.3–2.5 M, all reaction was through the complex with two silver ions:



When constant ionic strength was maintained by use of potassium nitrate, the appropriate rate expression was

$$\frac{-d[EtBr]}{dt} = \frac{k^\circ K[EtBr][Ag^+]^2}{1 + K[Ag^+]}$$

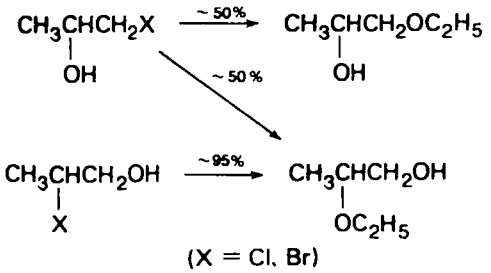
In water, the stability of Ag_2Br^+ is five orders of magnitude higher than that of $AgBr$[27], favouring the pathway with two silver ions. After displacement of Ag_2Br^+, AgBr is precipitated and the second Ag^+ (a true catalyst) released. It was calculated that at 10^{-3} M silver ion, one would expect equal amounts of reaction by one and two silver ion routes and the two silver ion route would be favoured above this concentra-

tion. Experimentally the formal orders were shown to be 1.7 in silver ion and 0.5 in total nitrate salt. The origin of the 0.5 order was not clear. It could just be a salt effect or it could indicate nitrate ion participation, as proposed by Colcleugh and Moelwyn-Hughes[96] and by Huq[97]. The possibility of a four-centred intermediate

$[EtBr\cdots{}^{Ag}_{Ag}\cdots NO_3]^+$ was mentioned. It was speculated that, since the $[Ag_3I]^{2+}$ ion also has high stability, a kinetic term corresponding to participation by three silver ions might be observed in reactions of alkyl iodides. It was subsequently found, however, that methyl iodide[50] shows only terms corresponding to involvement of one and two silver ions. The observation for reaction with methyl iodide of only the one silver ion term by Colcleugh and Moelwyn-Hughes[96] and by Huq[97] is not inconsistent with this picture since these workers used considerably lower (<0.1 M) concentrations of silver nitrate. Pathways involving either one or two silver ions were also found for the hydrolyses of ethyl iodide[51], isopropyl bromide[51] and (in aqueous ethanol) *t*-butyl chloride[73]: a series of compounds encompassing the entire S_N2 Ag^+–S_N1 Ag^+ spectrum.

Jaycock and Parfitt used the reaction between silver nitrate and ethyl iodide as a means of generating silver iodide in a study of its growth kinetics in ethanol[101]. Parfitt and coworkers[102] subsequently proposed that silver nitrate ion pairs were the reactive species but they pointed out that interaction of NO_3^- with a preformed $EtIAg^+$ complex would equally well rationalize their observations.

A study has been made[103] of the products from the reactions of 1-halogeno-2-propanols and 2-halogeno-1-propanols with silver nitrate in ethanol:



It was proposed that the reaction of $CH_3CH(OH)CH_2X$ proceeded via a protonated propylene oxide intermediate which can then ring open to either of the two products. Presumably, this intermediate is not formed from $CH_3CH(X)CH_2OH$ and an open carbenium ion was proposed. This reaction could, however, involve intermolecular S_N2 Ag^+ reaction as opposed to the intramolecular S_N2 Ag^+-type reaction.

Kevill and Horvath[104] studied the reactions of 1-adamantyl halides with ethanolic silver nitrate and perchlorate. The kinetics were found to be complex, suggesting that the use of ethanolic silver nitrate to give a semi-quantitative evaluation of the relative reactivities of bridgehead halides[105] requires a study under exactly equivalent conditions. For the reaction of 1-adamantyl chloride with silver nitrate or silver perchlorate at 25°C, it was found that the kinetic orders were 1.5–1.7 for 1-adamantyl chloride, about 1.6 for silver nitrate, and in excess of unity when silver perchlorate was used (with the value increasing with increasing $[AgClO_4]$). It was proposed that an intermediate formation of clusters containing silver ions, counterions, 1-adamantyl carbocations and halide ions was involved. One surprising feature of the study was the over 10^4-fold rate increase on replacing chlorine by bromine, since in hydroxylic solvents this value has usually been found to be in the range 30–100[106]. A second surprising

feature was the formation, even at very low (0.005 M) silver nitrate concentrations, of predominantly the nitrate ester as opposed to the ethyl ether. The extent of the solvolysis increased in the order 1-AdCl < 1-AdBr < 1-AdI and decreased as the silver nitrate concentration increased or as tetraethylammonium nitrate was added. Tetraethylammonium nitrate caused a slight deceleration of the reactions with silver nitrate, suggesting that nucleophilic assistance by nitrate ion was not occurring, although silver nitrate reacted a little faster than silver perchlorate within the concentration range studied. The cage structure present in 1-adamantyl derivatives would, of course, prevent any classical S_N2 reaction. The cluster model, suggested by the kinetics, can explain the dominant formation of the anionic substitution product and the dependence of the product ratio upon the identity of the leaving group. For unassisted reactions of 1-adamantyl derivatives, even in the presence of relatively large concentrations of appreciably nucleophilic anions, only solvolysis products are obtained; for example, 1-adamantyl *p*-toluenesulphonate solvolyses in 0.15 M ethanolic tetraethylammonium chloride without any detectable 1-adamantyl chloride formation[107].

Meléndez and Prévost[108] studied the effect of variation of the composition of an acetone–water mixture upon the reaction of methyl and ethyl bromide with silver nitrate, perchlorate and trifluoroacetate. For each salt, at low water content, the methyl bromide reacted faster than ethyl bromide and this situation was reversed at higher water content. The effect on the rates for either substrate of increasing the water content was an increase throughout the range (up to 72% water content) for silver perchlorate, an initial decrease with a minimum at about 30% water content for silver nitrate in the 2–72% water content range, and an increase to a maximum at about 8% water content followed by a minimum at about 40% water content for silver trifluoroacetate. Since, at least, one must consider changes in solvation of the silver ion and the counterion, in the nucleophilicity of the solvent, and in the stability of the $[RBrAg]^+$ complex, interpretation would be extremely difficult.

The same workers studied[109] the kinetics of the reaction of silver nitrate with continuous chain alkyl bromides of up to seven carbons. With 2% water–98% acetone, they found third-order kinetics, but in 50% aqueous acetone the reaction was of second order. Methyl and ethyl bromides had similar rates, an appreciable rate reduction was observed for *n*-propyl bromide, and relatively minor rate fluctuations occurred throughout the *n*-propyl to *n*-heptyl bromide range.

C. Mechanism Studies with Silver Arenesulphonates

Hoffmann prepared[110] *t*-butyl *p*-toluenesulphonate by the low temperature reaction of *t*-butyl bromide with an acetonitrile solution of the silver salt. It is interesting that, as in the reaction with silver nitrate[91], substitution is the dominant pathway, although similar reactions in the absence of silver ion give predominantly isobutylene[111]. He also found that, at -30°C, the reaction with silver tetrafluoroborate was only one-tenth as fast as with silver *p*-toluenesulphonate, paralleling the subsequent comparison of *t*-butyl chloride with silver nitrate and silver perchlorate[91].

Arenesulphonate ions are of appreciable nucleophilicity, especially in aprotic solvents, and they will carry out S_N2 reactions in acetonitrile upon powerful methylating agents such as methyl trifluoromethanesulphonate[112], methyl fluorosulphonate[78], trimethyloxonium ion[113] and methyl perchlorate[79]. The rates vary appreciably when *meta* and *para*-substituents are introduced and in each case the Hammett ρ value is close to -1.1.

The reactions of methyl iodide with silver arenesulphonates have also been studied in acetonitrile [112]. For each salt, the kinetics approximate to 2.5-order, although the

values increase somewhat with silver salt concentration throughout the 0.005–0.16 M range studied. The Hammett ρ values decreased over the above range from −1.09 to −0.98, all the values being very close to those obtained with other powerful methylating agents, where there is considerable evidence for conventional S_N2 reaction. If the scheme previously proposed[67,82,96] for silver nitrate reaction is considered, there is no appreciable development of bonding to the attacking anion

$$RX + Ag^+ \rightleftharpoons [RXAg]^+$$

$$NO_3^- + [RXAg]^+ \xrightarrow{\text{Slow}} NO_3^-R^+X^-Ag^+$$

within the rate-determining step and, for a parallel reaction with arenesulphonate ions, one would not expect any considerable influence by *meta* and *para* substituents. In actual fact, the influence is identical to that observed for S_N2 reactions, strongly suggesting that the rate-determining attack involves a conventional S_N2 Ag^+ reaction:

$$RX + Ag^+ \rightleftharpoons [RXAg]^+$$

$$ArSO_3^- + [RXAg]^+ \xrightarrow{\text{Slow}} ROSO_2Ar + X^-Ag^+$$

It must be emphasized, however, that this has only been demonstrated for methyl iodide. Alkyl halides which are normally considered to react in the S_N1–S_N2 borderline region, such as 2-octyl halides, may proceed by other mechanisms, such as the one previously proposed[67,82,96].

The data for the methyl iodide–silver *p*-toluenesulphonate (AgOTs) reaction have been analysed in terms of the Pocker and Wong equation, where $[AgY]_s$ is the

$$\text{rate} = \alpha k_2^{\circ}[RX][AgY]_s + \alpha^2 k_3^{Y^-}[RX][AgY]_s^2,$$

stoicheiometric silver salt concentration and α is the degree of dissociation of the salt. With other powerful methylating agents, it had been demonstrated[78,112,113] that bimolecular reaction with (> 0.005 M) arenesulphonate ions swamps out any background solvolysis and the first term (representing reaction without anionic assistance) should, therefore, be unimportant. Values of α at various concentrations were obtained by assuming that only free ions are appreciably nucleophilic in a consideration of the second-order rate coefficients for the reaction

$$MeOClO_3 + AgOTs \longrightarrow MeOTs + AgClO_4$$

While the fit to the equation was not too unreasonable, a minimum value for k_3^{exp}/α^2 (i.e. $k_3^{Y^-}$) in the middle of the concentration range was observed and one would predict that extrapolation to lower or higher concentrations would lead to considerable variation in the value:

$$\text{Rate} = k_3^{expt}[RX][AgY]_s^2$$

While the degree of dissociation is indeed important, one would expect a superimposed salt concentration influence because of the interaction of oppositely charged ions in the rate-determining step. By comparison, tetra-*n*-butylammonium arenesulphonates react with neutral esters, such as methyl trifluoromethanesulphonate[112] or methyl perchlorate[79] with values for the second-order rate coefficient which are independent of the salt concentration. However, for reaction with the positively charged

trimethyloxonium ion[113], an appreciable decrease in the values for the second-order rate coefficient is observed as the salt concentration is increased. The reaction

$$ArSO_3^- + Me_3O^+ \xrightarrow{MeCN} MeOSO_2Ar + Me_2O$$

is of the same charge type as

$$ArSO_3^- + [MeIAg]^+ \xrightarrow{MeCN} MeOSO_2Ar + AgI$$

D. Mechanism Studies with Silver Perchlorate

Silver perchlorate is soluble in a wide variety of organic solvents within which silver nitrate is of very limited solubility, such as aromatic (but not aliphatic) hydrocarbons[114], acetone[114], diethyl ether[114], ethyl acetate[114] and nitromethane[115]. Conductivity measurements indicate that, in a 10^{-3} M solution of silver perchlorate in benzene, the concentration of free ions is extremely small[116]. Cryoscopic experiments have indicated the solution to contain mainly ion pairs at very low concentrations and predominantly quadrupoles and multipoles as the concentration is increased.[117,118]. In the considerably more polar nitromethane, solutions have appreciable conductivity and appreciable ionic dissociation is indicated[119].

Redies and Iredale[114] investigated the reaction of methyl iodide with silver perchlorate in benzene and found the kinetics to be of 2.5 order. The product was assumed to be methyl perchlorate and, indeed, this method has subsequently been used as a way of preparing solutions of methyl perchlorate[79,120]. Only very small amounts of the Friedel–Crafts product, toluene, are formed[121]. In view of the complex behaviour of silver perchlorate in benzene and the extensive and variable degrees of association of ion pairs over the concentration range studied, the observation of a constant kinetic pattern is rather surprising. Even more surprising, similar results were obtained in such widely varying solvents as acetic acid, acetone[82], ethanol, ethyl acetate, 50% aqueous dioxane and 50% aqueous ethanol. However, in diethyl ether pseudo-second-order kinetics were observed throughout each run, which were related to an overall third-order rate coefficient.

Pocker and Kevill[83] investigated the reaction of 2-octyl bromide with silver perchlorate in benzene. They found the kinetics to approach 2.5 order, first order in alkyl halide and 1.5 order in silver salt, at low ($< 10^{-2}$M) salt concentrations. The order in silver perchlorate increased with the concentration within the remainder (up to 0.1 M) of the range studied. Especially at low silver salt concentrations, extremely small concentrations of added tetra-*n*-butylammonium perchlorate had a marked accelerative effect but a limiting velocity was soon attained. Also an autocatalysis observed in the absence of added tetra-*n*-butylammonium perchlorate was suppressed; presumably, this was a competitive acid catalysis, which was destroyed by complexing with perchlorate ion. In addition to perchloric acid, 38% of alkene and 61% 2-octyl perchlorate were also formed. Using optically active 2-octyl bromide it was shown that the cycle took place with 60% retention of optical purity. If we assume a Walden inversion

$$HClO_4 + ClO_4^- \rightleftharpoons H(ClO_4)_2^-$$

$$\underset{(+)}{C_8H_{17}Br} \xrightarrow[C_6H_6]{AgClO_4} \underset{(-)}{C_8H_{17}OClO_3} \xrightarrow[MeCN]{Et_4NBr} \underset{(+)}{C_8H_{17}Br}$$

in the second stage, then this value is for the first step, otherwise it represents a minimum value. If we assume a basic, simplified scheme, then the acceleration and

$$RBr + Ag^+ClO_4^- \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} RBr\cdots Ag^+ClO_4^-$$

$$ClO_4^- + RBr\cdots Ag^+ClO_4^- \xrightarrow{k_2} \begin{cases} ROClO_3 \\ \text{Octenes} \end{cases}$$

subsequent limiting rate observed on adding other perchlorate salts can be explained if k_{-1} is of the same order of magnitude as $k_2[ClO_4^-]$. At the higher silver perchlorate concentrations, the complex would be more accurately represented as $RBr(AgClO_4)_m$, where $m = 2,3$, etc. The optical results give some indication for formation of a carbocation intermediate in the reaction sequence. Nucleophilic attack could possibly be on a $R^+Br^-Ag^+ClO_4^-$ quadruplet, formed by ionization within the adduct shown above and within which reorientation of the R^+ group can then occur prior to attack by ClO_4^-, $Ag^+ClO_4^-$ or n-$Bu_4N^+ClO_4^-$.

Meléndez and Prévost[109] studied the reaction of silver perchlorate in toluene with the continuous chain C_2 to C_7 alkyl bromides at 60°C. The specific rates of reaction fluctuated but were all within 50% of the fastest reaction (with ethyl bromide). The observation that the rates were three times slower than in acetone was ascribed to the formation of a complex between the silver salt and the toluene.

Silver perchlorate is considerably dissociated in nitromethane[119] and a study of its reaction with methyl iodide has been made in this solvent[115,122] and also in nitrobenzene[122]. In both solvents, for a constant concentration of silver perchlorate, the rate initially increases with increasing methyl iodide concentration, but eventually a limiting rate is reached. This phenomenon can be explained by assuming that a pre-equilibrium is present and the products are formed from the alkyl halide–silver ion

$$CH_3I + Ag^+ \overset{K}{\rightleftharpoons} [CH_3IAg]^+$$

complex. The kinetics followed the Michaelis–Menten pattern, common in enzyme kinetics[123], with the silver ion equivalent to the enzyme and the alkyl halide representing the substrate. The association constant (K) had a value of 8.1 M^{-1} in nitromethane and of 35 M^{-1} in nitrobenzene. The higher value in nitrobenzene was considered to be consistent with a reduced solubility and with reduced dissociation, as indicated by conductivity measurements[119], for the silver perchlorate.

With the methyl iodide concentration kept constant and the silver perchlorate concentration varied, the order in silver perchlorate approached unity at low concentrations but it increased with concentration reaching a value of about 2.7 for reaction with 0.22 M silver perchlorate in nitromethane. Possible explanations include long-range interactions with additional silver ions, specific interaction with more than one silver ion[3,49], or a situation within which the ability to transfer a silver ion deviates from a linear relationship with concentration, especially at the higher concentrations. The latter explanation was considered[115] to be appealing because of the similarity to the acid-catalysed reactions of alkyl fluorides[17,23], where the rates followed the h_0 function rather than stoicheiometric acid concentration. It is possible that, if more reactions were studied, 'electrophilicity functions' (paralleling the acidity functions) could be set up for silver ion-assisted reactions. The major product (~80%) was methyl perchlorate, but an uncharacterized red amorphous solid was also isolated. A similar study was made of the reaction with neopentyl iodide in nitromethane[124]. The neopentyl iodide reacted with an identical kinetic pattern to methyl iodide. The association constant for the complex was 27 M^{-1}. With 0.11 M alkyl iodide and 1.6×10^{-2} M silver perchlorate, the neopentyl iodide reacted 33 times faster than methyl iodide; after

correction for the differing degrees of association, the values for reaction of the $[RIAg]^+$ complex differed by a factor of 21. It was believed that this value could be accommodated within the range of possible inductive influences[125], without the need to invoke anchimeric assistance. This conclusion is consistent with the isolation of optically inactive 2-methylbutan-2-ol-3*d* from the hydrolysis of neopentyl-1-*d* iodide in the presence of silver nitrate[126].

Acetonitrile is a weakly nucleophilic solvent and, in contrast to reactions in benzene[83,120] and nitromethane[115,127], alkyl perchlorates even if they were to be formed would solvolyse quite rapidly[78,83]. There is no evidence for alkyl perchlorates having been observed from a reaction between an alkyl halide and silver perchlorate in acetonitrile. At fairly low salt concentrations, reactions with silver perchlorate are slower than those with silver nitrate and the tendency for silver perchlorate to favour S_N1 Ag^+ reactions and silver nitrate to favour S_N2 Ag^+ reactions can be considered to provide an approximate measure of the susceptibility of substrates with halide ion leaving groups towards nucleophilic assistance[95]. For example, allyl bromide with 0.04 M salt[128] shows a $AgNO_3/AgClO_4$ rate ratio of 1600, α-bromo-*p*-phenylisobutyrophenone with 0.16 M salt[129] a value of 130, 2-bromooctane with 0.03 M salt[67,94] a value of 80, γ-methylallyl chloride with 0.20 M salt[95] a value of 48, α-methylallyl chloride with 0.20 M salt[95] a value of 8.1 and *t*-butyl chloride with 0.16 M salt[91] a value of 2.0.

It has been proposed[82] that perchlorate ion in acetonitrile can enter into the rate-determining step without completing the substitution process (Scheme 1) but this was on the erroneous assumption that perchlorate esters, if formed, would be unreactive towards the solvent; the rate expression with isopropyl iodide was approximately third order but only a limited concentration range (0.1–0.3 M) of silver perchlorate was

$$\text{Rate} = k_3[(CH_3)_2CHI][AgClO_4][AgClO_4 + LiClO_4]$$

investigated. The products were considered to be condensation products, formed via $CH_2{=}C{=}NC_3H_7$.

A more detailed study of the dependence on silver perchlorate concentration in reaction with 2-octyl bromide in acetonitrile[94] showed, for silver perchlorate concentrations of up to 1.5×10^{-2} M, second-order kinetics, first order in substrate and first order in silver perchlorate. At higher concentrations, the order gradually rises; for 0.3 M silver perchlorate, the order is a little higher than two. Added tetraethylammonium perchlorate had only a slight accelerative effect with 1.5×10^{-2} M silver perchlorate but a more pronounced effect with 0.15 M silver perchlorate. For reaction with *t*-butyl chloride[91], at low salt concentrations silver nitrate and silver perchlorate react at the same rate and with second-order kinetics. The values for the second-order rate coefficients rise with increasing salt concentration but more modestly for the perchlorate salt. For the perchlorate, it was suggested that the increase was probably, at least in part, associated with the ease of transferring a silver ion from solution to the alkyl halide increasing at a greater rate than the stoicheiometric concentration.

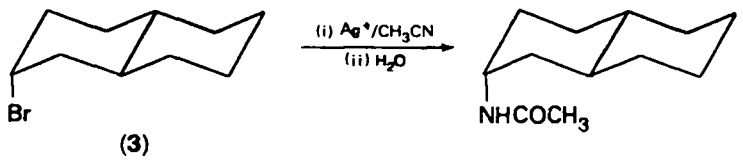
Pocker and Wong studied the reaction of an acetonitrile solution of silver perchlorate with neopentyl iodide[88], *t*-amyl iodide and 1-adamantylcarbinyl iodide[90]. They proposed in each case that, with correction for the partial dissociation (α) of a stoicheiometric concentration $[AgClO_4]_s$, the kinetics can be represented by

$$\text{Rate} = \alpha k_2^{\circ}[RI][AgClO_4]_s + \alpha^2 k_3^{ClO_4^-}[RI][AgClO_4]_s^2$$

There appears, however, to be a major approximation in that the α values used are those for silver nitrate and not those for silver perchlorate, whereas conductivity measurements[67] indicate more dissociation for silver perchlorate. It has also been

suggested[79] that it is necessary to consider the perturbations due to reaction involving positively ($RIAg^+$) and negatively (ClO_4^-) charged species in the analysis of the second term of the rate equation.

Cohen and Solash[130] have made a stereochemical study of the reaction of axial *trans*, *trans*-2-bromodecalin (**3**) with silver perchlorate or fluoroborate in refluxing acetonitrile. They reported that only the axial *N*-(*trans*, *trans*-2-decalyl)acetamide (**4**) was

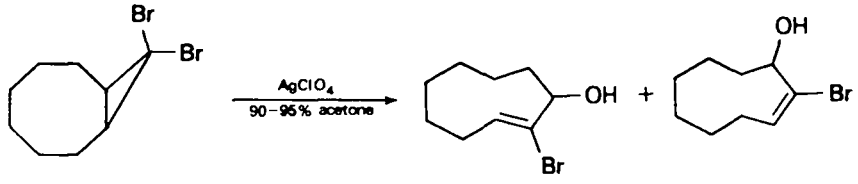


(3) (4)

produced. Two possible explanations were proposed. Either the counterion (ClO_4^- or BF_4^-) shields the backside of the carbon from attack, so that acetonitrile comes in from the front side, or the actetonitrile is donated from the attacking $Ag(CH_3CN)_2^+$ ion, in what could be considered as an S_Ni process.

Bach and Willis[131] have found a further example of reactions proceeding with a second-order dependence on silver ion concentration in the reaction of 2-octyl bromide with silver perchlorate in methanol to give approximately equal amounts of methyl ether and 2-octenes (*cis*:*trans* = 1:3). The total perchlorate salt concentration was maintained at 0.35 M by sodium perchlorate addition and the silver perchlorate contribution was 0.05–0.35 M. The overall retention of optical purity (ROH → RBr → ROMe) was 67%. The mode of interaction proposed for the two silver ions was essentially identical to that put forward earlier by Rudakov[3,49–51,73].

The silver ion-catalysed solvolytic ring opening of 8,8-dibromobicyclo[6.1.0]nonane (**5**)[132] was found to have a rate expression with terms of both first order and second order in silver ion[133]. It was assumed, for both the contributing mechanisms, that the first silver ion was assisting the removal of bromide ion, but it could not be determined whether the second was also interacting at the bromine or whether it was assisting directly in the rearrangement since silver ion-catalysed rearrangements of halogen-free small ring compounds, such as cyclopropanes, are well documented[134]. In aqueous acetone, the reaction produced both *trans*-(**6**) and *cis*-2-bromocyclononen-3-ol (**7**).



(5) (6) (7)

Loozen and coworkers[135] postulated, on the grounds that the amount of *cis*-isomer decreases as the solvent nucleophilicity increases, that an open *trans*-cation was initially formed which, competitive with solvent capture, isomerizes to the *cis* cation. Warner and Palmer[136] found the *cis*:*trans* product ratio to be a function of the silver ion concentration and a correlation was found between the ratio and the amounts of reaction proceeding by the one silver ion and two silver ion routes. It was suggested that the *trans* isomer was formed by both routes but the *cis* isomer only by the one silver ion route. This proposal explained why, in methanolysis, Reese and Shaw[132],

using a high (1 M) concentration of silver perchlorate, favouring the two silver ion route, had observed formation only of the *trans* isomer. It was further shown[136] that the silver ion-assisted hydrolysis of the monobrominated *exo*-8-bromobicyclo-[6.1.0]nonane favours much more the second-order process in silver ion than the corresponding hydrolysis of the geminal dibromo compound. Silver ion-assisted hydrolysis of *exo*-8-bromobicyclo[5.1.0]octane has been shown[137] to give a high yield of *cis*-cycloocten-3-ol, apparently obtained by isomerization of the initially formed *trans* isomer.

E. Mechanism Studies with Silver Nitrite

Silver nitrite is of limited solubility in most organic solvents. It will dissolve readily in acetonitrile, but conductivity measurements[67] indicate that the mode of dissociation is complex:

$$2\,AgNO_2 \rightleftharpoons Ag^+ + Ag(NO_2)_2^-.$$

It would, obviously, be unwise to choose silver nitrite for a fundamental study of the mechanism of electrophilic assistance to reaction at a C—X bond, and, indeed, studies have largely centred on the question of the dual reactivity (ambident character) of the nitrite ion in substitution reactions with alkyl halides:

$$RX + AgNO_2 \longrightarrow AgX + RONO + RNO_2.$$

The extensive work by Kornblum[138–145] on these reactions has been surveyed within reviews dealing with the dual reactivity of ambident anions[146,147].

The reaction of 2-octyl bromide with silver nitrite in acetonitrile has been briefly studied[94]. The reaction is subject to autocatalysis but the initial rates correspond, for a 0.01–0.08 M silver nitrite concentration range, closely to a 2.5-order reaction:

$$\text{Rate} = k_{2.5}[C_8H_{17}Br][AgNO_2]^{3/2}$$

The reactions are much slower than the corresponding S_N2 reactions with an equal concentration of tetraethylammonium nitrite. On adding tetraethylammonium nitrite to the reaction with silver nitrite, the increase in rate is initially very modest, due to removal of the added nitrite ions:

$$NO_2^- + AgNO_2 \rightleftharpoons Ag(NO_2)_2^-$$

With excess nitrite ions the rate then increases in exactly the pattern expected for S_N2 reaction between the 2-octyl bromide and the excess, uncomplexed nitrite ions.

When reactions of primary alkyl bromides or iodides with silver nitrite are carried out at slightly below room temperature, with diethyl ether as diluent[141], formation of nitrate ester side products[138–140] can be avoided. Continuous chain compounds gave 73–83% nitro compound and 10–14% nitrite ester. Branched chain compounds gave lower yields, even with longer reaction times. With secondary alkyl bromides or chlorides, even at slightly below room temperature[142], about 15% nitro-compound, about 30% nitrite ester, alkenes, nitrate esters and adducts of alkenes with oxides of nitrogen are observed. It was postulated that nitrous acid, accompanying the alkene formation, can decompose to oxides of nitrogen which can then give adducts or oxidize the nitrite ion to nitrate (which can then lead to nitrate esters). Tertiary alkyl chlorides gave small amounts (< 5%) of nitro compound and 50–64% nitrite ester plus adducts of alkenes with oxides of nitrogen. With tertiary alkyl bromides and iodides, no nitro compound was observed. 2-Bromooctane and 2-iodooctane gave a high degree of inversion in the conversion to both the 2-nitrooctane and the 2-octyl nitrite[143]. Con-

current racemization of the reactant was observed and it was proposed that, after allowance for the racemization, the degree of inversion would be close to 100%.

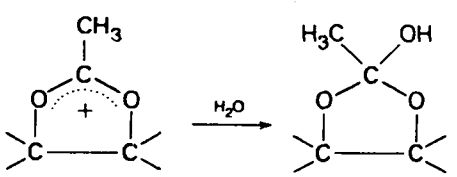
These results were rationalized by what, in a generalized form, has become known[146,147] as Kornblum's rule. The decrease in RNO_2 and increase in RONO on going from primary to secondary to tertiary alkyl halides suggested[144] that the higher the carbenium ion character of the attacked carbon the greater the tendency to react at the more electronegative atom (oxygen in the NO_2^- ion). Results with substituted benzyl bromides were consistent with this hypothesis[144]. With the electron-withdrawing *p*-nitro group, 84% RNO_2 and 16% RONO were formed but, with the electron-supplying *p*-methoxy group, 39% RNO_2 and 61% RONO were formed. The coordination of the halogen by the silver ion favours carbenium ion character at the α-carbon and increased nitrite ester formation. Accordingly, better yields (55–62%) of nitro compound are obtained from secondary alkyl halides when sodium nitrite is substituted for silver nitrite in *N,N*-dimethylformamide[148] or dimethyl sulphoxide[149].

The principle of hard and soft acids and bases[5–8] can be applied[147]. In the ambident anion, one atom is usually more electronegative (harder base) and the other more polarizable (softer base). Also, the greater the development of carbenium ion character, the more the polarizability at the α-carbon diminishes (i.e. it becomes a harder acid) and reaction with the more electronegative atom of the nucleophile becomes increasingly favoured.

The stereochemistry of the reactions of 2-bromooctane and α-phenylethyl chloride with silver nitrite[145], either homogeneously in acetonitrile or heterogeneously in diethyl ether, benzene or petroleum ether, parallels exactly (for formation of both RNO_2 and RONO) that for nitrate ester formation with silver nitrate under the same conditions[86].

F. Mechanism Studies with Other Silver Salts

The solvolyses of vicinal dibromides and of vicinal acetoxybromo compounds in acetic acid containing silver acetate played an important role in early studies of neighbouring-group effects in substitution reactions. Solvolyses of *threo-* and *erythro*-2-acetoxy-3-bromobutanes, *d,l-* and *meso*-2,3-dibromobutane, *trans*-1-acetoxy-2-bromocyclohexane and *trans*-1,2-dibromocyclohexane all gave diacetates with high retention of configuration[150]. In contrast, under the same conditions, 2-bromooctane gave inverted 2-octyl acetate with 72% retention of optical purity. This was considered a typical S_N1 result, but silver bromide-promoted racemization of unreacted substrate could account for some of the loss of optical activity[143]. The retentions of configuration were explained in terms of the intermediate formation of bromonium ions, or an ion with a bridging acetate group (**8**) in an S_N1Ag^+ process. In all the above reactions, the presence of a small amount of water resulted in a stereochemical shift towards inversion and a product containing monoacetate, which is only slowly esterified. The water seems to be involved only in the replacement of the second bromine of the dibromides[151]. These observations were rationalized in terms of intermediate formation of an orthomonoacetate (**9**).



(**8**) (**9**)

In anhydrous hydrogen fluoride, silver tetrafluoroborate reacts readily with *t*-butyl chloride with precipitation of silver chloride to give a carbenium ion. However, with primary and secondary bromoalkanes, silver bromide is released only after several hours or days. In anhydrous hydrogen fluoride, an electrochemical study[152] at a silver electrode in the presence of RBr led to identification by potentiometric titration of $(RBr)_nAg^+$ species. With ethyl bromide, distinct complexes were observed with $n = 1$, 2 or 3. Silver bromide precipitated from these complexes only slowly. With *n*-propyl and *n*-butyl bromides, complexes with $n = 1$ or 2 were observed and, due to faster silver bromide precipitation, the temperature had to be lowered to −25°C. No complexes were observed by this technique for isopropyl or *sec*-butyl bromides, but the oxidation curve of silver was shifted in the presence of isopropyl bromide, indicating unstable intermediates to be present. With ethylene dibromide, evidence for a $Ag(C_2H_4Br_2)_2^+$ complex was found. This work gives support to the kinetic[122] and gas-liquid partitioning[47] evidence for initial formation of discrete intermediates of this type prior to silver halide precipitation.

G. Consideration of the Alkenes Produced in Elimination Reactions

Reaction of 2-octyl bromide with silver nitrate in acetonitrile led to 2% 1-octene and 14% of a mixture of *cis*- and *trans*-2-octene[67]. Smith and Watson[153] carried out a detailed study of the reactions of *n*-butyl and *sec*-butyl bromides with a solution of silver nitrate in water or with a saturated solution, plus a heterogeneous phase, of silver nitrate in *t*-butyl alcohol. They determined the product distribution between 1-butene, *cis*-2-butene and *trans*-2-butene. At 73°C, with either of the reaction conditions, the *n*-butyl bromide gave predominantly 1-butene and the *sec*-butyl bromide predominantly 2-butenes. For all the reactions, the *trans/cis* ratio in the 2-butenes was 1.0–1.4:1. However, in this study, the possibility of heterogeneous reaction was completely disregarded. Heterogeneous reaction could occur either with undissolved silver nitrate or with precipitated silver bromide and a surface reaction might be expected to favour *cis* elimination.

Bartsch and Pruss[154] also carried out experiments with 2-butyl bromide and silver nitrate in *t*-butyl alcohol and showed that *in situ* generated (but not added) silver bromide can even lead to an excess of *cis* product over *trans* product. Accordingly, the *trans/cis* ratios observed by Smith and Watson[153] were almost certainly lower than the value that would apply to homogeneous reaction. Autocatalysis by silver bromide can be avoided by carrying the reaction out in several (but not all) aprotic solvents and under these conditions, at 50°C, the alkenes from 2-butyl bromides or iodides were 6.8–9.5% of 1-butene, 55–68% of *trans*-2-butene, and 25–35% of *cis*-2-butene with *trans/cis* ratios in the range 1.58–2.68. Reaction with silver perchlorate, silver acetate or silver nitrite also gave values within these ranges. In *E*2 reactions, values for the *trans/cis* ratio of 3.0–4.0 have been observed[155], and for a free cation values of unity would be expected. It is interesting that silver nitrate in pyridine, where considerable nucleophilic participation (by pyridine) has been observed[77], gives by far the largest *trans/cis* ratio; the value of 2.68 approaches the 3.0–4.0 predicted for *E*2 reactions. Since the ratios varied with leaving group (iodide or bromide and, also, silver or mercury ion assistance) a free 2-butyl cation was excluded. However, the strong preference for Saytzeff alkenes does indicate considerable carbenium ion character.

H. Heterogeneous Catalysis to Formally Homogeneous Reactions

A suspension of silver oxide in aqueous ethanol or an alcohol is effective in converting alkyl halides to alcohols and ethers. The reaction proceeds more quickly if a

soluble silver salt such as the nitrate or acetate is used, but it was proposed[2,156] that in all cases the reaction takes place largely on the surface of insoluble silver salt and, since this includes the silver halide formed during reaction, these reactions were considered to be very susceptible to autocatalysis. It has been suggested that the reactions take place on the surface of the silver salt with the help of adsorbed silver ions[2] and, when autocatalysis is observed, this is indeed generally accepted[154] to be the mechanism of the autocatalytic pathway.

Heterogeneous catalysis of formally homogeneous reactions, as typified by autocatalysis from precipitated silver halide, is not as general as the above description might suggest. For reactions of silver nitrate with alkyl halides in acetonitrile, it has been shown [62,67,82] to be very weak or non-existent. Similarly, based on the observation that heterogeneous reaction gives product distribution ratios for the butenes which are different from the homogeneous reaction, the reactions of 2-butyl halides with silver salts[154] were assumed to be without any important autocatalytic components in dimethylsulphoxide, *N,N*-dimethylformamide, acetonitrile, *N*-methyl-2-pyrrolidone, *N,N*-dimethylacetamide and pyridine; however, a strong autocatalysis was observed in tetramethylenesulphone (sulpholane). Kinetic evidence for autocatalysis was obtained for the reaction of methyl iodide with silver perchlorate in nitromethane[115], but not for the same reaction in benzene[114].

With respect to heterogeneous catalysis, silver ion-assisted reactions in protic solvents are almost as unpredictable as the reactions in aprotic solvents. Reactions of alkyl halides with silver nitrate have been found to be subject to autocatalysis in ethanol[60,63,64,72,104], aqueous ethanol[60,63,69,71,156], aqueous acetone[72], *t*-butanol[153,154] and water[64]. However, two other investigations in water[49,97] have found no evidence for autocatalysis, and it was also absent in the reaction of silver lactate with ethyl iodide in ethanol[62].

As a general rule, autocatalysis is more likely to be observed for reactions in protic solvents than for reactions in aprotic solvents but there are several well documented exceptions.

Spiro and coworkers have made the most detailed study to date of heterogeneous catalysis to reactions in protic solvents. The reaction of ethyl iodide with silver nitrate in water to give ethyl alcohol was found[68,157], consistent with the much earlier experiments by Senter[64], to be considerably catalysed by silver halides. With freshly prepared compounds, the relative efficiencies were AgI > AgBr > AgCl. Commercial silver iodide has a reduced efficiency, comparable to that of freshly prepared silver bromide. Charcoal was a very good catalyst, falling not far behind silver chloride in its efficiency. Quantitative data could not be obtained because surface areas differed greatly from one solid to another and the condition of the silver iodide formed in the reaction is influenced by the nature of the precipitate already present. The picture presented by Hughes and Ingold[2,156] was supported by application of the Pearson theory of hard and soft acids and bases[5–8]. Barium sulphate with hard acid and hard base sites was ineffective and the best catalyst was silver iodide with both soft acid and soft base sites, best suited for coordination with the 'soft' iodine atom of ethyl iodide and the soft silver ion, so as to bring these reactants together on the surface. The activation energy for the homogeneous reaction of 19.6 kcal mol^{-1} was reduced to 8.5 kcal mol^{-1} for the silver iodide-catalysed reaction and to 10.4 kcal mol^{-1} for the charcoal-catalysed reaction[157].

Similarly, it was found[158] that the S_N1 solvolysis of *t*-butyl bromide in 80% aqueous ethanol was catalysed by silver metal and several insoluble silver and mercury salts but not by silica, platinum metal, carbon or barium sulphate. The silver bromide-catalysed process was selected for detailed study and a model was developed within which the kinetics could be rationalized in terms of competitive adsorption of *t*-butyl bromide

and bromide ions, produced during reaction or added as potassium bromide, on the silver bromide surface. In contrast to the homogeneous reaction, the heterogeneous reaction produced no alkene and, in addition, the ether/alcohol ratio was increased. These variations were believed to be due to the reactions of the intermediate carbenium ion taking place in the vicinity of the silver bromide surface and, therefore, being influenced by changes in the solvent structure within the interfacial region.

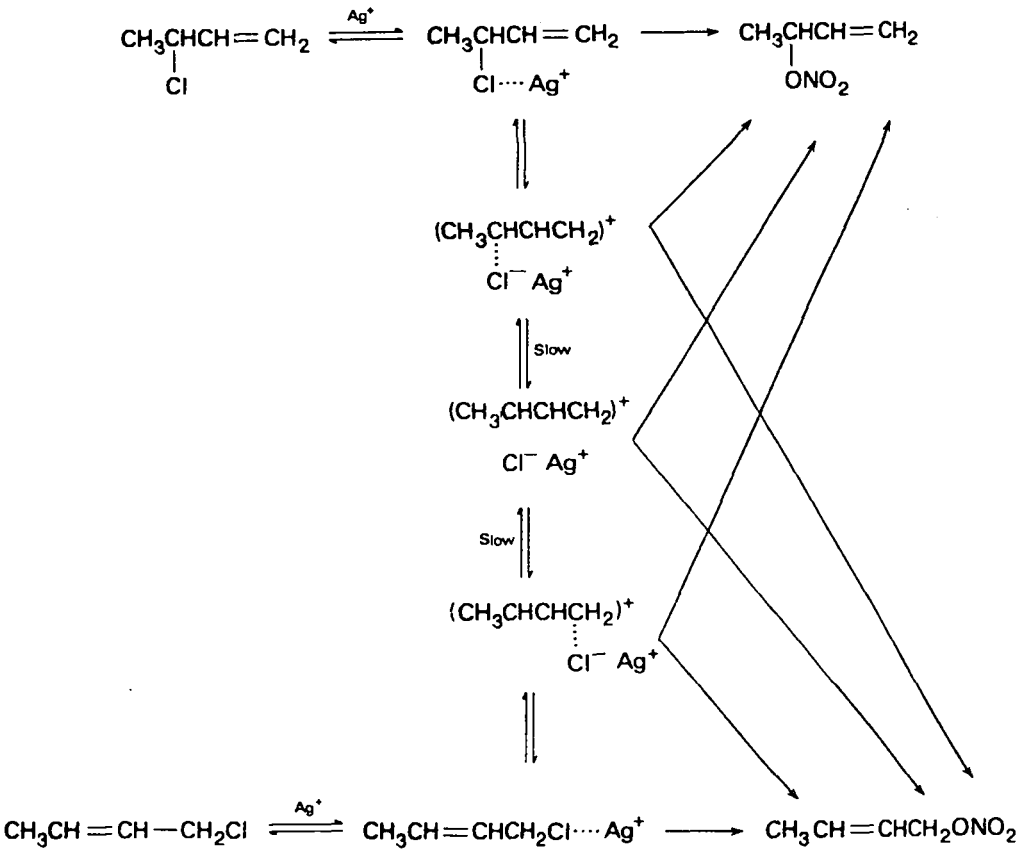
A study has also been carried out of the influence of solid catalysts on the Menschutkin reaction of triethylamine with ethyl iodide in benzene[159]. There was no influence upon the rate of reaction when silica or alumina was added. Carbon caused a mild retardation and silver iodide a large retardation, suggesting non-reactive adsorption of reactants. As one would expect, based on previous studies[83,114], silver ions in solution (added as silver nitrate) greatly accelerated the reaction. The best conditions were found to be with both silver ions in solution and either silver iodide or carbon as a heterogeneous phase. Under these conditions increases in the reaction rate of the order of 10^4-fold were achieved. A simple mechanism involving adsorption of the three reactants (triethylamine, ethyl iodide and silver ions) on the catalytic surface was proposed. However, any detailed mechanism would have to consider the complex aggregation of silver salts dissolved in benzene[116–118], the question as to the extents to which silver ions in solution are complexed by benzene and by triethylamine, and the question as to whether it is ethyl iodide or a preformed $[EtIAg]^+$ complex which is adsorbed on the catalyst.

IV. SILVER ION ASSISTANCE TO REACTIONS OF OTHER ORGANIC HALIDES

A. Allyl Halides

The extensive work by Young and coworkers on nucleophilic substitution and rearrangement reactions of allylic systems included some studies within which silver ion assistance was utilized[160–162]. These studies and one by Oae and VanderWerf[163] have been reviewed earlier in this series[164] and elsewhere[165]. This discussion will concentrate on more recent reports concerning silver ion-assisted reactions of allylic halides.

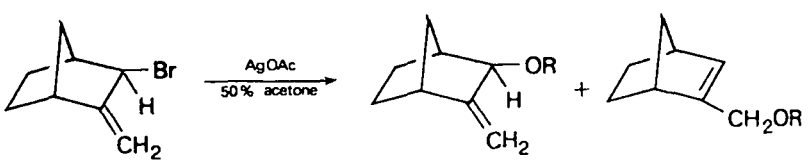
It was shown[128] that allyl bromide and allyl chloride react with 0.005–0.16 M silver nitrate in acetonitrile with very close to the 2.5-order kinetics previously observed[67] with 1-octyl bromide and with 2-octyl bromide or chloride under the same conditions. With allyl bromide, silver nitrate reacted over a thousand times as readily as silver perchlorate, indicating considerable nucleophilic assistance by nitrate ion. The same kinetic pattern was observed in the reactions of α, β and γ-methylallyl chlorides with an acetonitrile solution of silver nitrate[95] and, at 45°C, the relative rates were allyl (1.0), β-methylallyl (2.2), α-methylallyl (5.3), *cis*-γ-methylallyl (15) and *trans*-γ-methylallyl (19). In contrast, the accompanying silver ion-assisted allylic rearrangements[166] and the (eight to 50 times slower) reactions with silver perchlorate were faster for the α-isomer than for the γ-isomers. The *trans*-γ-methylallyl chloride (0.3 M) reacted with silver nitrate (0.2 M) without allylic isomerization and 88% *trans*-γ-methylallyl nitrate and 12% α-methylallyl nitrate were formed. After correction for products formed after an initial isomerization, α-methylallyl chloride gave 79% α-methylallyl nitrate and 21% γ-methylallyl nitrate. These results were rationalized in terms of Scheme 4. Since facile allylic isomerization does not occur, a barrier to isomerization was accomplished by introducing the concept of initially formed unsymmetrical ion pairs which return to precursor or react faster than they equilibrate[84,167]. In a recent study of unassisted alcoholyses of allylic chlorides, Georgoulis and Ville[168] also observed reaction to both unarranged and rearranged ethers and they proposed either concurrent



SCHEME 4

S_N2 or S_N2' reactions or reaction at a stage of an ion pair less ionized than an intimate ion pair, such as is the situation in Scheme 4.

It is believed that the 2-methylene-3-norbornyl cation must be considered as classical because of the swamping out of any non-classical participation in favour of allyl participation[169]. When *exo*-3-bromo-2-methylenenorbornane (**10**) is allowed to react with silver acetate in 50% aqueous acetone, the products are as indicated[170] (R = H or CH_3CO):



(**10**)

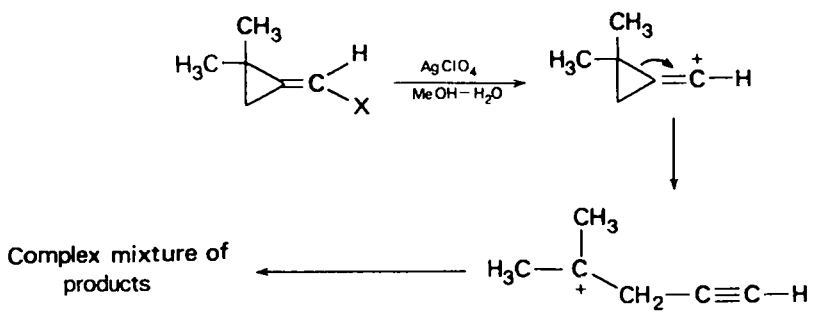
This suggested that reaction was through an allylic cation and, in particular, the absence of any *endo*-C-3 product showed that the *exo*-stereospecificity was a property of classical as well as non-classical 2-norbornyl cations and the stereospecificity cannot, in itself, be taken as evidence for non-classical character.

B. Vinyl Halides

For many years, it was believed that vinyl cations were species of too high energy to be generated by S_N1-type reactions, even with silver ion assistance. Indeed, it is true that simple alkyl-substituted vinyl halides do not readily precipitate silver halide with ethanolic silver nitrate[171]. However, with the new 'super' leaving groups, such as trifluoromethanesulphonates, simple alkylvinyl cations can now be generated by S_N1 reactions. Also, with suitable substituents, it has proved possible to generate this species by the silver ion-assisted reactions. In a recent monograph dealing with vinyl cations, the chapters devoted to bond heterolysis and to formation of arylvinyl cations via solvolysis contain details of studies involving silver ion assistance towards these processes[172] and the consideration in this chapter will accordingly be briefer than would otherwise have been the case.

Publications dealing with silver ion assistance towards the formation of vinyl halides have come from the laboratories of Bergman[173–175], Hanack[176,177], Lee[178–183], Rappoport[184–186] and others[187–190].

In 1969, Bergman[173] and Hanack[176] and their coworkers simultaneously published communications outlining their generation of cyclopropyl-stabilized vinyl cations from 1-cyclopropyl-1-haloethylenes with silver acetate in acetic acid. The major product was the corresponding acetate. Similar structures lacking the cyclopropyl ring were shown to be extremely unreactive even at considerably elevated temperatures. Kelsey and Bergman[174] showed that (*E*)- and (*Z*)-1-iodo-1-cyclopropylpropenes gave randomization of stereochemistry in the reaction. An identical linear vinyl cation which can rearrange, but with little driving force, to allylic ions (and to an even smaller extent to allenic ions) in competition with solvent capture to the same mixture of (*E*)- and (*Z*)-acetates was suggested. Ghencuilescu and Hanack[177] also showed that the following reaction takes place readily at room temperature:



Unlike the situation in acetic acid, silver ion-assisted formation of cyclopropylvinyl cations in aqueous ethanol is usually followed by ring expansion[188].

Rappoport and Apeloig addressed the question of the stereochemistry of vinyl cation formation through a study of triarylvinyl bromides with silver acetate in acetic acid. *Cis*- and *trans*-1,2-dianisyl-2-phenylvinyl bromides could be solvolysed with or without silver ion[184]. In both cases, the same product mixture was obtained, consisting of roughly equal parts of the *cis* and *trans* acetates. A more detailed study[186] showed that either of the bromide isomers gave 54% *cis*-acetate and 46% *trans*-acetate and also, perhaps of more interest in the context of the present chapter, at incomplete reaction the bromide had been partially isomerized and silver ion accelerated both the solvolysis and the isomerization. Such isomerization had also been observed by Kelsey and Bergman[174]. Both groups of workers assumed silver acetate to be little dissociated in acetic acid and the pathway for the isomerization to involve return of halide from an equilibriated $(Vinyl)^+[Ag(OAc)X]^-$ ion pair.

Kernaghan and Hoffman[187] used a heterogeneous phase of silver trifluoroacetate in isopentane, which is a very powerful electrophilic reagent, to generate less stable vinylic cations from, for example, the (*E*)- and (*Z*)-1-bromo-1-phenylpropenes. An overall net retention (ca. 13%) was plausibly explained in terms of reaction occurring on the silver salt surface. However, for homogeneous reaction in diethyl ether an even greater net retention was observed and this was explained in terms of a double inversion process via an oxonium ion. Since inversions have never been observed in other reactions of acyclic vinylic systems, reaction via a tight ion pair prior to equilibration might be considered an attractive alternative[174]. Yet another alternative[191] would be steric factors favouring attack upon a linear vinyl cation from the side of the hydrogen atom rather than from the side of the bulkier methyl group; such a steric control would lead to the observed excess retention for the (*E*)-isomer, the only one studied in the (initially) homogeneous reaction.

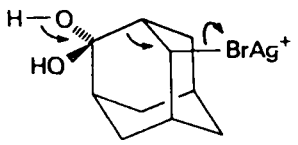
Another area of interest in vinyl cation chemistry is the occurrence of 1,2-aryl shifts across the double bond in triarylvinyl cations and silver ion assistance has been used in the generation of the required cations. During a study of the rearrangement of 2,2-dianisyl-1-phenylvinyl bromide to equal amounts of the 1,2-dianisyl-2-phenylvinyl acetates using silver acetate in acetic acid, internal return of bromide to give isomerized reactant was also observed[185]. Lee has carried out studies of degenerate rearrangements using ^{13}C or ^{14}C labelling. While the silver ion is used primarily to accelerate the reaction, it does sometimes serve to avoid competing electrophilic addition–elimination mechanisms by a selective acceleration of the S_N1 mechanism, such as in the generation of triarylvinyl cations from the bromides in trifluoroacetic acid[182]. One can, also, occasionally observe 1,2-hydride shifts, as in the reactions of the isomeric β-bromostyrenes with silver acetate in acetic acid[180].

C. Halogenated Ketones

The history of α-acylcarbenium ions resembles that for vinyl cations in that for many years they were considered to be of too high energy to be generated by a heterolytic bond fission, only eventually to become respectable members of the family of chemical intermediates. Charpentier-Morize and coworkers have developed a technique for the generation of these cations from α-haloketones and the silver salts of super acids in methylene chloride. A detailed account of their work, with consideration of the structure and reactions of the ions, has recently been given[192] and will not be repeated here. It is interesting to note that the reagent will also dehalogenate 2-bromo-2-nitrobornane, where the α-carbon bears a powerfully electron-withdrawing nitro group[193]. The reaction led selectively to 4-nitrocamphene and the importance of anchimeric assistance was confirmed by the inertness of 1-bromo-1-nitrocyclohexane. This also suggested that the halogen is more deactivated towards electrophilic reagents by a nitro group than by a carbonyl group.

The reactivities of several α-chlorinated carbonyl compounds towards silver nitrate in ethanol have been compared to that for *n*-butyl chloride[194]. S_N2 reactions of these compounds are usually considerably aided by the adjacent carbonyl group, in contrast to the powerful retardation of S_N1 reactions. The presence of the α-keto group caused a modest decrease in rate, consistent with a balance between S_N1 and S_N2 influences. The relative rates observed were $CH_3CH_2CH_2CH_2Cl$ (1.0); $PhCOCH_2Cl$ (0.56); $C_2H_5OCOCH_2Cl$ (0.28); CH_3COCH_2Cl (0.27). Nucleophilic assistance was shown to be an important factor in the reaction of silver nitrate in acetonitrile with α-bromo-*p*-phenylisobutyrophenone[129]. Unlike the same reaction[195] (or the reaction of α-bromoisobutyrophenone[196]) in aqueous ethanol, which gave quasi-Favorskii rearranged acid, good yields of the direct replacement α-nitrato product were obtained.

This reaction was 130 times faster than the reaction with silver perchlorate. Other examples of quasi-Favorskii rearrangements of α-haloketones by silver ion in aqueous ethanol have been reported[196–198]. There has also been a report[199] of a similar rearrangement of a β-bromoketone. The 4-*e*-bromoadamantanone reacts with silver perchlorate in aqueous acetone to give only 3% (*a* + *e*)-4-hydroxyadamantanone and largely bicyclo[3.3.1]-2-nonene-7-carboxylic acid. These quasi-Favorskii rearrangements have been considered to involve addition of solvent across the carbonyl group prior to attack by the silver ion, such that regeneration of the carbonyl group provides a push to accompany the pull by the silver ion[196]. For example, the following process has been postulated[199]:

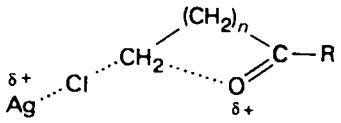


A detailed study[200] of the silver perchlorate-induced reaction of α-bromoisobutyrophenone in aqueous ethanol has revealed that a little of the unrearranged alcohol and ether accompanies the rearranged[196] acid and ester. The reaction was sensitive to the presence of acid and subject to autocatalysis. Although constant ionic strength was maintained using lithium perchlorate, the kinetics were quite complex. A rapid acid-catalysed addition of solvent to the carbonyl group to give an equilibrium amount of intermediate which then reacted via transition states also incorporating Ag^+, Ag^+ and H^+, or $2Ag^+$, respectively, was postulated

$$\text{Rate} = k[Ag^+][RBr] + k_H[Ag^+][RBr][H^+] + k_{Ag}[Ag^+]^2[RBr]$$

Phenacyl halides ($C_6H_5COCH_2X$) have been shown[201] to react with silver perchlorate in 80% aqueous ethanol with good second-order kinetics and no rearrangement; approximately 70% ether and 30% alcohol were formed. The reaction was almost entirely insensitive to *para* substituents (ranging from *p*-methoxy to *p*-nitro) and a highly concerted S_N2 Ag^+ process was postulated.

Although neighbouring-group participation does not seem to be present for phenacyl chloride, strong evidence for it has been found in the homologues of structure $RCO(CH)_nCH_2Cl$ (R = Ph, *n* = 1–4 or R = isopropyl, *n* = 2–4)[202]. The detailed nature of the interaction of the carbonyl group with the incipient carbenium ion centre (generated by using silver nitrate or perchlorate in 80% aqueous ethanol) is not fully understood but the formation of cyclic ketals (R = phenyl) and cyclic enol ethers (R = isopropyl) requires participation, at least in the product-forming stage. Good second-order kinetics, with no evidence for autocatalysis by precipitated silver chloride, were obtained using silver perchlorate. For R = isopropyl, the rate decreases as *n* is increased from 2 to 4. For R = phenyl, the rate increases as *n* is increased from 0 to 2 and then decreases as *n* is increased from 2 to 4. Since the phenyl and isopropyl derivatives have similar rates, a transition state with appreciable charge on carbonyl carbon (which would be considerably stabilized by an attached phenyl group) was considered unlikely. The transition state was visualized[202] as follows:



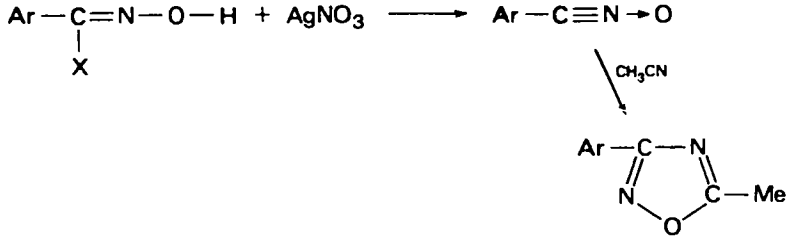
D. Acyl Halides

The addition of silver salts to simple acyl halides results in immediate precipitation of silver halide. For example, reaction of acetyl chloride and silver perchlorate in acetic anhydride[203] or in anisole[204] is immediate and a powerful acetylating agent, presumably acetyl perchlorate, is produced. Paralleling the behaviour of alkyl halides, acyl fluorides (but not chlorides) are subject to acid catalysis under solvolytic conditions and acyl chlorides can also be subject to such catalysis in aprotic solvents[205]. Because of the rapidity of the silver ion-assisted reactions, studies of the mechanism have concentrated on the corresponding reactions of chloroformate esters (ROCOCl), which usually allow kinetic studies to be performed at around room temperature. In contrast to reactions of alkyl chlorides, reactions of alkyl chloroformates with silver nitrate in acetonitrile involve either silver ion or nitrate ion attack, but not the two acting in unison[206,207]. Reaction initiated by silver tetrafluoroborate or hexafluoroantimonate is a convenient route to high energy aliphatic carbenium ions; bridgehead carbenium ions generated in this way can alkylate nitrobenzene[208,209]. There is an

$$ROCOCl \xrightarrow{Ag^+} (ROCO)^+ \longrightarrow R^+ + CO_2$$

obvious similarity between the carboxylium ion decomposition and the more familiar diazonium ion decomposition. The reactions of chloroformate esters with silver salts have been reviewed previously in this series[210] and also elsewhere[211].

In so far as reaction is at a carbon atom which is doubly bonded to a heteroatom, the silver nitrate-induced dehydrohalogenation of 3,5-dichloro-2,4,6-trimethylbenzohydroxamoyl chloride and bromide[212] is probably best considered within this section. In acetonitrile, the dehydrohalogenation is followed by a slow 1,3-cycloaddition to a solvent molecule to give a 1,2,4-oxadiazole derivative (**11**). For X = Cl,



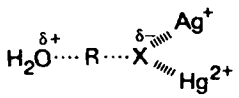
(**11**)

the first step was first order in both the hydroxamoyl chloride and silver nitrate and, for X = Br, this term was accompanied by a second term which was first order in hydroxamoyl chloride and second order in silver nitrate. With 10^{-3} M silver nitrate, the bromide reacts 2000 times faster than the chloride. A mechanism was proposed in which concerted silver ion assistance at the halogen and base assistance at the proton were operative. The base was also acetonitrile when X = Cl and either acetonitrile or nitrate ion when X = Br. It is a little difficult to why the identity of X should have so profound an effect upon the choice of the base removing the γ-hydrogen and a mechanism involving concerted attack by two silver ions at the bromine[49] should, at least, be considered as an alternative to assistance by nitrate ion.

V. MERCURIC ION ASSISTANCE TO REACTIONS OF ORGANIC HALIDES

Consistent with its classification as a soft acid, mercury(II) catalyses the hydrolyses of alkyl chlorides, and bromides[32,48] but not the hydrolysis of *t*-butyl fluoride[23]. Unlike

the situation with silver ion, where catalysis can involve either one or two silver ions, there is no evidence for a catalytic pathway with more than one mercury ion coordinated to a halogen[3]. However, in the hydrolysis of ethyl bromide in the presence of both silver and mercuric ions[25], there is evidence for a term in the rate expression which is first order in each of the three species, presumably corresponding to a transition state:



The hydrolysis of ethyl bromide catalysed by mercuric nitrate[47] has been found to give second-order kinetics, first order in each of the additives. The stability of the $[EtBrHg]^{2+}$ complex could be evaluated by consideration of the ethyl bromide distribution between gas and mercuric nitrate solution and the variation observed in the kinetic pattern with varying mercuric ion concentration. The inert strontium nitrate was used to maintain constant ionic strength. The $HgBr^+$ species was much less active than the Hg^{2+} species, consistent with a much lower affinity for bromide ion. With 0.5 M mercuric nitrate at 25°C the product consisted of 60% ethyl nitrate and 40% ethanol.

Nicholet[213] showed that mercuric halides were efficient catalysts in the alcoholyses of isopropyl halides but the catalyst was deactivated by complexation with halide ion, to give HgX_4^{2-}. In diethyl ether, isopropyl iodide could be converted to the chloride by treatment with mercuric chloride and the reaction was subject to a strong autocatalysis by the formed mercuric iodide[214]. Mercuric chloride in benzene in the presence of excess sodium iodide can bring about reactions of the reverse type and *t*-butyl iodide and benzyl iodide have been prepared from the chlorides[215]. The mechanism appears to be complex and reaction does not occur when soluble iodide salts or primary or secondary alkyl chlorides are substituted.

Mercuric nitrate can be substituted for silver nitrate in the assisted hydrolysis of neopentyl iodide to the rearranged tertiary alcohol[216].

Roberts and Hammett[11] studied the kinetics of the mercuric nitrate-promoted hydrolysis of benzyl chloride in aqueous dioxane. They concluded that the principal reactant was the unionized mercuric nitrate which interacted with essentially second-order kinetics to lead to a benzyl cation which then reacted with nitrate ion or water. Other forms of the mercuric ion[217] were also considered to be involved, but to a lesser extent. Mercuric perchlorate reacted slightly faster than the nitrate and gave only the alcohol. Benfey[218] extended these studies to ethyl, *n*-propyl, isobutyl, isopropyl and cyclohexyl bromides. In 70% aqueous dioxane, the kinetics were perturbed by the equilibrium $Hg^{2+} + HgBr_2 \rightleftharpoons 2HgBr^+$ and it appeared that $HgBr^+$, and also $HgBr_2$, were of much lower activity than Hg^{2+}. The relative second-order rate coefficients at 25°C were Et (7.3), *n*-Pr (3.5), *i*-Bu (1.0), *i*-Pr (1060), cyclohexyl (282). A similar order (Me > Et < *i*-Pr < *t*-Bu) had been found for the mercuric bromide-promoted hydrolysis of alkyl bromides in aqueous acetone[219].

Oae and VanderWerf[220] used mercuric nitrate in 70% aqueous dioxane to study the reactions of $CH_3(CH_2)_nBr$ (n = 1–4) and $C_6H_5(CH_2)_nBr$ (n = 2–5). Second-order rate coefficients gave no evidence for alternation effects[221] and the rationalization by Benfey[218] in terms of hyperconjugation, coupled with inductive effects, was offered. The assumption that continuous chain primary alkyl halides react in 70% aqueous dioxane by an $S_N1 - Hg^{2+}$ mechanism appears, in the light of present knowledge of solvolysis mechanisms, very unlikely and the authors[218,220] were probably observing $S_N2 - Hg^{2+}$ reactions for these substrates.

For hydrolysis of benzyl chloride in aqueous acetone, the mercuric chloride-promoted (0.15–0.35 M) reaction is approximately first order in each reactant[222]. Evidence for a 1:1 yellow coloured complex was obtained. Mercuric chloride was considered to be a relatively weak catalyst because it exists in an unionized form. Later, it was shown[223] by osmotic and ebullioscopic techniques that, in acetone, mercuric chloride is monomeric over a 0.038–0.25 M concentration range; mercuric bromide and iodide were also found to be monomeric, but a narrower range of concentrations was studied.

The solvolysis of *p*-chlorobenzyl chloride has been studied in a series of aqueous ethanol and aqueous-acetone solvents[224]. On the basis of the lower Grunwald–Winstein *m* values (which measure sensitivity to solvent ionizing power) for the catalysed reactions than for the uncatalysed reactions, it was claimed that the catalysed reactions are S_N2 in character. It seems unreasonable, however, to compare these values because the *m* values to a considerable extent measure the ability of the solvent to solvate the developing chloride ion, a function which has been partially taken over by the mercuric chloride in the catalysed reaction. Furthermore, it has been shown that the electrophilicity of the mercuric chloride varies with the solvent composition[225]. More convincing evidence[226,227] for S_N2 character is the observation of faster mercuric chloride-promoted reactions for the benzyl chlorides in 80% aqueous ethanol than in 80% aqueous acetone, despite a greater electrophilicity in the latter. Presumably, the higher nucleophilicity of 80% aqueous ethanol more than counterbalances the lower electrophilicity in this solvent. In contrast, the reactions are slightly slower in the aqueous ethanol for the $S_N1 - Hg^{2+}$ reacting *t*-alkyl chlorides.

The rates of solvolysis of compounds PhCH(R)Cl in aqueous acetone fall off as the R group is varied, Me > Et > *i*-Pr > *t*-Bu. The fall off is less marked when catalysis by mercuric chloride operates and inductomeric polarization of the alkyl groups by the catalyst was proposed[228]. A similar study was made of 1-(*p*-alkylphenyl)ethyl chlorides in aqueous acetone and aqueous ethanol solutions of mercuric chloride. The Baker–Nathan order (Me > Et > *i*-Pr > *t*-Bu) was followed. In the more aqueous mixtures, a superimposed inductometric effect was proposed[229].

Evans and coworkers have studied the equilibria involved when mercuric chloride is used to bring about formation of triphenylcarbenium ion from triphenylmethyl chloride in nitromethane[230]. With tri-*p*-tolylmethyl chloride and mercuric chloride in

$$Ph_3CCl + HgCl_2 \rightleftharpoons Ph_3C^+ \cdot HgCl_3^- \rightleftharpoons Ph_3C^+ + HgCl_3^-.$$

chlorobenzene or benzene[231], the corresponding ion pairs are formed but they do not dissociate. From benzene, stable crystalline complexes containing the carbenium ion and also excess $HgCl_2$ were isolated. The ionization of triarylmethyl chlorides by various Friedel–Crafts catalysts of type MCl_n, to give the ion pair, has been studied in acetic acid[232]. Mercuric chloride was found to be one of the weaker of these

$$Ar_3CCl + MCl_n \rightleftharpoons Ar_3C^+ . (MCl_{n+1})^-.$$

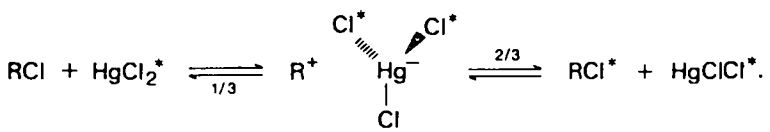
ionization-promoting reagents ($SbCl_5 \gg FeCl_3 \gg SnCl_4 \gg BiCl_3 > HgCl_2 > SbCl_3$). With very high concentrations of $HgCl_2$ (and $SbCl_3$), it appeared that additional metal halide molecules were involved in the solvation of the ion pair.

Bodendorf and Böhme[233] found that the racemization of α-methylbenzyl chloride was catalysed by metal halides ($SbCl_5 > SnCl_4 > HgCl_2$). In nitrobenzene and acetone the rates with varying $HgCl_2$ concentration (0.04–0.4 M) indicated an order of about 1.5. In ethanol, the product of the $HgCl_2$-assisted reaction was α-methylbenzyl ethyl ether, formed with partial inversion of configuration (a typical S_N1 stereochemistry). The hydrolysis of α-methylbenzyl chloride in 95% acetone, assisted by mercuric chloride (0.3–1.2 M), was found[234] to be second order in mercuric

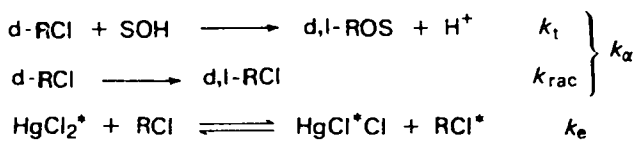
chloride, as was the identical reaction of α-methylbenzyl bromide catalysed by mercuric bromide.

Satchell[235] has shown that, in nitrobenzene, the racemization of α-methylbenzyl chloride induced by mercuric salts has orders of two in mercuric iodide and both one and two in mercuric bromide or mercuric chloride. The relative efficiencies when only one catalyst molecule is involved are bromide > chloride ≫ iodide. In acetone, an identical mixed-order kinetic pattern was observed for zinc halides, more powerful catalysts than the mercuric halides. When two catalyst molecules enter the transition state, both the catalytic efficiency and the ability to solvate the transition state were considered to be important[236]. The observation that, although arsenic trichloride does not itself induce racemization, it does accelerate the racemization induced by mercuric chloride suggested[237], in this case at least, that the solvation forces are of an ion-dipole nature and the ($R^{\delta+}\cdots Cl\cdots MX_2^{\delta-}$) transition state is better solvated by $AsCl_3$ than the positive poles of acetone or nitrobenzene. In extensions to other metal halides, aluminium and gallium chlorides and boron fluoride in diethyl ether[238] and stannic chloride in benzene[239] all showed only a first-order dependence on catalyst concentration. However, in diethyl ether, stannic halides showed both first- and second-order contributions, trichloro(phenyl)tin both first- and third-order contributions and antimony trichloride only a fourth-order contribution[240]. For each pathway, a transition state was proposed within which one catalyst molecule interacts specifically with the α-methylbenzyl chloride molecule and the transition state is solvated by either ether molecules or a combination of ether and metal halide molecules.

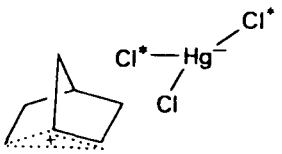
Winstein and coworkers have considered the influence of mercuric salts on ionization reactions in terms of the ion pair mechanism[241–244]. The racemization and radiochloride exchange involved in the interaction of *p*-chlorobenzhydryl chloride with mercuric chloride in acetone were monitored[241]. In the absence of catalyst the ratio of rate of racemization to rate of exchange (k_{rac}/k_e) was large, indicating internal return from stereochemically equilibrated ion pairs to be much more rapid than exchange with external chloride ion. Mercuric chloride increases both k_{rac} and k_e enormously and the k_{rac}/k_e ratio was reduced to 1.5. This is consistent with return to racemic RCl from $R^+HgCl_3^-$ ion pairs, within which the three chlorine atoms have equilibrated. Statistically, one would expect a ratio of 1.5, because only two-thirds of the return will be with incorporation of the label.



In 80% acetone[242], 55% of the $R^+HgCl_3^-$ ion pairs dissociate and collapse with water to the alcohol. The catalytic activity is reduced relative to acetone but k_{rac}/k_e remains close to 1.5. In acetonitrile[242], k_{rac}/k_e is unity and this can be explained if the internal return is after dissociation and equilibriation of the chlorines of $HgCl_3^-$ with the $HgCl_2$ reservoir. In benzene[242], the k_{rac}/k_e ratio is only 0.24 and, if the ion pair is $R^+HgCl_3^-$, only 16% of the ionization which gives rise to chlorine exchange is accompanied by racemization. In this solvent, it must be more difficult to equilibrate the faces of R^+ than the chlorine atoms in $HgCl_3^-$.



In order to study the extent of chlorine randomization in the presence of a more facile racemization process, the mercuric chloride-assisted ionization of *exo*-norbornyl chloride in acetic acid was studied[243]. The k_{rac}/k_e ratio was 2.0, suggesting that only two chlorine atoms in $R^+HgCl_3^-$ are equivalently associated with the bridged norbornyl



cation. The k_α/k_t ratio of 9.6 indicates that only 10% of the ion pairs give product and 90% regenerate *exo*-RCl. In formic acid, ion pair return is reduced, as indicated by a value of 1.95 for the k_α/k_t ratio. The k_t value for mercuric acetate was found[244] to be 1820 times higher than for mercuric chloride. The k_α values are probably a better estimate of the relative abilities to promote ionization and the ratio of these values was 228.

It has been found[245] that, in acetone, cobaltous chloride is a slightly better catalyst for both racemization and radiochloride exchange of α-methylbenzyl chloride than mercuric chloride. With mercuric chloride, terms both first order and second order in the salt are present in the rate equation. With 0.1 M salt approximately equal amounts of reaction follow each pathway. It was proposed that, in the $R^+(HgCl_3 \cdot HgCl_2)^-$ ion pair, dissociation (followed by chlorine randomization[242]), is favoured and $k_{rac}/k_e = 1$, as opposed to a value of 1.5 for the $R^+HgCl_3^-$ ion pair[241].

The observation[246] that the S_N1-Hg^{2+} reaction affords a convenient route to isothiocyanates is easily rationalized in terms of the Winstein picture for these reactions. In the transfer of the thiocyanate unit to the carbenium ion the exposed nitrogen atom is more favourably situated for attack than the mercury-attached sulphur atom and one obtains higher proportions of the isothiocyanate than in unassisted reactions.

$$RBr + Hg(SCN)_2 \rightleftharpoons R^+(Hg(SCN)_2Br)^-$$

$$R^+(Hg(SCN)_2Br)^- \longrightarrow RNCS + Hg(SCN)Br.$$

VI. ELECTROPHILIC ASSISTANCE TO REACTIONS OF ORGANIC HALIDES BY NON-METALLIC SPECIES

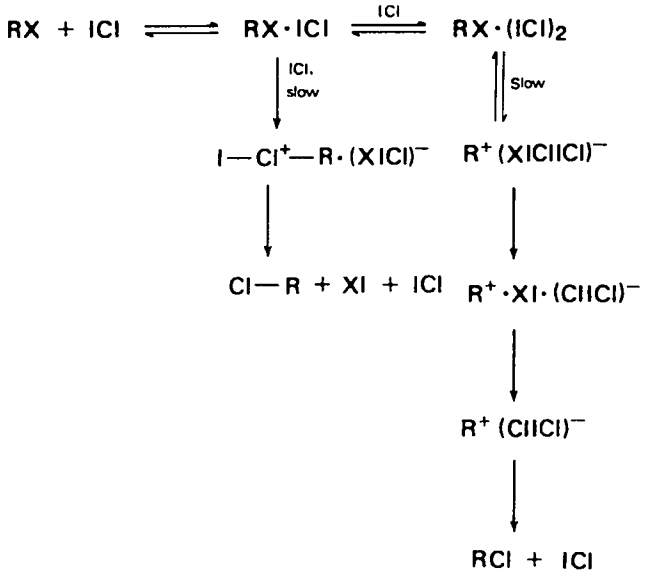
Assistance by protonic acids has been considered earlier (Section II).

Halogen molecules show appreciable Lewis acidity towards halide ions and, by considering the free energies of trihalide ion formation, an order ($ICl_2^- \gg BrCl_2^- > IBr_2^- \gg I_3^- > Br_3^- \gg Cl_3^-$) has been established[247]. Keefer and Andrews[248] showed that 1:1 molecular complexes formed between alkyl iodides and iodine have stability constants which vary with the alkyl group, Me < Et < *i*-Pr < *t*-Bu. This suggests an interaction within which the iodine of the alkyl iodide functions as the Lewis base and the iodine molecule as the Lewis acid ($RX \cdot X_2$). The interaction of methyl iodide was found to be considerably weaker with bromine than with iodine.

The kinetics of the interactions of benzyl iodide[249], benzyl bromide[249], isopropyl iodide[249] and *t*-butyl bromide[250] with iodine monochloride in carbon tetrachloride indicated, for each substrate, that a complex between the alkyl halide and the iodine monochloride was being attacked by a second molecule of iodine monochloride. In the presence of β-hydrogens, in addition to the alkyl chloride, the alkene chloroiodide was formed. Stereochemical studies of the reactions between 2-octyl iodide and

chlorine[251,252], iodine monochloride[251,252] or bromine[252] led, in a variety of solvents, to inversion plus racemization. Corey and Wechter[251] favoured a mechanism within which one halogen molecule acted as an electrophile and one as a nucleophile. However, neopentyl iodide in petroleum ether at − 78°C reacted with chlorine to give rearranged *t*-amyl chloride and halogen adducts of trimethylethylene[252], suggesting intermediate carbenium ion formation. Any plausible mechanism would have to be consistent with the observation that the inversion/retention ratio in the 2-octyl iodide reactions rose with the polarity of the solvent.

Taking iodine monochloride as an example, the simplest substitution scheme consistent with all the facts would involve bimolecular reaction with inversion on the molecular complex, leading to charge separation and ion pair formation, in competition with a unimolecular sequence involving tight ion-pair formation, favouring retention (although some racemization is possible).



There have been several studies involving the incorporation of labelled iodine into organic iodides. Many of these involve radical addition or radical abstraction mechanisms[253] but, when a relatively stable carbenium ion can be formed, heterolytic mechanisms can be observed. The data for compounds reacting heterolytically can be fitted to a rate equation of the form

$$\text{Rate} = k_1[\text{RI}] + k_2[\text{RI}][\text{I}_2] + k_3[\text{RI}][\text{I}_2]^2 + k_4[\text{RI}][\text{I}_2]^3$$

Usually two of the terms are sufficient to fit the data over a wide range of $[I_2]$[253]. A tight ion pair intermediate ($R^+I_3^-$) can be stabilized by interaction with other iodine molecules, a situation reminiscent of that found for catalysis by mercuric halide and related molecules (Section V). The exchange involves migration of R^+ from one end of the I_3^- anion to the other end. Consistent with an ionic mechanism, *t*-butyl iodide reacts about a hundred times more readily with iodine in 1,2-dichloroethane (dielectric constant of 10.1) than in hexane (dielectric constant of 1.9)[254]. Benzoyl iodide is believed to follow a polar mechanism in its exchange with radioiodine[255] and *p*-chloro and *p*-nitro substituents lead to a considerably reduced rate[256]; benzhydryl[257,258] and allyl iodides[253,259] are also believed to follow the polar mechanism.

Svetlakov, Moisak and coworkers[260–264] have carried out a series of experiments within which nucleophilic substitution reactions occur under what they describe as 'oxidative' conditions. Concentrated nitric acid converted alkyl iodides to alkyl nitrates[260]. Secondary alkyl iodides were more reactive than primary and alkyl iodides were more reactive than alkyl bromides. The products from *t*-butyl halides were formed via addition to isobutylene. Initially, electrophilic catalysis by the protons of the nitric acid was proposed but the observation[264] that dinitrogen pentoxide, acetyl nitrate or nitryl chloride in methylene chloride reacted to give nitrates, acetates or chlorides in 50–70% yield suggested a mechanism involving a common electrophilic assistance by the nitronium ion:

$$NO_2X \rightleftharpoons NO_2^+ + X^- \quad (X = H_2O^+, ONO_2, OAc \text{ or } Cl)$$

$$RI + NO_2^+ \rightleftharpoons R^+ + NO_2I(\rightarrow NO_2 + 1/2I_2)$$

$$R^+ + Y^- \longrightarrow RY(Y = ONO_2, OAc \text{ or } Cl)$$

Carbenium ion rearrangements can occur to an extent varying with the reaction conditions. For example, 1-iodobutane in 98% nitric acid gave 96% 1-butyl nitrate and only 4% 2-butyl nitrate but in nitromethane at 0°C for 15 min the percentages were 39 and 61, respectively. It is possible, especially with primary alkyl halides, that some of the reaction involves S_N2 attack on a $(RINO_2)^+$ complex.

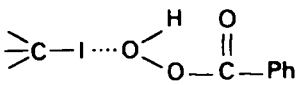
Dinitrogen tetroxide was found[264] to be effective, suggesting that the nitrosonium ion is also an effective catalyst.

By using alkyl iodides with 42% hydrochloric or hydrobromic acids in the presence of concentrated nitric acid, good yields of the alkyl chloride or bromide were obtained[261]. Optically active 2-iodooctane gave 2-bromooctane with inversion plus 73% racemization, a typical S_N1 stereochemical result, but 1-iodooctane gave a 92% yield of 1-bromooctane indicating minimal 1,2-hydride shift within any intermediate carbenium ion. Similar results were obtained on treating alkyl iodides or bromides with a mixture of concentrated nitric acid and liquid hydrogen fluoride[263]. These conditions are especially conducive to nitronium ion formation

$$HNO_3 + 2HF \longrightarrow NO_2^+ + 2F^- + H_3O^+$$

and subsequent capture of a carbenium ion by fluoride ion, or fluoride ion displacement of NO_2Hal from $(RHalNO_2)^+$. It was found[262] that a variety of oxidizing agents were effective in promoting the interaction of alkyl iodides with hydrohalic acids. These included HNO_3, N_2O_4, H_2O_2, $KClO_3$, $KMnO_4$, $NaNO_2$ and $Ca(OCl)_2$, with the proposed electrophilic reagents being NO_2^+, NO^+, OH^+, ClO_2^+, MnO_3^+, NO^+ and Cl^+, respectively.

Recent reports concerning peracid oxidation of alkyl iodides have suggested an alkyliodosyl species ($R—I^+—O^-$) as an intermediate[265,266], which can then rearrange to hypoiodite[265], undergo a *syn* elimination[265] or react by either S_N1 or S_N2 mechanisms[266] with displacement of hypoiodite ion. A transition state involving oxygen atom transfer has been proposed for the formation of the initial complex[266]. Such a scheme



is clearly only slightly different from the OH^+ attack proposed for H_2O_2 oxidation by the Russian workers[262]. Indeed, since one study was in non-polar solvents and the other in concentrated hydrohalic acid, each electrophile may well be the appropriate one for the conditions employed.

The utility of acetyl nitrate[264] as a reagent for converting alkyl halides into alkyl acetates via an alkyl halide–nitronium ion complex has been confirmed[267].

Stable salts containing nitronium and nitrosonium ion are now commercially available and this allows certain reactions to be carried out that would be difficult with *in situ*[260–264] generation. The Ritter reaction can be promoted by nitronium ion in acetonitrile at 0–25°C and the reactivities of the alkyl halides parallel the carbenium ion stabilities and the weakness of the C—X bonds[268]. The reaction was claimed to be

$$R_3CX \xrightarrow{NO_2^+BF_4^-} R_3C^+ \xrightarrow{R'CN} (R_3CNCR')^+ \xrightarrow{H_2O} R_3C-\underset{H}{N}-\underset{O}{C}-R'$$

especially useful for conversion of 1-adamantyl halides to a variety of *N*-(1-adamantyl) amides. However, it probably would not be effective with multiple bonds in the R′ group, a situation that has been handled by use of silver hexafluoroantimonate as the electrophilic species[269]. Optically active *exo*-2-norbornyl bromide lost all optical activity in conversion to the acetamide, suggesting a symmetrical norbornyl cation intermediate. The corresponding *endo*-compound gave 6% inversion[270]. These results were considered to be consistent with reaction via carbocations.

The nitrosonium ion can also promote these Ritter reactions but it is less effective than the nitronium ion[271]. From *n*-butyl iodide, approximately equal amounts of *N*-(1-butyl)acetamide and *N*-(2-butyl)acetamide were obtained. The nitrosonium ion does have an advantage over nitronium ion in that it does not attack arylalkyl halides at the ring[272]. It has been suggested that the $(RXNO)^+$ complex is attacked by nitriles by both S_N1 and S_N2 mechanisms, in many cases with S_N2 character predominating[272,273].

Dialkylhalonium ions (R_2X^+) are very effective alkylating agents[274]; dimethylbromonium hexafluoroantimonate is commercially available. These cations can be considered as relatively stable Lewis acid–Lewis base adducts, formally formed by electrophilic addition of a carbenium ion to an alkyl halide. Loss of an alkyl halide molecule then occurs much more readily than loss of halide ion[273]. Such reactions fit within the general pattern of electrophilic assistance to reactions at a C—X bond.

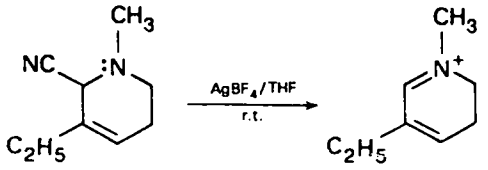
$$2RX \xrightarrow{HF/SbF_5} R\overset{+}{X}R \cdot SbF_6^-$$

$$Nu^- + R-\overset{+}{X}-R \longrightarrow NuR + XR$$

VII. ELECTROPHILIC ASSISTANCE TO REACTIONS OF ORGANIC CYANIDES, ISOCYANIDES AND AZIDES

Acetonitrile is frequently used as a solvent for interaction of electrophilic reagents such as silver or mercuric salts with alkyl halides. Silver salts do not react with acetonitrile even at high temperatures or during prolonged standing of solutions. It has been proposed[275] that silver ion can assist in the removal of cyanide ion from aminonitriles. For example, in tetrahydrofuran, silver tetrafluoroborate brings about the conversion of 1-methyl-2-cyano-3-ethyl-1,2,5,6-tetrahydropyridine (**12**) to the 1-methyl-3-ethyl-5,6-dihydropyridinium ion (**13**)[275]. Tetraalkylmethyleneimmonium nitrates have been prepared in a similar reaction[276]. However, it appears that participation by silver ion, other than in removal of the cyanide ion by precipitation, has not been firmly established.

There is convincing evidence that electrophilic assistance can play a role in reactions of alkyl isocyanides. In acetonitrile, triphenylmethyl isocyanide isomerized only slowly to triphenylmethyl cyanide but even 10^{-6} M concentrations of silver nitrate or silver



(12) (13)

$$R_2C(CN)-\ddot{N}R_2 + AgNO_3 \xrightarrow{EtOH} R_2C=\overset{+}{N}R_2 + NO_3^- + AgCN$$

perchlorate appreciably accelerate the reactions[277]. With concentrations of in excess of 10^{-4} M, the reactions become so fast that it is difficult to obtain accurate rate data. A silver nitrate–triphenylmethyl isocyanide complex was isolated at − 20°C. The assisted reaction was believed to be S_N1 Ag^+ in nature. By analogy with a suggestion

$$RNC + Ag^+ \rightleftharpoons RNCAg^+$$

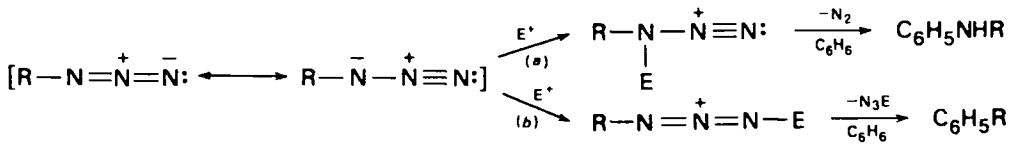
$$RNCAg^+ \xrightarrow{Slow} RCNAg^+$$

$$RCNAg^+ \rightleftharpoons RCN + Ag^+$$

for unassisted isomerizations[278], a three-centred transition state was proposed. For a triphenylmethyl substrate which is capable of forming a very stable carbenium ion, one might tend to favour bond heterolysis, followed by return of the cyanide ion from the silver ion with attachment at carbon rather than at nitrogen.

A wide variety of complexes have been prepared within which one or more isonitrile molecules are coordinated to a metal atom. The electron density is drawn towards the metal atom and nucleophilic substitution, with a metal-coordinated-cyanide nucleofuge, has been observed with complexes of benzyl and *t*-butyl isocyanides[279].

Organic azides are susceptible to electrophilic assistance in their reactions. There are two sites for electrophilic attack within the covalently bonded azido group[280]. Acyl, alkoxycarbonyl, aryl, α-carbonyl and sulphonyl azides all react with aluminium chloride in benzene via path (*a*) of Scheme 5. Attachment of the aluminium chloride is

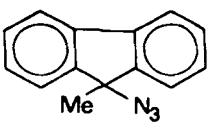


SCHEME 5

followed by loss of nitrogen and formation of *N*-substituted anilines[281,282]. Under the same conditions, some (but not all) alkyl azides react, at least in part, via path (*b*); attachment of the aluminium chloride is followed by loss of azide ion and alkylbenzene formation. Proton as well as Lewis acid-catalysed decompositions of organic azides usually follow path (*a*) and these reactions, which include the Curtius and Schmidt reactions, have previously been reviewed in this series[283,284]. Carbenium ions or antimony pentachloride have also been used as the Lewis acid catalyst[283].

Within this chapter, a strict interpretation of 'reactions at a C—X bond' will be adopted and only reactions involving loss of azide will be discussed.

Coombs showed that, in the presence of 98% sulphuric acid, 9-



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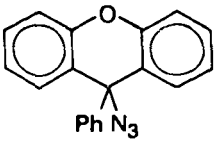

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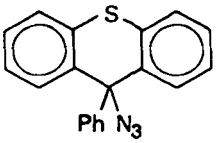


(16)

azido-9-methylfluorene (**14**)[285], 9-azido-9-phenylxanthen (**15**)[286] and 9-azido-9-phenylthiaxanthen (**16**)[286] were in equilibrium with the corresponding cation:

$$R_3CN_3 + H^+ \rightleftharpoons (R_3CN_3H)^+ \rightleftharpoons R_3C^+ + HN_3$$

Addition of water to a chloroform–sulphuric acid mixture containing (**15**) led mainly to unreacted substrate but a small amount of 9-hydroxy-9-phenylxanthen was also isolated[286].

Aluminium chloride in benzene appears to be a good system for promoting loss of azide ion in the competition with loss of a nitrogen molecule[280]. Cyclohexyl azide gave 30% cyclohexylbenzene, benzyl azide gave 50% diphenylmethane, and benzhydryl azide gave 8% triphenylmethane and 32% diphenylmethane (these two compounds were shown to participate within an equilibrium under the reaction conditions). In each case, about 50% of the reaction was with evolution of nitrogen gas, accompanied by formation of other products.

With bridgehead azides the balance between nitrogen molecule and azide ion loss is a delicate one. The 1-adamantyl azide, either with 95% sulphuric acid[287] or aluminium chloride in an aromatic solvent at 80°C[288,289], loses nitrogen and ring expands to give 3-hydroxy- or 3-aryl-4-azahomoadamantane. In contrast, 3-azidohomoadamantane with aluminium chloride in an aromatic solvent reacts exclusively with loss of azide ion, followed by ring of contraction of the 3-homoadamantyl carbocation to the less strained 1-adamantylcarbenium ion prior to alkylation of the solvent, to give >90% yield of the (1-adamantylcarbinyl)arene product[282].

Doyle and coworkers have investigated[290–292] the reactions of organic azides with nitrosonium tetrafluoroborate. They reasoned that the instability of nitrosonium azide and the formation of two non-nucleophilic molecules in its decomposition[293] could

$$NON_3 \xrightarrow{-50°C} N_2 + N_2O$$

provide a driving force for electrophilically assisted removal of azide ion. It is not known whether the initial attachment is to the inner or outer nitrogen of the azido group[290].

$$RN_3 + NO^+ \longrightarrow (RN_3NO)^+ \longrightarrow R^+ + N_2 + N_2O$$

Nitrosonium tetrafluoroborate in acetonitrile[290] reacted rapidly with triphenylmethyl azide to give an essentially quantitative conversion to triphenylmethyl tetrafluoroborate. With benzyl azide, a 99% production of the *N*-benzylacetonitrilium ion was obtained. With benzhydryl azide at − 30°C, about 8% of a carbonyl-containing product was obtained and 92% of the reaction was to the benzhydryl cation, followed by an equilibrium formation of some *N*-benzhydrylacetonitrilium ion.

Azidonitriles reacted with nitrosonium tetrafluoroborate in chloroform (heterogeneous conditions) to give 50–81% yields of fluoronitriles, much of the product being rearranged, with very little product from Curtius or elimination reactions[291,292]. Phenoxynitriles reacted similarly, except that a major competing reaction

$$N_3(CH_2)_nCN \xrightarrow[CHCl_3]{NO^+BF_4^-} F(CH_2)_nCN + CH_3CHF(CH_2)_{n-2}CN$$

produced 27–53% phenol, believed to arise via hydride abstraction from the carbon adjacent to the ether function[292]. Alkyl azides give little or no alkyl fluoride and Curtius rearrangement competes favourably both for azidocyclohexane (0% fluorocyclohexane) and for 1-azidohexane (5% 1-fluorohexane, 0% 2-fluorohexane)[292].

VIII. ELECTROPHILIC ASSISTANCE IN THE GAS PHASE

There is considerable current interest in nucleophilic substitution reactions in the gas phase[294,295]. Two powerful tools are available for the study of ion–molecule reactions in the gas phase, ion cyclotron resonance (ICR) spectroscopy, usually performed at low pressures, and negative ion chemical ionization mass spectrometry (CIMS), which is usually performed at much higher pressures. Because of the differences in the experimental conditions, results obtained by one technique are not necessarily directly comparable with results obtained by the other; in particular, the reaction environment has a profound influence on the formation of collision-stabilized ionic species[296].

Beauchamp and coworkers have investigated acid-induced nucleophilic displacement reactions under ICR conditions. For reactions of alkyl halides, they found two essential conditions: the substitution reactions must be exothermic and the competing proton transfer from the protonated substrate to the nucleophile must be endothermic[297,298]. The observed interactions were proposed to proceed as follows: either

$$RXH^+ + Y \longrightarrow \left[\begin{array}{c} R\overset{\curvearrowright}{\text{—}}X \\ \curvearrowleft \;| \\ Y\cdots H \end{array}\right]^+ \longrightarrow RY^+ + HX$$

or

$$RXH^+ + Y \longrightarrow RX + HY.$$

When Y = H_2O and using methyl chloride, deprotonation occurred, but, using ethyl chloride, protonated ethanol was formed. This was consistent with water having an intermediate proton affinity, greater than for methyl chloride but less than for ethyl chloride.

With alkyl fluorides and chlorides, halonium ion formation was a common reaction pathway in acid-induced reactions[299,300]. For example, in a mixture of methyl chloride and ethyl fluoride, the chloronium ion was formed.

$$\left.\begin{array}{l} MeClH^+ + C_2H_5F \\ \text{or} \\ MeCl + C_2H_5FH^+ \end{array}\right\} \longrightarrow \left[\begin{array}{l} CH_3CH_2\text{—}F \\ \quad\quad\quad\curvearrowleft \\ CH_3\text{—}Cl\cdots H \end{array}\right] \longrightarrow CH_3CH_2\overset{+}{Cl}CH_3 + HF$$

With methyl fluoride, the dimethylfluoronium ion was formed.

$$CH_3F^+ + CH_3F \longrightarrow CH_3FH^+ + CH_2F$$

$$CH_3FH^+ + CH_3F \longrightarrow CH_3\overset{+}{F}CH_3 + HF$$

The substitution mechanism proposed would require reaction to proceed with retention of configuration. Speranza and Angelini[301,302] have studied the stereochemistry of gas-phase, acid-induced inter- and intramolecular substitutions at a saturated carbon

atom. They used radiolytically generated Brønsted (CH_5^+, $C_2H_5^+$) or Lewis ($C_2H_5^+$, $CH_3FCH_3^+$) acids (GA^+) at relatively high (atmospheric) pressure.

Chloromethylcyclohexanes gave high degrees of inversion of configuration in the substitution process[301]. 3-Halo-2-butanols[301,302] ($CH_3CHXCH(OH)CH_3$; X = F, Cl)

$$GA^+ + RX \xrightarrow{-G} [RXA]^+ \xrightarrow{H_2O} \overset{+}{R}OH_2 + XA$$

gave a very high degree of inversion in the intramolecular formation of protonated 2,3-epoxybutanes and a double inversion (retention) in the formation of the minor product, 2,3-butanediols. The stereochemical results suggested electrophilically assisted S_N2 processes. Such a scheme is similar to that for the acid-catalysed S_N2 hydrolysis of

$$H_2O: + \rangle C{-}X\cdots H\cdots OH_2^+ \longrightarrow H_2\overset{+}{O}{-}C\langle + X{-}H\cdots OH_2$$

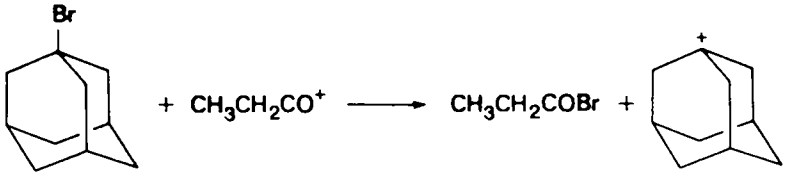
alkyl fluorides in solution (Section II.A). It was proposed that electrostatic interactions dominate at lower pressures[297] but clusters which are formed at higher pressures are deactivated by collisions and inversion is promoted[301,302].

It has been confirmed[296] that under ICR conditions nucleophilic displacement of halide ion from methyl halides under the influence of hydronium ion does not occur. However, under CIMS conditions, water generates the hydronium ion which was found to promote a gas-phase nucleophilic substitution by other water molecules on

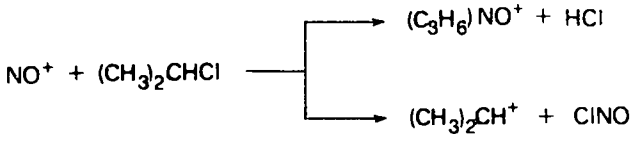
$$H_2O^+ + H_2O \longrightarrow H_3O^+ + OH$$

CH_3X (X = F, Cl) to yield protonated methanol, which in some instances was solvated by one or by two water molecules. In these highly polar gaseous media, other (rather complex) factors are involved in addition to the relative proton affinities[297] and clustering and collision deactivation are important considerations. A minute peak at the *m/e* value corresponding to $[CH_3\cdots X\cdots H\cdots OH_2]^+$ was observed[296]. This is formed in an excited state, involving stabilization by a collision with another water molecule. Further collisions lead to less excited proton-bound intermediates or directly to substitution product.

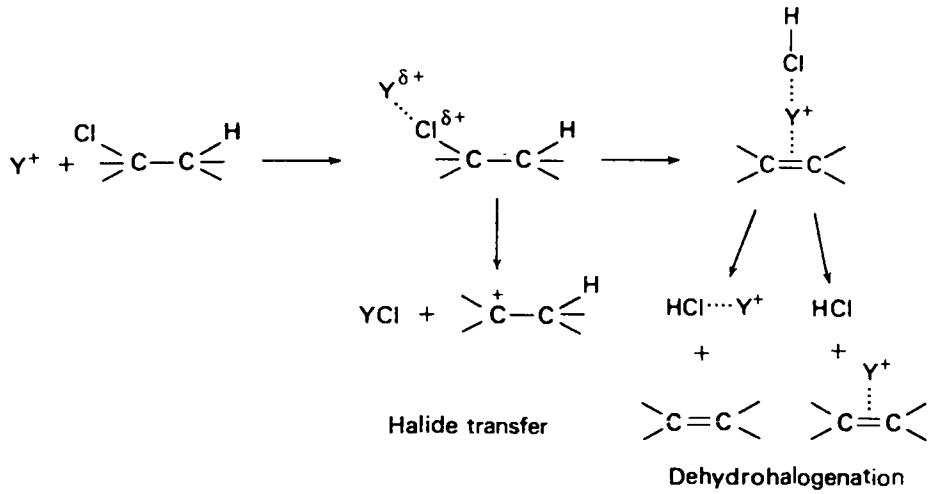
Just as halide ions can be interchanged between carbenium ions[299,300], bromide ion can be transferred from 1-adamantyl bromide to the propionyl cation under ICR conditions[298].



The nitrosonium ion has been found[303] to function as a Lewis acid towards alkyl halides under ICR conditions. With *t*-butyl chloride and with benzyl fluoride, the carbocations were formed. With isopropyl chloride, the carbocation was accompanied



by propene complexed to the nitrosonium ion. With isopropyl fluoride, the NO^+ was also found bound to the HF as well as to the propene. A generalized scheme can be applied (Scheme 6).

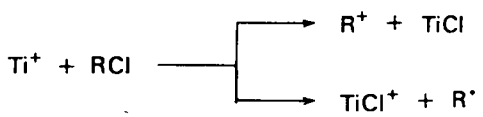


SCHEME 6

Using a thermionic source within the source region of the ICR cell, lithium ion was found to behave similarly and both dehydrobromination and halide transfer was observed with propionyl bromide[304]. Sodium ion brings about the dehydrochlorination of *t*-butyl chloride[305] forming, initially, $(C_4H_8)Na^+$. Lithium abstracts halide ion from benzyl chloride and 1-adamantyl bromide or chloride and Fe^+, Co^+ and Ni^+ abstract chloride ion from isopropyl chloride[305].

By use of a pulsed laser, volatilization and ionization of a variety of metals can be carried out in the ICR source and the interactions of the ions with a variety of organic halides have been investigated. Reports of the interactions of Cu^+ and Ti^+ have appeared and other ions are under investigation. Reaction with copper(I)[306] followed Scheme 6 for reaction with ethyl, propyl and butyl chlorides. With ethyl chloride, only the two dehydrohalogenation reactions were observed but the two propyl and the four butyl chlorides gave competitively from 55 to 100% halide ion abstraction, with the formed carbenium ions sometimes reacting with further alkyl chloride. Chloroform also reacted by halide ion transfer but methyl chloride reacted by chlorine atom or methyl radical transfer and $Cl^\cdot$ or $Me^\cdot$ generation.

Titanium(I)[307] reacted by direct chloride ion transfer with CCl_4, $CFCl_3$, $(CH_3)_2CHCl$ and $CHCl_3$ but there was a competing chlorine atom transfer. Many



substrates, including methyl and ethyl chlorides, reacted only by radical transfer. The $TiCl^+$ formed in the radical process can also act as an electrophilic reagent and C_2H_5Cl, CF_2Cl_2 and CH_2Cl_2 transferred a chloride ion to $TiCl^+$ but not to Ti^+.

$$TiCl^+ + RCl \longrightarrow R^+ + TiCl_2$$

IX. SYNTHETIC APPLICATIONS

Only a brief account can of necessity be given of the numerous applications in organic synthesis of electrophilic assistance to C—X bond reactions. For example, *Comprehensive Organic Chemistry* has over eight pages of the index devoted to silver

salts[308], largely concerning reactions of the type under consideration. There are also listings leading to synthetic applications for other reagents mentioned in this chapter. Another useful source of references is the series *Reagents for Organic Synthesis*[309].

Electrophilic assistance is important in the generation of stable carbocations. Alkyl halides, haloformates or halosulphites are often used as precursors, together with a powerful electrophilic reagent such as antimony pentafluoride–sulphur dioxide. A review of this area has recently appeared in the volume of *Topics in Current Chemistry* devoted to the memory of H. L. Meerwein[310]. Other reviews dealing with the formation of alkylcarbenium ions[311] and acylium ions (acyl cations)[312] are also available. Acylium ions are more usually generated from the acids or the anhydrides, but the acyl halides are sometimes used, especially when the salts are to be isolated[312].

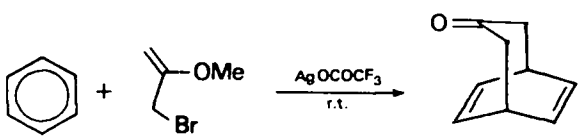
$$RCOF + AgSbF_6 \xrightarrow[-25°C]{SO_2} AgF\downarrow + (RCO)^+SbF_6^-$$

The *t*-butyl and 1-adamantyl hexafluoroantimonates have been isolated from the reactions, in 1,1,2-trifluorotrichloroethane at − 25°C, of the fluorides with antimony pentafluoride[313]. The *t*-butyl salt decomposes above − 20°C but the 1-adamantyl salt is stable at room temperature.

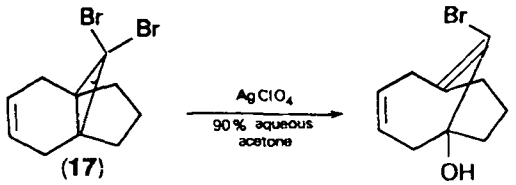
A technique has been developed for preparing stable solutions of carbenium ions which easily isomerize or which are formed from unsaturated precursors; molecular beams of the organic halide and antimony pentafluoride are deposited on a surface cooled to liquid nitrogen temperature[314].

A convenient way of obtaining reactive esters of powerful inorganic acids is by heterogeneous reaction of an alkyl halide with the silver salt in a low-boiling saturated hydrocarbon or in benzene. Alkyl perchlorates[315], alkyl trifluoromethanesulphonates[316], 1-adamantyl arenesulphonates[107,317] and isopropyl perbromate[318] have been synthesized in this way. A review of the syntheses, usually by reactions involving electrophilic assistance, and preparative applications of electrophilic reagents such as acyl, sulphenyl and sulphonyl trifluoromethanesulphonates and dialkylhalonium ions has recently appeared[319]. Silver oxide in refluxing anhydrous alcohols has been used to convert bridgehead bromo compounds to alkoxy compounds useful in the perfume industry[320,321]. Kornblum has written a review of synthetic aspects of the interactions of silver nitrite with alkyl halides[322].

In the syntheses of seven- and five-membered rings by cycloaddition of allyl cations, Hoffman and coworkers have found it convenient to generate the allyl cations by reaction of an allyl halide with silver trichloroacetate or silver trifluoroacetate in isopentane or benzene at reduced temperatures[323]. The heterogeneous reaction was found to be preferable to homogeneous reaction (for example, in ether). The driving force of the silver ion-assisted reaction is such that 2-methoxylallyl bromide reacts with benzene to form bicyclo[3.2.2]nona-6,8-dien-3-one, with sacrifice of the aromaticity, in addition to phenylacetone[324].



Bridgehead alkenes can be prepared by ring opening of cyclopropyl cations, generated by silver ion removal of halide ion. For example, 10,10-dibromo[4.3.1]propell-3-ene (**17**) is believed to give an intermediate bridgehead alkene, which then proceeds to other products[325].



(17)

The reactions of allyl, tertiary and benzylic chlorides and bromides with silver salts, containing $SO_3CF_3^-$, BF_4, PF_6^-, SbF_6^- or ClO_4^- as the counterion, in the presence of suitable heterocyclic monomers (such as tetrahydrofuran or styrene oxide) lead to cationic polymerization[326–329]. Silver hexafluoroantimonate and acyl chlorides interact in methylene chloride to give oxocarbenium ions which also initiate the polymerization of tetrahydrofuran[330]. Olefinic monomers have been polymerized by carbenium ions formed by the reaction of benzyl or benzhydryl chloride with silver hexafluoroantimonate[331].

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CHAPTER **21**

Molecular interactions involving organic halides

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I. INTRODUCTION

A. Scope of This Review

In the last few years a large number of books and papers concerning molecular interaction phenomena have been published. An important part of the information presented in these publications concerns the molecular associations of organic halides and pseudo-halides. This is because such compounds may play several roles.

Some of these compounds may play the role of electron donor in the presence of an acceptor. Others may play the role of an acceptor in the presence of a donor. And, with certain particular compounds, a hydrogen bond may be formed: these compounds may play the role of proton acceptor or the role of proton donor.

These comments suggest that we need to restrict the scope of this study, although we would like it to be as complete as possible. Taking as the starting point two of the previous volumes of this series[1,2] and a review about the same topic written by one of us in 1968[3], we have had to take into account at least 16 basic books[4–16] and more than 2000 papers. We have restricted the scope of our study by using the following criteria:

(1) The properties of some pseudo-halogen molecules, e.g. $(SCN)_2$, reveal some similarities with those of halogens X_2, whereas the organic halides and the organic pseudo-halides are less similar, particularly with respect to molecular associations. Furthermore, the organic halides may be considered as a much more important family of compounds in organic chemistry than the pseudo-halides. Finally, the associative properties of several pseudo-halides (organic compounds with OCN, NCO, SCN, etc., groups) have been reported by Hadži and Milićev in a recent volume in this series[2]. We will therefore restrict our study basically to the case of molecular associations concerning the organic halides.

(2) Among the studies referred to, a large number may be classified as 'routine', that is to say without any precise scientific objective, while some others are non-systematic studies or else either use doubtful methodologies or reveal a lack of skill in the use of a technique (see 'Methodological comments' below). Only a few such publications will be referred to.

(3) The earlier volume of this series on the chemistry of the carbon–halogen bond[1] was largely concerned with complexes formed by hydrogen bonding (26 pages) and only briefly referred to some specific donor–acceptor complexes (three pages about complexes formed with Lewis acids), and to an even lesser degree (two pages) to some lesser known complexes which were described as 'arising from the polarizability of the carbon–halogen bond'. We will denote these latter interactions by the symbol C—X···Y, in which X represents a halogen atom and Y its neighbour in the interaction. Y may be a heteroatom, or the π electron system of an organic base. A large number of studies[4–16] on hydrogen bonded complexes and, more generally, on donor–acceptor complexes have appeared. That is why the only topic treated here in detail is that of C—X···Y interactions. As a result of the lack of related studies, these were only superficially analysed in the previous edition.

(4) The study of 'C—X···Y' interactions will be developed in so far as we believe that it may be considered 'new', but it is similar to the 'hydrogen bond' interaction and this fact is of a fundamental importance.

(5) If we accept the agreement in (4) above (which is developed below in Sections V and VI), a large number of studies, some of them quite recent, in which the C—X···Y interaction is ignored, are no longer pertinent. For instance, such a case would be the interaction between an aromatic halide and an electron donor studied in a solvent such as an aliphatic halide which can interact with the electron donor. These considerations should also be taken into account with regard to (2) above.

(6) Finally, it is important to stress that fluorides will quite often, in comparison with other halides, exhibit specific properties. Since this is well known, specific details will not be presented beyond a few introductory comments.

For instance, in the case of the molecular association properties of aromatic halides (Section IV), it is well known that the influence of the fluorine enables hexafluorobenzene (HFB) to be associated with electron donors, and HFB is one of the most studied and best known aromatic halides. However, in the case of the interaction between aliphatic halides and organic bases, the fluorine bonded to the carbon is relatively inert (Section VI). The inertness of the Freon solvents reflects the unreactivity of carbon–fluorine bonds: the only interaction with an aliphatic fluoride may be formation of a hydrogen bond, in which the fluorine atom acts as a proton acceptor (Section II).

Accordingly, a summary of our study is as presented in the table of contents. Sections V and VI will be particularly developed, as a consequence of the selected criteria described above.

B. Methodological Comments

(1) In order to study the functions and the properties of molecular interactions, methodological criteria must be taken into account and physical techniques should be chosen according to criteria which are dependent upon the components of the system under study.

Moreover, in the case of weak molecular interactions (i.e. those having weak association constants, between 0.1 and 5 l mol^{-1}, or small free energies of association, between 1.5 and 3 kcal mol^{-1}) we are obliged to consider all of these criteria, for otherwise the results may be considered invalid.

These criteria have recently been discussed in several reviews, such as those of Hanna and Lippert, Tamres, and Swinton and Foster, published in the books edited by Foster[5,6], whose main concern is electron donor–acceptor (EDA) – or charge transfer (CT) – molecular complexes.

Methodological considerations of hydrogen bonded complexes may be found in several reviews included in the books edited by Schuster, Zundel and Sandorfy[7].

Among other things, it is possible to find in these reviews the analysis of problems arising from the determination of weak values of association constants[6], the need to use activity coefficients[5,6] and the so-called 'solvent effects on molecular associations'[5,6,14]. Most of the questions concern the classical debate about the eventual distinction between so-called 'specific' and 'non-specific' interactions. In the case where solvent effects are detected, the questions concern the distinction between 'normal' effects (e.g. those which may be explained in terms of non-specific solute–solvent interactions) and 'abnormal' effects (e.g. those that refer to specific solute–solvent interactions).

Finally, it is possible to find in the above reviews comparative analyses of the different physical techniques used in the study of molecular interactions[6]. Most of these are referred to as hydrogen-bonded or EDA complexes[5–7].

(2) It is well known how difficult it is to classify the strengths of forces of interaction. This is due to the fact that classifications based on a single parameter are notoriously insufficient. Furthermore, the criterion which may be used to establish a classification is not unique. For example, some studies use as a criterion the distance between interacting atoms (such as the shortening of Y···Z distances or the stretching of the X—Y distance in the case of X—Y···Z interactions). Spectrometric studies may use another criterion (e.g. the $\Delta\nu$ shift) and thermodynamic calculations may lead to values for the enthalpy and the free energy of association. McGlashan and coworkers[17] have recently stressed the difficulty of choosing one of these two thermodynamic criteria. Whatever is the criterion adopted, if certain interactions become too strong or too weak one may have trouble classifying other interactions whose values fall in between: in such cases the choice of the criterion used is a decisive one. Under such circumstances, classification of the strengths of the interactions will be discussed here only when strictly needed or when cited papers insist upon it.

Three other methodological comments will be presented in Section VI. More specific than comments (1) and (2) above, they aim to introduce the results which are related to the study of weak 'interactions between aliphatic halides (not proton donors) and organic bases' (see Section VI.A).

II. INTERACTIONS WITH PROTON DONORS

Like all the other hydrogen bonded complexes, the hydrogen bond associations between organic halides and proton donors were extensively studied between 1950 and 1970. The principal aspects of these associations are summarized by Smith[18] in a review published in a previous volume of this series. Furthermore, some general studies referred to in Section I above, such as the recent books by Green[12] and by Vinogradov and Linnell[13], contain much information on inter- and intramolecular associations of the type A–H···X–C.

In the last ten years the number of studies of hydrogen bonding and of associations of the type A–H···X–C has considerably diminished.

Also, chelation in *ortho*-halophenols, so widely studied in the recent past, is at present the subject of only rare theoretical treatments.

Consequently, it will be sufficient here to set out the main conclusions of the numerous previous studies and to dwell on the few recent ones.

A. General Remarks

The proton-accepting character intrinsic to halogens linked to carbon atoms may only be studied rigorously in intermolecular associations, because these permit the most favourable configuration of the H, X and C atoms, i.e. colinearity; intramolecular associations can give rise therein to bent hydrogen bonds in which the energy is considerably modified.

Also, the α-halo or *ortho*-halo configuration of the halogen substituent which permits intramolecular association is likely to introduce an entropy factor which may be important. In the particular case of the *ortho*-halophenols, it is worth noting that the halogen substituents, being in close electronic interaction with the aromatic ring, are not comparable to the halogen substituents in aliphatic molecules such as halogen-substituted alcohols. However, intramolecular associations are the most frequently studied because they are experimentally more easily followed than intermolecular interactions. Also, those intramolecular associations that involve the most 'perturbed' *ortho*-halogens are precisely those that are the most studied. It must also be noted that there is inevitable competition between a given association under study (inter- or intramolecular) and the possible intermolecular auto-associations of the type XAH...A(H)X and / or XAH...XAH. Finally, the solvents which can be used are few in number (usually acyclic or alicyclic hydrocarbons). Chlorinated solvents remain widely used but they may interact with the proton donor or sometimes with the organic halide (see Sections II and VI). Even when a classical solvent such as CS_2 is used in these studies, it does not seem to be an inert solvent in the strict sense[19]. All of these considerations show how difficult it is to be sure of the properties of the hydrogen bond interactions AH···XC, in spite of the many studies on the subject. In the following study we will adopt the enthalpy of association as the criterion for classification of the proton acceptor power, because it is frequently used in the literature. Yet, as recently stated by McGlashan and coworkers[17], the choice of either the enthalpy or the free energy of association is open. For this study, the choice is not important; the interactions studied would be classified in an identical manner with either ΔH or ΔG, following the values published by Allan and Reeves[20,21] for the AH···X intramolecular associations of *ortho*-halophenols and those by Schleyer[22] for the intermolecular hydrogen bonds, AH···X, in the phenol–cyclohexyl halide systems.

Finally, a large number of classifications for interactions are emerging from comparative studies of frequency shifts (e.g. O—H stretching bands). These may be useful only to the extent that studies such as those by Schleyer and coworkers[22], and Kollman and coworkers[23], have established the limits of the validity of the Badger–Bauer rule relating shifts with hydrogen bond enthalpies.

B. The Proton Acceptor Character of Organic Halides

According to the results of Vinogradov and Linnell[13], organic halides seem to be mediocre electron acceptors. A halogen attached to carbon is a weaker acceptor than most other heteroatoms, e.g. N, O, S. Nevertheless, a classification of acceptor character for the series F, Cl, Br, I may be attempted, using (1) intermolecular associations of the type AH···XR; (2) intramolecular associations of the type AH···XB.

1. *Intermolecular associations*

Only a few studies have been published in this category[22,24–26]. The most pertinent results seem to be those of Schleyer and coworkers[22] concerning phenol and cyclohexyl halides; this study, carried out with the use of infrared spectrometry in CCl_4

TABLE 1. Thermodynamic properties and spectral shifts of hydrogen bonds of phenol to cyclohexyl halides (RX) in CCl_4 solutions[22a]

X	$\Delta\nu$, cm^{-1}	$-\Delta H°$, kcal mol^{-1}	$-\Delta F°^b$, kcal mol^{-1}	$-\Delta S°^b$, cal $°C^{-1}$ mol^{-1}
F	53	3.13	1.31	6.1
Cl	66	2.21	0.87	4.5
Br	82	2.05	0.85	4.0
I	86	1.72	0.82	3.0

[a]Determined in the near infrared.
[b]At 25°C.

solutions, leads to a sequence F > Cl > Br > I (Table 1). This sequence, based on the enthalpy of association as a criterion to classify the proton acceptor power, is quite the reverse of the spectral shifts order.

2. *Intramolecular associations*

A large number of studies (in particular with *ortho*-halophenols) deal with this topic. In the first authoritative study of the hydrogen bond, by Pimentel and McClellan[27], the sequence F > Cl > Br > I was stated, but in 1960 the validity and generality of the results were less certain than they appear at present.

In a previous volume of this series, Smith[18] refers to several studies involving intramolecular associations, and he has stressed the conflicting views concerning the above sequence.

Therefore no unchallengeable classifications of the proton acceptor character emerge from the review of Smith. More recently, Rothschild[28] has written '. . . the impressive amount of literature on the strengths of intramolecular H-bonds between OH and halogen shows that agreement is not universal. Furthermore, a valid unified theoretical approach apparently has not yet been achieved . . .'.

Nevertheless, we will present the more recent results, distinguishing experimental from theoretical studies, and studies of aliphatic from studies of aromatic compounds.

a. Experimental studies. These studies will be discussed under two headings: (i) haloalcohols and (ii) halophenols.

(i) Haloalcohols. If we examine only the infrared results published by one group[29] for two series of haloalcohols, the following results are obtained: for the 2-haloethanols, F > Cl ~ Br > I in CCl_4 as solvent; for the 2-halocyclohexanols, I > Br > Cl in CS_2. The criterion used for classification was, in both cases, the enthalpy of the intramolecular association.

This finding exemplifies Rothschild's conclusion concerning apparent contradictions. And it may be related to the methodological comments in Section II.A (e.g. concerning the influence of solvents).

(ii) Halophenols. The results obtained by Carlson and coworkers[30] in the gas phase and in solution (by infrared spectrometry) have been compared by them to a large number of other results in the literature: several inconsistencies emerge from these comparisons concerning the relative positions of F, Cl, Br and I. The most probable order seems to be Cl > Br > I, with the position of F remaining in doubt (Table 2).

b. Theoretical studies. These studies will again be considered under two headings: (i) haloalcohols and (ii) halophenols.

(i) Haloalcohols. The Schroeder–Lippincott potential function model for bent hydrogen bonds has been applied to 'OH···halogen' intramolecular hydrogen bonds by Robinson and coworkers[29]. The sequence I > Br > Cl, found for the 2-halocyclohexanols, is consistent with the experimental classification above;

TABLE 2. Enthalpies of intramolecular hydrogen *bonds in o*-halophenols (*o*-XC_6H_4OH)[30]

X	$-\Delta H$, kcal mol^{-1}	
	Vapour phase	Solutions in C_6H_{12}
F	1.63	1.44
Cl	1.63	1.62
Br	1.53	1.57
I	1.32	1.45

however, the sequence I > Br ~ Cl > F found for the 2-haloethanols seems to be inverse of the experimental order. Therefore, no consistent conclusion is possible.

(ii) Halophenols. The model used by Robinson and coworkers[29] once again leads to a classification, I > Cl > Br > F, which is opposed to the one obtained experimentally (see Section II.B.2.a above).

In a recent in-depth analysis, Kollman and coworkers[23] proposed the following conclusions: the Cl > Br > I order is consistent, irrespective of the theoretical method used (CNDO/2 or *ab initio*), and only the relative position of F varies (CNDO/2 places F between Br and I and the *ab initio* method places it between Br and Cl).

In the specific case of the halophenols, it thus seems possible to detect some change from the uncertain position of Rothschild[28]. Thus, on the basis of the results presented here, the sequence for the proton acceptor character of the halogens in *ortho*-halophenols seems to be Cl > Br > I, both from experimentation and from calculation. Only the relative position of the fluorine remains to be determined.

3. *Conclusions about the proton acceptor character of organic halides*

With the information so far available, the sequence for this character seems to be Cl > Br > I, for both inter- and intramolecular hydrogen bonds. Fluorine, like the other halogens, is a proton acceptor, but its position within the sequence is not well established (though it is certainly a stronger proton acceptor than iodine).

C. Hydrogen Bonding, Sometimes an Unsatisfactory Explanation

Some authors have recently maintained that perhalogenated solvents such as CCl_4 or C_2Cl_4 can form hydrogen bonds with proton donors[25,31,32]. This hypothesis was used, some years ago, to explain among other things the apparent decrease in the value of the formation constant for hydrogen-bonded complexes, in such solvents (S). The existence of hydrogen bonding solvation A—H···S, in competition with A—H···B, was postulated at the time. The reduced stability of A—H···B complexes in such solvents can be explained, however, in terms of a B···S interaction, which is now well known, as will be shown in Section V.B. Guerin and coworkers have studied several kinds of interactions of this type, such as B···CCl_4 and B···C_2Cl_4[19,33,34]. Also, Tucker and Lippert[35] have recently referred to several studies supporting the view that CCl_4 does not have the character of a 'proton acceptor'.

III. INTERACTIONS WITH ELECTRON ACCEPTORS (NOT PROTON DONORS)

Aliphatic halides were cautiously considered by Mulliken and Person[11] as 'sometimes' n electron donors and the aromatic halides as mediocre π donors, the halogeno substituents not being considered as 'electron-releasing substituents'. It is not

surprising therefore that studies of aliphatic halide–electron acceptor complexes are relatively few in number. Only strong electron acceptors, such as those of *v* type (with vacant orbital according to Mulliken's classification), yield reasonably important interactions with aliphatic halides. But, one may also note the study carried out by Olah and coworkers[36] of a complex involving an aromatic halide: $C_6H_5F \rightarrow AlBr_3$. Another study by Voigt[37] of the complex C_6F_6–tetracyanoethylene showed that C_6F_6 may act as an electron donor with an electron acceptor as strong as tetracyanoethylene.

Within this group of interactions with *v*-type acceptors, the associations with trihalides of the elements of group IIIB have been most studied, on account of their relevance to the mechanism of Friedel–Crafts reactions. We will take note (Section III.A) of some complementary aspects of these interactions and of their connections with mechanism. Smith[18] developed this topic in a preceding volume of this series and it seems that little progress has been made since then.

In order not to limit our study to classical Lewis acids (of *v* type, such as $AlCl_3$), in Section III.B we will briefly consider interactions involving a classical $x\sigma$ acceptor, such as I_2. But in this case, the well known complexes 'I_2–aromatic hydrocarbon' entail the existence of variably stable interactions between I_2 and aromatic halides.

A. *v*-Type Electron Acceptors: Trihalides of Group IIIB Elements

EDA complexes formed between BF_3 and aliphatic halides seem to be essentially molecular[18]. However, those formed by $AlCl_3$ or $AlBr_3$ with several aliphatic halides seem to lead, according to recent studies[38–40], to an ionic dissociation which releases a carbocation under some circumstances (liquid HCl; saturated solutions of $AlBr_3$ in di- or trihalomethane). The issue of the ionic nature of the '$RX–MX_3$' interactions has been debated since 1964, and the use of Raman spectrometry by Rice and Bald[41] and of infrared spectrometry by Perkampus and Baumgarten[42] has pointed towards the existence of a non-ionized species. Such a conclusion was put forward by Rice and Bald[41], suggesting that $R–Br \rightarrow AlCl_3$ is a molecular complex rather than an ion pair $R^+ AlBr_4^-$. However, the solvent used by these authors, cyclohexane, is non-ionizing. Similarly, again using a non-ionizing solvent (CS_2), Adema and coworkers[43] determined the formation constants at 24 °C of the complexes $AlBr_3 \cdots n$-PrBr (1.3 l mol^{-1}) and $AlBr_3 \cdots i$-PrBr (7.3 l mol^{-1}) using microwave spectroscopy. These values, which are small when compared with those of other donors such as amines, confirm the mediocrity of organic halides as *n* donors.

It is worth commenting on the role played by the 'organic halide–Lewis acid' interactions in the mechanism of well known reactions such as Friedel–Crafts and Prins reactions. For the former, Smith has already stressed[18] the role played by the 'organic halide–MX_3' complex. More information on this subject is reported by Bamford and Tipper[44], citing the work of Brown and Olah. More recently, Olah and coworkers[45] presented results on the inter- and intramolecular selectivity of the competitive benzylation of toluene and benzene, 'supporting the suggestion that the nature of the "organic halide–Lewis" complex is primarily determining intermolecular selectivity but is rather unimportant in affecting the isomer distributions. . . . In addition, the order of reactivity of benzyl halide (for a given catalyst) is F > Cl > Br'.

Finally, Nakane and coworkers[46] suggested the formation of a more or less ionized complex of the type $C_2H_5XMX_3$, which would be involved in Friedel–Crafts reactions in non-polar solvents.

The role played by the 'organic halide–MX_3' complexes in the mechanism of the Prins reaction was referred to in a previous volume of this series by Chivers[47], who

reported the addition complex hexachlorocyclopentadiene···$AlCl_3$. A related addition complex, 4-perchloro-1-methylenecyclopentane···$AlCl_3$, is totally ionized with carbocation formation, according to a spectrometric (infrared and ultraviolet) study[48].

More recently, several organic syntheses published by West and coworkers[49,50], involving haloalkenes as reactants and $AlCl_3$ as catalyst, have also suggested the formation of a haloalkene–$AlCl_3$ complex as a pair of ions: 'carbocation, $AlCl_4^-$'.

Finally, some halogen exchange reactions between alkyl halides and boron trihalides also seem to have mechanisms involving initial formation of $RXBX_3$ adducts[51].

B. An xσ-type Electron Acceptor: Iodine

In the understanding of the interactions of organic halides with this type of electron acceptor, the separate study of aliphatic halides and aromatic halides seems useful, the latter in fact being likely to intervene, in spite of the presence of halogeno substituents, as π donors.

At the same time, and whatever may be the type of the organic halide and the phase considered (gas or solution in *n*-heptane), charge transfer bands (in the ultraviolet) appear[11,52–54] in all cases. The interactions, which would be effectively of the CT or EDA type, are generally rather weak, especially in the case of aliphatic halides, and certain CT bands are even attributed to contact complexes.

Nevertheless, the CT nature of these interactions remains proven by the correlations which have been found between the observed absorption energies ($h\nu_{CT}$) and the ionization potentials of the organic halide donors; at least, this is so in the case of a single series of halides (e.g. RI or RBr).

1. *Association with aliphatic halides*

In the case of the aliphatic halides, studied in solution[53] in an inert solvent (*n*-heptane), correlation of band maxima with the ionization potentials of the alkyl halides clearly suggests the charge transfer character of the bands. The linear dependence of absorbance on either the iodine or alkyl halide concentration is consistent with the view that the spectra arise from contacts (Table 3).

The values of the equilibrium constants determined by ultraviolet spectrometry are weak and yet these values indicate, in a meaningful way, the existence of an association in excess of random collisions (if, as according to Scott[55], the equilibrium constant obtained by the Benesi–Hildebrand procedure corresponds to this excess).

TABLE 3. First and second ionization potentials (I_D^V, eV) of alkyl iodides and spectral characteristics of alkyl iodide–iodine systems in *n*-heptane at 24°C[53]

			λ_{max}, nm[a]		
Systems	First I_D^V	Second I_D^V	Band 1	Band 2	Band 3
MeI	9.50	10.13	297.6	269.0	245.5
EtI	9.34	9.93	303.0	271.5	247.5
n-PrI	9.27	9.82	304.7	270.5	245.0
i-PrI	9.19	9.75	307.9	275.0	248.7

[a]From resolution of two Gaussian curves (assuming the third band has a negligible contribution); band 1 and band 2 attributed to two contact charge transfers; band 3 attributed to a blue-shifted $n—\sigma^*$ transition of the alkyl iodide.

TABLE 4. Equilibrium constants (K_c) for iodine complexes with alkyl or aryl halides

Compound	K_c, l mol^{-1}	Compound	K_c, l mol^{-1}
Benzene	0.175[a]	Toluene	0.26[b]
Methylbenzene	0.25[a]	*o*-Fluorotoluene	0.12[b]
Fluorobenzene	0.06[a]	*m*-Fluorotoluene	0.10[b]
Chlorobenzene	0.07[a]	*p*-Fluorotoluene	0.11[b]
Bromobenzene	0.11[a]	1-Chlorobutane	0.11[a]
Iodobenzene	0.34[a]	Chlorocyclohexane	0.15[a]
1,2-Dichlorobenzene	0.00[a]	1-Bromopropane	0.27[a]
1,3-Difluorobenzene	0.015[b]	2-Bromopropane	0.33[a]
1,3,5-Trifluorobenzene	0.004[b]	Iodomethane	0.67[a]
		Iodoethane	0.82[a]
		1-Iodopropane	0.79[a]
		2-Iodopropane	0.77[a]

[a]In CCl_4 at 25°C[56].
[b]In heptane at 21°C[58].

Even if certain aspects (e.g. the choice of CCl_4 as solvent) may undermine the recent work of Clark and Kolb, this study[56] presents a systematic methodology: it allows us to observe the decreasing stability of RX–iodine complexes in the order I > Br > Cl > F (Table 4).

2. *Association with aromatic halides*

The formation of CT complexes, which is observed by ultraviolet spectrometry in solution in numerous cases, is evidently linked to the π electron donor character of the aromatic ring (often benzene, or toluene) bearing the halogeno substituents.

Studies of classic correlations (e.g. between $h\nu_{CT}$ and the ionization potential of the donor or between this potential and the stability of the complex) have been effected, and are to be found in the review by Hanna and Lippert[57].

It appears, however, that these correlations, as well as the classification of the influence of the halogeno substituent, are questionable for a number of reasons. In fact, it is difficult to make comparisons in a given series, for the various authors sometimes employ solvents, such as CCl_4[56], which eventually interact, so one may suppose, with the donor and/or the acceptor. Yet, the principal fact observed in all of these cases appears to be evident, and may be summed up as follows: the adjunction of a halogeno substituent to an aromatic ring lowers the stability of the complex formed by the iodine with this aromatic compound. This destabilization effect increases, as in the case of aliphatic halides, with the electronegativity of the halogen, which reduces the electron donor character of the aromatic ring.

Some values of the stability constants of complexes between RX (or ArX) and molecular iodine, recently published[56], are given in Table 4; for comparison's sake, we also refer in this table to the earlier results of Tamres[58].

IV. INTERACTIONS BETWEEN AROMATIC HALIDES AND ELECTRON DONORS

Mulliken[11a] has classified as $x\pi$ electron acceptors 'aromatic or unsaturated hydrocarbons with electronegative or electrophilic substituents, for example trinitrobenzene . . .'. One may expect, therefore, to find many studies of EDA

interactions between n or π electron donors and (1) halo (or cyano) ethylenes; (2) halo (or cyano) benzenes.

For the first group it could be demonstrated that π electron donors, e.g. tetracyanoethylene, show the properties of a 'π electron acceptor' proposed by Mulliken. Related compounds such as tetrabromoethylene enter into interactions of a different type, involving 'halogen bonds' as described below (Sections VI.A.1 and VI.A.2), particularly with n electron donors.

For the second group, reported studies are mainly concerned with the interactions of hexafluorobenzene or 1,2,4,5-tetracyanobenzene with, particularly, π electron donors.

For halogenobenzene it is necessary that six of the most electronegative substituents (i.e. C_6F_6) be present in order for interaction with π electron donors to take place. But, in the case where the substituents are groups such as cyano or nitro, fewer substituents are needed, and the effects are generally stronger. It will be shown (Section IV.A.1) that the existence of interactions between hexafluorobenzene and π electron donors is itself controversial; few authors agree to classify it as an EDA, as would follow from Mulliken classification.

A similar analysis could be carried out for halo- or cyanoquinones, which are well known electron acceptors. According to Mulliken, a quinone will be a '$k\pi$ electron acceptor, with resonating $=C=O$ structures'. Thus the tetrahalo- or tetracyanoquinones will present *a fortiori* an enhanced electron acceptor character because they contain four electronegative substituents. The EDA complexes formed by such an electron acceptor are not central to this chapter and will not be further discussed here. Also, many reviews on the subject have been published recently (e.g. Foster[59]).

A. An Aromatic Halide: Hexafluorobenzene

Most of the information concerning this compound has been presented in reviews by Swinton[60a,60b]. All of the results to be presented here without specific reference come from these reviews. Only reference to work carried out since the later Swinton review[60b] will be specifically quoted.

1. *Studies in the solid state*

Several studies of solid–liquid phase diagrams suggest the existence of (1:1) solid addition complexes between C_6F_6 and π or (n and π) donors, but rarely with n electron donors.

It is worth noting that planar aromatic molecules such as pyridine and furan, which are (n and π) donors, do give addition compounds whereas the corresponding n donors such as Et_3N and tetrahydropyran do not.

These latter considerations, and the fact that phase diagrams do not give any decisive proof of the existence of a specific interaction, led several authors to consider that these 'unlike interactions' are the result of packing effects. This hypothesis seems to be confirmed by some X-ray crystallographic studies. In fact, Dahl[61a,61b] noted that the molecular species are arranged alternately face-to-face in stacks. This configuration is reminiscent of π–π donor–acceptor complexes except for the mean separation between planes (about 0.350 nm), which is substantially greater than those observed for π–π complexes. However, few papers have been published on the crystal structures of the solid complexes formed with C_6F_6. One reason for this is that the solids display a considerable degree of molecular motion over a wide scale of temperature. For the solid formed by C_6F_6 with benzene, the relative rotation of the two molecules and the activation energy for this were studied by Fyfe[62].

2. *Studies in the liquid and gas states*

Studies in the liquid state have mainly been carried out in fairly dilute solutions of C_6F_6 and an organic base.

a. Organic bases: benzene and methyl derivatives of benzene. Swinton and coworkers[60a] have determined the enthalpies and formation constants (K_x) for the complexes between C_6F_6 and several aromatic hydrocarbons using excess free energy values (Table 5).

Two additional arguments supporting the specific character of these interactions may be found in an infrared study of the C_6F_6–C_6H_6 system (in comparison with the C_6H_6–C_6H_{12} system) and in the small value (0.1–0.3 D) observed for the dipole moment of this complex. However, Bailey and Ferri[63] have very recently shown by infrared and Raman spectrometry that no preferential orientation of the two molecules was observed in the time range of 0–1.5 ps, and this seems to indicate that only collision complexes are present.

Finally, no CT band has been observed in these systems.

b. Organic bases: amines and oxides. We have already stated that most of the more important interactions involve aromatic compounds. In the case of the anilines, the results obtained by Beaumont and Davis (in Swinton[60a,60b]) (Table 5) are the most reliable, having been obtained by different methods (ultraviolet spectrometry, calorimetry) and confirmed by the existence of specific transitions in the ultraviolet.

TABLE 5. 'C_6F_6–organic base' interactions[60a]

Organic base	K_x	$-\Delta H_{complex}$, kcal mol^{-1}
Benzene	2.03[a]	2.3
Methylbenzene	2.58[a]	2.7
1,4-Dimethylbenzene	3.56[b]	2.8
N,N-Dimethylaniline	3.9[b]	1.9
N,N-Diethylaniline	3.0[b]	2.2

[a]At 313.2 K.
[b]At 298.2 K.

3. *The nature of interactions between hexafluorobenzene and electron donors*

As reported by Swinton[60a], the nature of these interactions raises particular problems because the acyclic (or alicyclic) perfluorocarbons themselves have several properties which are interpreted as strong evidence for unexpectedly weak, unlike interactions in these systems.

Moreover, as in all cases of weak interactions, some questions of interpretation are raised:

(i) In the solid state, are the observations due to molecular interactions or to packing effects?

(ii) Is the interaction specific or non-specific?

(iii) What is the physical nature of the interaction? For instance, do the C_6F_6–organic base complexes of interest here result mainly from CT effects (according to Mulliken), or from classical electrostatic and polarization effects (which are of major importance in this respect according to Hanna and Lippert[57]). This question is discussed in detail by Swinton[60a].

These questions, which have already been raised in Section I, will not be further developed here, but they will be analysed in more detail when the analogous problem

of the nature of the interaction between aliphatic halides and organic bases is examined in Section VI.C, and related to the classic debate concerning the nature of weak hydrogen bond interactions. For the interactions between C_6F_6 and organic bases, it will suffice to refer to the conclusions of recent studies (cf. Sections IV.A.1 and IV.A.2) and to take into account the general comments made about 'weak, unlike interactions' present in perfluorocarbons. The interactions between C_6F_6 and bases are only weak, and they seem to require 'structural' conditions (e.g. the possibility of stacking C_6F_6 and electron donors in parallel planes, but without substantial shortening of intermolecular distances).

If in some cases the specific character of the interactions is not in dispute, there are cases in which collision complexes seem likely to be involved. This type of interaction does not seem to be followed by chemical reactions, in relation to which the complex formation would thus be the first stage. On this latter point it will be shown that there are substantial differences between C_6F_6–base interactions and other associations, such as those between aliphatic halides and bases (or between tetracyanoethylene and bases), which appear to be much more clearly characterized, and in many cases are followed by chemical reactions.

V. HYDROGEN BONDING BETWEEN ALIPHATIC HALIDES (AS PROTON DONORS) AND PROTON ACCEPTORS

A. Hydrogen Bonding as a Satisfactory Explanation

The protons attached to carbon atoms carrying halogen atoms have a well known ability to form hydrogen bonds with organic bases. A large number of studies have been reported in which the proton donor character has been studied as a function of the nature and number of halogens as well as the nature of the hydrocarbon chain.

It is both difficult and unhelpful to refer to all the available studies, given that the topic has recently been reviewed by Green[12]. It is enough to say that one of the most studied 'proton donors' has been chloroform. This molecule has several advantages: very weak self-association[65] (like CH_2Cl_2, if we assume that its behaviour is like its deuteriated derivative[66]), and C_{3v} symmetry, which makes it easier to account for data obtained from dielectric measurements of its complexes (Section V.B).

However, many other halogen-containing compounds with acidic protons may engage in hydrogen bonding. Guerin and coworkers[67] have recently studied the interactions between dichloroethylene and several bases. Such a molecule may also engage in weak self-association of the kind already referred to[65].

Nevertheless, we will restrict the presentation of the results to examples concerning only the most studied, and thus better known, of the proton donors. We will examine mainly the interactions between the C—H bond of chloroform or dichloromethane and n or π electron donors. In these cases, no surprising results are expected: for n donors, the C—H bond is generally placed along the axis of the electron pair, and in the case of π donors along an axis perpendicular to the π electron system. However, it will be shown in Section V.B that surprising results are sometimes obtained. This is particularly true when the halogen has a high atomic number (Br or I). Studies by Sheridan and coworkers[68–70] and by Dumas, Geron, Guerin and Gomel[33,71–74] are the most recent, systematic and comprehensive. They will be presented below.

Meanwhile, it is interesting to note the existence of isomeric complexes: when chloroform interacts with an organic base which has non-independent n and π electron systems, interaction is possible with either electron system[74]. This result was reported by Castagna and coworkers[75] after a study of a different proton donor, pyrrole (which has weak self-association and C_{2v} symmetry). In this case, however, the π system of the

pyrrole may interact with the π electrons of the base and the observed isomerism may be erroneously attributed. The use of a compound without π electrons such as chloroform has resolved this ambiguity[74,76,77].

B. Is Hydrogen Bonding Always the Only Interaction?

We will now consider the case of organic halides in which there are several halogen atoms, such as the haloforms. Whatever the halogens present, one would expect these compounds to interact with *n* electron donors in the manner already described in Section V.A, namely C—H···*n* electrons. However, an interesting study of the 1:1 complex between iodoform and 1,4-dithiane by Bjorvatten and Hassel[78] proved that in the solid state the C, I and S atoms are colinear and not the C, H and S atoms, as might be expected. The result implies the existence of an S···I interaction (with an observed separation of 3.32 Å compared with the expected 4.00 Å). These results could have been caused, at least partially, by a 'crystal packing effect' and the situation could have been different in the liquid or gaseous states (cf. Section VI.A.1.a). The cases presented below in Section VI.A, with examples chosen to avoid ambiguity introduced by hydrogen atoms, show that in the liquid state there is a specific C—X···Y interaction, particularly with heavy halogens such as Br and I. Furthermore, after the first crystal structure determination[78], several other studies have confirmed the formation of complexes of CHI_3 in the solid state in which the electron donor atom is placed along the C—I bond. The main results are summarized in Table 6.

The studies by Sheridan and coworkers[68–70] and those by Dumas, Geron, Guerin and Gomel[33,71–74] of the $C_nH_pX_q$···base systems in the liquid state may be summarized as follows. The simultaneous presence of hydrogen atom(s) with acidic character and halogen atom(s) able to interact with a base leads to a new kind of 'isomeric complex' in which the C—X···Y interaction competes with the C—H···Y interaction. The stabilization energy of the former interaction (C—X···Y) in free energy terms probably increases (Section VI.E) with the increasing atomic number of the halogen. For the latter interaction (C—H···Y), it will decrease. This is likely to complicate the interpretation of the thermodynamic data. Sheridan and coworkers[68–70] arrived at this conclusion mainly on the basis of thermodynamic considerations based on gas–liquid chromatography. Dumas, Geron, Guerin and Gomel[33,71–74] based their conclusions mainly on dielectric measurements. Also, Baron and coworkers[79] have attempted to clarify the interpretation of some thermodynamic terms (such as K, ΔH) obtained by various techniques on the same molecular complex, when isomeric complexes may exist.

TABLE 6. Structural data on n–σ^* 'HCI_3–base' complexes[64]

Base	d(I···Y)[a]	$r_{(I)} + r_{(Y)}$[b]	Interbond angle[c]
Hexamethylenetetramine	(I···N) 2.94	3.65	180
Quinoline	(I···N) 3.05	3.65	176.5
1,4-Dioxane	(I···O) 3.04	3.55	173.2
1,4-Dithiane	(I···S) 3.32	4.00	175
1,4-Diselenane	(I···Se) 3.465[d]	4.15	178.6[d]
	3.514[d]		160.3[d]

[a]Intermolecular contact (Å).
[b]Sum of van der Waals' radii (Å).
[c]Interbond angle at the acceptor atom in degree.
[d]Different values given by original authors[64].

In fact the precise meaning of such terms is difficult to define in these cases, since it depends on the technique being used. For instance, dielectric polarization (DP) studies lead to $K_{DP} = K_{C-H\cdots Y} + K_{C-X\cdots Y}$, whereas infrared (IR) studies will lead to $K_{IR} = K_{C-H\cdots Y}$. It is not suprising therefore, to find that $K_{IR} < K_{DP}$. Baron and coworkers[79] have examined the following techniques: dielectric polarization, infrared and NMR spectroscopy and microcalorimetry. This work may be related to ultraviolet and NMR studies of the conformational isomerism of tetracyanoethylene–aromatic hydrocarbon complexes[80] and to general comments concerning isomeric 1:1 complexes[4a]. It is worthwhile to note that the possibility of isomeric complexes in solution was first suggested by Orgel and Mulliken[81].

In Green's review on C—H···Y interactions[12a], the possibility of isomeric complexes (C—H···Y and C—X···Y) was suggested, but it was supported only by the data on the 1:1 solid compound CHI_3···1,4-dithiane[78]. Recently, NQR data for this latter molecular complex were determined[82]. Dielectric measurements also allowed Sutton[83] in 1974 to demonstrate the existence of a C—I···N interaction for iodoform and 1,1,1-triiodoethane with nitrogen bases. In this case one might expect, in the liquid state, only a hydrogen bond to form (C—H···N). Similar isomeric complexes, C—H···(π electrons) or C—Br···(π electrons) in bromoform–toluene (or xylene) systems were studied by Singh and Verma[84] using NMR and calorimetric methods. However, the NMR study did not include corrections for magnetic anisotropy or for solvent effects. Such considerations also apply to the more systematic NMR study of Bertrán and Rodríguez[85] (three haloforms and 24 electron donors were studied) in its support for the existence of isomerism of the type C—H···Y and C—X···Y (Table 7).

TABLE 7. Estimated range of the contribution of the C—X···Y interaction in the haloform–base (solvent) interactions[85,a]

Solvent group	Br_3CH	I_3CH
Weakly basic (halogenated hydrocarbons)	0–10%	0–15%
Esters and ketones	≈0	0–15%
Ethers	≈0	10–30%
Amines	0–5%	60–95%

[a]Evaluation of the relative importance of the C—X···Y interaction from deviation of solvent shifts of haloform protons (Br_3CH and I_3CH) from linear dependence with solvent shifts of CCl_3H (CCl_3H was used as the solute for comparison), the haloform–base interaction involved being the C—H···Y hydrogen bond.

A recent work[73] offers a tentative approach to a rigorous methodology for studying the structural problem of the isomeric 1:1 complexes C—H···Y and C—X···Y. More details regarding this methodology are given on p. 1002 below.

In conclusion, the study of $C_nH_pX_q$ interactions with bases has produced, over the last few years, some interesting results, contributing to a better understanding of the C—X···Y interaction and to a more systematic approach to the study of the isomerism of the two types: isomerism of the complexes C—H···(n electrons) and C—H···(π electrons) on the one hand and C—X···Y and C—H···Y on the other. As will be shown in Section VI.C, the quadrupole resonance study[86] of several chloroform···N-containing base complexes is the only case to our knowledge in which a determination of the associated charge transfer from nitrogen to chlorine atoms has been carried out (Tables 8 and 9).

TABLE 8. ^{35}Cl quadrupole resonance in $CHCl_3$–amine complexes[86]

Compounds	ν, MHz	Enhancement of charge for the three Cl atoms
$CHCl_3$	38.281	
Pyridine + $CHCl_3$	37.764	~0.03 electron
Et_3N + $CHCl_3$	37.100	~0.06 electron

TABLE 9. ^{14}N quadrupole resonance in $CHCl_3$–amine complexes[86]

Compounds	ν, MHz	Diminution calculated for the charge on the N atom
Pyridine	3.892–2.984	
Pyridine + $CHCl_3$	3.8332–2.9691	~0.01 electron
Et_3N	3.7654	
Et_3N + $CHCl_3$	3.5842	~0.017 electron

Finally, we present in Tables 10 and 11 some thermodynamic data concerning the interactions discussed in this section, particularly those involving CHX_3 and CH_2X_2: 1:1 isomeric complexes occur essentially with the bromo and iodo derivatives, as judged by the difference between the K_{DP} and the K_{IR} and K_{NMR} values.

It would have been possible to treat the case of 'hydrogen bonding' between aromatic halides (proton donors) and proton acceptors (electron donors) in an analogous manner to the discussion above, involving aliphatic halides as proton donors. In fact:

(i) It may be assumed that the presence of several halogen substituents in an aromatic ring (e.g. several fluorine atoms) will increase the acidic character of the remaining hydrogen atoms. Thus the pentafluorobenzene molecule probably has a highly acidic proton.

(ii) Like Green[12b], one can also point out that the *para*-hydrogen of a compound such as $C_6H_5CX_3$ was formerly considered to be the most acidic, though this is controversial.

TABLE 10. Equilibrium constants (in litres per mole), enthalpies (in kilocalories per mole) and entropies (in entropy units) of complex formation for the systems (CHX_3 or CH_2X_2)–(n bases) determined by gas–liquid chromatography at 30°C

Halomethane		Di-*n*-octyl ether[68]	Di-*n*-octyl thioether[68]	Di-*n*-octyl methylamine[69]	Tri-*n*-hexyl amine[69]
$CHCl_3$	K	0.393	0.418	0.472	0.203
	$-\Delta H$	2.38	1.93	3.52	3.39
	$-\Delta S$	9.69	8.09	13.11	14.36
$CHBr_3$	K	0.411	0.733	0.645	0.241
	$-\Delta H$	2.17	2.28	3.19	2.97
	$-\Delta S$	8.92	8.14	11.39	12.61
CH_2Cl_2	K	0.280	0.359	0.206	0.093
	$-\Delta H$	1.52	1.34	2.41	1.81
	$-\Delta S$	7.54	6.45	11.10	10.70
CH_2Br_2	K	0.297	0.455	0.247	0.104
	$-\Delta H$	1.79	1.38	1.88	1.28
	$-\Delta S$	8.32	6.12	8.98	8.71

TABLE 11. Equilibrium constants (in litres per mole)[a] at 25°C and enthalpies (in kilocalories per mole)[a] for the systems (CHX_3, CDX_3 or CH_2X_2)–(π or n bases) in C_6H_{12}

Halomethane		Et_3N[73]	Tetrahydropyran[73]	Tetrahydrofuran[73]	1,3,5-Trimethylbenzene[74]
$CHCl_3$	K_{DP}	0.4	1.5	1.4	0.3
$CDCl_3$	K_{IR}	0.45	1.2	1.2	0.15
$CHBr_3$	K_{DP}	0.9	1.5	1.5	0.7
$CDBr_3$	K_{IR}	0.45	0.8	0.6	0.1
CHI_3	K_{DP}	3.2	1.6	–	0.9
	K_{IR}	–	–	–	0.03
CH_2Cl_2	K_{DP}	0.2	0.6	0.6	–
	K_{NMR}	–	–	0.3	–
	$-\Delta H_{NMR}$	–	–	2.0	–
	K_{cal}	–	–	–	0.3
	$-\Delta H_{cal}$	–	–	–	2.1
CH_2Br_2	K_{DP}	1.7	2.1	2.9	–
	K_{NMR}	–	–	0.3	–
	$-\Delta H_{NMR}$	–	–	2.6	–
	K_{cal}	–	–	–	0.35
	$-\Delta H_{cal}$	–	–	–	1.8
CH_2I_2	K_{DP}	1.8	1.6	2.0	–
	K_{NMR}	–	–	0.3	–
	$-\Delta H_{NMR}$	–	–	2.6	–
	K_{cal}	–	–	–	0.45
	$-\Delta H_{cal}$	–	–	–	1.8

[a] K and ΔH determined by the following methods: dielectric polarization, K_{DP}; infrared spectroscopy, K_{IR}; NMR, K_{NMR}, ΔH_{NMR}; calorimetry, K_{cal}, ΔH_{cal}.

These considerations are the main reasons why the aromatic systems were not discussed here. The major properties of the polyhalobenzenes seem to us to be as follows: proton acceptor properties (Section II), electron donor properties (Section III), and, in the case of hexafluorobenzene (Section IV), possibly electron acceptor properties.

VI. INTERACTIONS BETWEEN ALIPHATIC HALIDES (NOT PROTON DONORS) AND ORGANIC BASES: 'HALOGEN BONDING'?

A. Studies of Interactions between Aliphatic Halides and Organic Bases

We will consider here only the case of saturated and unsaturated aliphatic halides without hydrogen atoms in order to exclude the possible ambiguity caused by potential hydrogen bonding (Section V.B).

The general expression 'organic base' will be used for the associative partner with the halide. Thus no implicit assumption about the nature of the association will be introduced before Section VI.C. To speak of an electron donor would necessarily suggest charge transfer.

1. Saturated halides

a. Aliphatic halides: CX_4. The early review of Smith[18] was almost exclusively concerned with CCl_4 and referred to dielectric polarization as the main methodology. This did not allow many generalizations to be made. Some of the early work referred to by Smith, such as that of Sharpe and Walker[87,88], though methodologically

debatable (e.g. it lacks an assessment of the effect of the solvent on the dielectric polarization), showed correct intuition about the nature of the interactions.

In a review published in 1968, Gomel[3] related these results to other spectrometric studies as well as to the reactivity of the CCl_4–organic base systems. The possible existence of a well defined, specific interaction between a base and an organic halide, favoured by the polarizability of the halogen and probably involving a weak charge transfer to the organic halide acceptor, was suggested.

A large number of studies followed this suggestion. The most systematic ones confirmed the idea. However, some conflicting conclusions concerning the hypothesis still exist, and they will be considered below.

Several methods which were used to study the interaction will be introduced at appropriate places in the text. Binary systems were studied in the solid and the gaseous phases, as well in the liquid phase, including binary liquid mixtures and concentrated and dilute solutions of two solutes in an inert solvent.

Three methodological remarks are presented below, to complete those already presented in Section I.

(A) The first studies in the solid phase, particularly those of Hassel (using X-ray crystallography), which were reviewed by Smith[18], aided the suggestion of a possible C—X (halogen)···Y (electron donor) interaction that, as will be shown in Section VI.C, is analogous to the hydrogen bond. In some of these studies, C, X and Y were considered to be colinear (even in the case of the association CHI_3···Y, in which the C, H and Y atoms were expected to be colinear, C—H···Y). Nevertheless, research in the early 1960s paid little attention to these results since 'crystal packing effects' in the solid state might be assumed to be responsible for the particular configurations observed.

Other solid state studies using NQR did not lead to meaningful results because they were not systematic. Despite this, these studies were useful in supplying information on charge transfer data.

(B) The results in liquid mixtures are difficult to interpret since secondary effects related to the creation and disappearance of so-called 'non-specific' interactions introduce great complexity into the phenomena. This is particularly true for colligative methods, purely thermodynamic methods and NMR spectrometry, and also for dielectric polarization studies. These comments, which also apply to studies carried out in concentrated solution in an inert solvent, are not important in the case of highly diluted binary mixtures in an inert solvent (ternary system). In this case (see Section I) the usual procedure is to make sure that a sufficiently accurate evaluation of the 'normal' effect of the solvent is carried out. As a general rule, it is convenient to perform systematic and comparative studies with a large number of mixtures. In particular we will refer in Sections VI.A and VI.B to some studies that, so we believe, provided evidence for the existence of a molecular interaction of the type C—X···Y before – or at the same time as – the gas-phase studies reported below (cf. (C) below).

Although more than a thousand studies of these interactions have been reported since 1962, the previous considerations lead us to consider only some results which seem particularly reliable.

(C) In the gas phase, interactions which are very weak are particularly difficult to observe. The high pressures or low temperatures which are often used complicate the experiment. Moreover, of the important techniques, only infrared and microwave spectrometries are useful for gas-phase studies. That is why only two groups have carried out studies (one with infrared, the other with microwave). Although few and non-systematic, these studies strongly support the existence of the C—X···Y interaction. In fact they have established the existence of such complexes with well

defined linear geometry, C—X···Y. This configuration, and the fact that the data (see Tables 14 and 15) show that such interactions involve an amount of energy similar to that of the hydrogen bond, strongly support the idea that these interactions are of a 'specific' type. Whether or not electrostatic or charge transfer effects are the main cause of the complex formation (see Section VI.C) is, however, open to question. This question is not specific to C—X···Y interaction, and also concerns the well known hydrogen bond interaction.

The above considerations will be related to a recently published analysis by Hanna and Lippert[57]. These authors give particular importance to the works which they have called 'primary', concerning the frequencies of charge transfer absorption bands, the geometry of solid complexes, and NQR measurements on solid complexes. But, further more, they make the following statement:

> '. . . many weak complexes of interest do not form stable solids or have not had their structures determined. Second, whether or not geometry of a complex in solution with a definite stoichiometry will be the same as the geometry in a solid where there can be infinite chains is an open question, which at the present time is difficult, if not impossible, to answer'.

Finally they conclude their analysis with the following 'proposals for future work':

1. A first priority item is work to place all of the "secondary" data . . . on a firmer footing. A good start has been made in this direction by Deranleau, but activity effects still need consideration and the necessary thermodynamic information for handling them needs to be obtained.
2. If the above problem is solved, measurement of a large number of complex dipole moments needs to be undertaken.
3. Experimental data to test the adequacy of the electrostatic computations need to be obtained. It would be especially valuable to have reliable values of molecular quadrupole moments. This is a difficult experiment to perform, but not much effort has been devoted to it.
4. More gas-phase data on complex properties need to be obtained. It would be especially useful to measure dipole moment changes in the gas phase'.

Relevant information collected from recent studies, using some of the same criteria as Hanna and Lippert, is presented below.

(i) Interactions between CX_4 and aromatic hydrocarbons. Interactions between CCl_4 and benzene or its methyl derivatives have been observed by McGlashan and coworkers[17] in calorimetry studies of stability constants (K), and it was found that the stability increases with the number of methyl substituents. This suggests a charge transfer type of interaction. These results were confirmed by another study[89] using ultraviolet spectrometry.

In the case of these mixtures the polarization is strictly additive[90], and the modifications detected in the electronic spectrum of benzene and its methyl derivatives in CCl_4 are not necessarily the consequence of specific interaction[90]. This last result is consistent with the conclusions of Janini and coworkers[91], who have criticized almost all results obtained from ultraviolet spectrometric studies of CCl_4–aromatic hydrocarbon mixtures by referring to several sets of data which invalidate the results. In contrast, Foster[4] has collected a list of studies published prior to 1969 and, like McGlashan, argues in favour of the existence of such interactions. it was to be expected that NQR studies of the many known 1:1 solid complexes would show direct evidence of charge transfer involving the halogen atom. In a recent review,

TABLE 12. Some infrared (IR) and Raman (R) vibrational frequencies of the solid $CBr_4 \cdots p$-xylene complex; comparison is made between p-xylene in solution or in the liquid[92]

Assignment	ν, cm^{-1}	$\Delta\nu$, cm^{-1} [a]
νCH	3050 (R)	− 4
	3018 (IR)	− 3
	3041 (IR)	− 7
δCH	1025 (IR)	+ 3
	1123 (IR)	+ 5
γCH	800 (IR)	+ 6
	1900 (IR)	+11
	1807 (IR)	+14
ωCC	1613 (R)	− 4
	1575 (R)	− 2
$\delta C-CH_3$	384 (R)	− 5
	298 (IR)	+ 7
$\gamma C-CH_3$	316 (R)	+ 3
	159 (IR)	+13

[a] $\Delta\nu = \nu\ p\text{-}C_6H_4(CH_3)_2\text{–}CBr_4$ (solid complex) $-\nu\ p\text{-}C_6H_4(CH_3)_2$ (in solution (IR) or in the liquid (R)), at 25°C.

however, Semin and coworkers[15] arrived at the following conclusions: NQR spectra of these molecules (CX_4) are complicated; systematic studies are few in number, and known results are conflicting. However, in the case of infrared[92] and Raman[92,93] spectra of the complexes between CBr_4 and aromatic hydrocarbons obtained in the solid state[92] (Table 12) and in solution[93] an interaction is observed. According to the authors, the relative weight to be attributed to the charge transfer is small. Janini and coworkers[91] estimate that the interaction is weak and unobservable by NMR or dielectric polarization studies, but they do not indicate whether solvent effect corrections were introduced. Other work[90] using dielectric polarization has shown an increased polarization in the case of the $CBr_4 \cdots$1,3,5-trimethylbenzene system.

Concerning solid state work, Prout and Kamenar[64] have recently referred to crystallographic studies by Strieter and Templeton on the complex between CBr_4 and p-xylene which, according to Prout and Kamenar, is a $\pi-\sigma^*$ complex (see Table 13). Fyfe[62] has at the same time noted the existence of internal rotation in the complex with an activation energy of 2.8 kcal mol^{-1}.

(ii) Interactions between CX_4 and oxygen derivatives (ethers or phosphorus oxides). These interactions, which are relatively strong, seem to be well characterized; several studies using gas–liquid chromatography[68], infrared spectrometry in solution[94], dielectric polarization[33,90], cryometry[95] and calorimetry[95] have shown the existence of

TABLE 13. Structural data on the p-xylene$\cdots CBr_4$ complex[64]

Stoicheiometry	1:1
Type of complex	π-donor σ^*-acceptor
Remarks	Two bromine atoms of CBr_4 are bonded, each with the π-aromatic plane of a xylene molecule, the distance between the Br nucleus and the centre of the aromatic ring being 3.34 Å, which is markedly lower than the sum of the van der Waals' radii (3.80 Å).

these associations for CBr_4, which are more stable than they are for CCl_4 (Tables 14 and 15).

A recent work[96] on CCl_4–alcohol and CBr_4–alcohol mixtures also finds an interaction between halogen and oxygen, once again more stabilizing for bromine than for chlorine. Therefore, it seems that the idea of hydrogen bond 'O—H···Cl—CCl_3 (or CBr_4)' interactions is now discredited (see Section II.C).

(iii) Interactions between CX_4 and amines. Although these interactions are generally stronger than the previous ones, NQR studies[15] reported in 1975 did not provide enough evidence to characterize them. In a recent study, Gur'yanova and coworkers[97] have examined the NQR spectra of complexes formed between CBr_4 and aliphatic and aromatic amines. The authors confirm the involvement of the bromine atom and also observed charge transfer bands in the ultraviolet.

In 1973 Martire and coworkers[69] studied two aliphatic amines and found by gas–liquid chromatography that the complexes with CBr_4 are more stable than those with CCl_4 (Table 14). From 1973 to 1978, Dumas, Gomel and Guerin published a series of systematic studies (particularly involving dielectric polarization studies) of the associations between CCl_4 and CBr_4 with pyridine and its methyl derivatives[33,71,90,95,98]. Their results (Table 15) are consistent with those of Martire and coworkers with respect to the CCl_4–CBr_4 comparison and show the enhancement of polarization on formation of complexes: these last results show an analogy between these interactions and weak hydrogen bonds that will be discussed later (see Sections VI.C and VI.D). Very recently, Huyskens and Mahillon[99] have evaluated the increase of the enthalpy of solution of a series of pyridines with CCl_4 in cyclohexane. This increase, as well as that of the dipole moment, correlates with the pK_a of these bases in water. The 'chemical reactions' between CX_4 and amines, probably following the formation of a complex, are discussed in Section VI.D.1.

(iv) Miscellaneous. Other interactions of CCl_4 or CBr_4 have been studied with a number of bases; for example, organic sulphur compounds[68] yield more stable complexes than do ethers (Table 14). The interactions between CCl_4 and several metallocenes have also been studied, for they are of particular interest in photochemistry[100]. Studies of these latter interactions could be described along with the interactions between tetracyanoethylene and metallocenes.

b. Aliphatic halides: $CX_pX'_q$. After having suspected since 1967 the existence in the gas phase of the complex $CF_3I\cdots NMe_3$ because of infrared data[101], in 1971 Pullin and coworkers published a more thorough study of the subject[102]. This was complemented

TABLE 14. Equilibrium constants (in litres per mole), enthalpies (in kilocalories per mole) and entropies (in entropy units) of complex formation for the systems (CX_4 or CX_3X')–base[a]

CX_4 or CX_3X'		Di-*n*-octyl ether[68]	Di-*n*-octyl thioether[68]	Di-*n*-octyl methylamine[69]	Tri-*n*-hexyl amine[69]
CCl_4	K	0.066	0.138	0.060	0.026
	$-\Delta H$	1.60	1.35	0.70	0.75
	$-\Delta S$	10.66	8.38	7.89	9.71
CBr_4	K	0.121	0.931	–	–
	$-\Delta H$	2.51	3.02	–	–
	$-\Delta S$	12.47	10.09	–	–
CCl_3Br	K	0.106	0.293	0.206	0.073
	$-\Delta H$	2.49	1.59	2.75	2.38
	$-\Delta S$	12.65	7.70	12.21	13.06

[a]Determined by gas–liquid chromatography at 30°C.

TABLE 15. Equilibrium constants (in litres per mole) and enhancement of dipole moments (in debyes) of complex formation for the systems CX_4–base at 25°C

CX_4		Pyridine[90]	4-Methylpyridine[98]	2,6-Dimethylpyridine[98]	Tetrahydrofuran[90]	Tetrahydropyran[90]
CCl_4 in cyclohexane	K	0.14	0.32	0.10	0.08	0.13
	$\Delta\mu$	0.29	0.23	0.37	0.20	0.20
CBr_4 in heptane	K	0.83	1.16	0.41	0.46	0.93
	$\Delta\mu$	0.92	0.82	1.10	0.36	0.40

by a systematic study of several complexes formed by perfluoroorgano bromides and iodides with various bases in condensed phases by using infrared and NMR methods[103–106]. These authors were able to detect a new band at 77 cm^{-1}, arising from the association, and evaluated the N···I or N···Br bond stretching force constants. Values for the $F_3CI\cdots NMe_3$ complex are given in Table 16.

Using these values and some reasonable hypotheses, these authors gave a good description of the $F_3CI\cdots NMe_3$ complex within the theoretical framework of Mulliken: the formation of this donor–acceptor complex takes place with a charge transfer of 0.17 electron[105]. It must be noted that Sheridan and coworkers[68,69] have evaluated the thermodynamic characteristics of the related $Cl_3CBr\cdots$ether (or thioether) complexes by gas–liquid chromatography: their results (Table 14) demonstrate the greater stability of the CBr_4 complex compared with the CCl_4 complex.

Finally, the recent work of Millen and coworkers[107] on $CF_3I\cdots NMe_3$ deserves particular attention because 'the microwave spectrum of a charge transfer complex formed between two molecules having closed electron shells has been observed for the first time'.

Moreover, these authors have established unambiguously the C_{3v} symmetry of the complex, and that the new bands observed (Table 16), resulting from the charge transfer complexation, are equi-spaced.

In these circumstances, it is therefore possible to show that in the gas phase, in which molecules are freely oriented and no reaction field (as defined by Onsager) is to be considered, the carbon atom, the halogen (acceptor) and the electron donor are colinear, giving the complex a well defined geometry. Taken with the energy values for complex formation (see Table 14) this gives credence to the suggestion that the interaction is a specific interaction. We will further develop this point when the 'nature' of this interaction is treated (see Sections VI.C and VI.E). It is important to stress the existence of this 'new' intermolecular bond on account of the importance of the other related intermolecular bond – the hydrogen bond in various fields of chemistry and biology.

TABLE 16. The $F_3CI\cdots NMe_3$ complex

New bands	
New bands are found at 77 cm^{-1} using IR_g[102]; six equispaced bands are found between 26.760 and 32.830 MHz using microwaves[107].	
N···I bond stretch force constant[105]	
Gas phase (room temperature)	0.19 ± 0.04 mdyn $Å^{-1}$
Solution in CCl_4 (room temperature)	0.29 ± 0.03 mdyn $Å^{-1}$
Liquid phase (room temperature)	0.31 ± 0.03 mdyn $Å^{-1}$
Solid phase (80 K)[a]	0.53 ± 0.09 mdyn $Å^{-1}$
N···I bond length[107]	
From the microwave spectrum, r(N···I) = 2.93 Å.	

[a]For the N···Br bond in a $F_3CBr\cdots NMe_3$ complex, the same authors[105] give 0.29 ± 0.05 mdyn $Å^{-1}$.

2. *Unsaturated halides*

Not many results are available at present concerning the interactions between unsaturated halides and organic bases. Essentially, these results are for the solid state. They involve the X-ray crystallographic studies (generally those of Hassel and his coworkers, reported by Prout and Kamenar[64]) of complexes formed by *n* donors and C_2Br_4 or C_2I_4 or C_2I_2 (Table 17). Quite recently, NQR data for complexes of C_2I_4 (or

TABLE 17. Structural data on n—σ^* 'C_2X_4–base' and 'C_2X_2–base' complexes

Complex	$d(X\cdots Y)^a$		$r_{(X)} + r_{(Y)}{}^b$	Interbond angle[c]
C_2Br_4–pyrazine[64]	(Br···N)	3.018	3.45	174.8
C_2I_4–pyrazine[64]	(I···N)	2.979	3.65	175.2
C_2I_4–1,4-diselenane[64]	(I···Se)	3.43	4.15	180
C_2I_2–1,4-dioxane[148]	(I···O)	~2.65	3.55	~180
C_2I_2–1,4-dithiane[148]	(I···S)	3.27	4.00	180
C_2I_2–1,4-diselenane[148]	(I···Se)	3.34	4.15	180
C_2I_2–cyclohexane-1,4-dione[64]	(I···O)	2.94	3.55	165
		2.95		166

[a]Intermolecular contact (Å).
[b]Sum of van der Waals' radii (Å).
[c]Interbond angle at the acceptor atom in degree.

C_2I_2) with some n donors were determined[15]. These complexes in the solid state are considered by Prout and Kamenar as belonging to the n–σ^* type. They present a linear configuration of the atoms C—X···Y (Y being the n donor atom), and are thus quite likely to involve the interaction already suggested in Section VI.A as 'halogen bonding'. Virtually no studies have been devoted as yet to such complexes in a liquid state or in the gaseous state. Most of the studies dealing with the interactions in liquid mixtures 'C_2Cl_4–organic bases' are concerned with excess functions, but without comparison with others mixtures as references. Consequently, their conclusions appear doubtful. Only the dielectric study of the C_2Cl_4–pyridine and the C_2Cl_4–tetrahydrofuran associations[19,33] seems to us to have been conducted with sufficient methodological precautions. Table 18 lists the values of association constants and the moments of the complexes formed (and thus the enhancement of molar polarization, due to their formation).

Even after having admitted the 'halogen bonding' character of the interactions between unsaturated halides without a H atom and organic bases, we feel that the order of interaction strength proposed by Bent[108], i.e. X—C (sp hybridized) > X—C (sp^2) > X—C (sp^3), is not conclusively supported by all the evidence, and it will thus not be retained in our own conclusions in Section VI.E.

TABLE 18. Equilibrium constants (in litres per mole) and enhancement of dipole moments (in debyes) of complex formation for the systems C_2Cl_4–base in C_6H_{12} at 25°C

	Pyridine[33]	4-Methylpyridine[34]	2,6-Dimethyl-pyridine[34]	Tetrahydrofuran[33]	Tetrahydropyran[34]
K	0.09	0.39	0.10	0.15	0.06
$\Delta\mu$	0.27	0.19	0.24	0.25	0.15

B. Studies Concerning Solvent Effects of Aliphatic Halides on Various Molecular Associations

The term 'solvent effect' has several meanings: one is the influence of the solvent on a physical, non-thermodynamic property, such as the dipole moment or the absorption spectrum (ultraviolet, infrared, etc.); a second is the influence of the solvent on thermodynamic variables, in particular those characteristic of molecular associations such as the free energy of formation of a complex.

The variation of the free energy (or of the equilibrium constant) of the formation of a molecular complex in solution may depend to a greater or lesser extent upon the nature of the solvent. This influence of the solvent is caused by the solvation of each of the constituents of the complex and of the complex itself. 'Non-specific' solvent effects always exist but they are generally weak. 'Specific' solvent effects arise from a particular interaction between one or more constituents of the system with the solvent molecules; the influence on the equilibrium constant may be considerable.

The observation of a specific solvent effect upon a given complex formation may reveal a particular interaction between the solvent and one or both of the precursors of the complex. For the specific interactions which lead to aliphatic halide–organic base complex formation, it will be shown that the stability of hydrogen-bonded complexes (used as reference), i.e. of a 'proton donor–organic base' type, decreases when the solvent is an aliphatic halide (Table 19). This decrease in stability, in comparison with that in an inert solvent such as cyclohexane, may be quantitatively attributed to the specific interaction between the aliphatic halide and the organic base. This analysis, first proposed by Gomel[3] in 1968, was quantitatively verified by Guerin and Gomel[112]. These authors have focused their attention particularly upon the correction for the effects of solvents on the physical variables (dielectric polarization, infrared absorption) used for studying the stability of the hydrogen-bonded complex which was used as a reference[33]. Furthermore, they have verified in a complementary way, using activity coefficients, that the so-called non-specific solvent effects are not the main cause of the reduction in stability which is observed when the solvent or a cosolvent is an aliphatic halide[67]. Finally, Gomel and Guerin tried to generalize their approach to this problem by putting forward an interpretation of the effects or organic solvents on the hydrogen bond[19]. The general approach to the influence of the solvent on complex formation (hydrogen bonded or EDA) has recently been analysed by Katritzky and coworkers[113], Foster[80], Christian and coworkers[114] and Kamlet and coworkers[115]. Very recently, Arnaud and Bonnier[116] similarly analysed the solvent effects on an EDA complex of tetracyanoethylene. A large number of authors, who are particularly interested in the contribution of the 'non-specific' (so-called 'normal') effect of the solvent on the free energy of complex formation in solution, have developed several approaches aimed at quantitative evaluation of this contribution. In particular, the general studies of 'non-specific interaction models' by Christian[114], of 'electrostatic effects' by Dack[117], and of 'dipolar contributions to solvent effects' by Kamlet and coworkers[118] may be mentioned. Several of these authors consider the non-specific effect as a very general one, sufficient to explain, for the most part, the whole effect of solvents in all cases, including the aliphatic halides of interest here. It is at this level that different approaches to the problem appear. Thus certain authors propose to explain the effects by using activity coefficient effects (Christian and coworkers[114,119], Dack[117], Litt and Wellinghoff[120]). Other authors try to establish 'linear free energy

TABLE 19. Solvent effect on the equilibrium constant K_c (in litres per mole)[a] of the pyrrole–pyridine complex

Solvent	K_c
Cyclohexane[110]	5.56
CCl_4[110]	2.6
C_2Cl_4[110]	3.35
Heptane[111]	5.3
Heptane–CBr_4 mixture (1.29 mol l^{-1})[111]	2.8

[a]Determined by infrared spectroscopy at 25°C.

relationships' (Dack[117], Katritzky and coworkers[113], Kamlet and coworkers[115,118]). Still others try to explain the solvent effects by applying 'non-electrolyte solution theories' (cf. the works of Arnett, Buchowski, Drago, Guggenheim, etc., cited by Christian[114]).

In these attempts to make more explicit the non-specific effects of the solvent, central studies are those in which the evaluation of the energy of solvation is based on classical electrostatic theory. This latter aspect is exemplified by the work of Abraham and coworkers[121–125], Baba and coworkers[126], Malecki and coworkers[127,128], Barriol and coworkers[129,130] and in the reviews of Kamlet and coworkers[118] and of Jauquet and Laszlo[131].

On this aspect of the problem we have found[19] that when the influence of aliphatic halide solvents on the stability of the hydrogen bonded complexes in solution was calculated by using the expressions proposed by Abraham and coworkers[121–125] and by Rivail and coworkers[130], there was a satisfactory agreement of the results in both treatments. Furthermore, the evaluation of the non-specific effect of the solvents predicts a reduction in the stability of a proton donor–organic base complex which is much smaller than that observed in aliphatic halide solvents. Thus the influence of these solvents on the stability of proton donor–organic base complexes cannot be attributed exclusively to the non-specific effects of the solvents. The main factor seems to be the specific interactions already mentioned.

Several authors have already reported that theoretical relationships as well as empirical ones are exclusively valid in selected solvents, in which only electrostatic interactions take place, rather that hydrogen bond or CT interactions (Abraham[125], Kamlet and coworkers[115]). Thus certain empirical relations are not valid for aromatic solvents and polyhalogenated solvents. In order to extend the interpretation of solvent effects to aliphatic halides, some authors do not take into account the difference between specific and non-specific effects. An example is the work of Kamlet and coworkers[115], who support a 'linear solvation relationship' with several parameters, or the work of Kehiaian and coworkers[132–134] in which thermodynamic data obtained for several mixtures are interpreted on the basis of interchange parameters between molecular surfaces.

In conclusion, regardless of the approach used, it appears that in order to understand the influence of the aliphatic halide solvents upon molecular associations involving an organic base, it is necessary to take into account the specific as well as the non-specific (normal) effects of this type of solvent.

The specific molecular interactions responsible for this specific effect of the solvent would be, in this case, intermolecular 'halogen bonds', already referred to in Section VI.A.

C. The Nature of the Interactions between Aliphatic Halides and Organic Bases

Some years ago the nature of the C—X···Y interaction was thought to be summed up by the title of the section by Smith[18]: 'Complex formation arising from the polarizability of the carbon–halogen bonds'.

We have seen in Section VI.A some reasons why such concepts have evolved. Moreover, to observe a correlation between the stabilization by these interactions and the polarizability of the halogen does not necessarily mean that electrostatic energies (defined by Hanna and Lippert[57] as the sum of Coulombic, induction and dispersion energies) play the essential role and that processes such as charge transfer are not important: I_2···base complexes are known to be more stable than the corresponding Cl_2···base complexes, and although I_2 is more polarizable than Cl_2, it is known that charge transfer from the donor to the acceptor molecule also plays a key role.

Because of this, since 1968 Gomel and Dumas[3,135] have considered several reasons

in favour of a classification of the CX_4···base complexes within the category 'donor–acceptor complexes'. A charge transfer process, even though a weak one, as well as purely electrostatic energies, are necessary for the formation of such complexes. Such an interpretation has been experimentally supported by work carried out up until 1978 by these authors as well as by other work carried out by them in collaboration with Castagna, Geron and Guerin[33,71,73,74,90,98].

A summary of their conclusions will be presented, as well as other, sometimes contradictory, contributions by other authors.

We have already seen[18] that some years ago the existence in solution of a 'specific' C—X···Y interaction was not commonly accepted, several researchers having argued that it was in fact a non-specific interaction explicable in terms of a 'continuum' model. The interesting studies carried out by Barriol and coworkers concerning an improvement of the Onsager model of liquid dielectrics took into account anisotropy of the solute molecules[136–138] and gave hope for a better evaluation of the so-called non-specific effects. However, on the halide–base interactions, Gomel and Guerin have reported[19,33] that, even when anisotropic effects were taken into account in order to correct for the non-specific effects, there still remained significant evidence for the existence of specific C—X···Y interactions. Gomel and Guerin were able, in collaboration with Dumas and Geron, to determine the values of the enhancement of the molar polarization, ΔP, or the dipole moment $\Delta\mu$, which characterize them[71,74,90,98]. For information on the attempts to formulate a methodology to evaluate the non-specific effects, the reader should consult the works of Guerin, Geron, Gomel and coworkers[19,33,79].

We have already referred in Section VI.A to several results obtained by other researchers which suggest the specific character of the C—X···Y interaction, even though in some circumstances such an interaction is energetically weak (e.g. when the donor is an aromatic hydrocarbon). It seems worthwhile to refer, in support of this argument, to a comment made by Pople after Sandorfy's communication[139] in a recent colloquium. He pointed out that the weak interaction (0.8 kcal mol^{-1}) for the couple CH_4···H_2O shows all the characteristics (linearity, force constant, etc.) of an 'ordinary' hydrogen bond, as in the couple H_2O···H_2O, where the interaction is much stronger.

If the specific character of the C—X···Y interaction is assumed, the problem of its nature still remains to be resolved. The possibility of purely electrostatic effects has been referred to by Sheridan and coworkers[68,69,91,140]. One of the arguments used by these authors is the absence of charge transfer bands. However, C—X···Y complexes are weak (n–$k\sigma$ type, according to Mulliken), and even in the case of a n–ν complex as strong as NH_3–BCl_3, the CT band was not observed.

Thus it seems more reasonable to take into account (see Section VI.A) the results of Gomel and coworkers[33,71–74,90,98], Millen and coworkers[107], Pullin and coworkers[105] and Gur'yanova and coworkers[97] which give enough arguments and experimental support in favour of the existence of a charge transfer in the halide–base complex, even if it is a weak one and electrostatic effects including mutual induction are obviously present. It may also be noted that even very weak complexes such as those formed by CBr_4 with aromatic hydrocarbons will, according to Lebas and Julien-Laferrière[92], be weak charge transfer complexes because of the analogous spectroscopic properties (infrared and Raman) of these complexes with the crystal $C_6H_6CuAlCl_4$.

In such circumstances the value of the enhancement of the dipole moment $\Delta\mu$ (or of the molar polarization ΔP) which corresponds to the formation of an intermolecular bond C—X···Y (e.g. C—Cl···N) can be mainly attributed to the transfer of charge, $\Delta\mu_{CT}$, and to mutual induction effects, $\Delta\mu_i$. A determination of $\Delta\mu_i$ by Geron and Gomel[74] gave a value of 0.25 D. Yet the experimental global value $\Delta\mu$ found by these authors for this interaction is 0.9 D, which seems to indicate that at least qualitatively the effect of charge transfer cannot be neglected. Such results may be compared with

the calculated values reported by Hanna and Lippert[57] for a well known CT complex such as the benzene–tetracyanoethylene complex, for which $\Delta\mu_i = 0.64$ and $\Delta\mu_{CT} = 0.43$.

Concerning energetic aspects, certain authors[68–70] have stressed the stabilization effect of the electrostatic interactions. Such arguments do not contradict the specific character of C—X··· Y interactions, for in several recently published works concerning a typical specific interaction such as the hydrogen bond[141,142], the importance of the electrostatic interaction energy has been taken into account. Also, in the general case of donor–acceptor complexes without hydrogen bonds, such as those of I_2, Br_2 or tetracyanoethylene with benzene or *p*-xylene, Hanna and Lippert[57] have stressed that these typical specific interactions, though called 'charge transfer interactions', also involve large contributions of electrostatic and repulsion energies.

In 1969, Mulliken and Person[11] revealed how the problem of interactions between organic halides and bases might be best considered to belong to the donor–acceptor type. In such studies the organic halide was first described as presenting a 'conditional donor behaviour' requiring the electrostatic influence of the solvent, and the σ acceptor was considered to be no more than a 'dissociative acceptor'. Mulliken and Person suggested the existence of n–$k\sigma$ complexes (no work substantiated them till 1952) and considered them to be stabilized essentially by electrostatic interactions[11b].

Yet in 1964, and by reference only to work of Hassel on the complex between CHI_3 and 1,4-dithiane[78] in the solid state, Mulliken considered that the interaction presented one or more favourable orientations and did not eliminate the possibility of a 'contact charge'[11c]. This last case does not exclude the simultaneous stabilization by quadrupole interactions (e.g. between CX_4 and dioxan or dithiane) or by dipole–quadrupole interactions (between CHX_3 and the same bases).

Finally, one may wonder how worthwhile it is in the case of C—X··· Y interactions to distinguish sharply between so-called electrostatic effects and so-called charge transfer effects. In fact, there is still such a debate about hydrogen bonding. It seems difficult after the work of Mulliken and Person[11] on donor–acceptor complexes to separate into completely different categories hydrogen bonded complexes (HB) and electron donor–acceptor complexes (EDA). Hanna and Lippert[57] concluded their theoretical study on the ground state structure of molecular complexes as follows: 'such a complete theory would apply equally well to hydrogen-bonding interactions since hydrogen-bonded complexes and donor–acceptor complexes are formally identical. The major difference is that hydrogen bonded complexes do not usually have an observable charge transfer band'. A relevant work is that of Ratajczak and coworkers[143], who used a very large number of hydrogen bond interactions of varying strengths and, on the basis of the charge transfer theory of Mulliken, established a relationship between interaction energies in hydrogen bonded complexes and modifications of vibrational spectra. Moreover, comparing the experimental behaviour (spectrometric, dielectric, etc.) of the two categories of complexes (HB and EDA), Dumas and Gomel have stressed their closely analogous behaviour[144].

From a theoretical point of view, Umeyama and Morokuma[141] have recently noted that the characteristics of a weak hydrogen bond (e.g. NH_3···H_2O) are not very different from those of a corresponding EDA complex without a hydrogen bond (e.g. NH_3···ClF). According to these authors, strong hydrogen bonds show greater similarly to EDA complexes of high energy. In general, like previous authors such as Kollman and Allen[145] and others referred to by Schuster[142], these authors[141] systematically disect the energy of a hydrogen bond into five terms. The first two, the electrostatic interactions, ES, and the charge transfer interactions, CT, appear to be the most important in determining the characteristics of a hydrogen bond. According to Umeyama and Morokuma[141], the CT term will be more important when the hydrogen bond is weak.

Experimental manifestations of charge transfer accompanying hydrogen bond formation may be found in some recent works: pure quadrupole resonance (of chlorine and nitrogen) in the case of $CHCl_3$–amine complexes seems to confirm the existence of charge transfer[86]. Recent works by Nagakura and coworkers[146,147] reveal the existence of charge transfer bands when some hydrogen bonds are formed. Such observations seem to undermine the last distinctions remaining between HB and EDA complexes.

In conclusion, it is possible to use the same arguments in the analysis of C—X···Y bonds as were used in the debate about 'ordinary' hydrogen bonds.

Taking into account the generality of the theory proposed by Mulliken for donor–acceptor complexes, Gomel, Dumas, Geron and Guerin[71,98] are convinced that the C—X···Y interaction involves a charge transfer of the type n–$k\sigma$ or b–$k\sigma$, even though it may be a weak one.

The purpose of these authors was mainly to examine, using a phenomenological approach, different characteristics of the interaction in order to compare it with hydrogen bond (HB) interactions as well as with well known donor–acceptor (EDA) interactions without hydrogen bonds. They considered[71,98] CX_4···base complexes as models for complexes with a weak charge transfer energy (inner complexes, related to weak hydrogen bonds unaccompanied by proton transfer). These authors have established an analogy between the behaviours of the 'acid' CX_4 and a 'weak proton donor' (pyrrole) which helps to justify, along with other considerations (cf. Section VI.E), the name of 'halogen bond' for the interaction C—X···Y.

In summary, the C—X···Y interaction may be considered as a new intermolecular bond and, like the hydrogen bond, may be described[105] at a theoretical level within the framework of the donor–acceptor theory of complexes by Mulliken. However, electrostatic effects obviously also play a stabilizing role in these complexes.

Such a definition of the 'halogen bond' seems to us preferable to the recently proposed classification by Bent[108] which designates as 'Hassel donor–acceptor interactions' a set of interactions such C—X···Y, X_2 (or XX')···Y (n or $b\pi$–$x\sigma$-type complexes) and distinguishes them from hydrogen bonding.

The summary given by Bent of the characteristics of the 'Hassel donor–acceptor interaction' may be used partially in the description of the 'halogen bond'. However, this review[108] seems to us to be almost exclusively based upon crystallographic data (cf. Section VI.A for discussion of its limitations) as well as on considerations, even hypothetical ones, about reactivity; results obtained in the gaseous and liquid phases[14] are not referred to.

Finally, if the existence of the 'halogen bond' and its characteristics seem established for systems involving halogen–carbon bonds, problems of interpretation remain when the halogen is bonded to silicon (see Section VI.D.1), and we do not believe that the O–X···Y or N–X···Y interactions are at present sufficiently well understood. Consequently, the generalizations proposed by Bent[108] are not justified. Therefore, only conclusions that seem to us well established will be presented in Section VI.E. It is worth noting the interesting review[148], in which Bent regrouped very early (1968) all the information concerning the structures of binary systems in the solid state, in particular including organic halides, and the later review (1971) by Prout and Kamenar[64].

D. Does the Concept of 'Halogen Bonding' Contribute to an Explanation of Some Aspects of Reactivity or Biological Activity?

(1) Several chapters of this book, as well as the previous volume[1], contain details on the chemical reactivity of the carbon–halogen bond with organic bases. Moreover, many references on the subject were mentioned, in 1965, by Kosower[149], in a review

in 1968 by Gomel[3], and later in the books of Foster[4,109]. Thus, it will be sufficient to describe here some recent complementary studies among those that are concerned with the formation of a halide–base complex as a first step in the reaction. Some of the works on this subject, such as those by Miller and coworkers[150–152] between 1970 and 1976, are worth noting. However, these works and that of Lindsay Smith and coworkers[153–155], and others, also, use a third reagent (oxygen) or a catalyst, e.g. Pyrex glassware, metal salts, metals or ultraviolet irradiation in the reaction. The complexity of the mechanism is such that it seems difficult to consider the specific halide–base interaction as the principal factor of the different mechanisms.

(2) The mechanism of the Menschutkin reaction, particularly that involving organic iodides, seems to involve the formation of a charge transfer complex between, for example, Et_3N (donor) and EtI (acceptor) prior to the formation of the ion pair $Et_4N^+I^-$. Furthermore, the influence of solvents, particularly organic halide solvents, on the kinetics[156–158] and also on some theoretical and thermodynamic aspects (Abraham and coworkers[125,159]) is now well studied. Part of the effect of these solvents could be attributed to their effect on the stability of the halide–base complex (Section VI.B). Nevertheless, some of the interactions between halogen-containing solvent and reactant may, in some circumstances, be other than 'halogen bonding'; for example they may be 'hydrogen bonding'[157,158]. In conclusion, the specific 'halogen bonding' interaction is probably involved in the mechanism of the Menschutkin reaction, but not enough is known about its contribution to the overall mechanism.

Dumas and coworkers[90,111,160] have recently referred to the analogies and the differences between the behaviour of corresponding carbon and silicon halides interacting with organic bases.

(3) The use of halogen-substituted organic compounds as general anaesthetics has led to mechanistic investigation of this role. It is known that general anaesthetics such as halogenated hydrocarbons operate at the membrane level. The relation between their solubility in lipids and their effectiveness as anaesthetics suggests that they act at the hydrophobic sites of the membranes (cf. the unitary theory of Overton, who does not differentiate between anaesthetics according to the way they act[161]).

However, recent work by Sandorfy and coworkers[162,163], using infrared spectroscopy, shows that hydrogen bonds in 'model' molecules that have the functional groups of the membranes are perturbed by halogenated hydrocarbons. Consequently, these authors suggest that general anaesthetics such as halogenated hydrocarbons can act in a specific way on some of the main constituents of the cell membrane (lipids, proteins), at which other interactions may take place concurrently: the halogenated hydrocarbons with H atoms, such as $CHCl_3$ and $CF_3CHClBr$, give hydrogen bonds (Section V.A). The chloro- or bromofluorocarbons containing no protons would also interact with the membrane in a similar way, and Sandorfy has suggested that these latter interactions could also lead to a partial break-up of existing hydrogen bonds in the membrane. Moreover, we think that these interactions may be 'halogen bonds' in type because their importance increases with the atomic number of the halogen.

E. Provisional Conclusions, and Some Current Developments

1. *Provisional conclusions*

a. A summary of the properties of the 'halogen bond' bridging a carbon (C)–halogen (X) bond to an electron donor. The possibility of an intramolecular bond of this type has not yet been established. The properties of this new intermolecular bond may be described as follows.

It is a specific interaction, usually with a substantial energy, leading to the formation of complexes with well defined geometry. Such an interaction is independent of the nature of the carbon atom bonded to the halogen, i.e. whether it is tetrahedral, trigonal or digonal.

If no particular constraints are present, the C—X bond will be oriented linearly to the Y electron donor atom, or oriented perpendicular to the aromatic system of π electrons.

In the case where the Y donor atom (bonded to an atom Z) has one lone pair of electrons or more, results obtained in the solid state show that the angle XYZ is roughly tetrahedral if Y—Z is a single bond, about 120° if it is a double bond, and 180° where it is a triple bond.

In the case of any given base, the stability of the complex (in terms of free energy) will increase with the atomic number of the halogen and with the number of electron-attracting atoms attached to the carbon atom. The stability will be particularly marked in the case of the carbon tetrahalides. The stability almost certainly decreases if the carbon bound to halogen is replaced by silicon, at least in the case of Si—X···Y complexes formed by Si—X with some donors.

In the case of an organic halide, the stability of the complex formed obviously depends upon the electron donor. As in the case of the hydrogen bond, nitrogen bases seem to lead to very stable complexes, whereas aromatic hydrocarbons lead to complexes with low stability.

It is difficult to analyse the ΔG values in terms of the influence of the enthalpy and the entropy factors on the nature of the halogen, the number of halogens present, the other substituents attached to the carbon atom, the nature of the base, etc. However, it is often observed that stability (in terms of enthalpy) increases with the atomic number of the halogen. This stability may in general be about the same as that of hydrogen bonded complexes formed by weak proton donors with the same bases. The energetics and the stereochemistry of the 'halogen bond' may therefore be considered as well established: the 'halogen bond' may now be considered as a well defined, specific interaction, leading to molecular complexes.

Naturally, in the case where one or more hydrogen atoms are attached to the carbon linked to the halogens, a hydrogen bond may also form (Section V).

b. The concept of halogen bond as an 'economic' one. Studies reported in Section VI.A support the physical reality of this concept. Moreover, such a concept, put forward as an hypothesis, has made possible the qualitative interpretation of the following phenomena reported in Sections V.B and VI.B: (i) the structural and thermodynamic 'anomalies' characterizing 'the' complex formed by hydrogen bonding between a halomethane (particularly in the case of a heavy halogen) and bases (Section V.B); (ii) the important and anomalous influence of halogenated solvents on the stability of complexes formed (through hydrogen bonding) in these solvents.

2. *Some current developments*

The following list contains only a brief description of some possible future studies. The list is clearly open to other possible developments.

(i) In the study of reactivity we still need to evaluate experimentally the 'normal' effect of a solvent on the polarization of a solute as well as on the stability of a complex formed in solution. Such an evaluation requires in particular a new systematic test of the expressions to be established by theoreticians. Such research[164] will help to set the limits, if any, for the distinction between so-called specific and non-specific interactions.

Also worthy of study, using quantum computational methods, would be the geometries and the energies which correspond to the interactions computed between a CX_4 molecule and a simple electron donor such as Me_3N[165].

Another question concerns the reasons for the detected differences between carbon–halogen bonds and silicon–halogen bonds, as a function of changing the electron donor. Some donors are 'inert'; others engage in 'halogen bonds', or are involved in addition reactions by coordination with the silicon; and others are engaged in reactions involving a double decomposition[165].

(ii) In the domain of biological properties, a general study of the action of anaesthetics, particularly organic halides, has been undertaken by Sandorfy and coworkers[166]. Finally, the influence of polarizability on the biological behaviour of organic halides with anaesthetic properties is also being examined by Sandorfy and some of us[164,166].

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CHAPTER **22**

Formation of carbon–halogen bonds

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INTRODUCTORY REMARKS

The following review on the formation of carbon–halogen bonds is meant to be a self-contained survey of the most important and most essential methods of preparation of halogen compounds. It is divided according to the nature of the carbon–halogen bond. Condensation of a topic which is normally covered in monographs of many thousands of pages to the present abbreviated number of pages required a very careful screening. Papers containing other than synthetic aspects and papers where yields of products were not reported were, with a few exceptions, omitted. Where there was a choice between sources of data, more recent examples from readily available journals were quoted preferentially. Samples of the carbon–halogen bond-forming reactions are illustrative and by no means exhaustive, and their selection is a result of the authors' critical and necessarily somewhat subjective choice, influenced sometimes by their own laboratory experiences.

Since the formation of carbon–halogen bonds has been thoroughly documented in *Houben-Weyl's Methoden der Organischen Chemie* (Volumes 5/3 and 5/4), where countless tables and procedures show the yields and conditions of individual reactions, this review concentrates on typical representatives of the main preparative methods, and emphasizes procedures which have been developed during the past 20 years up to the end of 1980.

Tables correlating halogenating agents with the starting materials and halogenated products are included at the end of the review. They were originally published in *Organic Preparations and Procedures International*, **10**, 181–194 (1978), and permission for their reproduction was kindly granted by the Editor, Dr J.-P. Anselme.

FORMATION OF CARBON–FLUORINE BONDS

I. INTRODUCTION

The chemistry of the organic compounds of fluorine lagged behind that of the other halogens by some 50 years. It was not until the end of the last century that laboratory methods for the preparation of organic fluorine compounds were developed, mainly by F. Swarts, and not until the early 1930s that industrial applications were found, mainly as a result of the work of A. L. Henne. Since then fluorine chemistry has caught up rather rapidly; at the time of writing the number of organic fluorine compounds has exceeded 265 000, and the number of monographs has surpassed significantly that of books dealing with the other halogens. References 1–14 list the most comprehensive – but by no means all – the monographs on fluorine chemistry.

This review is heavily weighted toward the past decade's literature since more thorough surveys of carbon–fluorine bond formation were published earlier by one of the authors[12] and are contained in Houben-Weyl's compendium[14]. A list of review papers is given on p. 478 of Ref. 9.

Because of some unique properties of fluorine – i.e. the extraordinarily low dissociation energy of the fluorine–fluorine bond (37 kcal mol^{-1}), the very high dissociation energies of the hydrogen–fluorine bond (136 kcal mol^{-1}) and the carbon–fluorine bond (108–116 kcal mol^{-1}), and its extreme electronegativity (4.0) – reactions suitable for the formation of carbon–halogen bonds cannot be applied across the board.

Rather, special methods had to be developed for the synthesis of organic fluorine compounds. While the reaction with elemental fluorine is used not nearly as much as the reactions with other elemental halogens, reactions of organic compounds with metal fluorides found much wider applications than the analogous reactions with other metal halides.

II. EQUIPMENT AND TECHNIQUES

Since hydrogen fluoride, impure fluorine and some fluorides react with glass, reactions involving such corrosive reactants must be carried out in special equipment. For reactions taking place at atmospheric pressure dishes, beakers, flasks and bottles made of polyethylene, poly(chlorotrifluoroethylene) (Kel-F®, Fluorothene®), poly(tetrafluoroethylene) (Teflon®, Fluon®) or poly(fluoroethylenepropylene) (FEP®) are very satisfactory.* Polyethylene equipment stands temperatures up to about 100°C; the polyfluorinated materials listed above can be used up to 150–180°C quite safely. Stirring is best achieved using Teflon-coated magnetic stirring bars and magnetic stirrers.

Reactions which require elevated pressures are best run in mild steel, stainless steel, or Monel metal bombs or autoclaves. Connections between the individual reaction vessels are made of copper or stainless steel tubes with brass or stainless steel swage-lock fittings and valves with Teflon seats.

When choosing the size of the pressure vessels it is essential to take into account the possibility of overheating of the reaction mixture above the critical temperature of the components. Then all the compounds can be present in the vapour phase and the pressure inside the container will obey the gas law. Careful calculations of the possible pressures and a wide safety margin are recommended, especially for previously untried experiments when unexpected reactions can generate additional heat.

III. MOST COMMON FLUORINATING AGENTS

Physical properties and applications of the most common fluorinating agents are listed in Table 1. Some of the agents require special handling, different from that used for introduction of other halogens. Reactions with potentially dangerous and corrosive gaseous and liquid fluorinating agents are best run under good hoods behind protective shields of shatter-proof glass or thick plastic. The person carrying out such experiments must wear a plastic face-shield, a laboratory coat or a plastic apron, and leak-proof rubber gloves. It is advisable to work with small quantities of such reagents at a time. More detailed directions about protection and about treatment of possible injuries are published in the literature[4].

Anhydrous hydrogen fluoride is available in steel cylinders. The best way to withdraw the necessary amount from the cylinder is by distillation using the assembly shown in Fig. 1. Before opening the valve of the cylinder, the more distant polyethylene receiver is first immersed in a dry ice–acetone bath. In this way water vapour present in both receivers, as well as that entering the assembly, will condense. After 5–10 min both receivers are immersed in the dry ice bath, the cylinder with hydrogen fluoride is warmed up to about 30–40°C, the valve is opened, and hydrogen fluoride is condensed in the receiver closer to the cylinder. It is useful to have this receiver tared and calibrated for direct reading of the volume or for weighing of the condensed hydrogen fluoride. The receiver can be then used as a reaction vessel. Use of a face-shield, a laboratory coat or apron and of gloves is imperative for any work with anhydrous hydrogen fluoride since it not only dissolves glass but also rapidly attacks tissues.

Aqueous solutions of hydrogen fluoride – hydrofluoric acid – are available in plastic containers at concentrations of 40%, 48%, 70%, etc. Azeotropic hydrofluoric acid contains 38.26% of hydrogen fluoride and has a boiling point of 112.0°C at 750 mm[15].

*Kel-F is a registered trade name of 3M Co.; Fluorothene of Union Carbide Corp.; FEP and Teflon of E. I. du Pont de Nemours & Co.; and Fluon of ICI.

TABLE 1. Most common fluorinating agents

Formula	Molecular weight	Melting point, °C	Boiling point, °C	Density[a]	Method of application: Addition	Replacement of: H	Hal[b]	O	N
HF	20.01	−83.36	19.51[c]	1.0015/0°C	•		*	•	*
KF	58.10	858	1502	2.528	*[d]		*	*	
CsF	151.91	703	1253	3.586	*[d]		*		
AgF	126.88	435	~1150)	5.852/15.5°C			*		
AgF_2	145.88	~690		4.57–4.78	*	*	*		
HgF	219.60	570	Decomp.	8.73/15°C			*		
HgF_2	238.60	645	Decomp.	8.95/15°C	*		*		
BF_3	67.82	−127.1	−101.1	3 g l^{-1}/20°C				*	
$BF_3 \cdot Et_2O$	141.94	−60.4	125.7	1.125				*	
HBF_4	87.83		130, decomp.						*
$NaBF_4$	109.81	384	Decomp.	2.47/20°C					*
TlF	223.39	327	655				*		
H_2SiF_6	144.10		Decomp.	1.463/25°C[e]					*
HPF_6	145.98	31.5 ($HPF_6 \cdot 6H_2O$)	Decomp.						*
AsF_3	131.91	−5.97	57.13	2.666			*		
SbF_3	178.76	292	319	4.379/21°C			*		
SbF_5	216.76	8.3	141	2.993/22.7°C	*		*		
SF_4	108.01	−121.0	−40.4[f]	1.91/−70°C			*	*	

ClF	54.46	−154	−108.8[j]	1.62/−101°C	*			
ClF_3	92.46	−76.34	11.75[k]	1.88	*	*	*	
$FClO_3$	102.46	−147.74	−46.67[l]			*		
BrF	98.92	−33	−20		*			
BrF_3	136.92	8.77	125.75	2.79/27°C	*	*	*	
IF_5	221.91	9.43	100.5	4.31/20°C	*		*	
MnF_3	111.94			3.54	*	*	*	
CoF_3	115.94	~1200	~1400	3.88	*	*	*	
$KCoF_4$	174.04				*	*	*	
XeF_2	169.30	~140		4.32	*	*		
CF_3OF	104.01	−215	−95		*	*		
$C_6H_5PF_4$	260.07		133–136					*
$(C_6H_5)_2PF_3$	242.19		106–107/2 mm					*
$(C_6H_5)_3PF_2$	300.29	136–140						*
$C_6H_5SF_3$	166.16	~0	47/2.6 mm					*
$(C_2H_5)_2NSF_3$[m]	161.14		—[m]					*
$(C_2H_5)_2NCF_2CHClF$	189.61		33/6 mm					*
p-$CH_3C_6H_4IF_2$	256.03	112			*			

[a] Densities are either relative densities (where no units are given) or absolute densities. Temperatures following a solidus indicate that temperature at which density was determined, in degrees Celsius.
[b] In most of this first part of the chapter, 'halogen' refers to chlorine, bromine and iodine, but usually not fluorine.
[c] Critical temperature 230°C.
[d] Under special conditions.
[e] 60.8% solution in water.
[f] Critical temperature 90.9°C.
[g] Critical temperature 89.0°C; by-product in reactions of SF_4.
[h] Critical temperature ~290°C.
[i] Critical temperature −129°C.
[j] Critical temperature ~14°C.
[k] Critical temperature 174°C.

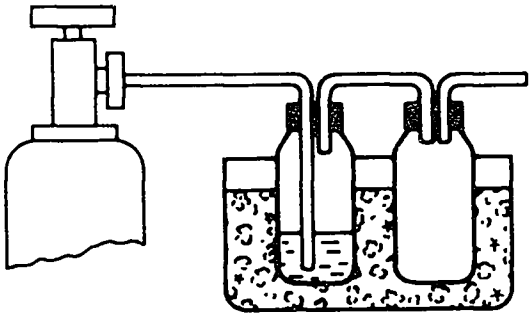


FIGURE 1. Distillation assembly for withdrawal of anhydrous hydrogen fluoride.

Hydrofluoric acid reacts rapidly with glass. Rubber gloves are highly recommended since even relatively dilute solutions can cause painful injuries, especially around the nails.

Anhydrous hydrogen fluoride dissolves readily in nitrogen-, oxygen- and sulphur-containing organic solvents such as acetone, diethyl ether, tetrahydrofuran, dioxane, dimethyl sulphoxide, tetramethylene sulphone, morpholine, pyridine and other amines.

A solution of anhydrous hydrogen fluoride in pyridine is especially useful. It is known as Olah's reagent and is prepared either by condensing hydrogen fluoride in anhydrous pyridine at $-78°C$[16,17] or by adding anhydrous pyridine dropwise into anhydrous hydrogen fluoride with efficient stirring and cooling with dry ice[18a] until the composition of the solution is 70% of hydrogen fluoride and 30% of pyridine (9 mol HF:1 mol C_5H_5N). Such a solution, now available commercially, is a liquid which can be stored in polyethylene bottles in a refrigerator, and even at room temperature as its vapour pressure is fairly low. It can be used in many instances instead of anhydrous hydrogen fluoride up to temperatures of 50–55°C at atmospheric pressure[17].

Most solid metal fluorides can be handled in glass equipment. They frequently etch the surface, but several reactions can be run in the same equipment before its walls become dangerously thin. As long as the contamination with impurities resulting from the reactions of the fluorides with glass is not critical, it is more convenient to use common glassware than expensive and less available apparatus made of plastics or metals. However, when high temperatures and especially when elevated pressures are required, metal equipment becomes indispensable.

Xenon difluoride (XeF_2), a solid crystalline compound, is quite safe provided that it is not contaminated with higher fluorides (XeF_4, XeF_6), which are hydrolysed with moisture to the explosive XeO_3. If no hydrogen fluoride is involved in xenon difluoride reactions, glass equipment may be used.

Reactions with some liquid or gaseous fluorinating agents can be run in glass equipment at atmospheric pressure if no hydrogen fluoride is produced during the reaction. Nevertheless, it is safer to carry out such reactions in metal apparatus.

Work with elemental fluorine requires special precautions. Undiluted fluorine is extremely dangerous and must be handled in metal equipment. This must be free of moisture and organic contaminants such as grease which could cause explosions or fire. Fluorine diluted with an inert gas is much safer, and some reactions with very dilute fluorine can be carried out in glass apparatus. Mixtures of fluorine with nitrogen in ratios between 1:5 and 1:1000 are now commercially available.

Metal equipment is necessary for work with the highly corrosive halogen fluorides, some of which (ClF_3) are almost as reactive as fluorine.

On the other hand, some gaseous fluorides, such as perchloryl fluoride ($FClO_3$) and trifluoromethyl hypofluorite (CF_3OF), can be handled in all-glass equipment. However, an explosion was experienced when exit gases of a reaction mixture containing perchloryl fluoride were condensed in a dry ice trap[18b], and some explosions have been recorded in work with trifluoromethyl hypofluorite. These events may be a cause for not manufacturing these two reagents any more.

Sulphur tetrafluoride is frequently used in reactions which produce hydrogen fluoride. If such reactions do not require elevated pressures or temperatures any higher than room temperature, they can be carried out in plastic equipment by bubbling the gas through the reaction mixture. For work at higher temperatures metal equipment is necessary. Selenium tetrafluoride, molybdenum hexafluoride and diethylaminosulphur trifluoride (DAST), which all act upon organic compounds similarly to sulphur tetrafluoride, can be handled in plastic equipment and sometimes even in glass. However, DAST should not be heated above 40°C as an explosion occurred during a distillation at that temperature[18c]. Distillation at 10 mm or below is considered safe.

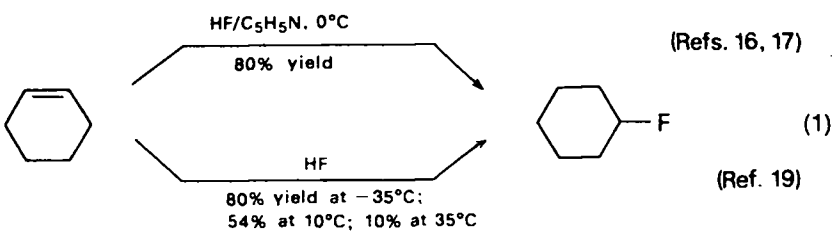
Work with fluorophosphoranes ($PhPF_4$, Ph_2PF_3 and Ph_3PF_2), chlorotrifluorotriethylamine ($CHClFCF_2NEt_2$) and aryl iodide difluorides ($ArIF_2$) is usually carried out in glass equipment.

IV. METHODS OF PREPARATION OF ORGANIC FLUORIDES

Preparation of organic fluoro compounds by formation of carbon–fluorine bonds is based essentially on addition of fluorine across multiple bonds and on substitution of fluorine for other elements.

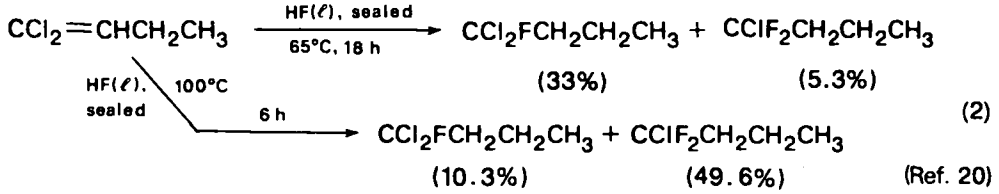
A. Addition of Hydrogen Fluoride across Multiple Bonds

One of the most simple ways to prepare monofluoro compounds is by addition of hydrogen fluoride to alkenes, alkynes and compounds having carbon–nitrogen double bonds. The reaction is regiospecific and obeys Markovnikov's rule: a proton attacks the more electronegative end of the double bond. Yields of the fluoro compounds vary, depending on the olefin and on the reaction conditions, especially the temperature and the catalyst[19]. An undesirable side reaction is polymerization of the alkene. Successful addition of hydrogen fluoride to alkenes was carried out using poly(hydrogen fluoride)–pyridine reagent[16,17] (equation 1).



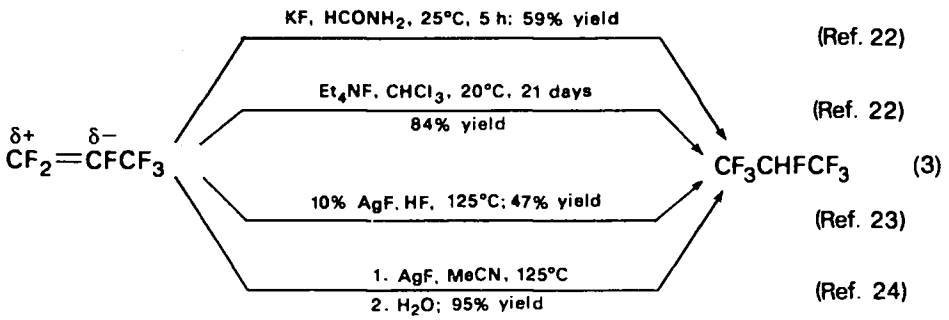
(Refs. 16, 17) (1) (Ref. 19)

When hydrogen fluoride reacts with chloroalkenes, it not only adds across the double bond but also replaces the chlorine, especially at higher temperatures[20] (equation 2).



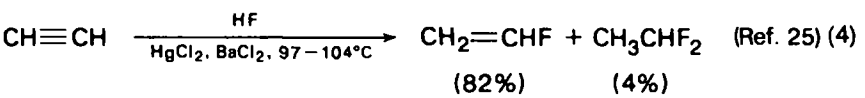
(2)

Polyhalogenoalkenes are rather resistant to the addition of hydrogen fluoride and the reaction requires catalysis, best with boron trifluoride[21]. Poly- and perfluoroalkenes do not undergo addition of hydrogen fluoride under electrophilic conditions. However, they are prone to nucleophilic addition of a fluoride ion followed by a proton from the solvent or the reagent[22–24] (equation 3).



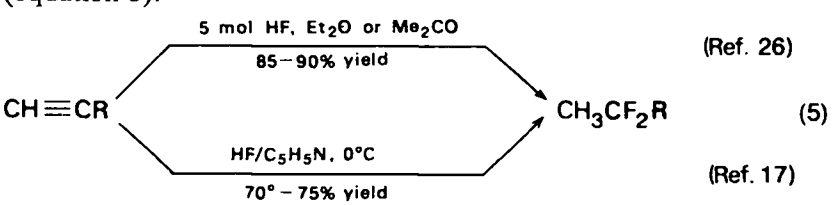
(3)

Acetylene reacts with hydrogen fluoride to form vinyl fluoride and 1,1-difluoroethane. With different catalysts one or the other product predominates[25] (equation 4).



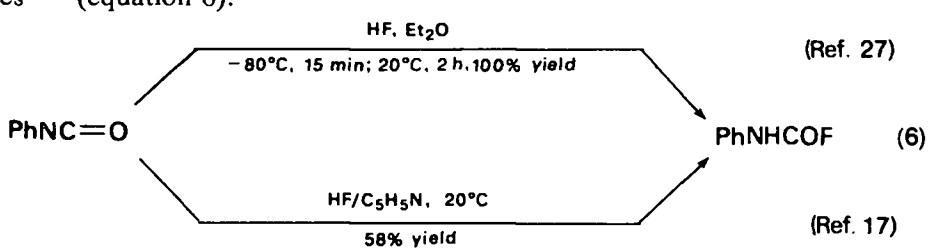
(4)

Homologous acetylenes react with hydrogen fluoride so avidly that it is difficult to intercept monofluoroalkenes. Usually, geminal difluoroalkanes are the main products[16,17,26] (equation 5).



(5)

Alkyl and aryl isocyanates add hydrogen fluoride to give alkyl or aryl carbamyl fluorides[17,27] (equation 6).



(6)

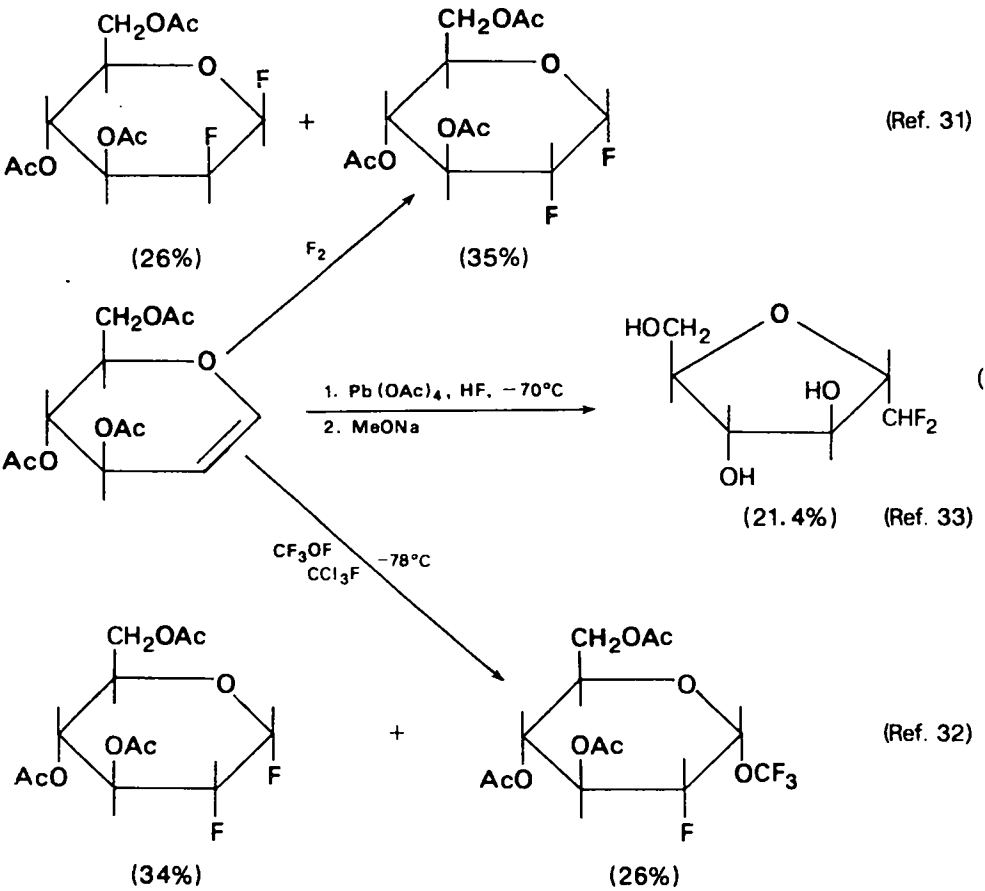
B. Addition of Fluorine across Multiple Bonds and to Aromatic Systems

Addition of fluorine to unsaturated hydrocarbons and their derivatives can be accomplished by a host of reagents.

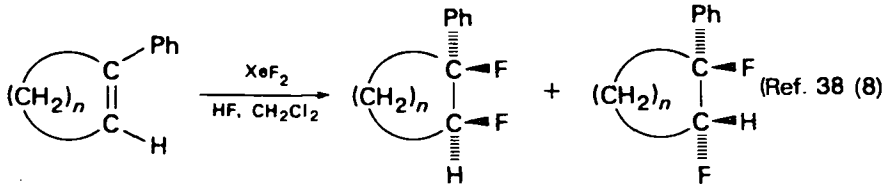
Elemental fluorine can be used at low temperatures if diluted with an inert gas. The reaction is usually not stereospecific, and *syn* addition seems to predominate. Side reactions which sometimes considerably decrease yields of the desired product are replacement of hydrogen or other elements and dimerization of free radicals produced by the initial attack of the alkane by fluorine. Chlorofluoroalkenes and perfluoroalkenes added fluorine in yields of 23–88%[28]. 2-Methylindene gave 15% of *cis*- and 28% of *trans*-1,2-difluoroindane[29], and $\Delta^{4,5}$-cholestenone yielded 60–70% of *cis*-4,5-difluorocholestanone[30]. 3,4,6-tri-*O*-acetyl-D-glucal was fluorinated with fluorine to a mixture of 35% of 3,4,6-tri-*O*-acetyl-2-deoxy-2-fluoro-α-D-glucopyranosyl fluoride and of 26% of 3,4,6-tri-*O*-acetyl-2-deoxy-2-fluoro-β-D-mannopyranosyl fluoride. Both products are results of a *syn* addition without rearrangement[31]. Other fluorinated agents give different results[32,33] (equation 7).

The work with elemental fluorine can be avoided by using other fluorinating reagents which are sometimes more available in conventional laboratories.

Xenon difluoride adds fluorine atoms across double and triple bonds. The reaction requires either irradiation to initiate a free radical addition,[34] or else catalysis with



anhydrous hydrogen fluoride[35], trifluoroacetic acid[35], or better still a boron trifluoride–diethyl ether complex[34,36,37], to facilitate ionic addition. The reaction is not stereospecific, giving both *syn* and *anti* addition in different ratios[35,38–40] depending mainly on the structure of the alkene[38] (equation 8).



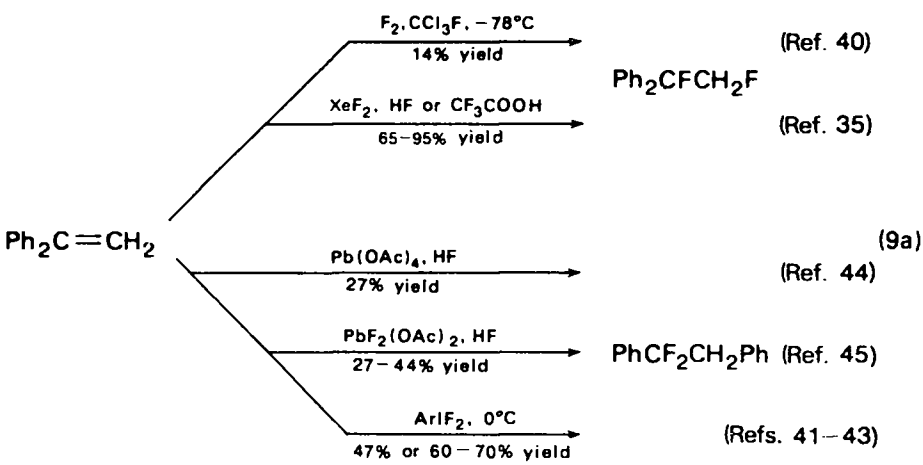
(Ref. 38 (8))

n	Yield of *syn* product	Yield of *anti* product
3	21%	79%
4	50%	50%
5	65%	35%

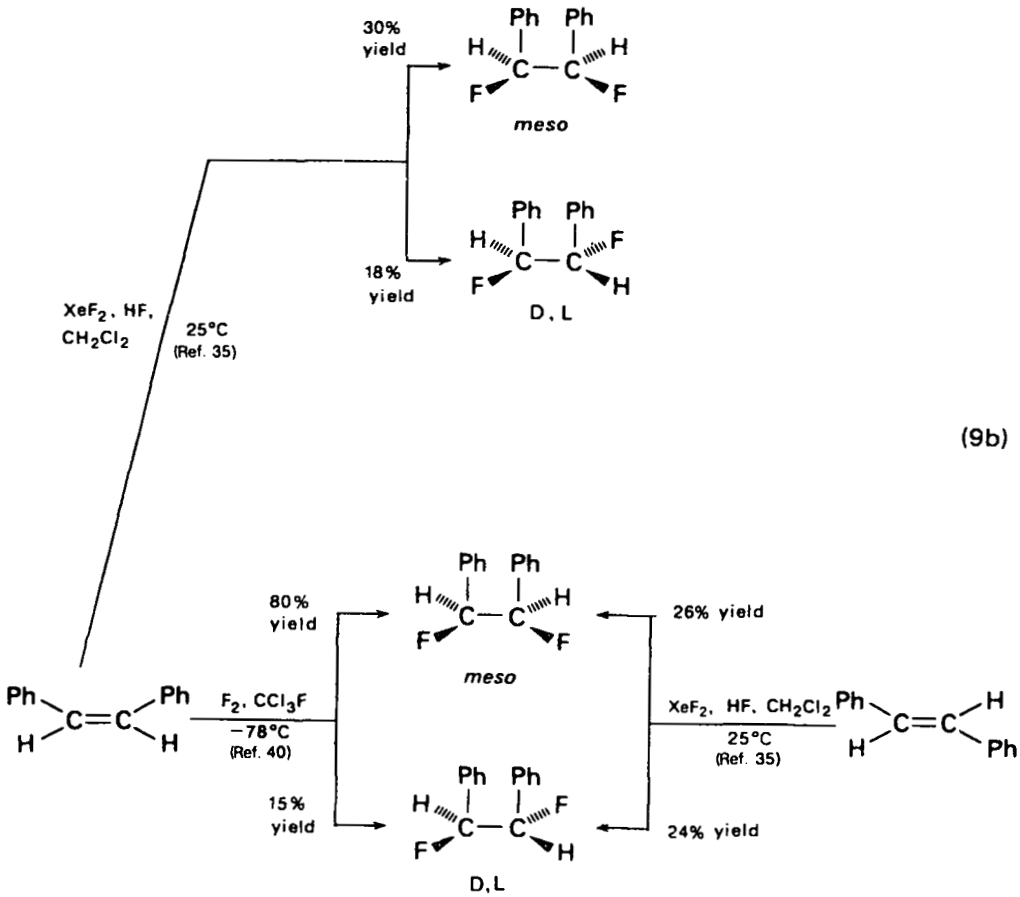
A thorough investigation of the reactions with xenon difluoride in the series of norbornene[34,36] and diphenylethylenes[35] demonstrated that various rearrangements take place during the reactions and lead frequently to mixtures of products. Examples of the addition of fluorine to diphenylethylenes by means of xenon difluoride and other fluorinating agents[40–45] are shown in equations (9a) and (9b).

To a much more limited extent, aryl iodide difluorides were used to add two fluorines to alkenes[41–43]. Aryl iodide difluorides having various substituents in the ring are prepared by reaction of the aryl iodide with xenon difluoride[41], aryl iodide dichloride with hydrofluoric acid and mercuric oxide[42], or aryliodoso compounds (ArIO) with hydrofluoric acid and mercuric oxide[43]. The reaction of aryl iodide difluorides with 1,1-diphenylethylenes gave rearranged products, always containing geminal instead of the expected vicinal difluorides (equation 9a).

Addition of fluorine to unsaturated derivatives can also be achieved when a mixture of lead tetraacetate and anhydrous hydrogen fluoride is used[33,44]. The reagent responsible for adding two fluorine atoms to a double bond was found to be lead difluoride diacetate[45], not the expected lead tetrafluoride (equation 9a). Also, lead

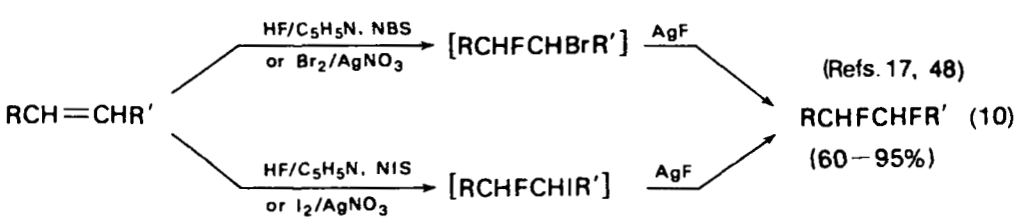


(9a)

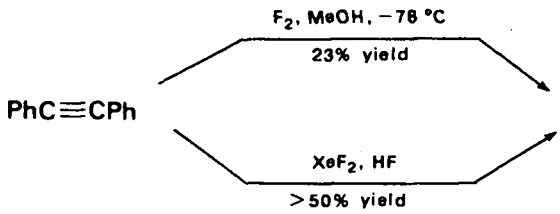


superoxide PbO_2 with anhydrous hydrogen fluoride[18a,46] or sulphur tetrafluoride[47] add fluorine in good yields to some alkenes in a non-stereospecific way[47].

An elegant method for the addition of fluorine to alkenes is the reaction of alkenes with a solution of anhydrous hydrogen fluoride in pyridine (Olah's reagent) containing either *N*-bromo- or *N*-iodosuccinimide (NBS or NIS) or iodine or bromine and silver nitrate. If silver fluoride is then added to the reaction mixture, the following steps are involved in a one-pot conversion of alkenes to vicinal difluorides[17,48] (equation 10).



Addition of fluorine to acetylenes was accomplished, though in unsatisfactory yields, using elemental fluorine at low temperatures[49], or xenon difluoride[50] (equation 11).



(Ref. 49) (11) (Ref. 50)

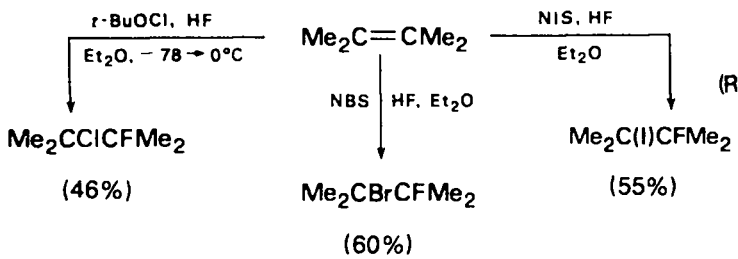
Clean-cut addition of fluorine to aromatic systems is very rare. It was achieved with elemental fluorine and hexachlorobenzene[51]. Usually the addition is inseparable from replacement of either hydrogens or halogens by fluorine. As a result, mixtures of unsaturated and saturated polyfluoro compounds are obtained. If the reaction is carried out under forcing conditions, perfluoroperhydroaromatics are the final products.

Fluorine also adds to heterogeneous double bonds. Carbonyl fluoride is thus converted to trifluoromethyl hypofluorite, a useful fluorinating agent[52].

C. Addition of Halogen Fluorides across Multiple Bonds

A general method for adding halogen fluorides across double and triple bonds lies in a reaction of an unsaturated compound with a source of the so-called 'active halogen' in the presence of a fluoride ion: most often hydrogen fluoride, less frequently potassium or silver fluoride. Since the addition is ionic, it usually follows Markovnikov's rule and normally takes place in an *anti* mode. Additions of mixed halogens are carried out in polyethylene or Teflon flasks or bottles at temperatures ranging from −78°C to room temperature and give good yields of vicinal halofluorides.

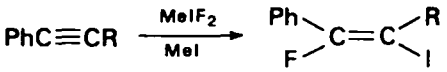
The sources of chlorine are most often *t*-butyl hypochlorite[48] and *N*-chlorosuccinimide (NCS)[53], the sources of bromine are *N*-bromoacetamide[53–55], *N*-bromosuccinimide (NBS)[48] and 1,3-dibromo-5,5-dimethylhydantoin[56], and the source of iodine is *N*-iodosuccinimide (NIS)[48,57] (equation 12).



(Ref. 48) (12)

An improvement in the halofluorination is the use of 'Olah's reagent', pyridine–poly(hydrogen fluoride)[17,58], and *N*-halo compounds, or bromine or iodine and silver nitrate[17]. Halofluorination is frequently used in the fields of steroids[53] and saccharides[59].

Unlike aryl iodide difluorides, methyl iodide difluoride adds iodine and fluorine across double[60] and triple bonds[61] regiospecifically (Markovnikov) and stereospecifically (*syn*) (equation 13). The presence of products of the opposite configuration in the reaction mixtures is due to the subsequent, time-dependent epimerization[61].

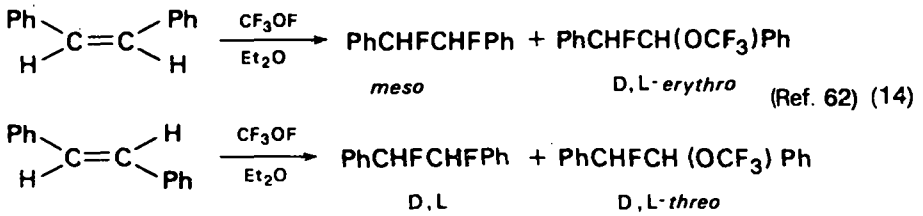


(65–80%) (Ref. 61) (13)

R = H, Me, Pr, *t*-Bu, Ph

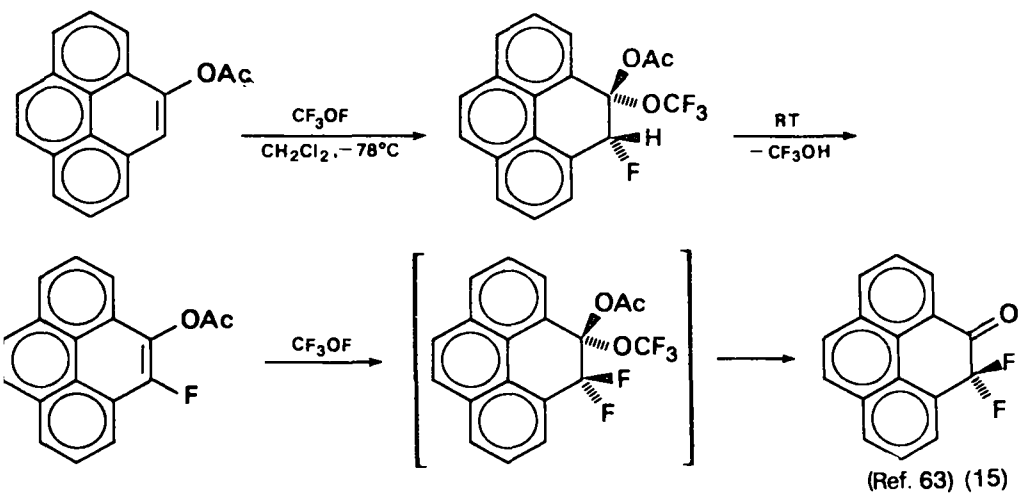
D. Addition of Fluorine and Other Groups to Multiple Bonds

Trifluoromethyl hypofluorite adds two fluorines[32] (equation 7) or fluorine and trifluoromethoxy group in a *syn* mode across double bonds[32,62] (equation 14).



(Ref. 62) (14)

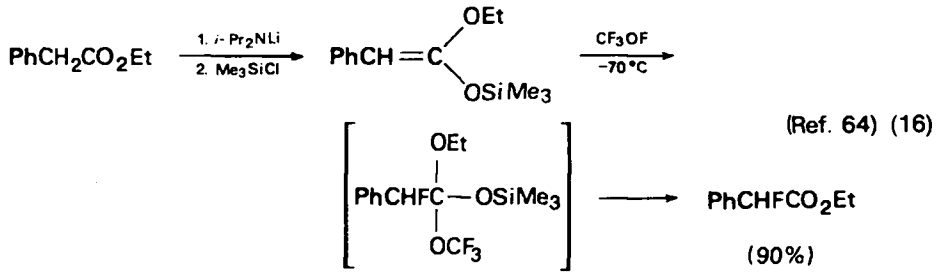
Reaction of trifluoromethyl hypofluorite with enol esters of ketones results first in regiospecific *syn* addition of fluorine and the trifluoromethoxy group across the double bond. Elimination of hydrogen and the trifluoromethoxy group from the neighbouring carbons gives α-fluoroenol ester which may react with another molecule of trifluoromethyl hypofluorite to yield α,α-difluoro ketone (equation 15)[63].



(Ref. 63) (15)

Monofluoro aldehydes, ketones, acids, esters or amides result from the reaction of trifluoromethyl hypofluorite with trimethylsilyl ethers of the enols of the carbonyl compounds[64]. Again, the first phase of these reactions may be the addition of trifluoromethyl hypofluorite across the double bond of the enols (equation 16; see also equation 31, p. 1040).

α-Fluoroketones were also prepared in 45–87% yields by treatment of enol acetates with a suspension of sodium trifluoroacetate in Freon through which elemental fluorine was passed. The trifluoroacetyl hypofluorite formed then reacted similarly to trifluoromethyl hypofluorite[65].

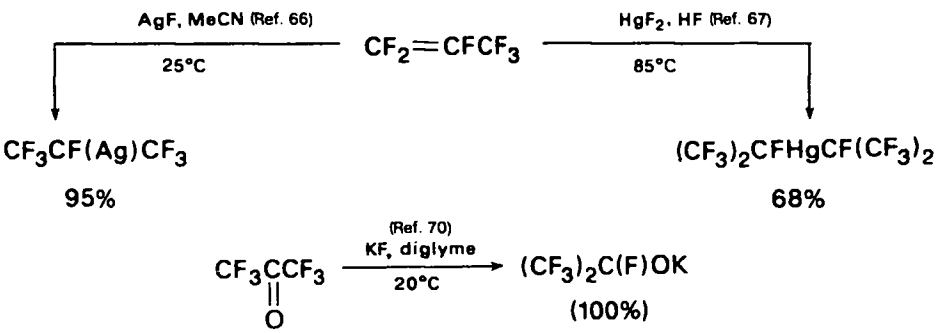


(Ref. 64) (16)

Addition of fluorine and a nitro group to alkenes to give vicinal fluoronitroalkanes in 40–80% yields was achieved by means of a mixture of nitronium tetrafluoroborate and pyridine–poly(hydrogen fluoride)[17].

Addition of fluorine and a metal takes place in a reaction of polyfluoroalkenes or perfluoroalkenes with silver fluoride[66] or mercuric fluoride[67] to produce fluoro-organometallics, important intermediates in the synthesis of fluoro compounds (equation 17). Perfluoroacetylenes form perfluorovinyl organometallics[68].

Addition of potassium fluoride and caesium fluoride across a carbonyl bond in perfluoroacyl fluorides[69] and perfluoroketones[70] yields alkali perfluoroalkoxides (equation 17).



(17)

E. Replacement of Hydrogen by Fluorine

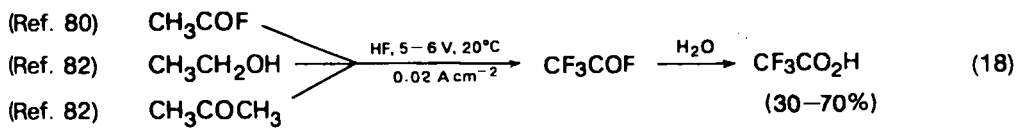
Direct fluorination – replacement of hydrogen by fluorine using elemental fluorine – is not nearly as common as the analogous reaction of other halogens. The reason is the extremely high heat of reaction (104.6 kcal mol^{-1}), more than four times as large as that of chlorination (24.9 kcal mol^{-1}) and larger than the bond dissociation energy of a carbon–carbon bond (70–92 kcal mol^{-1}). Consequently, direct fluorination is accompanied by fragmentation of the carbon skeleton and degradation to low molecular weight species, ultimately to carbon tetrafluoride.

However, it is possible to fluorinate organic compounds with elemental fluorine under strictly controlled conditions. In the liquid phase, fluorine is diluted with nitrogen or helium at low temperatures (−78°C), organic compounds are dissolved in solvents inert to fluorine, and the stream of diluted fluorine is dispersed by special devices. In the vapour phase, specially designed jet reactors may be used which provide for slow and gradual mixing of organic vapours with fluorine and inert gas, or the reaction may be carried out in reactors filled with metals such as silver- or gold-coated copper which not only help to dissipate the reaction heat but also act as catalysts (see Simons[1a], p. 373, and Stacey and coworkers[2a], p. 104). All these modifi-

cations often lead to mixtures of polyfluoro compounds since fluorination with elemental fluorine is a very non-selective reaction. Replacement of individual hydrogens by fluorine using elemental fluorine was successful only in fluorination in aqueous medium of aliphatic nitro compounds or their alkali salts[71], of primary or secondary amides[72], and in a few exceptional cases.

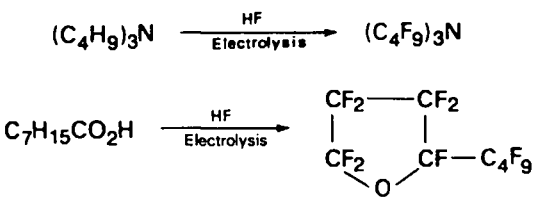
For the preparation of highly fluorinated and perfluorinated compounds which are desirable for their thermal and chemical stability, other methods such as the use of high valency metal fluorides or electrochemical fluorination processes were found to be more practical (*vide infra*). Quite recently fluorination with elemental fluorine in special cryogenic apparatus was successfully applied to the preparation of perfluoroalkanes[73,74], perfluoro cyclic and polycyclic hydrocarbons[74,75] and oxygen-[76,77] and nitrogen-containing[78] compounds. This method, reviewed recently[79], is especially suited for fluorination of non-volatile materials. It has been used for conversion of graphite to poly(carbon monofluoride) and for fluorination of polymers.

Complete (exhaustive) fluorination of all types of organic compounds can be accomplished by electrochemical fluorination. This process consists of electrolysis of solutions of organic compounds in anhydrous hydrogen fluoride at a potential lower than that necessary for evolution of fluorine (about 6V). In specially designed apparatus[80,81] fluorination takes place in the anodic space and results ultimately in the replacement of all hydrogens by fluorine[80]. Some functional groups (carboxyl, sulphonyl) are preserved[80,81]; others (alcoholic and carbonyl functions) are modified[82] (equation 18). Electrochemical fluorination is a free radical process with quite a few



(18)

side reactions; the yields of the main products sometimes leave much to be desired. However, the method is very practical for the synthesis of perfluorocarboxylic acid fluorides[80] and perfluoroalkanesulphonyl fluorides[81] as well as some perfluoroethers and -amines (equation 19), some of which are used as inert solvents and recently as



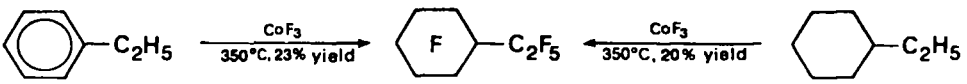
(19)

blood substitutes because they dissolve oxygen. Thorough reviews of the electrochemical fluorination process have been published in monograph contributions by Stacey and coworkers[2a] (p. 129) and by Tarrant[5a] (p. 77).

Another method for the synthesis of poly- and perfluoro compounds is fluorination using high valency metal fluorides (see Stacey and coworkers[2a], p. 166). Compounds such as silver difluoride, cobalt trifluoride, manganese trifluoride, cerium tetrafluoride and bismuth pentafluoride, decompose at 150–300°C to lower oxidation state fluorides and fluorine. Such reactions are endothermic: dissociation of cobalt trifluoride to cobalt difluoride and fluorine requires 52 kcal mol^{-1}, i.e. just one-half of the reaction heat developed in replacing hydrogen by fluorine. If cobalt trifluoride or other similar fluorides are heated with organic compounds, fluorination takes place and the organic compound is converted to poly- or perfluoro derivatives, often with

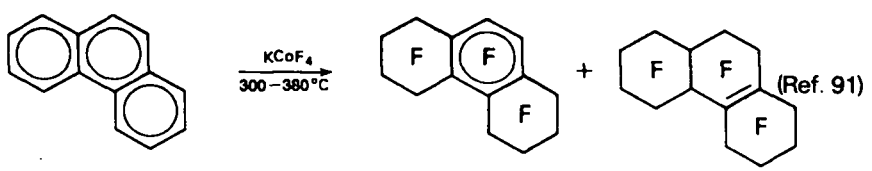
less degradation than if elemental fluorine were used. A special metal apparatus is necessary[83] in which vapours of compounds to be fluorinated are brought into contact with stirred powdered metal fluoride heated gradually to a higher temperature in such a way that the starting material encounters the fluoride at the lowest temperature, and the fluorinated material, much more resistant to degradation, is fluorinated to perfluoro compounds at the highest temperature. In this way, cobalt trifluoride converts alkanes to perfluoroalkanes[84] and aromatic and hydroaromatic hydrocarbons to perfluorocycloalkanes[85] (equations 20, 21).

$$C_7H_{16} \xrightarrow[150-165°C,\ 275-300°C]{CoF_3} C_7F_{16} \quad (91\%) \qquad \text{(Ref. 84) (20)}$$



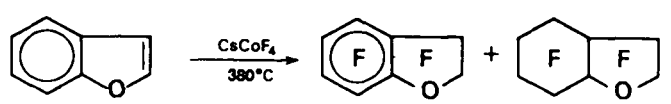
(Ref. 85) (21)

A somewhat milder reagent for poly- and perfluorination is potassium tetrafluorocobaltate[86], $KCoF_4$, prepared by fluorination of a complex salt of cobalt dichloride and potassium fluoride dihydrate. Fluorinations with $KCoF_4$ give mainly mixtures of polyfluoro- and perfluorocycloalkanes[87], polyfluoro- and perfluorocycloalkenes[88], and polyfluoro and perfluoro heterocyclic compounds[89], often in low yields. Functional groups such as nitriles are left intact[90]. Similar results are obtained with caesium tetrafluorocobaltate, $CsCoF_4$[91,92] (equation 22).



(5.6%) (14.3%)

(22)

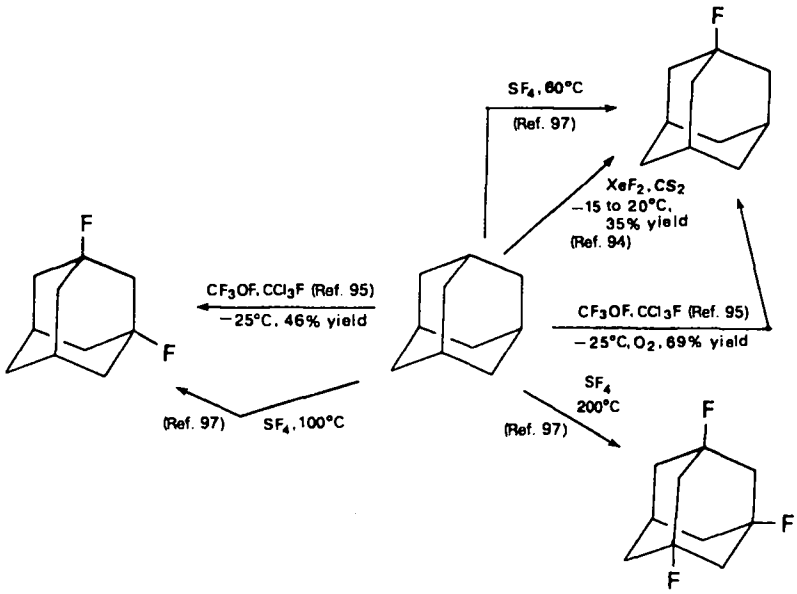


(20%) (20%)

The three methods of fluorination just described – fluorination with elemental fluorine, electrochemical fluorination, and fluorination with high valency metal fluorides – result usually in replacement of many hydrogens by fluorine. Substitution of fluorine for tertiary hydrogens in 4-*trans*-alkylcyclohexanol *p*-nitrobenzoates was achieved selectively by elemental fluorine[93], but special reagents such as xenon difluoride and trifluoromethyl hypofluorite have been used more frequently for the replacement of individual hydrogens by fluorine.

Hydrogen bonded to sp^3 carbons in alicyclic compounds was replaced by fluorine by means of xenon difluoride[94] and trifluoromethyl hypofluorite[95,96]. Replacement of hydrogen by using sulphur tetrafluoride is so far peculiar to adamantane (equation 23) and its derivatives[97] (equation 84).

Trifluoromethyl hypofluorite is very useful for introducing fluorine into positions 9,



(23)

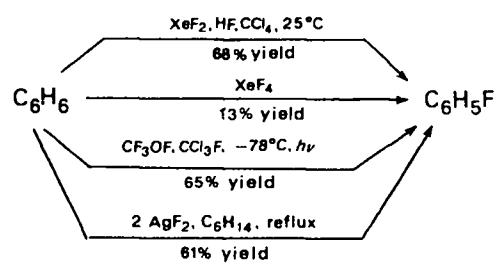
14 and 17 in steroids with retention of configuration[98]. It can also replace hydrogen by fluorine in secondary amides and sulphonamides[99].

Replacement of hydrogen by fluorine in aromatic compounds can be carried out by xenon fluorides[100,101].

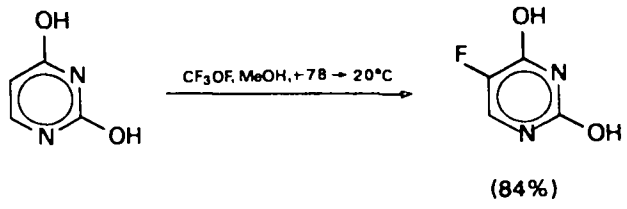
Xenon difluoride reacts with benzene and its homologues and derivatives like an electrophilic reagent. The reaction is catalysed by hydrogen fluoride[102,103] but the catalysis is not necessary[104]. The fluorination is carried out in solvents (CH_2Cl_2, CCl_4) at room temperature and gives monofluoro compounds in yields ranging from 10 to 70%. In this way phenols, phenol ethers[104], nitrobenzene[103], naphthalene[105,106], phenanthrene[107], pyrene[108] and even pyridine and hydroxyquinoline[109] were fluorinated. Treatment of naphthalene[106] with xenon difluoride gave, in addition to 45% of 1-fluoro- and 9% of 2-fluoronaphthalene, 15% of 1,4-difluoronaphthalene, and fluorination of pyridine gave 30% of 2-fluoro-, 20% of 3-fluoro-, and 11% of 2,6-difluoropyridine[109].

Similar results were obtained from treatment of aromatic compounds with xenon tetrafluoride[101] (which is safe only when pure and dry; moisture converts it to explosive compounds) or with an intercalate of xenon hexafluoride in graphite[110] ($C_{19.1}$ XeF_6).

Monofluorination of benzene and its homologues and derivatives was also achieved using trifluoromethyl hypofluorite[96] (equation 24). Toluene yielded 34% of *o*-fluorotoluene and 25% of benzyl fluoride[96], β-naphthol yields 9–20% of



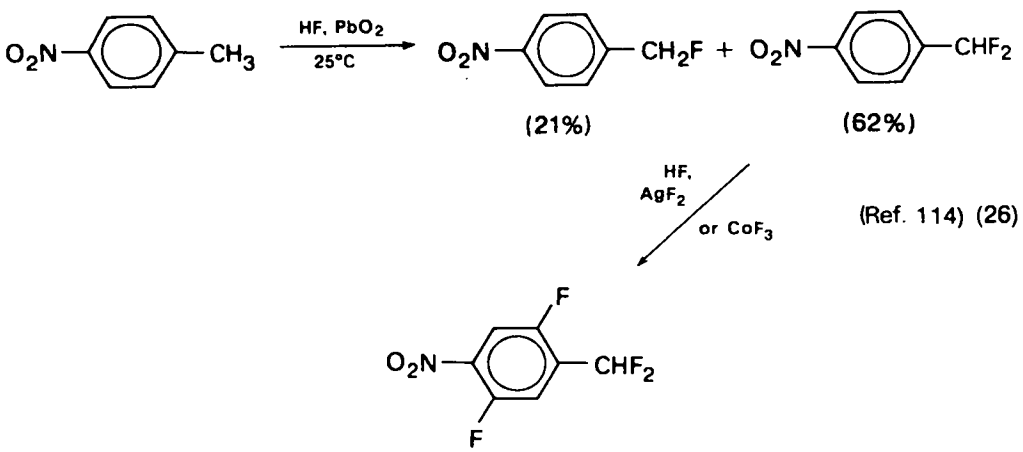
(Ref. 103)
(Ref. 101)
(24)
(Ref. 96)
(Ref. 113)



(Ref. 112) (25)

α-fluoro-β-naphthol and 20–40% of 1,1-difluoro-2-oxo-1,2-dihydronaphthalene[111], and uracil yields 84% of 5-fluorouracil[112] (equation 25).

Most recently, two more methods were reported for the selective fluorination of aromatic compounds. Surprisingly, silver difluoride and benzene gave, under mild conditions in hexane solution, 61% of fluorobenzene[113] (equation 24), and *p*-nitrotoluene was fluorinated in the side chain by a mixture of liquid hydrogen fluoride with lead superoxide and similar oxidizing agents[114] (equation 26). Some ring fluorination was accomplished by using silver difluoride or cobalt trifluoride but the results were of little preparative use[114] (equation 26).

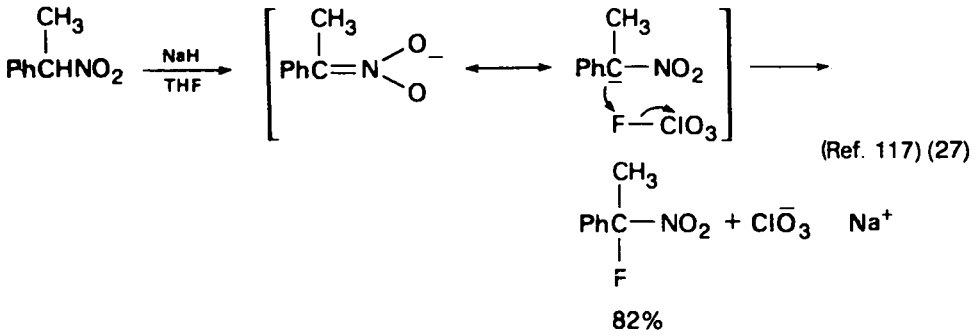


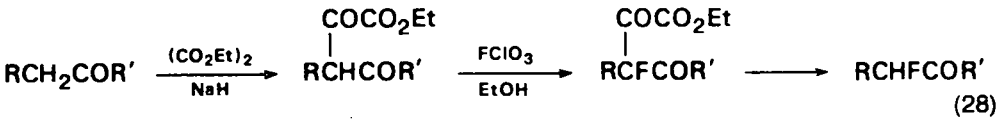
(Ref. 114) (26)

Hydrogen atoms in positions α to nitro groups, carbonyl groups and especially on carbon atoms flanked by two carbonyl or carboxyl groups are replaced by fluorine by means of perchloryl fluoride, $FClO_3$[115]. This gaseous compound is remarkably stable to heat and hydrolysis but was found to explode if condensed to a liquid in the presence of an organic compound[18b]. As long as it is handled in solutions the danger of an explosion is small. Nevertheless, all necessary safety measures should be observed when reactions with perchloryl fluoride are undertaken.

While the mechanism of the reactions of perchloryl fluoride is not entirely clear, it can be assumed that it reacts with enols either by an intramolecular transfer of fluorine[116] or by a nucleophilic displacement of the ClO_3 group from fluorine[117] (equation 27).

Enol ethers of aldehydes and ketones, enol esters, enamides and enamines react with perchloryl fluoride to give α-fluoroaldehydes and α-fluoroketones. Sometimes α,α-difluoro compounds are formed. This happens especially in the case of β-diketones, β-ketoesters[118] and malonic esters[119]. In order to prevent disubstitution, the carbonyl compound may be first treated with ethyl formate or diethyl oxalate, which condense with the carbonyl compound to form a derivative with only one

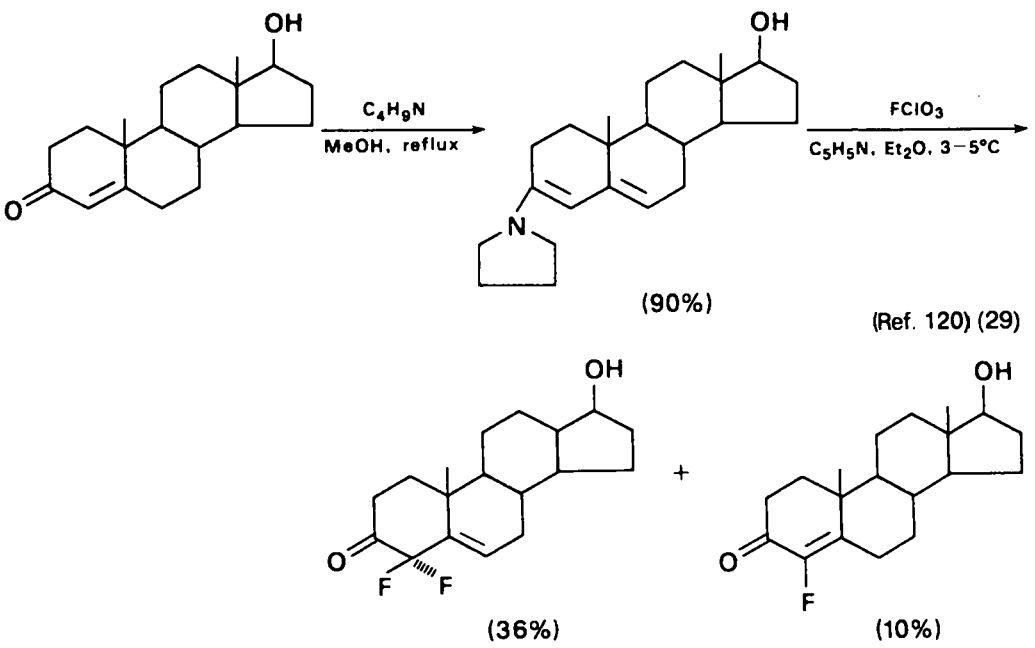


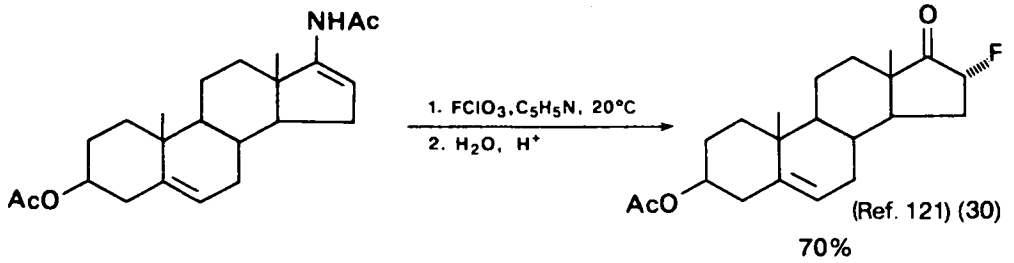


hydrogen atom available for replacement by fluorine (equation 28). The replacement of hydrogens using perchloryl fluoride was successfully applied in steroids for introduction of fluorine into different positions[120,121] (equations 29,30).

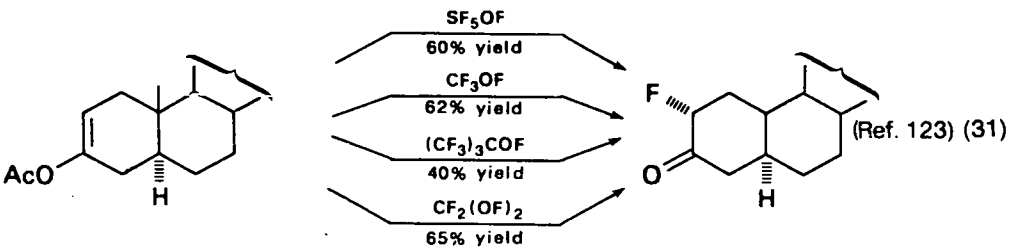
Applications of perchloryl fluoride in preparing fluoro compounds are very abundant[122]. However, the amount of work is declining with decreasing availability of the reagent.

A similar effect – introduction of fluorine into positions α to keto groups in steroids – was achieved by reacting steroidal enol acetates with perfluorooxy compounds (see p. 1040). Enol acetate of 3-cholestanone was thus converted to 2α-fluorocholestanone





in 40–62% yields by trifluoromethyl hypofluorite, perfluoro-*t*-butyl hypofluorite, and best by bis(fluoroxy)difluoromethane[123] (equation 31).



F. Replacement of Halogens by Fluorine

Replacement of halogens by fluorine constituted the first general method for the preparation of organic fluorine compounds when it was found that the most common methods used for the synthesis of other organic halides, direct halogenation and replacement of hydroxyl groups, were not successfully applicable to the preparation of organic fluorides. With the discovery of other fluorination methods the metathetical halogen–fluorine exchange lost some of its importance. However, there are still situations in which halogen–fluorine exchanges are useful and practical, especially in industry. Comprehensive reviews cover this mode of preparation of organic fluorides[2c].

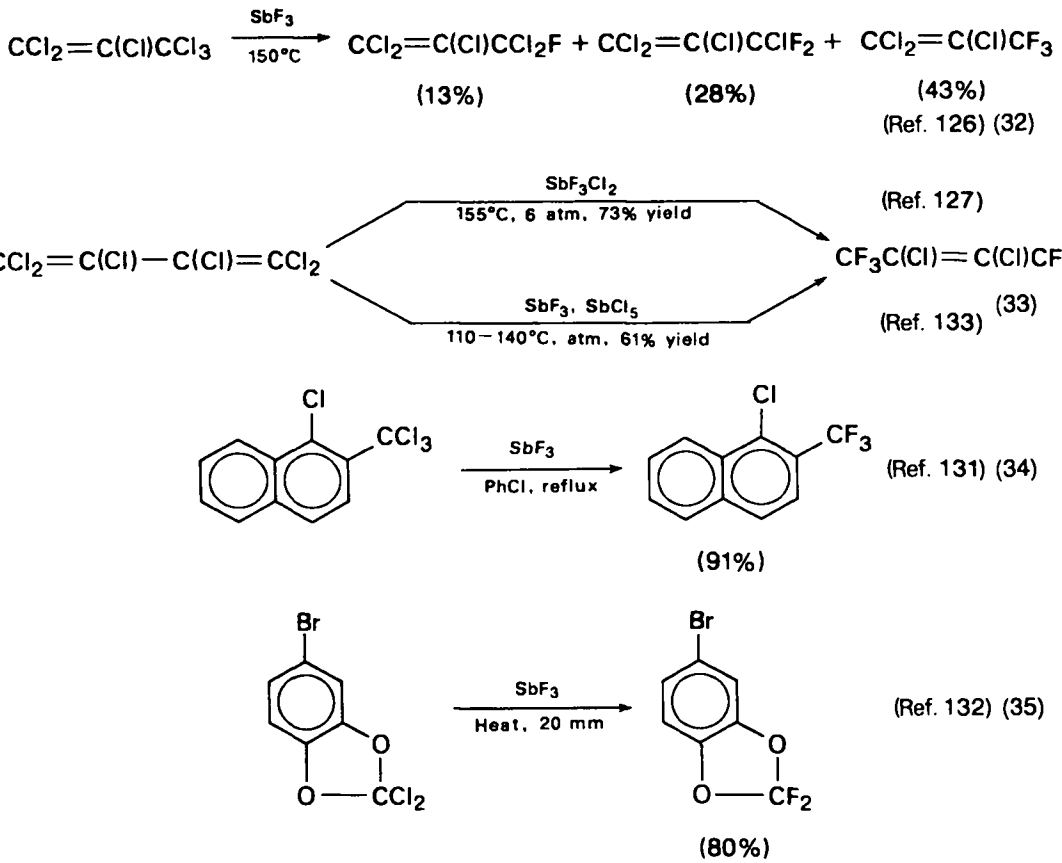
The cheapest source of fluoride ion for the metathetical reactions is anhydrous hydrogen fluoride. It is not surprising that it is used for large scale production of organic fluorides, especially polyhalogen polyfluorides. (Hydrogen fluoride is incapable of replacing single halogen atoms by fluorine.) Although anhydrous hydrogen fluoride converts polychloro organic compounds to polychlorofluoro compounds on its own at sufficiently high temperatures and pressures[124,125], it is convenient to use catalysts. The most common catalysts for liquid-phase reactions are antimony trichloride and, better still, antimony pentachloride. These salts are converted by hydrogen fluoride to antimony trifluoride and antimony dichlorotrifluoride and chlorotetrafluoride, respectively, which act as fluorine transfer agents at temperatures of 50–150°C (in autoclaves). Other catalysts such as tin tetrachloride are used much less frequently.

Polychlorides can be converted to polyfluorides and polychlorofluorides by hydrogen fluoride at atmospheric or moderate pressures in the vapour phase at temperatures of 350–450°C over catalysts based on salts of iron, aluminium, chromium and many others, usually supported on matrixes with a large surface area, e.g. activated charcoal and alumina.

Both liquid-phase and vapour-phase catalytic fluorinations with hydrogen fluoride are used extensively in industry for production of the fluorochloro derivatives of methane and ethane which have been used for some 50 years as refrigerants and

propellants under the trade name Freon and other trade names. The procedures are described mainly in the patent literature and are frequently reviewed in monographs[1a,2c,6].

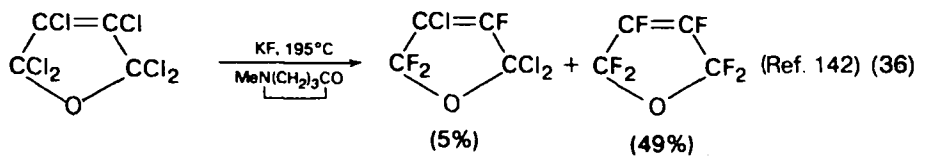
For a laboratory which is not equipped with autoclaves suitable for work with anhydrous hydrogen fluoride at higher temperatures, metal fluorides are more convenient for the replacement of halogens by fluorine. The fluoride which resembles most closely the action of hydrogen fluoride is antimony trifluoride. It is not very reactive, but its activity can be strongly enhanced if a part or all of the antimony is converted to its pentavalent state by addition of chlorine, bromine or antimony pentachloride; such mixtures – known as 'Swarts reagents' – are capable of replacing one to three halogen atoms linked to one carbon by fluorines. Single halogens are inert to the antimony fluorides. The extent of the replacement of halogens by fluorine depends on the amount of the reagent used, on the temperature, and on the nature of the halogen. Geminal and trigeminal allylic[126–128] and benzylic halogens[129] are, as a rule, replaced more readily than those in saturated chloro compounds[130]; vinylic[126,127] and aromatic[131,132] halogens and single halogens on sp^3 carbons[130] are unaffected (equations 32–35). Many reactions with antimony fluorides can be carried out even in glass equipment[129,133].

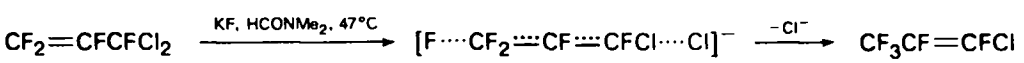


One of the most general reagents capable of converting organic halides to organic fluorides is dry potassium fluoride. (Potassium fluoride dihydrate is unsuitable; even

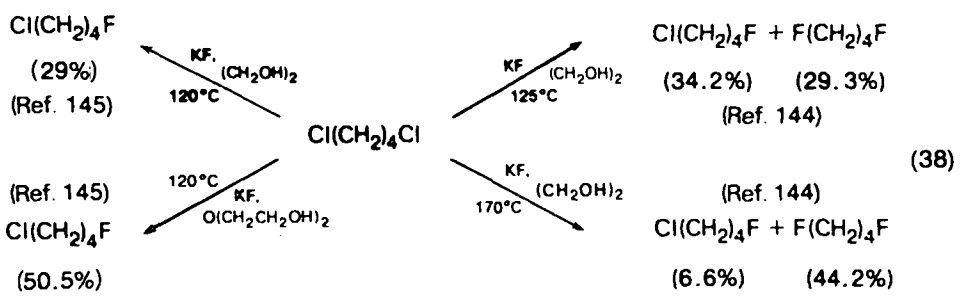
commercial anhydrous potassium fluoride must be carefully dried, preferably overnight in an oven at 150–160°C[133].) It was used in the past predominantly for reactions with reactive halides such as sulphonyl chlorides[134], acyl chlorides[135], allyl and benzyl halides[136], α-halocarbonyl and carboxyl compounds[137,138] and aromatic chlorides activated by nitro groups[139]. However, when strongly polar solvents such as acetamide, nitrobenzene, dimethyl sulphoxide, dimethyl sulphone, sulpholane, and especially ethylene glycol, di- and triethylene glycol, dimethylformamide and *N*-methylpyrrolidone[140] are used, just about any halogen can be replaced by fluorine in fair to high yields. The main reason for the success in replacement of even as unreactive halogens as vinylic and aromatic chlorines is probably the relatively high solubility of potassium fluoride in polar solvents (*N*-methylpyrrolidone dissolves up to 3%). The solubility of potassium fluoride even in relatively non-polar solvents can be dramatically increased by addition of crown ethers (18-crown-6 ether) which enhance the nucleophilicity of fluoride ion by solvating the cation, giving a naked F^- ion[141]. The introduction of the latter two solvents was a breakthrough since potassium fluoride can be used even for the preparation of perfluoro compounds[140].

Replacement of halogen by fluorine in polyhaloalkenes can take place either by the S_N2[142] or by the S_N2' mechanism[143] (equations 36 and 37, respectively).

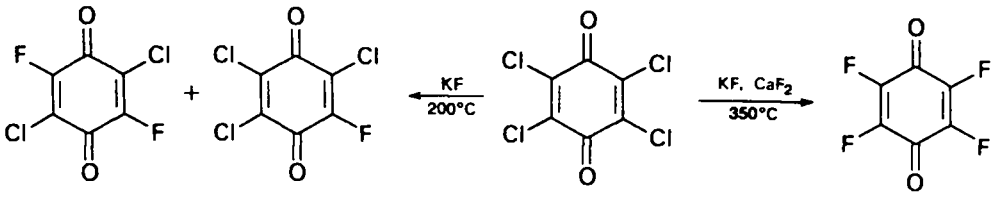




The effect of the solvent and the reaction temperature on the conversion of aliphatic α,ω-dihalides to halofluorides and difluorides is shown in equation (38)[144,145].

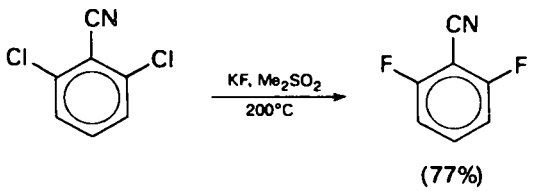


Poly- and perchloro compounds can be converted to poly- and perfluoro compounds by means of potassium fluoride, especially if the chlorines are activated by the proximity of polar groups such as carbonyl (equation 39)[146], carboxyl[147], cyano (equation 40)[148] or nitro (equation 41)[139], or a double bond (equation 42)[140]. The clue to the metathetical exchange of halogens in the latter case seems to be an S_N2' reaction of the fluoride ion, combined with elimination of hydrogen chloride and even chlorine under the conditions of the reaction. Because at high enough temperatures dehalogenation can take place, even completely saturated perchloro compounds are fluorinated (equation 43)[140].

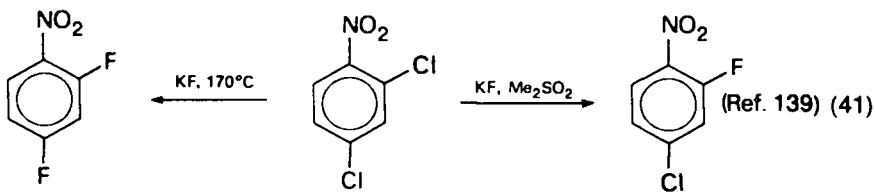


(60%) (14%) (25–30%)

(Ref. 146) (39)



(77%) (Ref. 148) (40)



(69.5%) (Ref. 139) (41)

$CCl_2{=}C(Cl){-}C(Cl){=}CCl_2$

KF, $MeN(CH_2)_3CO$, Heat, 65% yield → $CF_3CH{=}CFCF_3$* (Ref. 140) (42)

KF, $MeN(CH_2)_3CO$, Heat, 20% yield → $CCl_3C(Cl){=}C(Cl)CCl_3$

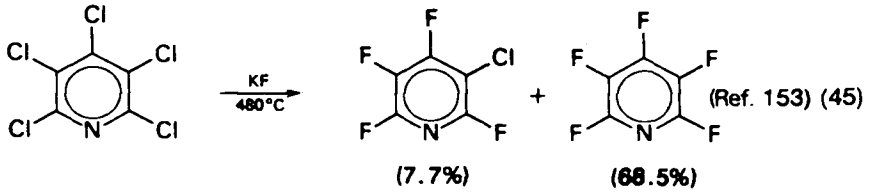
*Hydrogen comes from the solvent.

$$CF_3CCl_2CCl_2CF_3 \xrightarrow[MeN(CH_2)_3CO]{KF,\ heat} CF_3C(Cl)FC(Cl)FCF_3 + CF_3CF{=}CFCF_3 + CF_3C(Cl){=}CFCF_3 \quad (43)$$

(70%) (Ref. 140)

A far-reaching discovery was the reaction of perchloroaromatic compounds with potassium fluoride without solvent in autoclaves at 400–500°C. Under these harsh conditions as many as every one of the chlorine atoms are replaced by fluorine, even in otherwise non-activated compounds like hexachlorobenzene[149,150] (equation 44),

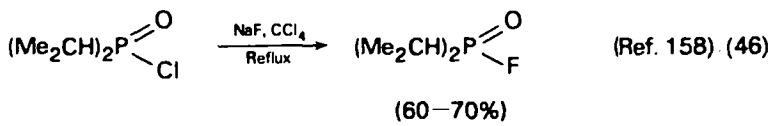
$$C_6Cl_6 \xrightarrow[460-470°C]{KF} \underset{(11-12\%)}{C_6Cl_3F_3} + \underset{(13-14\%)}{C_6Cl_2F_4} + \underset{(19-21\%)}{C_6ClF_5} + \underset{(20-22\%)}{C_6F_6} \quad \text{(Ref. 150) (44)}$$



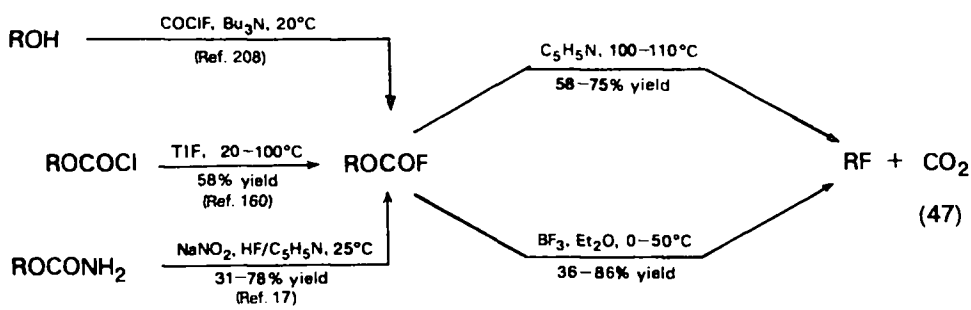
perchloronaphthalene[151], and many other perchloroaromatics[152] (cf. Tarrant[5g], p. 115). Under similar conditions aromatic heterocycles such as perchloropyridine[153] (equation 45), diazines[154] and others can also be converted to perfluoro compounds. Although perfluoroaromatics were prepared by other methods, e.g. by defluorination of perfluoroalicyclic compounds with iron or nickel, it was the metathetical halogen exchange which made perfluoroaromatics available on an industrial scale.

Halogen–fluorine exchange can also be effected by other alkali fluorides. Caesium fluoride is more efficient than potassium fluoride. Alone[155] or in a mixture with potassium fluoride[156], it gives usually higher yields than potassium fluoride.

Sodium fluoride has been used for replacement only of very reactive chlorine atoms such as those linked to phosphorus[157,158] (equation 46).



The special capability of thallium (thallous) fluoride lies in the conversion of alkyl chloroformates to fluoroformates[159,160], whose decomposition by pyridine or, better still, by boron trifluoride–ether complex, gives good yields of alkyl fluorides[160] (equation 47)[17,208].



Since potassium fluoride has developed into a universal reagent for the halogen–fluorine exchange, the importance of silver fluoride, mercurous fluoride, and mercuric fluoride, once popular fluorinating agents, has dropped considerably. Nevertheless, because of its solubility in water and acetonitrile, because of the very gentle reaction conditions, and because of the possibility of preparing it *in situ* from silver oxide and hydrogen fluoride[161], silver fluoride is used for substitution of fluorine for bromine and iodine in steroids[161,162] and carbohydrates[163]. The replacement usually takes place with inversion[161,163], but sometimes with retention of configuration.

Silver fluoride[164,165] (and also zinc fluoride[165]) was used for replacement of tertiary bromine atoms in adamantane by fluorine. 1-Fluoroadamantane, 1,3-difluoro-, 1,3,5-trifluoro and 1,3,5,7-tetrafluoroadamantanes were thus obtained. Another reagent used for the replacement of a tertiary bromine is silver fluoroborate, which

converted 3-bromo-3-methyl-2-butanone to 3-fluoro-3-methyl-2-butanone at room temperature in 87.5% yield[166].

Mercurous fluoride was used especially for replacement of bromine by fluorine. The reactivity of mercurous fluoride is considerably increased by the addition of bromine or iodine (up to one equivalent). Such a reagent replaced bromine by fluorine in brominated esters. In methyl α,β-dibromopropionate, fluorine replaces, surprisingly enough, β-bromine[167], whereas in ethyl α,α,β-tribromopropionate it replaces the α-bromine[168] (equations 48).

$$CH_2BrCHBrCO_2Me \xrightarrow[140-150°C]{HgF,\ I_2} CH_2FCHBrCO_2Me \quad \text{(Ref. 167)}$$
$$\text{(29\%)}$$
$$CH_2BrCBr_2CO_2Et \xrightarrow[140°C]{HgF,\ I_2} CH_2BrC(Br)FCO_2Et \quad \text{(Ref. 168)} \qquad (48)$$
$$\text{(24\%)}$$

Whereas mercurous fluoride, even if fortified by iodine, usually replaces only one of the geminal halogens, the more reactive mercuric fluoride frequently replaces two and even all three halogens[169,170] (equation 49). Instead of mercuric fluoride, a reagent made *in situ* from mercuric chloride[171] or mercuric oxide[172] and anhydrous hydrogen fluoride can be used.

$$CHCl_2CH_2Cl \xrightarrow[140°C]{HgF_2} CHClFCH_2Cl + CHF_2CH_2Cl$$
$$\text{(50\%)} \qquad \text{(8–10\%)}$$
$$\text{(Ref. 169)} \quad (49)$$
$$CHBr_2CHBr_2 \xrightarrow[150-160°C]{HgF_2} CHF_2CHBr_2$$
$$\text{(100\%)}$$

Conversion of acyl and sulphonyl chlorides to the corresponding fluorides[173] and partial replacement of trigeminal chlorines by fluorine was achieved using arsenic fluoride[174].

Sulphur tetrafluoride can be used for replacement of halogens by fluorine[175]; for example, 1-chloro-, 1-bromo- and 1-idoadamantane were converted to 1-fluoroadamantane in 61–84% yields at 85–140°C[176]. However, since rather high temperatures are usually necessary and other fluorides react more easily, sulphur tetrafluoride is hardly ever used for replacement of halogens by fluorine.

Organic fluorides such as tertiary amine tris(hydrofluorides)[177] or nitryl fluoride[178], prepared *in situ* from anhydrous hydrogen fluoride and fuming nitric acid, replace reactive halogens by fluorine under mild conditions[178] (equation 50).

$$CH_3CH(Br)C_6H_{13} \xrightarrow[78\%\ \text{yield}]{HF,\ 100\%\ HNO_3,\ 15-18°C} CH_3CH(F)C_6H_{13} \xrightarrow[78\%\ \text{yield}]{HF,\ 100\%\ HNO_3,\ -10°C} CH_3CH(I)C_6H_{13} \quad \text{(Ref. 178)} \quad (50)$$

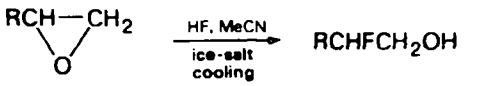
G. Replacement of Oxygen by Fluorine

While the replacement of hydroxyl and carbonyl oxygen by halogens is one of the favoured methods of preparing organic chlorides, bromides and iodides, analogous reactions leading to fluorinated derivatives were for a long time considered generally unfeasible. It has been only for the past 30 years that the replacement of oxygen by fluorine became competitive with other methods of preparation, owing mainly to the

development of new fluorinating agents. Fluorinated compounds are prepared by substitution of fluorine for oxygen in ethers, esters, alcohols, carbonyl compounds and acids and their derivatives.

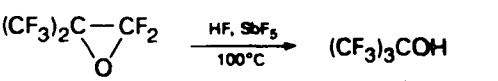
1. *Cleavage of epoxides and ethers*

Epoxides (oxiranes) are easily opened by hydrogen fluoride to fluorohydrins. Since the reaction is carried out in an acidic medium, fluorine becomes attached to the carbon which can better accommodate a partial positive charge in the transition state. The reaction is catalysed by Lewis acids and gives *trans*-fluorohydrins[179,180,181] (equations 51–53). In place of aqueous or anhydrous hydrogen fluoride, acid fluorides

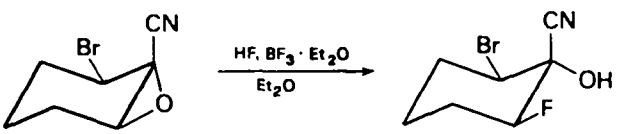


(Ref. 179) (51)

R	C_2H_5	C_4H_9	C_5H_{11}
Yield, %	32.6	33.3	32.4

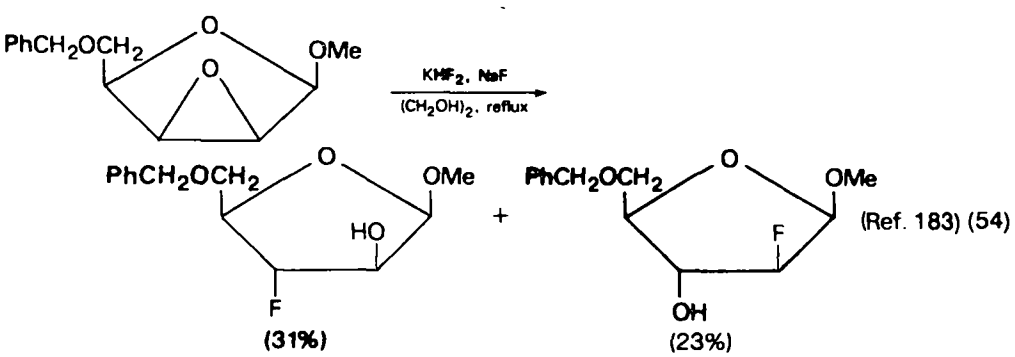


(Ref. 180) (52)



(Ref. 181) (53)

of potassium[182,183], ammonia[184], alkylamines[184], and pyridine (Olah's reagent)[185] were used successfully. The cleavage is not always regiospecific[183,184]. The reaction found wide application in the fields of carbohydrates[183] (equation 54) and steroids[182]. Steroidal epoxides were often converted to *trans*-fluorohydrins by means of boron trifluoride etherate at room temperature[186–188].



(Ref. 183) (54)

Open-chain ethers and five- and six-membered cyclic ethers are not cleaved by hydrogen fluoride. However, boron trifluoride in the presence of acetyl fluoride converted methyl bicyclo[2,2,2]octyl ether to 1-fluorobicyclo[2,2,2]octane in 70% yield at 10–20°C[189].

Alkyl silyl ethers react with alkyl or aryl tetrafluorophosphoranes to give high yields of alkyl fluorides[190] (equation 55).

$$C_2H_5OSiMe_3 + RPF_4 \xrightarrow{20°C} \underset{100\%}{C_2H_5F} + Me_3SiF + RPF_2O \text{ (Ref. 190)} \quad (55)$$

R = Et, Ph

2. Cleavage of esters

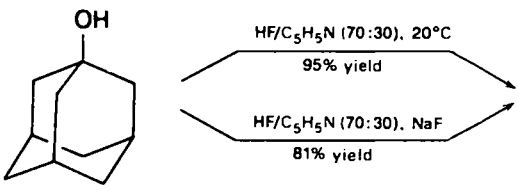
Carboxylic esters and lactones do not react with hydrogen fluoride[133] or most fluorides. However, the cyclic carbonate of ethylene glycol gave 50–55% of ethylene fluorohydrin on heating with potassium fluoride at 165–170°C[191], and carbohydrate hemiacetal esters – glycosyl benzoates – were converted to glycosyl fluorides by hydrogen fluoride at −10°C[192] with both retention and inversion of configuration.

Esters of alcohols with mineral acids are readily cleaved by potassium fluoride. The reaction is particularly useful in the case of alkyl methanesulphonates[193] and *p*-toluenesulphonates[194,195] and is carried out by heating the sulphonates with dry potassium fluoride, preferentially in diethylene glycol. Since the sulphonates can be prepared *in situ*[196], this method is a route from alcohols to alkyl fluorides. The best results for this one-step process are obtained if the alcohols are treated with methanesulphonyl fluoride[193] (equation 56). Tetrabutylammonium fluoride, which is soluble in organic solvents, can be used instead of potassium fluoride[197].

$$\underset{\text{(Ref. 193)}}{ClCH_2CH_2OH} \xrightarrow[20°C,\ 24\ h]{MeSO_2F,\ KF} [ClCH_2CH_2OSO_2Me] \xrightarrow[100°C,\ 300\ mm]{KF,\ O(CH_2CH_2OH)_2} \underset{\text{(53\%)}}{ClCH_2CH_2F} \quad (56)$$

3. Replacement of hydroxyl by fluorine

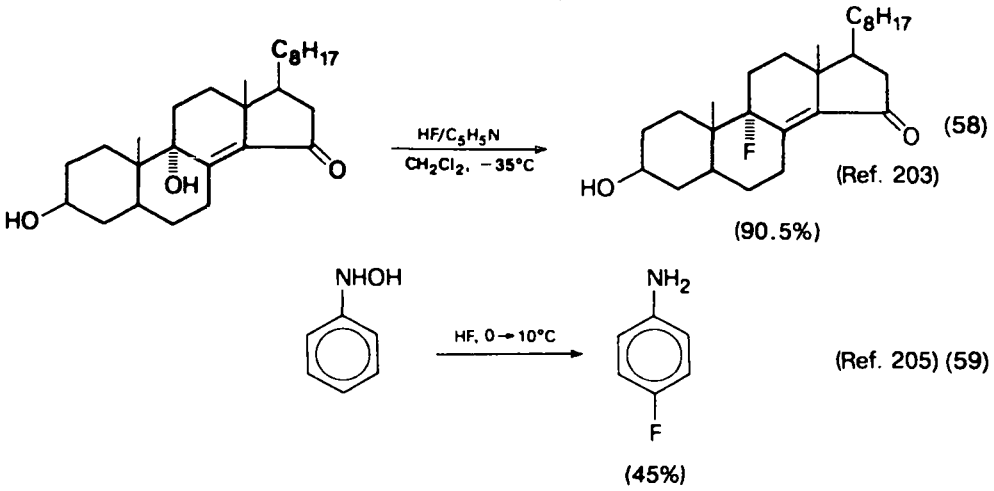
The most straightforward conversion of alcohols to fluoroalkanes is by their treatment with hydrogen fluoride. Unfortunately, this reaction is rather unpredictable: it has failed on many occasions and given alkenes or ethers as the main products. Successful conversion of *t*-butyl alcohol to *t*-butyl fluoride in 60% yield was achieved by heating the alcohol with 60% aqueous hydrofluoric acid to 60°C[198], by treating the alcohol with anhydrous hydrogen fluoride at −50°C (52% yield)[199], or by the use of pyridinium poly(hydrogen fluoride) (Olah's reagent) at 0°C (50% yield)[17,200] (equation 57). The last-mentioned reagent gives 30–99% yields of alkyl fluorides with



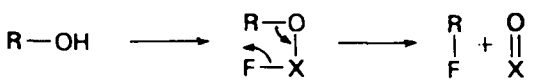
(Ref. 17) (57)

secondary and tertiary alcohols[17,200]. Primary alcohols are unreactive but are converted to alkyl fluorides in 30–88% yields if sodium fluoride is added to the reagent[17] (equation 57). The replacement of the hydroxyl group may take place with or without rearrangement[201,202] and usually with retention of configuration[202,203] (equation 58).

Trimethylbenzylammonium hydroxide was converted, by distillation with 20% hydrofluoric acid, in 60% yield to benzyl fluoride[204]. A peculiar replacement of a hydroxyl group by fluorine with a rearrangement takes place when phenylhydroxylamine is treated with hydrogen fluoride[205–207] (equation 59).



There is a series of reagents that convert hydroxy compounds to more or less stable intermediates which decompose or are decomposed – probably by a cyclic mechanism – to the corresponding fluoro derivatives (equation 60).



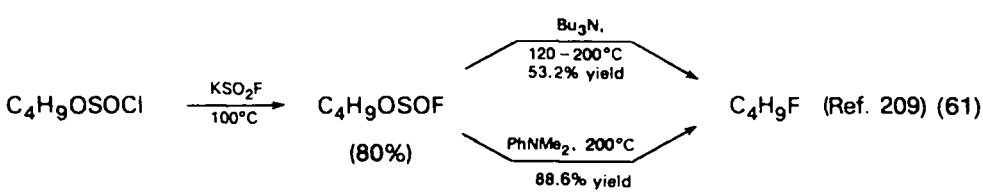
(60)

X = CO, CS, SO, SF_2, SOF_2, $CHClFCNEt_2$, Ph_3P, Ph_2PF, $PhPF_2$

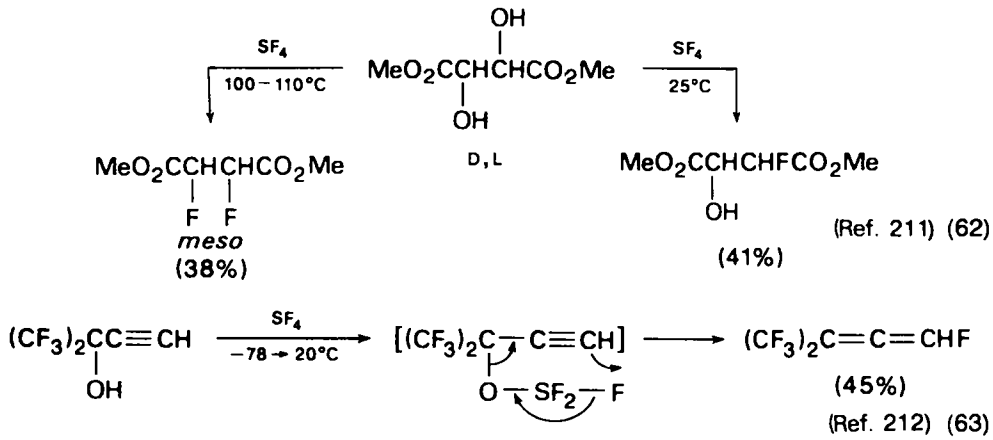
One of the above reactions is catalytic decomposition of alkyl fluoroformates, prepared from alkyl chloroformates and thallium fluoride[160], or from alcohols and carbonyl fluoride or chlorofluoride[208] and giving alkyl fluorides (equation 47).

Similar decomposition (catalysed by platinum) converts aryl fluoroformates, prepared from phenols and carbonyl chlorofluoride, to aryl fluorides[208].

Alkyl fluorosulphites prepared from alkyl chlorosulphites and alkali fluorides or potassium fluorosulphinate decompose in the presence of tertiary amines to alkyl fluorides[209] and sulphur dioxide (equation 61).



Alcohols are converted to the corresponding fluoro compounds by treatment with sulphur tetrafluoride[11,210]. The reagent is unsuitable for simple alcohols as the yields are decreased by the formation of ethers[210]. Acidic alcohols such as nitro alcohols[210], α-hydroxy acids[210,211], and polyhalogenated and polyfluorinated alcohols[210,212] give good yields of fluoro compounds. The replacement of the hydroxyl group by fluorine sometimes leads to rearrangements and takes place with retention or inversion of configuration, depending partly on the structure of the alcohol[133,213] (equation 62). Allylic and propargylic fluorinated alcohols undergo allylic rearrangements[212] (equation 63).



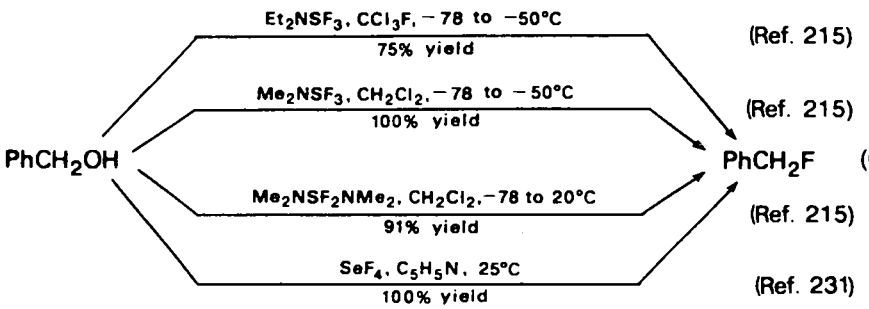
Amino alcohols and amino hydroxy acids yield fluoroamines and fluoroamino acids with sulphur tetrafluoride in anhydrous hydrogen fluoride at −78°C and atmospheric pressure. Under these conditions the protonated amino group does not react with sulphur tetrafluoride, and only the hydroxyl group is replaced by fluorine[213]. Mono- and bimolecular mechanisms both seem to be operating since products of carbonium-type rearrangements were found, and predominant inversion was observed together with some retention of configuration[213].

Hydroxyl groups in tropolones, carboxylic acids and sulphonic acids are readily replaced by fluorine in the reactions with sulphur tetrafluoride. Further reaction with sulphur tetrafluoride leads to the replacement of the carbonyl oxygen by fluorines in the acyl fluorides thus formed (equation 69).

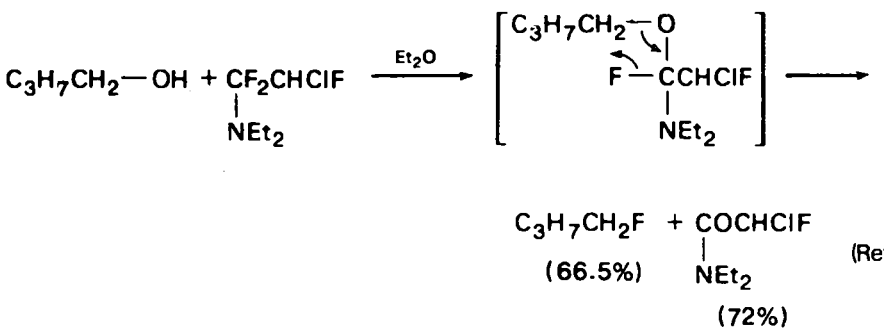
The reactions with the gaseous sulphur tetrafluoride (b.p. −40°C) are usually carried out at elevated pressures. The more recent fluorinating agents suitable for replacement of hydroxyl groups (and also carbonyl oxygen) by fluorine are obtained by treatment of sulphur tetrafluoride with trimethylsilyldialkylamines[214,215]. The most popular of this group is diethylaminosulphur trifluoride (DAST), made from trimethylsilyldiethylamine and sulphur tetrafluoride. This liquid reagent – safe at temperatures below 40–50°C[18c,215] – reacts with alcohols under milder conditions than sulphur tetrafluoride (at −78 to −50°C) and, therefore, does not require autoclaves[215].

The mechanism of the replacement of hydroxyl groups or carbonyl oxygen by fluorine is not entirely clear. With secondary and allylic alcohols much less rearrangement was noticed than in reactions with sulphur tetrafluoride[215]. The replacement takes place with retention of configuration, as demonstrated using many examples in steroids[216,217]. DAST can also be used for the replacement of hydroxyl groups by the ^{18}F isotope of fluorine if it is treated with $H^{18}F$ prior to the reactions with alcohols[218]. Other aminosulphur fluorides such as morpholinosulphur trifluoride[214,219] and bis(diethylamino)sulphur difluoride[215] react similarly to DAST with minor nuances (equation 64).

Another rather general and, at the same time, selective reagent suitable for the conversion of alcohols to fluorides is 1-chloro-1,2,2-trifluorotriethylamine, prepared by the addition of diethylamine to chlorotrifluoroethylene[220–222]. The product is a liquid of limited stability. It can be distilled *in vacuo* without decomposition but decomposes slowly at room temperature. However, it can be kept for weeks and even months in a freezer. Although the compound was first prepared by Pruett and coworkers[220], its usefulness for the selective replacement of a hydroxyl group in



alcohols and acids by fluorine was first recognized by Yarovenko and Raksha[221] (equation 65). The Yarovenko–Raksha reagent does not react, as a rule, with phenols and carbonyl compounds[133]. Its reaction with alcohols and acids is spontaneous and is autocatalysed by the hydrogen fluoride evolved during the reaction[133]. The replacement of the hydroxyl group takes place with retention[222,223] as well as with inversion of configuration[224]. Primary, secondary and tertiary alcohols are converted to fluorides in fair to good yields. The reagent is very useful in steroid series[222–224], although some side reactions and rearrangements may decrease the yields[224,225]. Similar reagents made by addition of secondary amines to perfluoropropene are claimed to be superior to the Yarovenko–Raksha reagent in terms of easier preparation and better stability[226].



Alcohols can also be transformed into fluorides by means of triphenyldifluorophosphorane[227], diphenyltrifluorophosphorane[228], and phenyltetrafluorophosphorane[229]. Whereas the first two reagents require heating of the alcohols to 150–170°C, the last-mentioned reacts with steroidal alcohols at room temperature and gives 24–64% yields of fluoro steroids with retention as well as inversion of configuration, depending on the structure of the alcohol[229].

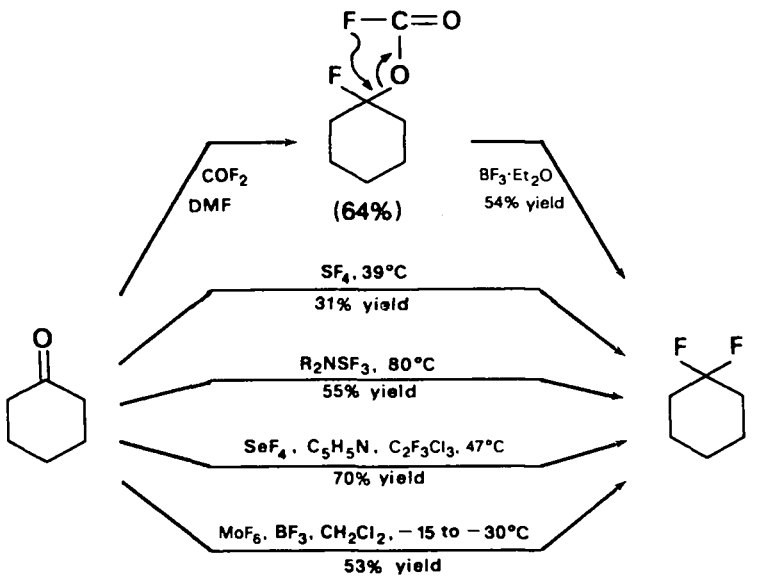
Phenyltetrafluorophosphorane reacts not only with alcohols but with their trimethylsilyl ethers, converting them in 30–95% yields into fluorides[230] (equation 55).

Finally, hydroxyl groups in alcohols can be replaced by fluorine by treatment with selenium tetrafluoride[231]. This reaction is superior to that of sulphur tetrafluoride since it can be carried out in glass or plastic equipment at atmospheric pressure and moderate temperature (50°C). It is also more general, and, provided that one equivalent of pyridine is added to the reaction mixture to neutralize the hydrogen fluoride generated in the reaction, alkyl fluorides are obtained in 56–100% yields practically without rearrangement[231] (equation 64).

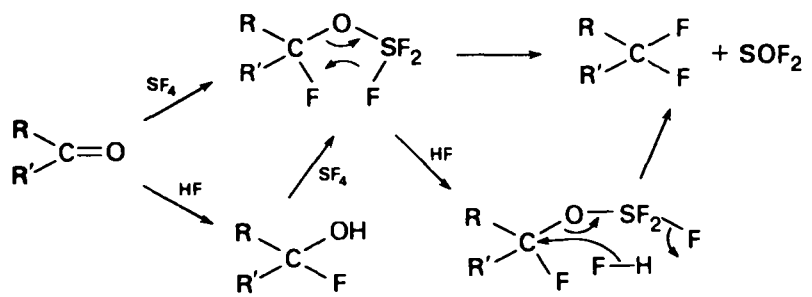
4. Replacement of carbonyl oxygen by fluorine

Replacement of carbonyl oxygen by fluorine is a very versatile reaction which converts aldehydes and ketones to geminal difluorides and carboxylic groups to trifluoromethyl groups.

The oldest reagent used for this conversion is sulphur tetrafluoride, by means of which aldehydes and ketones give the corresponding difluorides in 35–88% yields at temperatures of 50–150°C[210] (equation 66). The reaction is catalysed by Lewis acids such as boron trifluoride[210] or by hydrogen fluoride[232,233] and even water (which generates hydrogen fluoride in contact with sulphur tetrafluoride)[232]. Equation (67) shows in a simplified manner how the reaction probably operates.



(66)



(67)

With the catalysts the reaction takes place even at room temperature[232–234]. Applications are especially abundant in steroids[11]. Quinones require high temperature even in the presence of hydrogen fluoride[235]. In chloranil both carbonyl oxygens were replaced by fluorines in 78% yield while chlorine atoms survived even at 240°C[235].

The carbonyl oxygen is replaced very easily and in good yields by fluorine by means of diethylaminosulphur trifluoride and similar reagents[214,215]. Aromatic aldehydes

were converted to benzal fluorides at 60–80°C[214], and aliphatic aldehydes and ketones to geminal difluorides at 25–85°C[214,215]. The reagent was used, among other things, for introducing fluorines in lieu of carbonyl oxygen in steroid aldehydes[236], and for converting α-ketoesters to α,α-difluoroesters[237] (equation 68). The ester group is not affected.

$$PhCOCO_2Et \xrightarrow[40-60°C]{Et_2NSF_3} PhCF_2CO_2Et \quad (92\%) \qquad \text{(Ref. 237) (68)}$$

Other reagents capable of replacing carbonyl oxygen by fluorines are phenylsulphur trifluoride at 20–200°C in up to 80% yields[238], selenium tetrafluoride in the presence of pyridine[231] (65–100% yields of geminal difluorides at the reflux temperature of the solvent trichlorotrifluoroethane), and molybdenum hexafluoride in the presence of boron trifluoride[239] (now commercially available as a solution in dichloromethane) (equation 66). Carbonyl fluoride and dimethylformamide convert carbonyl compounds to α-fluoroalkyl fluoroformates, which are decomposed by boron trifluoride etherate to geminal difluorides in fair yields[240].

Carbonyl oxygen can also be replaced by fluorines in carboxylic acids and their derivatives. The reactivity of sulphur tetrafluoride towards the oxygen-containing groups in different compounds can be ranked as follows[210]: $-C(=O)-OH > RCH=O \sim RR'C=O > -COOH \sim -CONR_2 > -COOR \sim -COOCO-$.

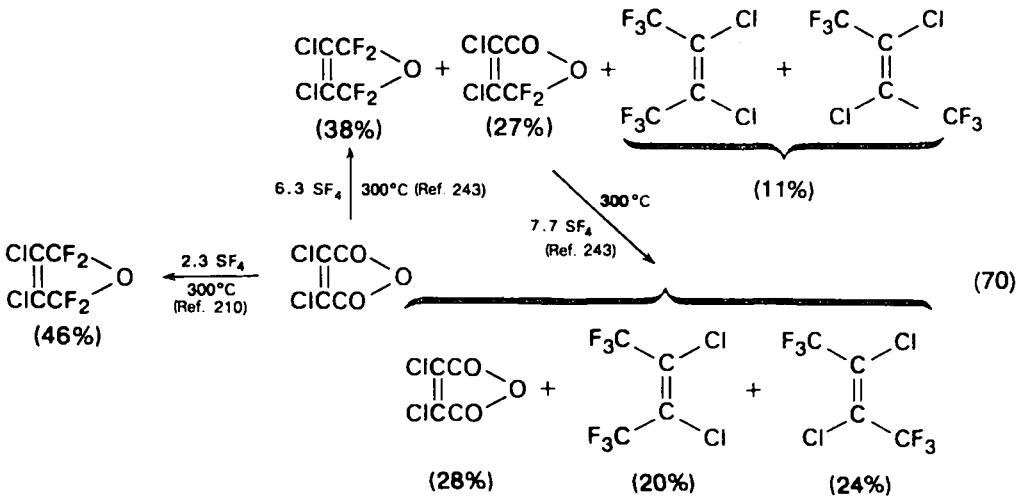
Carboxylic acids react with sulphur tetrafluoride most readily and in two stages[210,232]. First, acyl fluorides are formed, especially if only a limited amount of the reagent is used[210]. With an excess of sulphur tetrafluoride the carbonyl oxygen is also replaced by fluorine, giving trigeminal fluorides. The reaction is catalysed by boron trifluoride[210] or hydrogen fluoride[210,232] (or water[232]) and gives good to high yields even at room temperature[232] (equation 69).

$$HO_2C(CH_2)_8CO_2H \xrightarrow[120°C]{3\ mol\ SF_4} FCO(CH_2)_8COF\ (21\%) + CF_3(CH_2)_8COF\ (45\%) + CF_3(CH_2)_8CF_3\ (27\%)$$

$$\xrightarrow[120°C]{6\ mol\ SF_4} CF_3(CH_2)_8CF_3\ (87\%) \qquad \text{(Ref. 210) (69)}$$

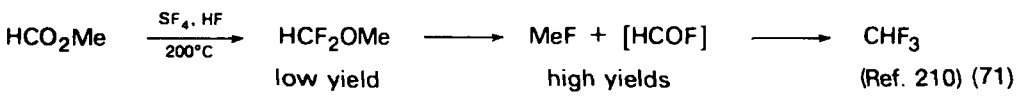
Dicarboxylic acids which easily form cyclic anhydrides give α,α,α′,α′-tetrafluoroethers[210,241]. It seems that monocarboxylic acids may form anhydrides under the reaction conditions, since tetrafluoro ethers were found as by-products in yields up to 34% even under very mild conditions (−15 to 18°C)[242]. This finding is rather surprising since anhydrides themselves require very high temperatures for fluorination[210,243] (equation 70).

Ketocarboxylic acids of the adamantane series were converted by sulphur tetrafluoride in the presence of hydrogen fluoride to adamantanes containing geminal and trigeminal fluorine groups[244]. Surprisingly, even tertiary hydrogens were replaced by fluorine, which is quite exceptional with sulphur tetrafluoride (cf. equations 23 and 84)[244].

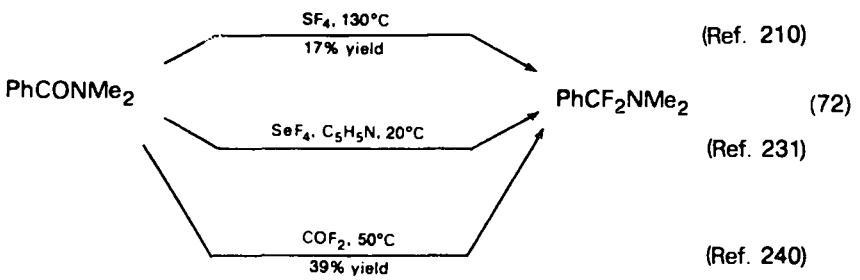


Carboxylic groups were also transformed in good yields into trifluoromethyl groups by treatment of carboxylic acids or their esters with molybdenum hexafluoride at higher temperatures (130°C)[245]. Halogen atoms in halogenated carboxylic acids were not exchanged for fluorine[245]. Other reagents, dialkylaminosulphur trifluoride[214] and selenium tetrafluoride[231], convert carboxylic acids only to their fluorides in yields up to 89%[214]. The latter reagent also formed acyl fluorides from acid anhydrides[231].

Esters of carboxylic acids are fairly resistant to sulphur tetrafluoride[210]. They are ultimately cleaved to alkyl fluorides and trifluoromethyl compounds, but only at temperatures in excess of 250°C in the absence of catalysts, at 130°C in the presence of boron trifluoride or titanium tetrafluoride, and at 200°C in the presence of hydrogen fluoride. α,α-Difluoroethers and acyl fluorides were identified as intermediates[210] (equation 71). Conversion of an ester group to a trifluoromethyl group was also achieved with molybdenum hexafluoride[245].



Amides, on the other hand, react much more readily with sulphur tetrafluoride (at 130–150°C without and at 60–100°C with boron trifluoride as the catalyst)[210]. Depending mainly on the structure of the amide, trifluoromethyl derivative, acyl fluoride, or α,α-difluoroamine are obtained in not very good yields[210]. The last mentioned product also results from the reaction of an amide with selenium tetrafluoride[231] or carbonyl fluoride[240] (equation 72).



Sulphur tetrafluoride is also used for replacing oxygen bonded to iodine[246] and phosphorus[247] by two atoms of fluorine, giving aryl iodide di- and tetrafluorides[246] and arylfluorophosphoranes[247], respectively (equations 73 and 74).

$$PhIO \xrightarrow[-20°C]{SF_4,\ CH_2Cl_2} PhIF_2 \quad (59-100\%)$$

(Ref. 246) (73)

$$PhIO_2 \xrightarrow[70\rightarrow150°C]{SF_4} PhIF_4 \quad (100\%)$$

(Ref. 247)

$$Ph_3P \xrightarrow[69\%\ yield]{SF_4,\ 50\rightarrow150°C} Ph_3PF_2 \xleftarrow[67\%\ yield]{SF_4,\ 50\rightarrow150°C} Ph_3PO \qquad (74)$$

$$Ph_3P \xleftarrow[90\%\ yield]{PhIF_4,\ Et_2O,\ 20°C} Ph_3PF_2$$

(Ref. 246)

Reactions of sulphur tetrafluoride with organic compounds are thoroughly documented in a recent review[11].

H. Replacement of Nitrogen by Fluorine

The most common and most important reaction in which fluorine displaces nitrogen is the replacement of a diazo and a diazonium group. Other reactions such as cleavage of azirines and aziridines have only limited applications.

1. *Replacement of diazo group*

The diazo group can be displaced by fluorine in some diazoalkanes and especially α-diazoketones and α-diazoesters. Thus, diazo compounds can be converted to monofluoro compounds by reaction with anhydrous hydrogen fluoride[248,249] or, more conveniently, by Olah's reagent[250] (equation 75a).

Hydrogen fluoride in the presence of *N*-halosuccinimide (NXS) converts diazo compounds to geminal fluorohalo compounds in 32–95% yields[250,251] (equation 75b).

$$RCOCHN_2 \xrightarrow{HF/C_5H_5N} RCOCH_2F \qquad (75a)$$

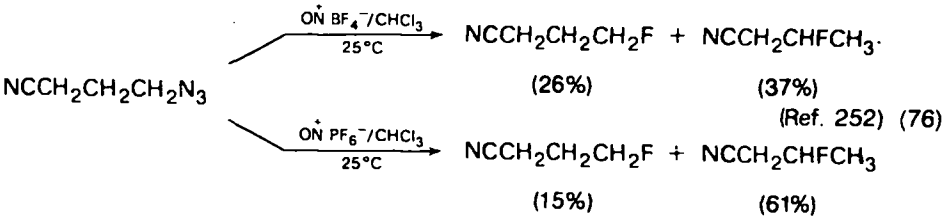
(Ref. 250)

$$RCOCHN_2 \xrightarrow[NXS]{HF/C_5H_5N} RCOCHXF \qquad (75b)$$

	Yield, %			
X	R = C_6H_5	R = cyclo-C_6H_{11}	R = C_2H_5	R = C_2H_5O
H	32	50	40	40
Cl	49	95	50	30
Br	63	38	32	50
I	62	80	80	50

2. Replacement of azido group

An interesting reaction takes place when some azides are treated with nitrosonium tetrafluoroborate or hexafluorophosphate[252] (equation 76). The highest yields of fluorides resulting from replacement of the azido group by fluorine were obtained in aliphatic α,ω-azidonitriles. Since rearrangements giving mixtures of fluoronitriles occur, carbonium ions resulting from elimination of N_2 and N_2O are believed to be intermediates[252].



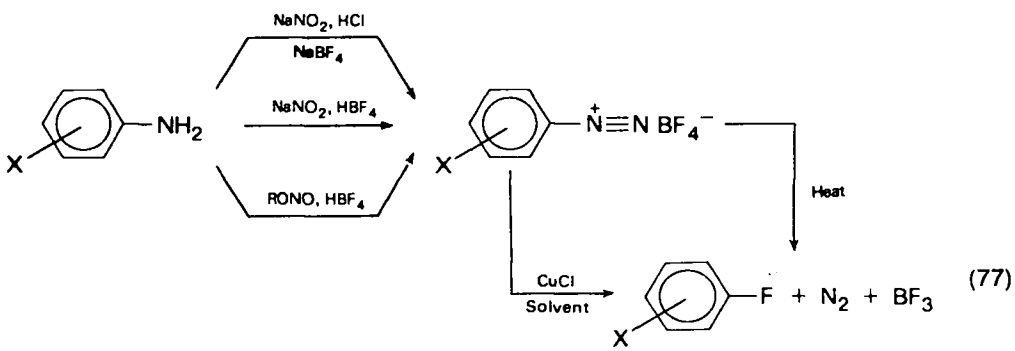
(Ref. 252) (76)

3. Replacement of diazonium group

Rare examples of replacement of transiently existing aliphatic diazonium groups are conversion of α-amino acids to α-fluoro acids in 38–98% yields[17] and conversion of alkyl carbamates to alkyl fluoroformates in 31–78% yields[17]. Both reactions were carried out with sodium nitrite in Olah's reagent (equation 47).

Replacement of amino groups in aromatic primary amines via the diazonium salts is by far the most general and most convenient method for preparing aromatic fluoro compounds. The best way of carrying out such reactions is by decomposition of arenediazonium fluoroborates prepared by diazotization of primary aromatic amines in the presence of fluoroboric acid or sodium fluoroborate. The reaction is known as the Balz–Schiemann reaction and has been thoroughly reviewed[2d,14,253].

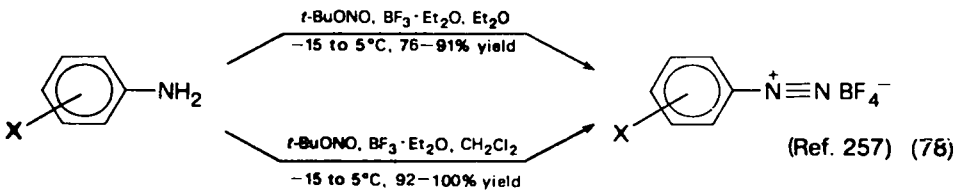
The main features of the Balz–Schiemann reaction are diazotization of the amines with alkali nitrite in a mineral acid, addition of fluoroboric acid or sodium or ammonium fluoroborate, filtration of the precipitated and sparingly soluble arenediazonium fluoroborate, and its decomposition after drying (equation 77). Diazotization can be carried out in aqueous fluoroboric acid. The decomposition is usually achieved by heating the dry arene diazonium fluoroborate to temperatures above 100°C, when nitrogen and boron trifluoride escape. The fluoro compound left as a residue is purified by steam distillation or other methods of purification. The decomposition can also be accomplished by heating the salt in a solvent.



(77)

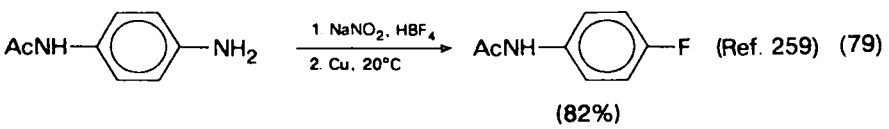
Some limitations of the Balz–Schiemann reaction are due to the structures of the aromatic amines, which affect physical properties and chemical and thermal stability of the diazonium salts.

Slightly basic amines (nitroamines which are sparingly soluble in dilute acids) may be diazotized with nitrososulphuric acid[254,255], or with alkyl nitrites in organic solvents and fluoroboric acid[256]. An elegant method giving high yields of diazonium fluoroborates is the treatment of the amine in ether, or, better still, dichloromethane, with *t*-butyl nitrite and boron trifluoride etherate[257] (equation 78). When the



X = H, Me, MeO, Br, Cl, NO_2, CO_2H

diazonium fluoroborates are too unstable to be isolated they may be decomposed *in situ* without[258] or with added catalysts[259] (equation 79).

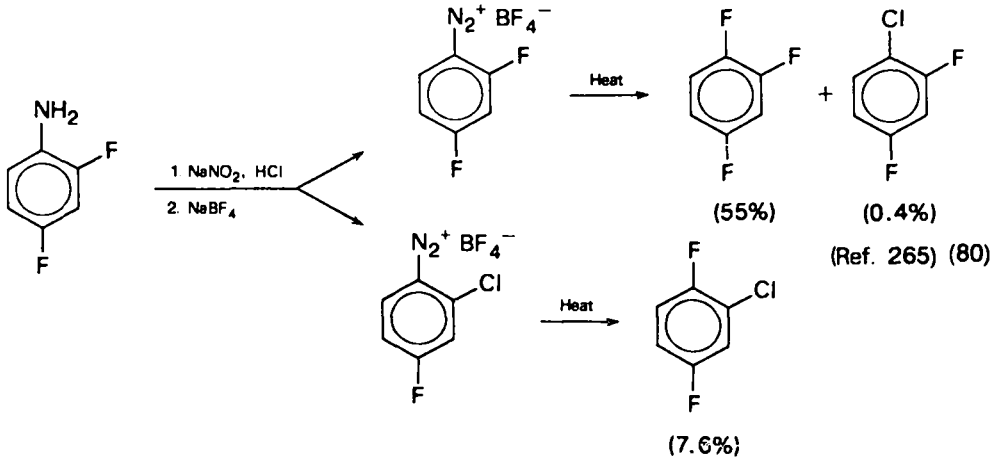


Temperature, rate of decomposition of the arenediazonium fluoroborates and yields of the fluoro compounds vary widely and depend on the structure and partly also on the purity of the salts. When tetrahydrofuran was used as a cosolvent in the precipitation of the fluoroborates, higher yields of the fluoro compounds were obtained[260].

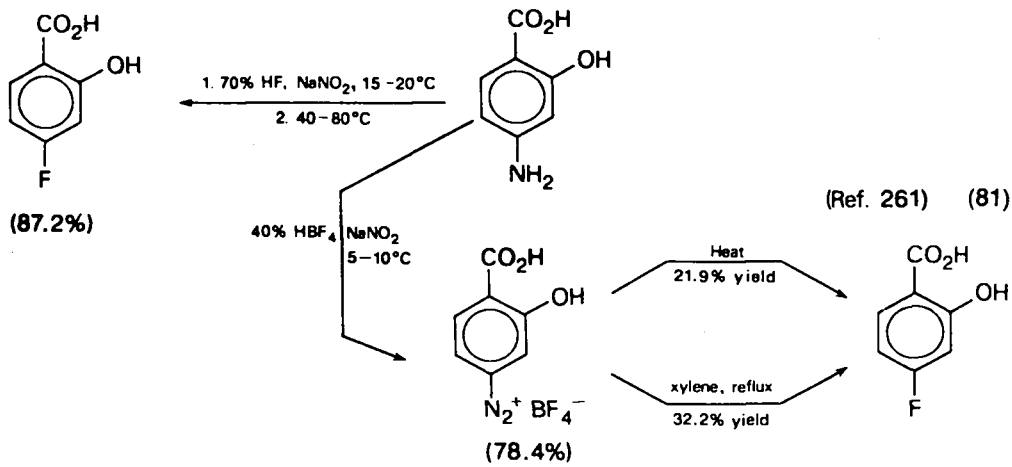
Most dry salts decompose regularly, but nitroarenediazonium fluoroborates may decompose violently. If larger quantities are to be decomposed, it is advisable to mix the salts with neutral solids such as sand or barium sulphate, or carry out the decomposition in solvents[260], sometimes even with better yields[261]. Copper or copper halides as catalysts are able to improve the yields[262]. Good results were also obtained by decomposition in solvents under ultraviolet irradiation[263,264] Such photochemical decomposition was successfully applied *in situ* for the synthesis of fluoroimidazole derivatives, which are unobtainable otherwise[264].

The yields of Balz–Schiemann reactions may be decreased by side reactions due to partial displacement of the diazonium group by the anion of the acid used in the preparation of the diazonium fluoroborates. Since the diazonium group strongly activates *ortho* and *para* substituents for nucleophilic bimolecular displacement, another displacement by the anion, usually chloride from sodium chloride coprecipitated with the diazonium tetrafluoroborate, sometimes occurs during the decomposition[254,265] (equation 80).

Decomposition of arenediazonium hexafluorophosphates[266] and bis(arenediazonium)hexafluorosilicates[267] gave better yields than the Schiemann reaction in cases where these salts are less soluble than the fluoroborates. α-Aminopyridine yielded 12–42% of α-fluoropyridine via bis(α-pyridinediazonium)hexafluorosilicate[267], and *o*-aminobenzoic acid gave 61.5% yield of *o*-fluorobenzoic acid via *o*-carboxybenzenediazonium hexafluorophosphate[266]. The respective yields of the two above compounds via the diazonium fluoroborates were 34.2 and 7.2%.

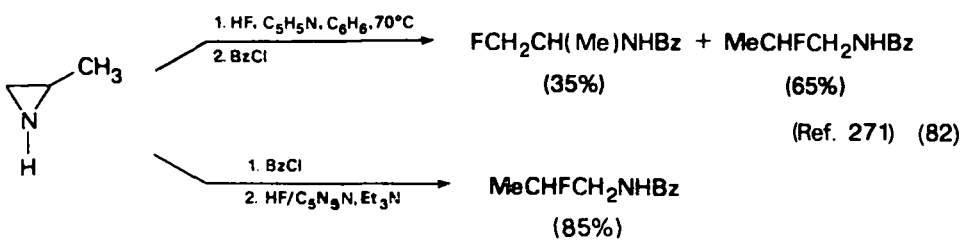


Better yields are occasionally obtained by simple diazotization of the aromatic amine in anhydrous hydrogen fluoride[268], and even in strong enough (65–70%) aqueous hydrofluoric acid[261,269] (equation 81).



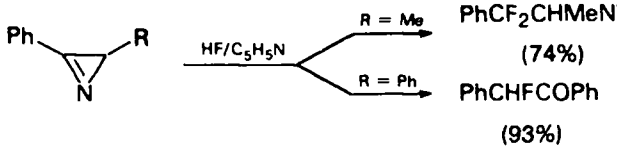
4. *Cleavage of aziridines and azirines*

Treatment of aziridines with Olah's reagent (70% hydrogen fluoride in pyridine) yields β-fluoroamines in up to 95% yields[270,271]. *N*-Acylated aziridines gave better yields and better regioselectivity than the non-substituted ones, especially when a less acidic reagent obtained by adding triethylamine was used[271] (equation 82)



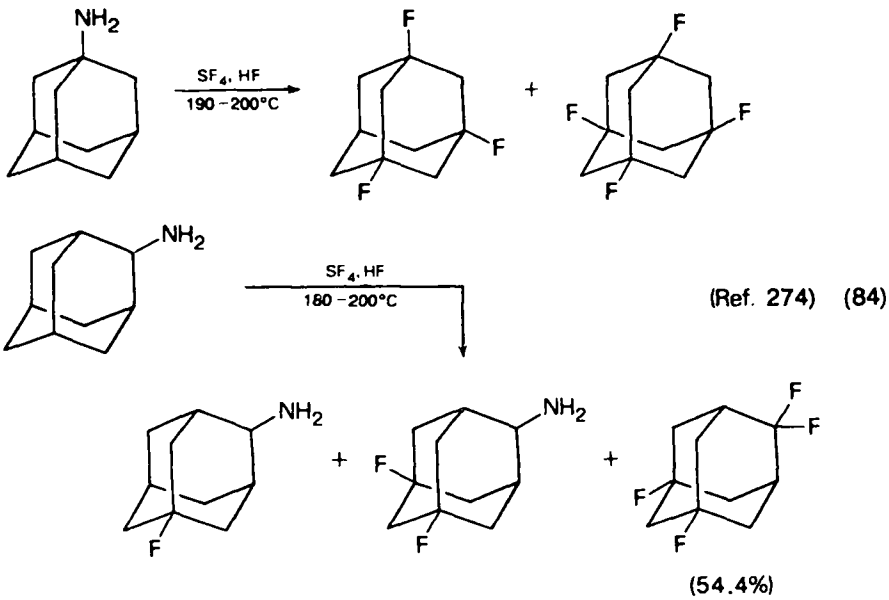
The ring cleavage is usually, but not always, regiospecific; it gives predominantly and often exclusively the isomer resulting from a transition state which can better accommodate partial positive charge. The non-stereospecific reaction of arizidines results in mixtures in which the *threo* form predominates over the *erythro* form (where applicable)[270].

Azirines treated with Olah's reagent first add 1 mol of hydrogen fluoride and then undergo ring-opening to give β,β-difluoroamino compounds, or an α-fluoroketone[272,273] (equation 83).



(Ref. 273) (83)

An unique replacement of nitrogen by fluorine took place in the reaction of aminoadamantanes with sulphur tetrafluoride and hydrogen fluoride. 1-Aminoadamantane gave a mixture of 1,3,5-trifluoro- and 1,3,5,7-tetrafluoroadamantane: 2-aminoadamantane yielded 5-fluoro-2-amino-, 5,7-difluoro-2-amino- and 2,2,5,7-tetrafluoroadamantane. The surprising replacement of tertiary hydrogens by fluorine took place before the replacement of the amino group[274] (equation 84).



(Ref. 274) (84)

I. Replacement of Other Elements by Fluorine

Replacement of a metal by fluorine takes place very easily in a reaction of perchloryl fluoride with organolithium and organomagnesium compounds[275] (equation 85).

Replacement of carbon by fluorine occurs usually as an undesirable fragmentation of the carbon–carbon chain whenever an organic compound is exposed to energetic action of elemental fluorine, an electrolytical fluorination process, or high valency metal fluorides. The cleavage of cyclopropane to 1-fluoropropane by Olah's reagent at 20°C in 75% yield has some preparative significance[17]. Anhydrous hydrogen fluoride

$$C_6H_5Li \xrightarrow[42\%\ \text{yield}]{FClO_3/THF,\ -78°C} C_6H_5F \xleftarrow[36\%\ \text{yield}]{FClO_3/THF,\ -78°C} C_6H_5MgBr \quad \text{(Ref. 275)} \quad (85)$$

at 130°C opened the ring of 1,1-dichlorocyclopropane regiospecifically and replaced one or both chlorines by fluorine, giving 25% of 1-chloro-1,1-difluoro- and 47% of 1,1,1-trifluoropropane[276].

V. APPENDIX

After this review of the formation of carbon–fluorine bonds had been completed an important survey of the most recent synthetic methods of fluorination was presented at the Fifth Winter Fluorine Conference, Daytona Beach, Florida, February 1–6, 1981.

A new reactor for fluorination of volatile organic compounds by elemental fluorine has been developed. It consists of two concentric tubes, the inner one made of porous metal or ceramics and the outer one, impervious, made of Monel metal. Fluorine diluted with nitrogen or sulphur hexafluoride diffuses slowly through the porous tube and mixes with the gaseous or vaporized organic material flowing through the outer tube. Yields of 50–80% of perfluorinated hydrocarbons, dimethyl ether, acetone, acetyl fluoride and trimethylamine were obtained[277].

Direct fluorination by fluorine diluted with helium converted organometallics with hydrocarbon ligands to perfluoroorganometallics[278].

Compounds containing only one or few fluorines per molecule were prepared by fluorination with elemental fluorine[279] or by an electrolytic fluorination process[280]. A new fluorinating agent NF_4BF_4 – tetrafluoroammonium tetrafluoroborate – prepared from fluorine, nitrogen trifluoride and boron trifluoride can add fluorine to aromatic compounds as well as replace hydrogen by fluorine in positions reactive for electrophilic attacks[281].

A survey of fluorinating agents of the sulphur fluoride family suitable for the replacement of oxygen by fluorine was given by W. J. Middleton[282]. Applications of the known diethylamino sulphur trifluoride, bis(dialkylamino) sulphur difluoride, and of trifluoromethyl hypofluorite led to a host of fluorinated pharmaceuticals, some of which with better properties than the parent compounds. A new reagent tris(dialkylamino)sulphonium difluorotrimethylsilicate $[(R_2N)_3S\ SiF_2Me_3]$ provides a very reactive fluoride ion soluble in organic solvents[282].

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FORMATION OF CARBON–CHLORINE BONDS

I. INTRODUCTION

Carbon–chlorine bonds can be formed by addition of either chlorine or chlorine-containing compounds across multiple bonds, or by replacement of hydrogen and other elements (or groups) by chlorine. Reactions resulting from additions of chlorine and carbon to multiple bonds and the formation of new carbon–carbon bonds are omitted from this review. Only the most essential and most important reactions for the introduction of chlorine into organic compounds are discussed. More detailed information should be looked for in monographs and reviews[1–4].

II. MOST COMMON CHLORINATING AGENTS

The physical properties and applications of most chlorinating agents are listed in Table 1.

Chlorine (bond dissociation energy 58 kcal mol^{-1} is a yellow-green gas stored in steel cylinders under pressure (3.8 atm at 0°C, 6.9 atm at 20°C, and 9.0 atm at 30°C). It is very toxic (0.005 mg l^{-1} is tolerable, 0.2 mg l^{-1} is dangerous, and 2.0 mg l^{-1} (2 p.p.m.) is a lethal concentration) and must be handled with proper precautions. Solubility in carbon tetrachloride is 8.5% at 19°C, in chloroform 20% at 10°C, in heptane 20% at 0°C, in acetic acid 11.6 g per 100 ml at 15°C, and in water 1 g and 0.65 g per 100 ml at 10°C and 25°C, respectively.

Chlorine adds to multiple bonds and, under irradiation, to aromatic rings. The most frequent use is in replacement of hydrogen by chlorine in practically all types of compounds. With proper precautions it is suitable for mono- as well as for polychlorinations. Less frequent applications are replacement of carboxylic groups and some other groups, and cleavage of carbon chains. Many reactions of chlorine with organic compounds require or go better with irradiation, and usually the best conditions involve the use of ultraviolet light. In such cases, quartz reaction vessels or immersion ultraviolet lamps are very useful.

Hydrogen chloride (bond dissociation energy 103 kcal mol^{-1}) is a gas available in steel cylinders. It is used for additions across multiple bonds and for replacement of hydroxyl groups in alcohols by chlorine; less frequently it is used for cleavage of epoxides, ethers and esters. It is very soluble in alcohols and ethers (35.6% and 24.9% in diethyl ether at 0°C and 20°C, respectively), in dimethylformamide (57.5% at 0°C), and in other polar solvents.

Its aqueous solution, hydrochloric acid, can be used for most of the above reactions. In addition it is used, in the presence of copper and its salts, in the decomposition of aromatic diazonium salts to aryl chlorides. Hypochlorous acid exists only in dilute solutions. An aqueous solution is prepared from its calcium or sodium salts, hypochlorites (bleach), by acidification with boric or phosphoric acid[5], or by passing chlorine into an ice-cooled suspension of sodium hydrogen carbonate in water until the solid dissolves[6]. An ether solution is obtained by ether extraction at −15°C and is unstable at room temperature[7].

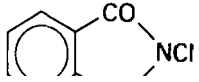
Hypochlorous acid adds chlorine and a hydroxyl group across multiple bonds. The same effect is achieved by treatment of unsaturated compounds in aqueous media with chlorine, organic hypochlorites and *N*-chloro compounds such as *N*-chlorosuccinimide (NCS) and others (*vide infra*).

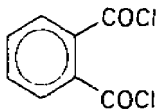
Alkaline hypochlorites, especially sodium hypochlorite, exist only in dilute aqueous solutions. Commercially available 'bleach' contains 5.25% of NaOCl. Alkaline hypochlorites are a source of 'positive' chlorine and are used for substitution of chlorine for 'acidic' hydrogen in acetylenes, in primary and secondary amines, amides and sulphonamides, and occasionally for chlorination of aromatic rings.

Tertiary butyl hypochlorite prepared by saturating a mixture of dilute sodium hydroxide and *t*-butyl alcohol with chlorine[8], or by treatment of a solution of *t*-butyl alcohol in fluorotrichloromethane with aqueous hypochlorous acid[9], adds across multiple bonds to give chlorohydrins or their ethers, replaces acidic hydrogens linked to nitrogen, and sometimes even hydrogen in aromatic rings.

Of many compounds with chlorine linked to nitrogen the most common are *N*-chloroacetamide[10] and *N*-chlorosuccinimide[11] (both commercially available); *N*-chlorophthalimide[12], *N*-chlorosaccharin[13], *N*-chloro-[14] or *N*,*N*-dichloro-*p*-toluenesulphonamide[10], *N*-chlorodialkylamine[15], *N*-chloro- and dichlorourea[16] and *N*,*N*-dichlorourethane[17] and others are employed only rarely. The common feature of the *N*-chloro compounds is their ability to add chlorine and a hydroxyl group across

TABLE 1. Most common chlorinating agents

Reagent	Molecular weight	Melting point, °C	Boiling point, °C	Density[a]	Applications: Addition	Replacement of: H	O	N	C	Hal.
Cl_2	70.91	−101	−34.6[b]	1.449/0°C	*	*			*	
HCl[c]	36.46	−114.8	−84.9[d]	1.187/−84.9°C	*		*	*		
HOCl	52.46	Only dilute solution in H_2O or Et_2O			*	*				
NaOCl	74.44	Only dilute solution in water				*				
Ca(OCl)OH	Approximate composition only									
Me_3COCl	108.56		77–78		*	*				
ClNHCONHCl	128.95	83			*	*				
Cl_2NCO_2Et	157.98	96	55–56/15	1.349	*	*				
AcNHCl	93.51	116–18			*	*				
$(CH_2CO)_2NCl$ (NCS)	133.53	149–50			*	*				
	181.57	183–5			*	*				

p-$MeC_6H_4SO_2NClNa.3H_2O$	281.69	167–170			*	*			
NOCl	65.46	−64.5	−5.5	2.99 (gas)	*	*			
NO_2Cl	81.46	<−31	5 −15 to −14	2.57 (gas)	*				
PCl_3	137.33	−112	75.5	1.574			*		
$POCl_3$	153.33	2	105.3	1.675			*		
PCl_5	208.24	178–81	Subl.	1.600			*		
$SOCl_2$	118.97	−105	78.8	1.655/10°C			*		
SO_2Cl_2	134.97	−54.1	69.1	1.667	*	*			
LiCl	42.39	614	1325–1360	2.068/25°C					*
CuCl	99.00	430	1490	4.14		*		*	
$CuCl_2$	134.44	620	993 decomp.	3.386/25°C		*		*	
$AlCl_3$	130.34	190/2.5 atm	182.7	2.44/25°C					*
$COCl_2$	98.93	−118	7.56	1.381/20°C			*		
$(COCl)_2$	126.93	−16, −10 to −8	63–64	1.478/20°C			*		
AcCl	78.50	−112	50.9	1.105			*		
BzCl	140.57	0	197.2	1.212/20°C			*		
	203.02	15–16	281.1	1.409/20°C			•		

[a] Temperatures following a solidus are those at which the density was evaluated.
[b] Critical temperature 144°C; critical pressure 76.1 atm.
[c] Aqueous HCl: concentrated, 37% (density 1.19 at 20°C); azeotropic, 20.4% (density 1.10).
[d] Critical temperature 51.4°C; critical pressure 81.6 atm.

multiple bonds (in aqueous medium), and to replace allylic and benzylic hydrogen by chlorine.

Phosphorus trichloride, oxychloride and pentachloride are used almost exclusively for replacement of hydroxyl groups in alcohols, acids and sulphonic acids by chlorine. Phosphorus pentachloride can, in addition to that, substitute chlorine for oxygen in aldehydes, ketones and amides, and occasionally for aromatic hydrogens (in pyridine).

Thionyl chloride acts similarly to phosphorus pentachloride in replacing hydroxylic and carbonyl oxygens. Sulphuryl chloride, on the other hand, accomplishes replacement of hydrogen by chlorine under free radical conditions. Compared to chlorine, it is usually more selective.

Applications of metal chlorides for chlorinations are limited to replacement of other halogens by chlorine (mainly by lithium chloride and aluminium chloride), of some hydrogens by chlorine (cupric chloride), and of aromatic diazonium groups by chlorine (cuprous and cupric chloride).

Acyl chlorides (commercially available) such as phosgene, oxalyl chloride, acetyl chloride, benzoyl chloride and phthaloyl chloride are suitable for conversion of carboxylic acids to acyl chlorides, and occasionally for replacement of carbonyl oxygen by chlorines.

Relatively new chlorinated phosphoranes such as dichlorotriphenylphosphorane (triphenylphosphorus dichloride), dichlorotriphenoxyphosphorane (triphenoxyphosphorus dichloride)[18], triphenoxybenzylphosphonium chloride[19], benzenephosphoric acid dichloride[20], and especially phosphorus pentachloride combined with carbon tetrachloride[21,22] and other organic chlorides act similarly to phosphorus pentachloride but are more selective.

III. ADDITION OF HYDROGEN CHLORIDE ACROSS MULTIPLE BONDS

Addition of hydrogen chloride to alkenes is an electrophilic reaction which occurs in a stepwise manner. First, a proton attacks that carbon which has the most hydrogen substituents (Markovnikov's rule), then chlorine joins the vicinal carbon[23] (equation 1). A better description of the regiospecific addition of hydrogen chloride is that a proton adds to the carbon with the higher electron density so as to give the more stable intermediate – a carbonium ion[24] (equation 2). The presence of peroxides does not change the direction of addition.

$$\overset{\delta-}{CH_2}=\overset{\delta+}{C}HCH_3 \xrightarrow[20°C]{HCl/FeCl_3} CH_3CHClCH_3 \qquad \text{(Ref. 23)} \quad (1)$$

$$\overset{\delta+}{CH_2}=\overset{\delta-}{C}HCF_3 \xrightarrow[20 \rightarrow 100°C]{HCl/AlCl_3} ClCH_2CH_2CF_3 \qquad \text{(Ref. 24)} \quad (2)$$

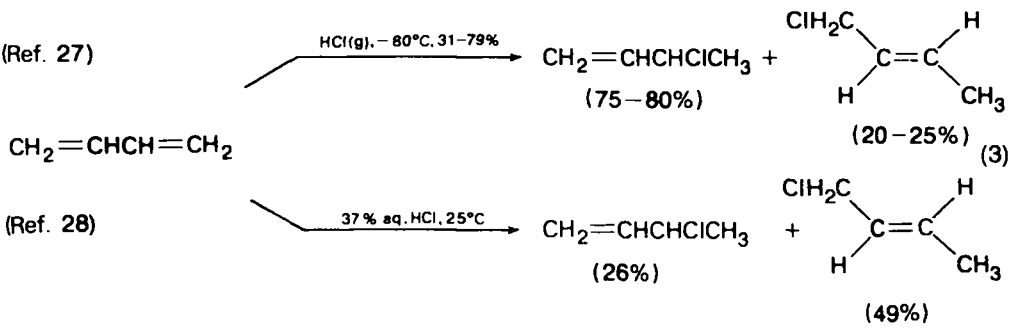
(24%)

Since carbonium ions are formed as intermediates, rearrangements occur – especially at higher temperatures. Secondary chlorides are formed in preference to primary ones, and tertiary chlorides in preference to primary or secondary ones. Classical examples are the addition of hydrogen chloride to camphene to form unrearranged 'camphene hydrochloride' together with rearranged isobornyl chloride, and the addition to pinene which forms 'pinene hydrochloride' at $-60°C$ and bornyl chloride at temperatures higher than $-10°C$ (Wagner–Meerwein rearrangement)[25].

The reaction requires gaseous hydrogen chloride (concentrated hydrochloric acid is rarely used), and frequently catalysis: aluminium chloride, ferric chloride and other strong Lewis acids are commonly used. This is especially true of the addition to

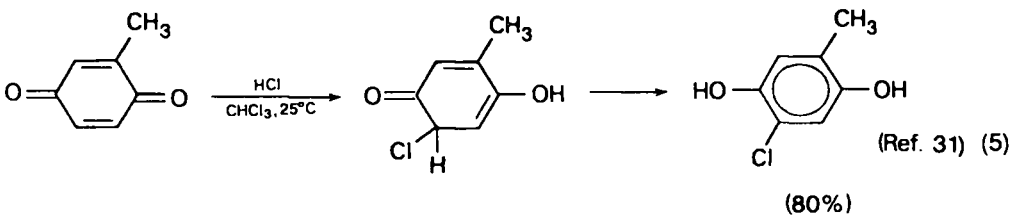
halogenated alkenes having vinylic halogens, for such haloalkenes react sluggishly. Chlorine joins the carbon having more chlorines or other halogens. Allyl chloride gives 1,2-dichloropropane (according to the Markovnikov rule)[26].

Conjugated dienes such as 1,3-butadiene usually react only with one molecule of hydrogen chloride, which adds either to the 1,2 positions to give 3-chloro-1-butene (kinetically controlled product), or to the 1,4 positions to give 1-chloro-2-butene (thermodynamically controlled product), in ratios depending on the catalyst and the temperature[27,28] (equation 3). Chloroprene (2-chloro-1,3-butadiene) gives 1,3-dichloro-2-butene by 1,4-addition in 58% yield[28] (equation 4).



When unsaturated alcohols are treated with hydrogen chloride at low temperatures addition across the double bond takes place in preference to the replacement of the hydroxyl group[29]. At higher temperatures (40–80°C) hydroxyl groups are replaced and the double bond is conserved[29] (equation 46, p. 1090).

α,β-Unsaturated aldehydes and ketones give β-chlorocarbonyl compounds under very gentle conditions in good yields (if stabilized to prevent polymerization)[30]. Quinones also react very easily. The primary product of 1,4-addition tautomerizes spontaneously to a chlorohydroquinone[31] (equation 5). Both α,β- and β,γ-unsaturated acids always give β-chloro acids.

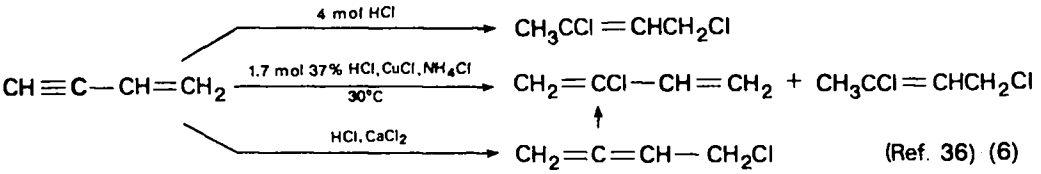


α,β-Unsaturated nitriles form β-chloronitriles with gaseous hydrogen chloride at room temperature in good yields[32]. On the other hand, addition of hydrogen chloride to the double bond of fumaric acid requires heating with hydrogen chloride in acetic acid to 100°C[33].

Addition of hydrogen chloride to a triple bond takes place in two stages. Acetylene and hydrogen chloride give either vinyl chloride or 1,1-dichloroethane, depending on the molar ratio, on the catalyst and on the reaction conditions. The best catalyst for the former product is mercuric chloride[34,35].

Vinylacetylene reacts with aqueous hydrochloric acid in the presence of a copper

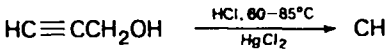
catalyst to give chloroprene and 1,3-dichloro-2-butene[36], and with calcium chloride as catalyst the major product is 4-chloro-1,2-butadiene (equation 6).



(Ref. 36) (6)

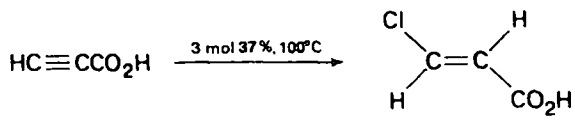
(61%)

Acetylenic alcohols and acids add hydrogen chloride to give unsaturated chlorinated derivatives[29,37] (equations 7, 8).



(Ref. 29) (7)

(75.7%)

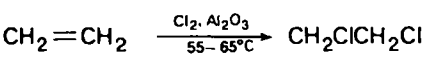


(Ref. 37) (8)

(100%)

IV. ADDITION OF CHLORINE ACROSS MULTIPLE BONDS AND TO AROMATIC SYSTEMS

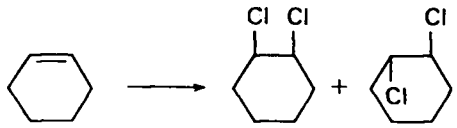
Addition of chlorine to alkenes is an exothermic reaction (30–35 kcal mol^{-1}) which takes place in the liquid and in the vapour phases. The mechanism of the addition in the liquid phase is usually ionic; in the vapour phase it is a free radical process. Liquid-phase reaction is faster and is catalysed by Lewis acids (iodine, chlorides of aluminium, iron, antimony, etc.)[38] but also by irradiation. Addition in the vapour phase has an induction period until traces of liquid are formed. It is enhanced by porous materials such as activated charcoal, alumina and silica, especially when impregnated with metal salts (equation 9). Normal stereochemistry of addition is *trans* (*anti*), but *cis* (*syn*) addition also takes place and sometimes even predominates. Because of the electrophilic nature of the addition of chlorine, electron-releasing groups increase the reaction rate, whereas electron-withdrawing groups (such as halogens) decrease it.



(Ref. 38) (9)

(94%)

The addition of chlorine to double bonds can also be effected by metal chlorides: cupric chloride adds chlorine non-stereospecifically[39,40] whereas molybdenum pentachloride[41–43] and antimony pentachloride[44] give predominantly if not exclusively[43] products of *cis* (*syn*) addition (equation 10). Addition of chlorine by means of iodobenzene dichloride was found to be both stereospecific[45] and non-stereospecific[46]. Skeletal rearrangement sometimes accompany the addition[44,45].



(10)

Reaction conditions	Yield of *syn* product, %	Yield of *anti* product, %
$SbCl_5$, CCl_4, 0–10°C[44]	44	48
$SbCl_5$, CCl_4, 76°C[44]	75	15
$MoCl_5$, CH_2Cl_2, −78°C[43]	68	<2

Addition of 1 mol of chlorine to conjugated dienes gives both 1,2- and 1,4-dichloro derivatives (equation 11)[47,48]; addition of 2 mol gives tetrachloro compounds[49].

$$CF_2{=}CF{-}CF{=}CF_2 \xrightarrow[h\nu]{0{\cdot}5\ mol\ Cl_2} \underbrace{ClCF_2CClFCF{=}CF_2 + ClCF_2CF{=}CFCClF_2}_{(61\%)} + \underset{(17\%)}{ClCF_2CFClCFClCF_2Cl} \quad \text{(Ref. 47)} \quad (11)$$

The addition of chlorine to unsaturated alcohols gives dichloro alcohols[50] under proper conditions but may be complicated by oxidation. Unsaturated ethers are converted to dichloro ethers[51].

An interesting reaction of a double bond with chlorine takes place between a trimethylsilyl enol ether and cupric or ferric chloride and gives an α-chloroketone[52] (equation 12).

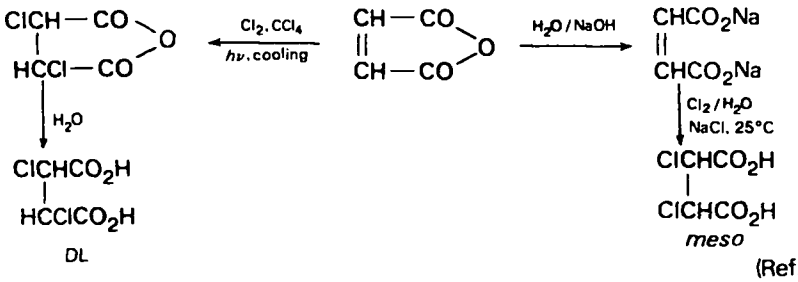
$$RCH{=}CR'{-}O{-}SiMe_3 \xrightarrow[DMF,\ 50°C]{CuCl_2\ or\ FeCl_3} \underset{(45-80\%)}{RCHClCOR'} \quad \text{(Ref. 52)} \quad (12)$$

α,β-Unsaturated aldehydes can be transformed into dichloroaldehydes or dichloroacyl chlorides[53,54] (equation 13).

$$CH_3CH{=}CHCHO \xrightarrow[\text{Ice-cooling, dark}]{Cl_2} \underset{(50.5\%)}{CH_3CHClCHClCHO} \xrightarrow[\text{Daylight, 100°C}]{Cl_2} \underset{(39\%\ \text{overall})}{CH_3CHClCHClCOCl} \quad \text{(Ref. 54)} \quad (13)$$

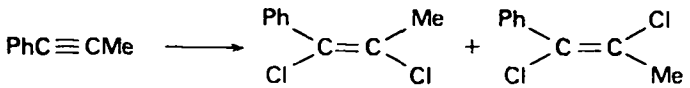
Unsaturated acids and their derivatives yield the corresponding dichloro compounds in good yields[55–57] (equation 14).

Compounds containing triple bonds react with one or two molecules of chlorine. Acetylene itself does not react with chlorine in the dark. Irradiation of the mixture may cause an explosion. Total saturation gives *sym*-tetrachloroethane, which is a base of chlorinated ethanes and ethylenes used as solvents and intermediates. The first molecule of chlorine adds *trans* (*anti*) or *cis* (*syn*) depending on reaction conditions. Chlorination with chlorine with or without catalysts results usually in *anti*-addition to give a *trans*-dichloroalkene[58]. Chlorination of acetylene with cupric chloride at 240–250°C gives 92% of *trans*- and 2% of *cis*-dichloroethylene[39].



(Ref. 56) (14)

The outcome of the chlorination of higher homologues of acetylene containing terminal and internal triple bonds depends on their structures and on the reagent used. Cupric chloride usually gives predominantly *E* isomers[59]; antimony pentachloride usually gives predominantly *Z* isomers[59] (equation 15).



(Ref. 59) (15)

Reaction conditions	Yield of *cis* product, %	Yield of *trans* product, %
$CuCl_2$, MeCN, LiCl, reflux	2	92
$SbCl_5$, $(CH_2Cl)_2$, 82°C	29	16
$SbCl_5$, $(CH_2Cl)_2$, 25°C	24	4

Chlorination of 2-pentyne and 4-octyne with a solution of molybdenum pentachloride in dichloromethane at −78°C afforded 38% and 36% of the corresponding *cis*-dichloro compounds, and less than 1% of the *trans*-dichloro compounds, respectively[43].

Reaction of chlorine with benzene and its derivatives under irradiation or in the presence of special catalysts results in addition of six atoms of chlorine to form hexachlorocyclohexane and its derivatives[60]. One of the nine possible isomers, γ-1,2,3,4,5,6-hexachlorocyclohexane, is an effective insecticide (gammexane).

V. ADDITION OF CHLORINE AND OTHER ELEMENTS OR GROUPS ACROSS MULTIPLE BONDS

Addition of chlorine and bromine to α,β-unsaturated acids and their esters was accomplished by treating them with *N*-bromosuccinimide in dilute (3 N) hydrochloric acid at −6°C. The electrophile – bromine – joined the more electron-rich α-carbon while the chloride anion went into the β-position to form α-bromo-β-chloro derivatives in 61–78.5% yields[61].

Chlorine and iodine were added to propylene by means of cupric chloride and iodine in acetonitrile at 50°C, giving 65% of 2-chloro-1-iodo- and 20% of 1-chloro-2-iodopropane[62].

Addition of chlorine and hydroxyl across double bonds produces vicinal chloroalcohols (chlorohydrins) and is accomplished most simply by treating the alkenes and other unsaturated compounds with hypochlorous acid, ready-made or prepared *in situ*[63] (equation 16). Chlorine as an electrophile combines with the carbon of higher electron density (equation 17).

Because of the intermediate formation of a chloronium ion, the addition is *trans* (*anti*). Cyclohexene and aqueous hypochlorous acid at 15–20°C gave 70–73% of

$$CH_3CH{=}CH_2 \xrightarrow{\text{aq. HOCl}} \underset{\underset{OH}{|}}{CH_3CHCH_2Cl} + CH_3CHClCH_2OH \qquad \text{(Ref. 63) (16)}$$

(95%) (5%)

$$ClCH_2CH{=}CH_2 \xrightarrow{\text{aq. HOCl}} \underset{\underset{OH}{|}}{ClCH_2CHCH_2Cl} + ClCH_2CHClCH_2OH$$

(65%) (35%)

(Ref. 63) (17)

$$HOCH_2CH{=}CH_2 \xrightarrow{\text{aq. HOCl}} \underset{\underset{OH}{|}}{HOCH_2CHCH_2Cl} + HOCH_2CHClCH_2OH$$

(25%) (75%)

trans-2-chlorocyclohexanol[64]. Instead of ready-made hypochlorous acid, chlorine in water can be used; it converts crotonaldehyde to 2-chloro-3-hydroxybutyraldehyde[65]. The concomitant formation of vicinal dichlorides can be supressed by addition of 0.1–1% of cupric chloride or ferric chloride[66]. Sodium hypochlorite was used to add chlorine and hydroxyl to the α- and β-carbons, respectively, of the double bond in cinnamic acid in 72% yield[67], and calcium hypochlorite in aqueous acetic acid converted 2-butene to 3-chloro-2-butanol in 55% yield[68].

Organic hypochlorites in acidic aqueous medium form chlorohydrins whereas in neutral medium they form chlorohydrin ethers[69] (equation 18). The latter group of compounds also result from the reaction of chlorine with the unsaturated compound in alcoholic solution.

$$\underset{\underset{OH}{|}}{PhCHCH_2Cl} \xleftarrow[H_2O,\,AcOH]{t\text{-BuOCl}} PhCH{=}CH_2 \xrightarrow[H_2O]{t\text{-BuOCl}} \underset{\underset{OCMe_3}{|}}{PhCHCH_2Cl} \qquad \text{(Ref. 69) (18)}$$

(84%) (30%)

Also, *N*-chloro compounds in aqueous media accomplish addition of chlorine and hydroxyl across double bonds. Cyclopentene and *N*-chlorourea in aqueous acetic acid afforded 52–56% of 2-chlorocyclopentanol[70].

Addition of one molecule of hypochlorous acid to acetylenes gives α-chloroaldehydes or ketones[71], while the reaction of alkynes with two molecules of the reagent yields α,α-dichloroaldehydes or -ketones[72].

VI. REPLACEMENT OF HYDROGEN BY CHLORINE

The mechanism of replacement of hydrogen by chlorine is different for the replacement of hydrogen bonded to an sp^3 carbon or to an aromatic sp^2 carbon. In the former case, the reaction takes place by a free radical chain process which is initiated by heat, by irradiation (ultraviolet light, sunlight and even diffused daylight) or by free radicals such as those derived from peroxides. It is inhibited by even minute concentrations of oxygen. Vapour-phase chlorinations of this type are frequently carried out in the presence of materials of large surface area such as activated charcoal, alumina, silica gel and others. In this way chlorine is substituted for hydrogen in

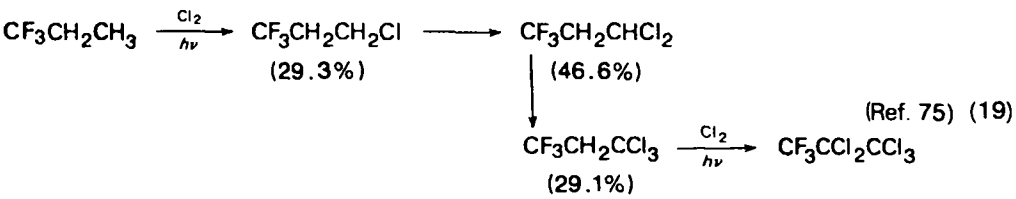
alkanes and functional derivatives with saturated chains or rings, in saturated side chains attached to aromatic rings, and in alkenes in positions α to the double bonds.

The other type of replacement of hydrogen is the substitution of chlorine for hydrogen linked directly to aromatic (homocyclic or heterocyclic) nuclei. Such a reaction is a true ionic electrophilic substitution which is catalysed by Lewis acids such as aluminium chloride, ferric chloride, antimony tri- and pentachloride, or by elements which are converted to Lewis acids *in situ* by chlorine (iron, iodine and others).

A. Replacement of Hydrogen by Chlorine in Alkanes, Cycloalkanes, Alkenes and Alkynes

Chlorination of alkanes results in the formation of monochloro- as well as polychloroalkanes. If monochloro compounds are desirable, a large excess of the hydrocarbon is necessary. Different types of hydrogens show different reactivities at different temperatures. At 300°C, the ratios of the reactivities of primary to secondary to tertiary hydrogens in the replacement by chlorine are 1:3.25:4.43[73]. Using these relative values together with the numbers of replaceable hydrogens of the individual types, an approximate distribution of the isomeric monochloroalkanes can be calculated. For example, the relative contents of propyl chloride and isopropyl chloride in the chlorination of excess propane with chlorine are, respectively, as follows: 39% and 61% at 65°C; 48% and 52% at 300°C; 58% and 42% at 550°C[73]. The calculated contents of the two isomers in chlorination at 300°C are 48% and 52%, respectively[73].

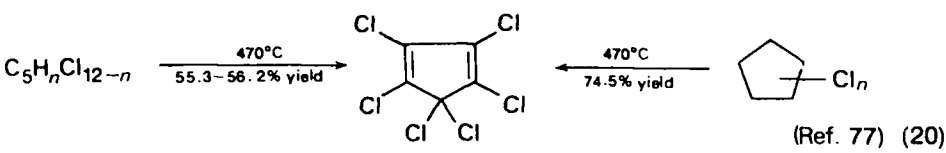
The distribution of polyhalogenated isomers is more difficult to predict. A selective reagent for predominant chlorination on the second carbon of the chain was found to be *N*-chloro-2,2,6,6-tetramethylpiperidine[74]. In chlorination of fluoroalkanes with chlorine, hydrogens on carbons adjacent to CF_2 or CF_3 groups are the most difficult to replace[75] (equation 19).



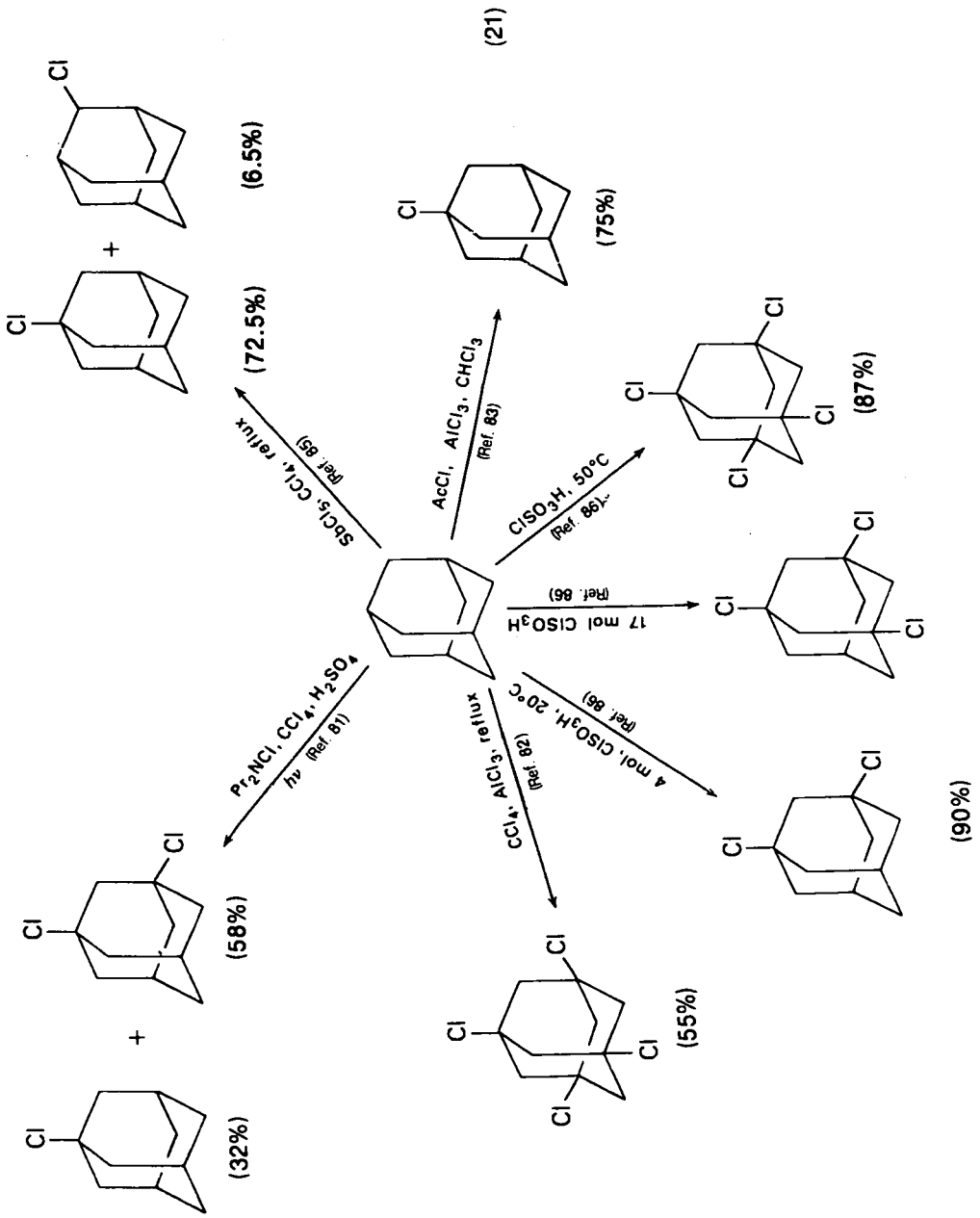
(Ref. 75) (19)

Replacement of many or all hydrogens by chlorine requires energetic conditions, strong irradiation (best with bright sunshine) or high temperatures. At temperatures around 500°C hydrogen chloride is usually eliminated in the last stages of chlorination and unsaturated stable perchloro compounds are formed: perchloro-1,3-butadiene from chlorinated butanes[76] and perchlorocyclopentadiene from chlorinated pentanes, isopentanes and cyclopentanes[77] (equation 20). Such chlorinations are accompanied by partial fragmentation to hexachloroethane, tetrachloroethylene and carbon tetrachloride.

Chlorination of cyclopropane yields different amounts of 1-chloro- and 1,3-dichloropropane depending on the reagent used: chlorine produced 15.4–47.3%



(Ref. 77) (20)

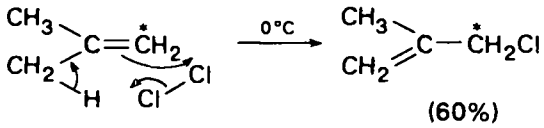

(21)
(6.5%)
(72.5%)
(75%)
(87%)
(90%)
(58%)
(32%)
(55%)
SbCl5, CCl4, reflux
(Ref. 85)
AcCl, AlCl3, CHCl3
(Ref. 83)
ClSO3H, 50°C
(Ref. 86)
17 mol ClSO3H
(Ref. 86)
4 mol. ClSO3H, 20°C
(Ref. 86)
CCl4, AlCl3, reflux
(Ref. 82)
P2NCl, CCl4, H2SO4
hν (Ref. 81)

of 1-chloropropane and 61.4–33.5% of 1,3-dichloropropane (in carbon tetrachloride), whereas *t*-butyl hypochlorite yielded 85% and 15% of the two isomers, respectively[78].

Chlorination of chlorocyclopentane and chlorocyclohexane with molybdenum pentachloride afforded high yields of almost pure *cis*-vicinal dichlorides[79] while chlorination of bromocyclopentane and bromocyclohexane with antimony pentachloride gave almost exclusively vicinal *trans*-bromochlorides[80].

Chlorination of adamantane usually gives good to high yields of monochloro- and polychloroadamantanes, depending on the reagents and conditions used[81–86] (equation 21).

Most alkenes add chlorine to the double bonds at moderate temperatures. The exceptions are isobutylene[87] and trimethylethylene, which give predominantly unsaturated derivatives with chlorine in a position α to the double bond even at temperatures below 0°C. The replacement of allylic hydrogens by chlorine takes place by an 'ene' mechanism, proven by isotope experiments and illustrated in equation (22)[88].

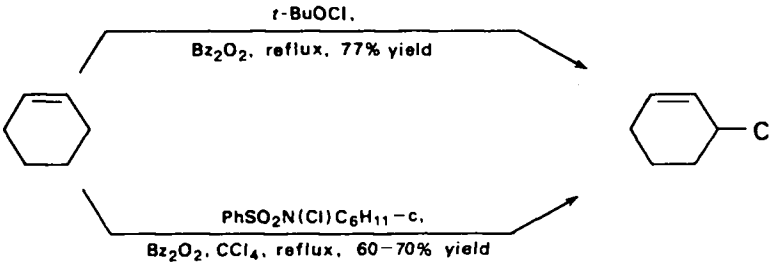


(Ref. 88) (22)

At elevated temperatures allylic substitution predominates over addition, and at temperatures above 400–500°C the substitution is almost exclusive. Propylene gave different yields of the substitution product at different temperatures as follows: 210°C, 25% yield; 400°C, 96% yield; 590°C, 99.7% yield[89]. The high temperature substitution chlorination of alkenes is a free radical process accelerated considerably by tetraethyllead and traces of oxygen (larger amounts inhibit the reaction), and enhanced by the presence of a liquid phase[90].

If there is no allylic hydrogen in the alkenes, the high temperature chlorination takes place at the double bond: ethylene is converted almost quantitatively to vinyl chloride at 300–500°C[91]. High temperature allylic chlorination is of great industrial importance for the production of monomers as well as intermediates for other products.

Replacement of hydrogen by chlorine in the allylic position is achieved not only by high temperature chlorination with elemental chlorine but also by a reaction of an alkene with *O*-chloro[92] and *N*-chloro compounds in the presence of dibenzoyl peroxide[93] (equation 23).



(Ref. 92) (23)

Alkynes and chlorine give only addition products, frequently with explosions. Replacement of the acetylenic hydrogens can be achieved only with alkali hypochlorites in the presence of excess alkalis[94]. However, when pentylacetylene was first transformed into its potassium salt by means of potassium amide the treatment with chlorine gave 1-chloro-1-heptyne in good yield[95] (equation 24). Another way of preparing 1-chloro-1-alkynes is a reaction with butylmagnesium chloride followed by treatment with sulphuryl chloride[96] (equation 24).

$$C_5H_{11}C{\equiv}CH \xrightarrow[NH_3]{KNH_2} C_5H_{11}C{\equiv}CK \xrightarrow{Cl_2} C_5H_{11}C{\equiv}CCl \quad \text{(Ref. 95)} \qquad (24)$$

$$PhC{\equiv}CH \xrightarrow[THF,\ C_6H_{14}]{BuMgCl} PhC{\equiv}CMgCl \xrightarrow{SO_2Cl_2} PhC{\equiv}CCl \quad \text{(Ref. 96)}$$

(48%)

B. Replacement of Hydrogen by Chlorine in Functional Derivatives at Saturated (sp^3) Carbons (Except Side Chains in Aromatic Systems)

Alcohols, when treated with chlorine, are first oxidized to aldehydes or ketones, and these are chlorinated to α-monochloro- and polychlorocarbonyl compounds. A classical example is chlorination of ethanol, which is first oxidized to acetaldehyde, which is subsequently acetalized with ethanol by hydrogen chloride, and the diethyl acetal is converted by a stepwise procedure up to chloral alcoholate, $CCl_3CH(OEt)_2$. Cyclohexanol is transformed by chlorine either to α-chlorocyclohexanone[97] or to 2,2,6,6-tetrachlorocyclohexanone[98] in good yields.

Ethers are chlorinated preferentially in α-positions at low temperatures (−25°C)[99]. At room temperature polychlorination on more carbons occurs, possibly as a result of elimination of hydrogen chloride followed by addition of chlorine. Tetrahydrofuran gave 2,3-dichlorotetrahydrofuran at 0–10°C in 61% yield[100]. Some ethers may explode in contact with chlorine.

Aldehydes are chlorinated in positions α to the carbonyl groups, especially in the presence of concentrated hydrochloric acid[101]. α,β-Unsaturated aldehydes are chlorinated in the γ-position; this chlorination is best carried out via the enol acetates[102].

Chlorination of enolizable ketones is an acid–base-catalysed reaction and gives exclusively α-monochloro- and α-polychloroketones. High yields are obtained if the chlorination is carried out in aqueous medium in the presence of calcium carbonate[103]. In 2-butanone, both α-carbons are chlorinated[103], copper chloride in dimethylformamide chlorinates carbon 3 preferentially[104] (equation 25).

$$CH_3COCH_2CH_3 \xrightarrow[CaCO_3,\ CaCl_2]{Cl_2,\ H_2O} CH_2ClCOCH_2CH_3 + CH_3COCHClCH_3 \quad \text{(Ref. 103)}$$

(22%) (62%)

(25)

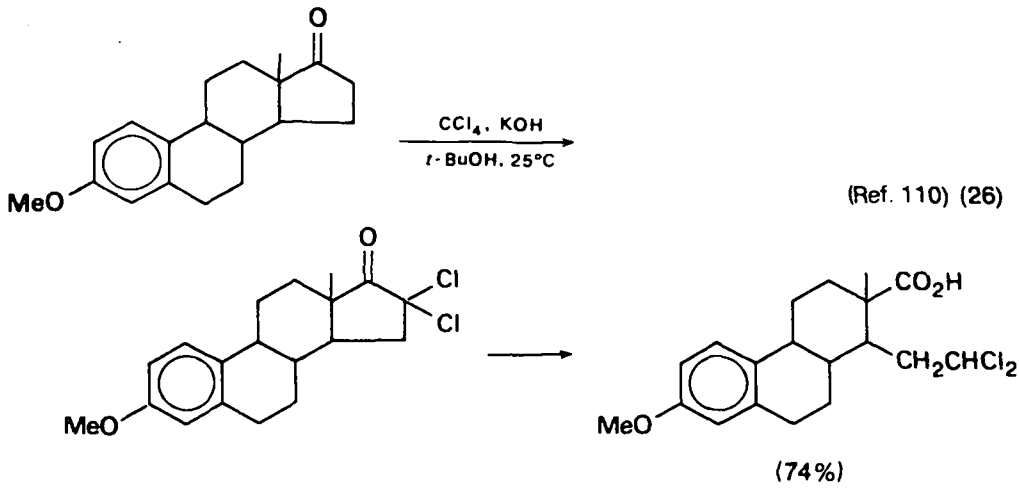
$$\xrightarrow[80-90°C]{CuCl_2,\ DMF} CH_3COCHClCH_3 \quad \text{(Ref. 104)}$$

(55–70%)

Chlorination of methyl ketones with sodium hypochlorite takes place exclusively in the methyl group. Since the reaction is carried out in an alkaline medium, cleavage to chloroform and the corresponding acid takes place – a valuable preparative method for degradation of methyl ketones to acids.

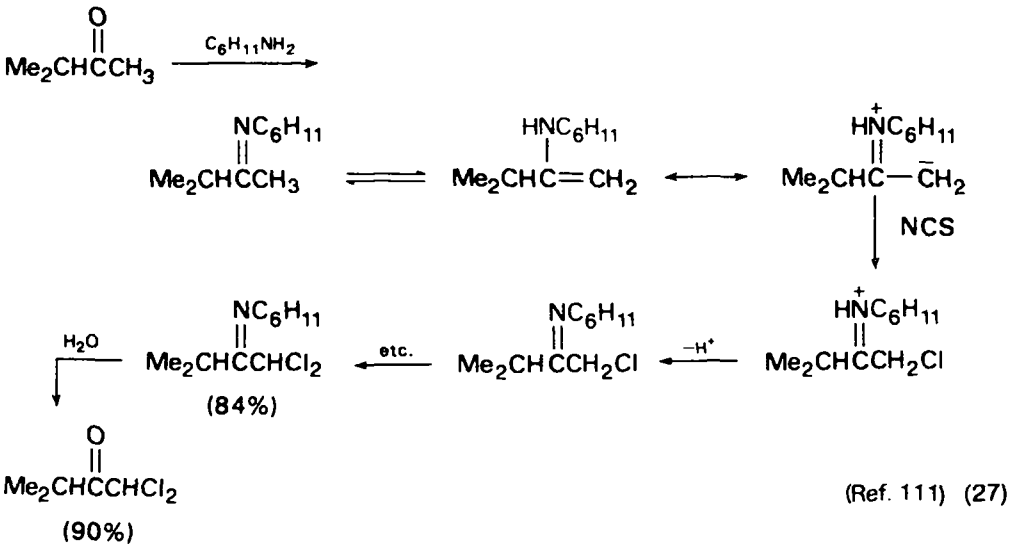
Cyclohexanone is chlorinated in water to give 61–66% yield of α-chlorocyclohexanone[105], and α-methylcyclohexanone is chlorinated with sulphuryl chloride to α-chloro-α-methylcyclohexanone in yields of 83–85%[106].

Acetophenone is chlorinated in acetic acid to give ω-monochloro-, dichloro- and trichloroacetophenone[107,108]. α-Tetralone is chlorinated to β-chloro-α-tetralone[109]. A curious 'haloform' reaction took place when a steroidal ketone was treated with carbon tetrachloride, potassium hydroxide and *t*-butyl alcohol: the α,α-dichloroketone was cleaved to give a dichloro acid[110] (equation 26).



(Ref. 110) (26)

A similar α,α-dichlorination was achieved by treatment of ketimines with *N*-chlorosuccinimide[111] (equation 27).



(Ref. 111) (27)

Carboxylic acids photochlorinated at boiling points give monochloro compounds with chlorine on almost any carbon. β-Chlorocarboxylic acids are usually most abundant[112]. Similar results were obtained in chlorination with *t*-butyl hypochlorite[113].

Predominantly α-chlorination is accomplished if phosphorus or phosphorus pentachloride is used as a catalyst[114], if the acids are chlorinated in solutions in sulphuric acid at 120–140°C[115], or if acids containing anhydrides or chlorides as catalysts are treated with cupric chloride in sulpholane at 135°C[116].

Acyl chlorides are photochlorinated in the liquid phase to give monochlorides with chlorine predominantly at the β-carbon[117]. Treatment of acyl chlorides with *N*-chlorosuccinimide at 85°C gave α-acyl chlorides in 60–87% yields[118].

Like acids and acyl chlorides, nitriles, too, are photochlorinated at all possible

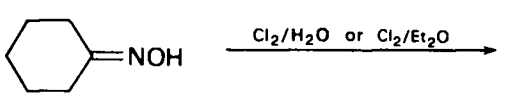
carbons, with the β-chloro derivatives most abundant[119]. Ethyl cyanoacetate was mono- and dichlorinated with sulphuryl chloride[120].

Esters of carboxylic acids are chlorinated non-selectively with chlorine when irradiated, with β-chlorination predominant[112]. α-Chlorination can be accomplished by treatment with *N*-chlorosuccinimide and dibenzoyl peroxide[121] or via carbanions using carbon tetrachloride as the chlorinating agent[122] (equation 28). Both methods give yields of 40–50% only. Chlorination of γ-butyrolactone with chlorine at 125–140°C resulted exclusively in α-chlorination in 78.5% yield[29].

$$RCH_2CO_2R' \xrightarrow[THF,\ -78°C]{i\text{-}Pr_2NLi} R\bar{C}HCO_2R' \xrightarrow[-78°C]{CCl_4} RCHClCO_2R' \quad (37-49\%) \qquad \text{(Ref. 122) (28)}$$

When oximes of aldehydes are treated with chlorine they form chloronitroso compounds which rearrange to chlorides of hydroxamic acids[123] (equation 29). Ketoximes form blue chloronitroso compounds[124] (equation 30). Chloronitrosocyclohexanone formed in this way decomposed violently or ignited spontaneously when exposed to temperatures around 30°C over a period of a few weeks[243].

$$CH_3CH{=}NOH \xrightarrow[aq.\ HCl]{Cl_2} CH_3CHClNO \quad (27.7\%) \xrightarrow[35-40°C]{Et_2O} CH_3CCl{=}NOH \qquad \text{(Ref. 123) (29)}$$



(83%) (Ref. 124) (30)

Aliphatic nitro compounds are best chlorinated in the form of their alkali salts[125], always in positions α to the nitro groups[126] (equation 31).

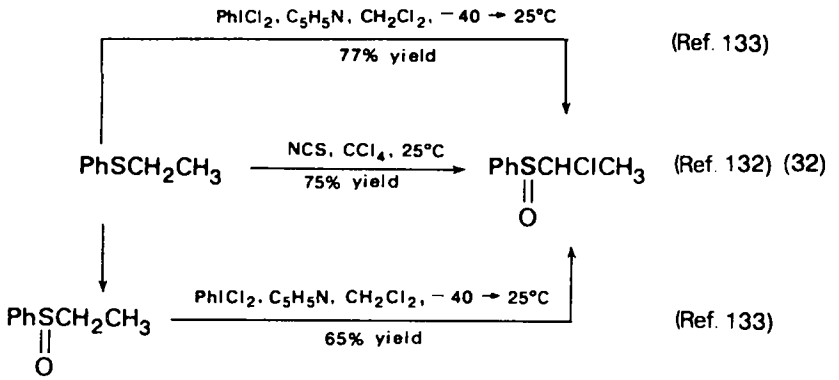
$$RCH_2NO_2 \xrightarrow[2.\ Cl_2,\ CH_2Cl_2,\ -78°C]{1.\ aq.\ KOH} RCHClNO_2 \quad (82-95\%) \qquad \text{(Ref. 126) (31)}$$

R = Me, Et, C_7H_{15}

Primary and secondary amines are chlorinated at the nitrogen atoms, giving *N*-chloro derivatives, many of which are good chlorinating agents. Aliphatic tertiary amines are chlorinated in the carbon chains, usually not in a position α to the nitrogen[127]. α-Chlorination of quinuclidine in 21% yield was accomplished by a free radical photochlorination with carbon tetrachloride[128].

In mercaptans, chlorine[129] or *N*-chlorosuccinimide[130] replaces the hydrogen on sulphur, giving alkanesulphenyl chlorides. Sulphides are chlorinated in a position α to sulphur in high yields with chlorine[131], *N*-chlorosuccinimide[132] and other chlorinating reagents[133] (equation 32). Sulphoxides are also chlorinated in α-positions with chlorine[134], sulphuryl chloride[135,136], *N*-chlorosuccinimide[134], and 1-chlorobenzotriazole[133] (equation 32). Some reagents like iodobenzene dichloride convert sulphides directly to α-chlorosulphoxides[133] (equation 32).

Hydrogen linked to carbon was replaced by chlorine in silanes[137] and siloxanes[138] using chlorine[137] or *t*-butyl hypochlorite[138].



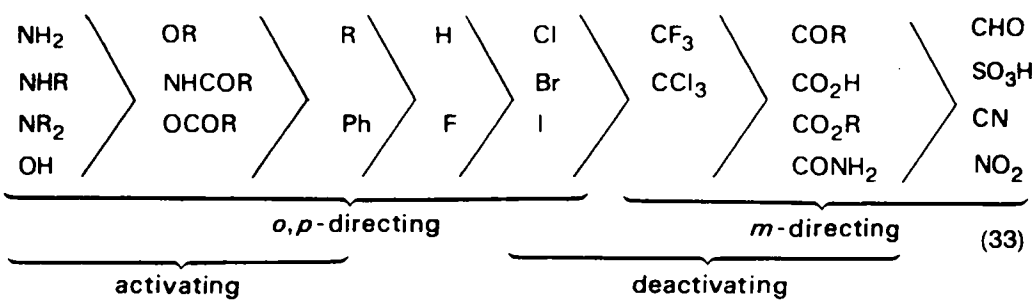
Chlorination of pentaborane in the presence of aluminium chloride gave 1-chloropentaborane (9)[139], that of decaborane gave 1- and 2-chlorodecaborane[140]. Carboranes were chlorinated to monochloro- and polychlorocarboranes by chlorine or carbon tetrachloride and aluminium chloride[141,142].

C. Replacement of Hydrogen by Chlorine in Aromatic Systems and Their Side Chains

Substitution of chlorine for hydrogen bonded to aromatic rings is an ionic reaction involving an electrophilic attack on the aromatic ring by a positive chlorine or its complexes. Free radical replacement of aromatic hydrogens occurs at high temperatures or in the presence of peroxides but has no practical value[143].

In benzene, its homologues and its derivatives, and in most aromatic systems, the reaction proceeds through a positively charged intermediate (Wheland complex) whose formation is rate determining. Because the attacking species carries a positive charge, the aromatic nuclei with electron-releasing groups enhance the reaction by inductive effects, while those with electron-withdrawing substituents make the reaction more difficult. In addition, the former increase, by resonance, electron density in *ortho* and *para* positions; the latter, with the exception of halogens, decrease the electron density in these positions so that the *meta* position becomes more reactive.

The following series illustrates the decreasing influence of substituents in the benzene ring on the electron density of the ring and its *ortho* and *para* positions:



(33)

Based on the above series it is possible to predict with fairly good accuracy the position of the predominant attack of chlorine. Halogens orient the entering chlorine into *ortho* and *para* positions but, with the possible exception of fluorine, slightly deactivate the ring. Whereas chlorination in *meta* positions usually gives highly pure

m-chloro derivative, substitution in *ortho* and *para* positions always gives a mixture with one or the other isomer predominating. The distribution between *ortho* and *para* products is affected by steric hindrance and other effects like coordination of the chlorinating agent with the substituent, which is important for *ortho* substitution.

If both activating and deactivating or less activating substituents are present in the ring, the position of the attack by chlorine is determined by the strongest activating substituent. In polynuclear aromatics where the aromatic nature of one or more rings is weak (anthracene, phenanthrene, etc.) the replacement of hydrogen by chlorine is a result of addition of chlorine followed by elimination of hydrogen chloride.

The electrophilic chlorination described above takes place in the dark and requires catalysis by Lewis acids (aluminium chloride, ferric chloride or iron, antimony chlorides, iodine, etc.), with the exceptions of very reactive compounds such as phenols, amines, polynuclear hydrocarbons and some aromatic heterocycles.

Aromatic compounds with side chains undergo another type of chlorination: side chains containing multiple bonds undergo addition of chlorine; saturated side chains undergo substitution chlorination at the sp^3 carbons. The former usually takes precedence over chlorination in the ring. The latter is a free radical process which requires heat or irradiation (or both), or peroxides, and which does not lead to ring chlorination. It is, thus, possible, by the proper choice of reaction conditions, to direct chlorine into the desired positions. Differentiation between ring and chain chlorination can also be achieved by choosing different chlorinating reagents[144–147] (equation 34).

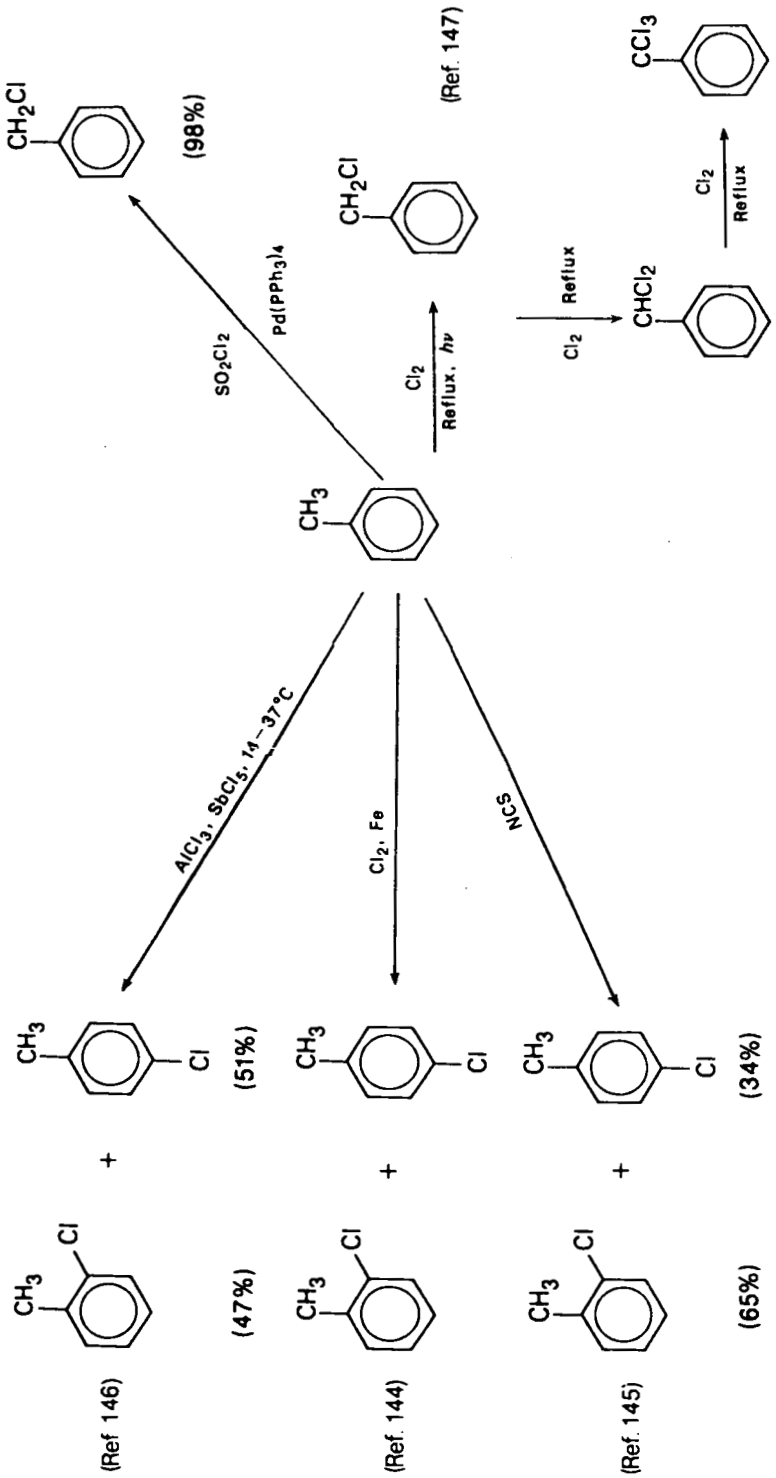
With an excess of chlorine, the proper catalyst, and sometimes harsher reaction conditions polychlorination may be accomplished up to perchloro compounds. A suitable chlorinating agent for conversion of chlorobenzenes to hexachlorobenzene is a mixture of iodine and chlorosulphonic acid[148].

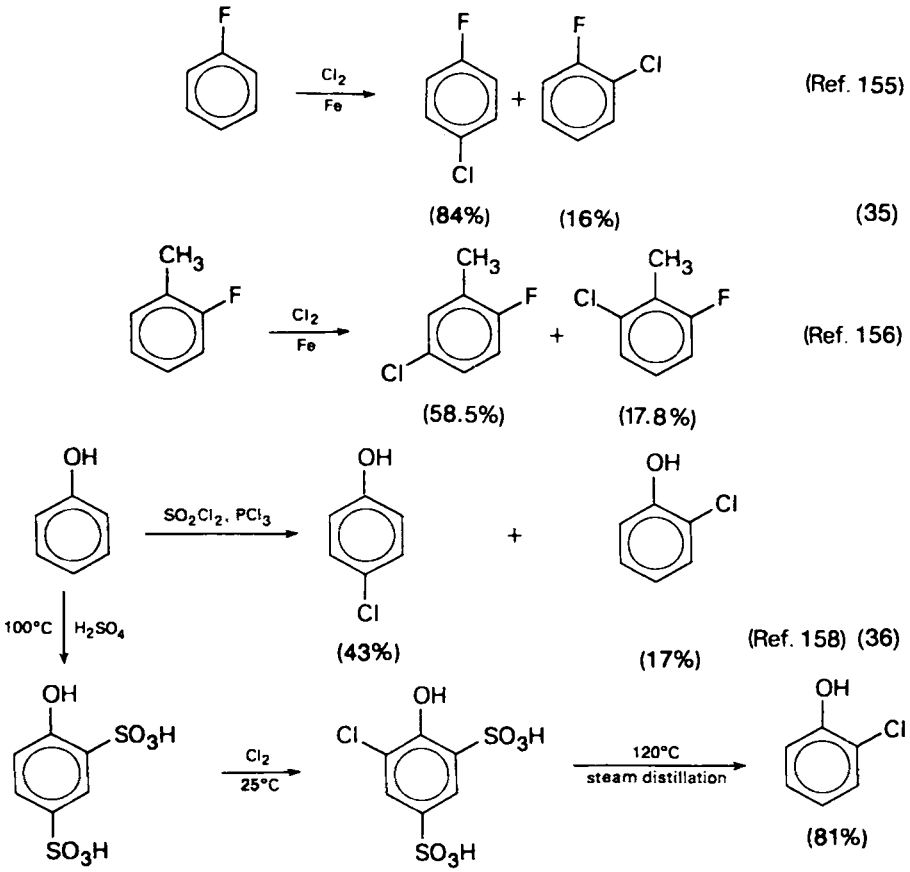
Polynuclear hydrocarbons are chlorinated more readily than benzene, sometimes even without a catalyst. Preferred positions in naphthalene are α (1-), and for dichlorination 1,4- and 1,5-. In azulene, cupric chloride chlorinates the five-membered ring in positions next to the bridgeheads[149]. Acenaphthene is chlorinated in positions 3 and 5[150] and fluorene in positions 2 and 7. The latter reactions are best carried out with *N*-chlorosuccinimide[151] or *N*,*N*-dichlorobenzenesulphonamide[152]. Both anthracene[152] and phenanthrene are chlorinated very easily in positions 9 and 10. 2,7-Dichloro-9,10-dihydrophenanthrene was obtained by chlorination with chlorine in triethyl phosphate as the solvent[153]. (This method is very useful for all halogenations since triethyl phosphate reacts with hydrogen halides and thus prevents possible side reactions[153].) Monochloropyrene was prepared by refluxing pyrene with cupric chloride in several solvents[154].

Halogenated aromatics undergo further chlorination in positions activated by the substituents, as illustrated in equations (35)[155,156].

Chlorination of phenols and phenol ethers is very easy and gives mixtures of *o*- and *p*-chloro derivatives in ratios depending mainly on the chlorinating agent. Chlorination with cupric chloride[157] and sulphuryl chloride[158] gave predominantly *p*-chloro derivatives (equation 36). Pure *o*-chlorophenol can be best prepared by first converting the phenol into phenol-2,4-disulphonic acid, chlorinating it in position 6, and hydrolysing to *o*-chlorophenol – all in one pot (equation 36).

Aromatic amines undergo oxidative side reactions unless their amino groups are protected by acylation. Chlorination of acetanilide under different conditions gives *p*-chloro- or 2,4-dichloroacetanilide either with chlorine[159] or with titanium tetrachloride in the presence of peroxy acids[160]. Complete chlorination of acetanilide results in the formation of *N*-2,4-trichloroacetanilide, itself a chlorinating agent[159]. Nitroanilines treated with *t*-butyl hypochlorite yielded monochloro or dichloro


CH2Cl
(98%)
SO2Cl2
Pd(PPh3)4
(Ref. 147)
CH2Cl
Cl2
Reflux, hv
Cl2
Reflux
CHCl2
Cl2
Reflux
CCl3
CH3
AlCl3, SbCl5, 14–37°C
Cl2, Fe
NCS
CH3
Cl
(51%)
CH3
Cl
CH3
Cl
(34%)
+
+
+
CH3
Cl
CH3
Cl
CH3
Cl
(47%)
(65%)
(Ref 146)
(Ref. 144)
(Ref. 145)



derivatives with chlorine atoms in positions *ortho* and *para* to the amino group[161].

Aromatic aldehydes react with chlorine at positions *meta* to the carbonyl group unless some activating substituents like a hydroxyl group orient the entering chlorine into other positions. Benzaldehyde thus gives 59% yield of *m*-chlorobenzaldehyde, the reaction occurring best in the presence of large amounts of aluminium chloride ('swamping catalyst')[162], while salicylaldehyde is readily chlorinated to 5-chloro-2-hydroxy- and 3,5-dichloro-2-hydroxybenzaldehyde[163]. At elevated temperatures (150–160°C) and with no catalyst present, *o*-chlorobenzaldehyde gave 70–82% of *o*-chlorobenzoyl chloride[164].

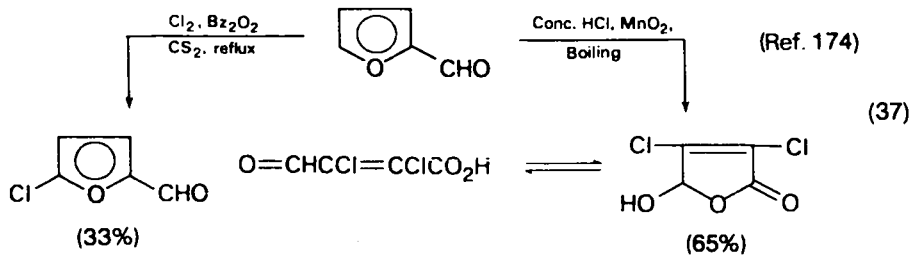
Aliphatic–aromatic ketones are chlorinated in the alkyl groups at positions α to the carbonyl. *Ortho*- and *para*-chlorinated acetophenones are prepared by Friedel–Crafts synthesis from chlorinated benzenes. *m*-Chloroacetophenone was prepared in 60% yield by chlorination of acetophenone in the presence of large amounts of aluminium chloride ('swamping catalyst')[162].

Chlorination of aromatic acids is not easy unless the ring has some activating substituents such as hydroxyl or amino groups. Benzoic acid was transformed into *m*-chlorobenzoic acid with chlorine in the presence of anhydrous ferric chloride[165], or with aqua regia[166]. Salicylic acid[167,168] and anthranilic acid[169], on the other hand, are readily converted to monochloro or dichloro derivatives in good yields. Amides of the two above acids were successfully chlorinated by *t*-butyl hypochlorite[170].

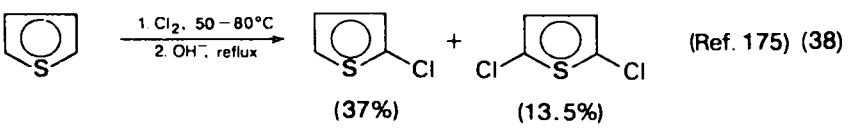
Nitrobenzene gave 50% yield of *m*-chloronitrobenzene accompanied by small amounts of 2,5-dichloronitrobenzene and *p*-chloronitrobenzene[171].

D. Replacement of Hydrogen by Chlorine in Aromatic Heterocycles

Chlorination of furan is a very delicate operation since fission of the ring by hydrogen chloride followed by polymerization takes place easily. Chlorination at −20 to −40°C in dichloromethane solution gave mainly 2-chlorofuran with smaller amounts of 2,5-dichloro- and 2,3,5-trichlorofuran[172]. 2-Furancarboxaldehyde chlorinated in the presence of dibenzoyl peroxide gave 5-chloro-2-furancarboxaldehyde[173]; under more vigorous conditions it was partly degraded to mucochloric acid[174] (equation 37).



Chlorination of thiophene gives not only substitution products but also addition products. To obtain 2-chloro- and 2,5-dichlorothiophene, chlorination must be followed by alkali treatment of the reaction mixture[175] (equation 38).



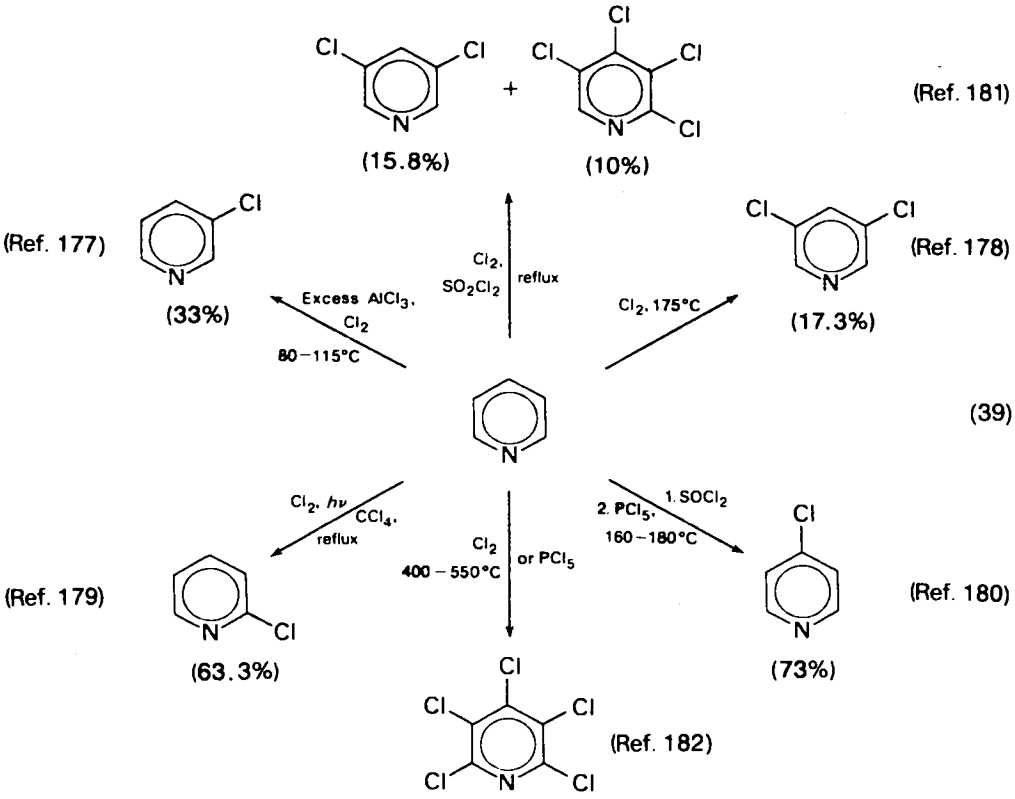
(Ref. 175) (38)

Pyrrole itself suffers polymerization and decomposition when treated with chlorine. On the other hand, pyrrole derivatives containing deactivating substituents, such as methyl 5-formylpyrrolecarboxylate or dimethyl pyrrole-2,5-dicarboxylate were converted to the corresponding 3,4-dichloro derivatives by *t*-butyl hypochlorite and sulphuryl chloride, respectively[176].

Pyridine is notorious for difficulties in its chlorination since its ring is even more strongly deactivated towards electrophilic substitution than that of nitrobenzene. Electrophilic chlorination with chlorine results in the formation of 3-chloro-[177] and 3,5-dichloropyridine[178] in not very good yields; photochlorination gives 63–78% of α-chloropyridine[179]; γ-chloropyridine is prepared by a special method[180]. Chlorine and sulphuryl chloride converts pyridine to 3,5-dichloro- and 2,3,4,5-tetrachloropyridine[181] while phosphorus pentachloride converts pyridine to pentachloropyridine[182]. These reactions are shown in equation (39).

Conversion of pyridine to pyridine oxide provides for easier chlorination, preferentially at the α- and γ-positions[183]. α-Aminopyridine undergoes easy chlorination in dilute sulphuric acid and gives 82% of 5-chloro-2-amino- and some 3,5-dichloro-2-aminopyridine[184]. Relatively easy chlorination of pyrimidine derivatives can be accomplished by heating with thionyl chloride[185].

Chlorination of indole-2-carboxylic acid with *N*,*N*-dichlorourethane gave complex mixtures of polychloro derivatives[186]. Likewise, quinoline[187] and carbazole[188,189] are polychlorinated in both rings by sulphuryl chloride.



VII. REPLACEMENT OF OXYGEN BY CHLORINE

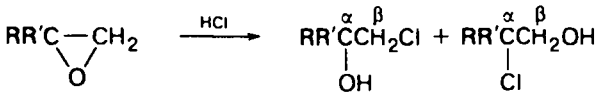
Carbon–chlorine bonds can be substituted for carbon–oxygen bonds by cleavage of ethers (epoxides) and esters (both carboxylic and sulphonic), by conversion of alcohols to alkyl halides, by conversion of carboxylic acids and sulphonic acids to acyl and sulphonyl halides, respectively, and by the replacement of carbonyl oxygen by two chlorines.

A. Cleavage of Ethers (Epoxides)

Although alkyl ethers are cleaved to alkyl chlorides by hydrogen chloride, this reaction is hardly ever of preparative value. On the other hand, cyclic ethers and especially epoxides (oxiranes) are frequently cleaved by hydrogen chloride to give chlorohydrins or other chloroalcohols.

Opening of the epoxide ring takes place by an S_N2 mechanism, i.e. a *cis*-epoxide gives a *threo*-chlorohydrin, and a *trans*-epoxide the *erythro* compound. Treatment of *cis*-epoxysuccinic acid with saturated hydrochloric acid gave 95% of *threo*-chloromalic acid[190]. The regiospecificity of the reaction is sometimes good (α,β-epoxy esters give β-chloro-α-hydroxy esters in Darzens glycidic ester synthesis[191]), but sometimes is unpredictable, as shown in equation (40)[192].

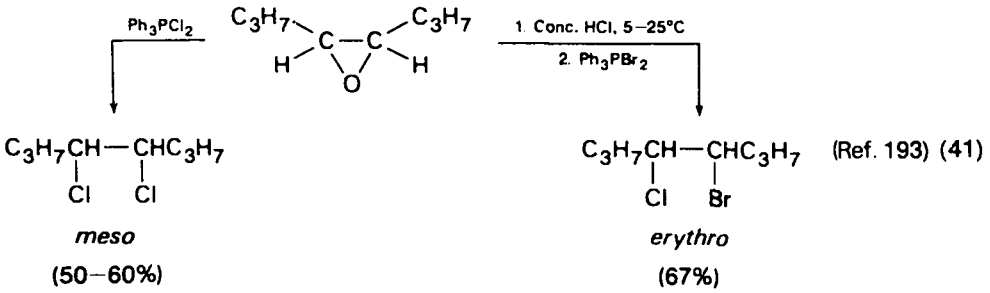
An interesting stereospecific cleavage of epoxides takes place in their reaction with triphenylphosphine dichloride (dichlorotriphenylphosphorane): *cis* epoxides give



(Ref. 192) (40)

R	R'	Yield of α-chloro-β-hydroxy compound, %	Yield of α-hydroxy-β-chloro compound, %
Me	H	75	25
Et	H	80	20
$HOCH_2$	H	90	10
$ClCH_2$	H	100	0
Me	Me	45	55

erythro (or *meso*) vicinal dichlorides; *trans* epoxides give *threo* (or D, L) vicinal dichlorides[193]. If the epoxide is subjected to successive reactions with hydrogen chloride and dibromotriphenylphosphorane, a *cis*-epoxide yields an *erythro* vicinal chlorobromo compound[193] (by a double S_N2 mechanism) (equation 41).



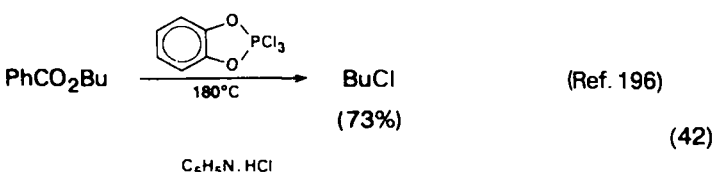
(Ref. 193) (41)

Cyclic ethers are cleaved to chloroalcohols or dichlorides, depending on the reaction conditions. Tetrahydrofuran gave 75–85% of 4-chlorobutanol with hydrogen chloride at 40°C[194]. With hydrogen chloride at 150°C or with thionyl chloride and zinc chloride at 130°C, 1,4-dichlorobutane was obtained in yields of 63% and 88%, respectively[194]. 4-Aminotetrahydropyran hydrochloride yielded 81% of 1,5-dichloro-3-aminopentane hydrochloride after heating with concentrated hydrochloric acid at 120–130°C[195].

B. Cleavage of Esters, Lactones and Sulpho Esters

Cleavage of carboxylic esters to alkyl chlorides is very rare and requires vigorous conditions. A few examples are shown in equations (42) and (43)[196–198].

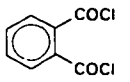
On the other hand, the acetyl group on carbon 1 in acetylated saccharides (hemiacetal-acetate group) is replaced by chlorine very easily in good yields when treated with hydrogen chloride in ether at 5°C[199].



(Ref. 196)

(42)

(Ref. 197)



$$CHClFCO_2Et \xrightarrow[ClSO_3H,\ 120-200°C]{} CHClFCOCl + C_2H_5Cl \quad \text{(Ref. 198)} \quad (43)$$

(50–88%)

Lactones are often used to prepare chloro acids or esters. β-Propiolactone is opened by sodium chloride to form β-chloropropionic acid[200]. More relevant is opening of γ-lactones with aqueous or alcoholic hydrogen chloride. Butyrolactone thus gave 77% yield of γ-chlorobutyric acid[201] and 91% of ethyl γ-chlorobutyrate[202], respectively. Butyrolactone and valerolactone yielded 76–88.5% of the corresponding γ- and δ-chloro esters by refluxing with thionyl chloride in alcohols[203], and treatment of butyrolactone with thionyl chloride and zinc chloride afforded 80% of γ-chlorobutyryl chloride[204].

p-Toluenesulphonates react with lithium chloride[205], ferric chloride[206], titanium chloride[206] or pyridinium chloride[197] to give high yields of alkyl chlorides. Since the tosylates are readily prepared from alcohols, this reaction represents an indirect method for the replacement of a hydroxyl group by chlorine.

C. Replacement of Hydroxyl by Chlorine

Substitution of chlorine for hydroxyl groups in alcohols gives alkyl chlorides; substitution in carboxylic acids and sulphonic acids gives acyl and sulphonyl chlorides, respectively.

1. Replacement of hydroxyl in alcohols

The most straightforward conversion of alcohols to alkyl chlorides takes place in the reaction of alcohols with hydrogen chloride or hydrochloric acid. Tertiary alcohols react with concentrated hydrochloric acid within minutes[207] (equation 44) while primary alcohols require heating with hydrochloric acid and calcium chloride or zinc chloride[208] (equation 44). Secondary alcohols react more slowly than tertiary ones, but considerably faster than the primary alcohols. Unsaturated alcohols and hydrochloric acid give unsaturated chlorides since hydrogen chloride does not usually add across the double bond under the conditions used. Primary allylic and benzylic alcohols react at a rate comparable to that of the secondary alcohols and give allyl and benzyl chlorides, respectively. The mechanisms are S_N2 for primary alcohols and S_N1 for the tertiary, allylic and benzylic alcohols. Primary alcohols may suffer some rearrangement, secondary alcohols usually rearrange to other secondary or tertiary chlorides, and allylic alcohols undergo allylic rearrangement to a mixture in which the most stable chloride, usually the primary one, predominates[209] (equation 45). Similar rearrangement takes place with α-hydroxyacetylenic alcohols[210].

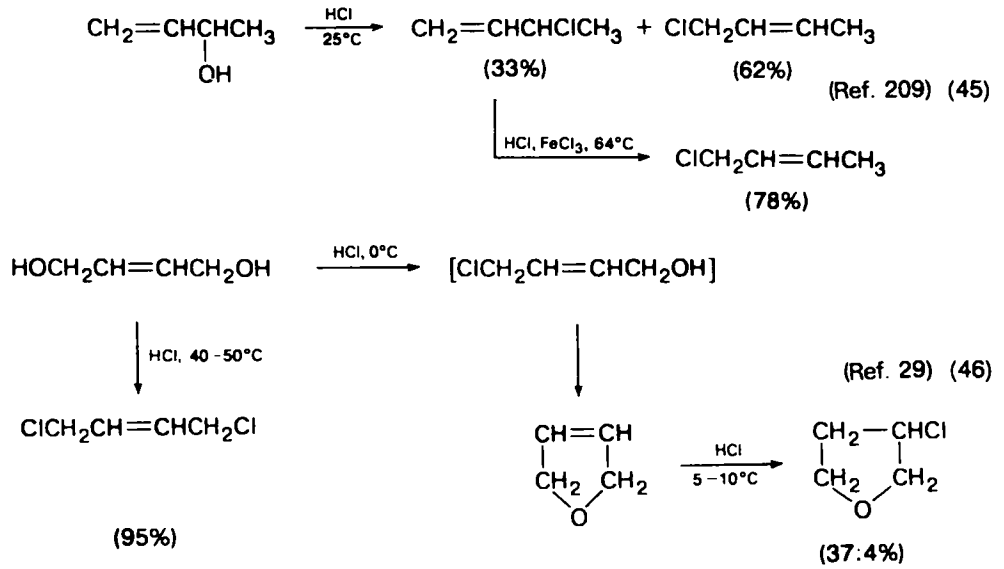
In addition to the carbonium ion-type rearrangements, chiral alcohols give chlorides with retention or inversion of configuration and/or with racemization. Polyhydric

$$(CH_3)_3COH \xrightarrow[20°C]{HCl} (CH_3)_3CCl \quad \text{(Ref. 207)} \quad (44)$$

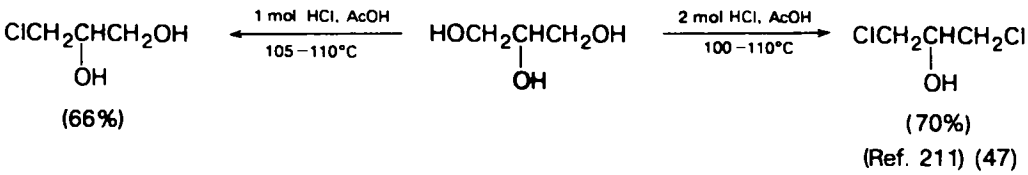
(78–88%)

$$CH_3CH_2CH_2CH_2OH \xrightarrow[ZnCl_2,\ \text{reflux, } 150-165°C]{HCl} CH_3CH_2CH_2CH_2Cl \quad \text{(Ref. 208)}$$

(76–78%)

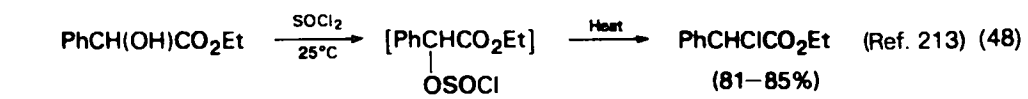


alcohols require more vigorous conditions (gaseous hydrogen chloride and higher temperature) than the monohydric ones[29,211] (equation 47).



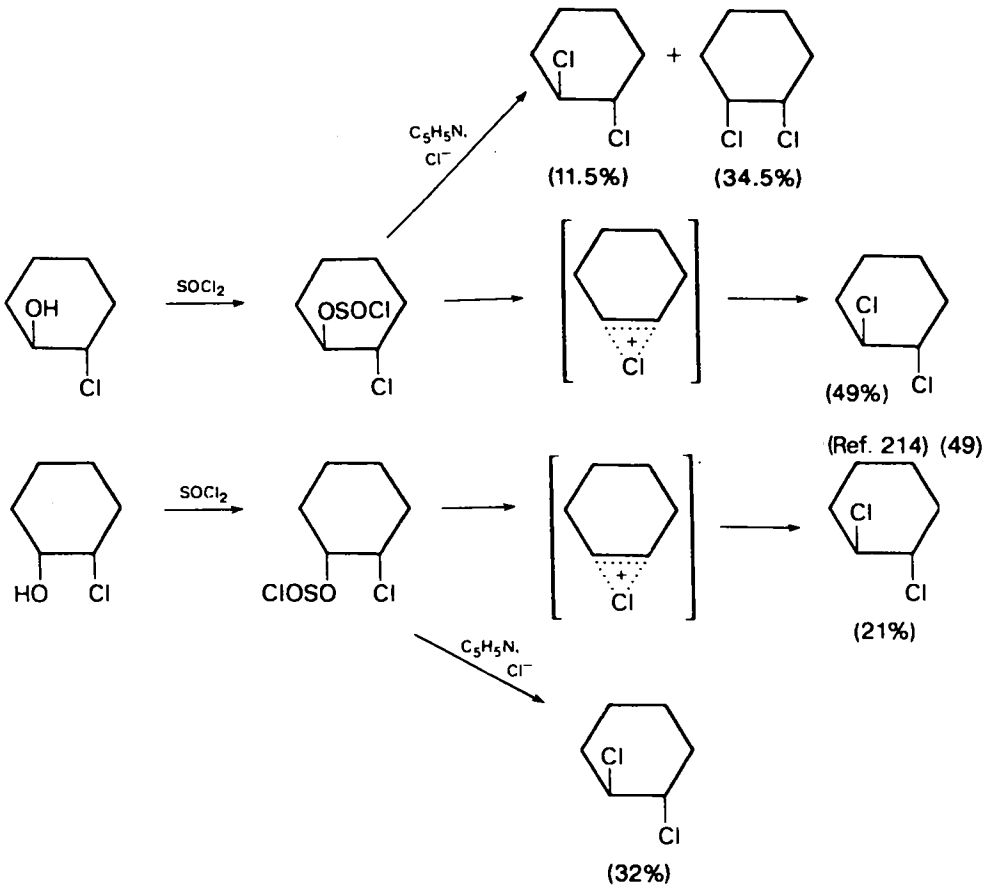
Different rates of reaction of alcohols with hydrochloric acid can be used to determine the class of alcohols by Lucas' test[212]. Lucas' reagent[212] (a 1:1 molar solution of anhydrous zinc chloride in concentrated hydrochloric acid) reacts with tertiary alcohols at 26–27°C, immediately producing turbidity and separation of a layer of tertiary chlorides. Secondary alcohols react within 5 min, and primary alcohols (except allylic and benzylic alcohols) do not react.

A very attractive method for conversion of alcohols to chlorides is the treatment with thionyl chloride[213] (equation 48). This reagent is especially suitable for the preparation of unsaturated chlorides from unsaturated alcohols[29].



The reaction proceeds via the alkyl chlorosulphinates, which are usually not isolated and which decompose on heating to alkyl chlorides and sulphur dioxide. Depending on the reaction conditions, the replacement of the hydroxyl group by chlorine can take place with retention or with inversion of configuration (in the presence of pyridine)[214]. This general statement does not hold without modifications. Whereas the reaction of thionyl chloride with *trans*-2-chlorocyclohexanol gives pure *trans*-1,2-dichlorocyclohexane in the absence of pyridine and predominantly *cis*-1,2-dichlorocyclohexane in the presence of pyridine, *cis*-2-chlorocyclohexanol

gives *trans*-1,2-dichlorocyclohexane regardless of whether thionyl chloride is used alone or with pyridine[214]. This somewhat surprising outcome may be rationalized by assuming a three-membered chloronium intermediate (equation 49).



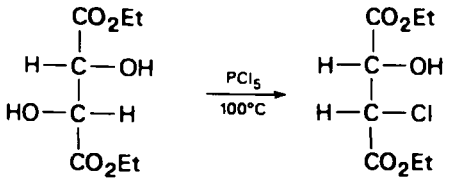
The stereochemical outcome of reaction of an alcohol with thionyl chloride also depends on the accessibility of the carbon at which the displacement takes place. In complex molecules like steroids the conformation of the hydroxyl group (axial or equatorial) affects the stereochemistry of the reaction.

Like hydrogen chloride, thionyl chloride can also give products of rearrangement[215], especially with allylic alcohols[216]. This is the case with phosphorus trichloride, too[209,216].

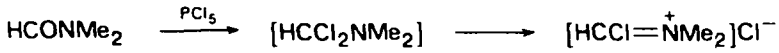
Replacement of hydroxyl groups by chlorine using phosphorus oxychloride[217] or phosphorus pentachloride was found to take place with inversion of configuration[218] (equation 50).

A reagent suitable for the replacement of hydroxyl groups by chlorine without rearrangement is cyanuric chloride[219]. Heating of an alcohol with this reagent 10–20°C below the boiling point of the mixture, filtration, and distillation of the product gave 71–92% yields of the halide.

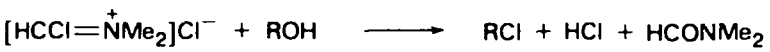
In the presence of dimethylformamide phosphorus pentachloride[220] and methanesulphonyl chloride[221] form 'Vilsmeier' reagents which convert alcohols to alkyl chlorides in good yields and with a minimum of rearrangement (equation 51).



(Ref. 218). (50)

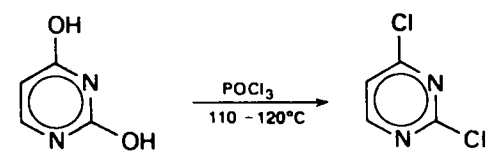


(Ref. 220) (51)

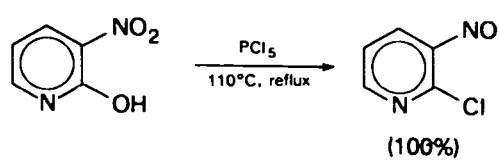


High yields (94–99%) of non-rearranged products were also obtained by treatment of alcohols with hexachloroacetone and triphenylphosphine at 0–25°C[222]. Optically active (*R*)-(−)-2-octanol was converted to (*S*)-(+)-2-chlorooctane with 81% inversion by reaction with cupric chloride and triphenylphosphine[223]. Similar inversions were obtained in reactions of alcohols with triphenylphosphine or triphenylphosphite and *N*-chlorosuccinimide or other *N*-chloro compounds (65–95% yields)[224]. Other reagents used for conversion of alcohols to alkyl chlorides are triphenylphosphite dichloride and triphenoxybenzyl phosphonium chloride[18,19].

Phenolic hydroxyl groups were replaced by chlorine only exceptionally: in tropolone in 90% yield by thionyl chloride[225], and in 3-hydroxy-2-naphthoic acid in 73% yield by phosphorus pentachloride[226]. On the other hand, hydroxyl groups in positions α or γ to nitrogen atoms in aromatic heterocycles are easily replaced by chlorine using phosphorus oxychloride[227,228] (equation 52) or phosphorus pentachloride[229] (equation 53).



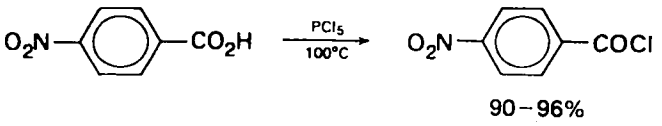
(Ref. 227) (52)



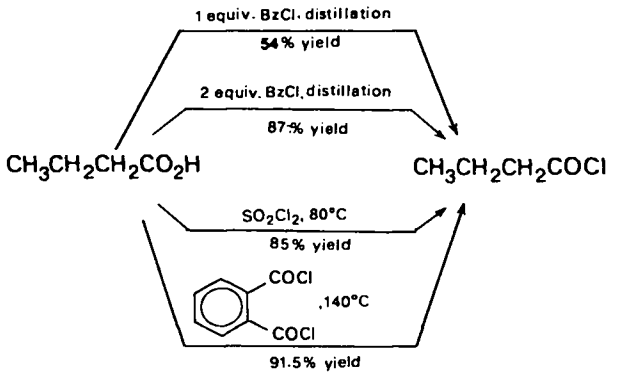
(Ref. 229) (53)

2. *Replacement of hydroxyl in carboxylic and sulphonic acids*

Conversion of carboxylic acids into acyl chlorides is usually accomplished by treatment with phosphorus pentachloride[230] (equation 54) or thionyl chloride[231] (equation 55). The choice of one reagent rather than the other is influenced by the boiling points of the products, which are best isolated by distillation. Thionyl chloride gives, as by-products, hydrogen chloride and sulphur dioxide, both gases which can be



(Ref. 230) (54)



(Ref. 232)

(Ref. 232)

(55)

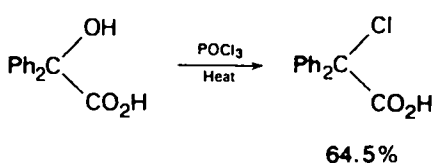
(Ref. 231)

(Ref. 233)

expelled from the reaction mixture by heating, and the product can be purified by distillation or crystallization. With phosphorus pentachloride, the by-product is phosphorus oxychloride (b.p. 106°C) which can be separated by distillation from products which boil at sufficiently different temperatures or which are non-volatile.

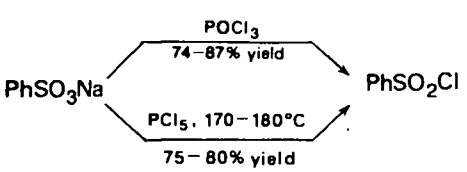
In addition to these two reagents, some acyl chlorides can effect the same conversion of carboxylic acids to acyl chlorides: i.e. benzoyl chloride[232], phthaloyl chloride[233,234], and oxalyl chloride[235] (equation 55). The choice of these reagents is dictated by the relation of their boiling points to those of the products and by-products so that the purification of the products by distillation be feasible.

Acyl chlorides can be also prepared by the reaction of phosphorus oxychloride with alkali carboxylates. The free acids do not react. This method is especially useful for conversion of hydroxyacids into hydroxyacyl chlorides. On the other hand, free hydroxyacids are converted by phosphorus oxychloride to chloroacids[236] (equation 56).



(Ref. 236) (56)

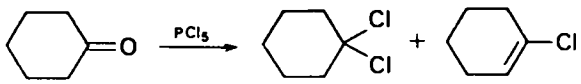
Thionyl chloride was used for transformation of sulphinic acids to sulphinyl chlorides[237]. Phosphorus pentachloride is the reagent of choice for the preparation of sulphonyl chlorides from free sulphonic acids or their alkali salts[238] (equation 57). Alkali salts of sulphonic acids are also converted to sulphonyl chlorides by the reaction with phosphorus oxychloride[238] (equation 57).



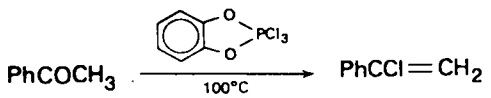
(Ref. 238) (57)

D. Replacement of Carbonyl Oxygen by Chlorine

Aldehydes and ketones react with phosphorus pentachloride[239,240] (equation 58) thionyl chloride[241] and some organic chlorides[196,242] (equation 59) to form geminal dichlorides. If there is a hydrogen atom at the neighbouring carbon, these dichlorides eliminate hydrogen chloride easily, sometimes even during the reaction itself, and afford the corresponding vinylic chlorides. This happens especially if such an elimination extends conjugation of the double bond with an aromatic ring. To prevent undesirable side reactions, the aldehyde or ketone should be added to a solution or suspension of phosphorus pentachloride in a solvent (not vice versa)[243].

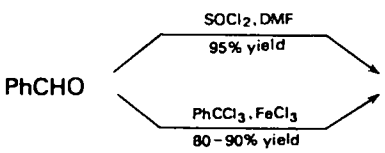


(21%) (46%) (Ref. 240) (58)



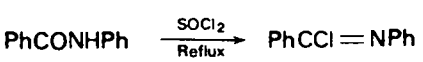
(64%) (Ref. 196) (59)

Benzaldehyde was converted to benzal chloride by treatment with thionyl chloride with a catalytic amount of dimethylformamide (pure thionyl chloride did not react). The chlorinating agent proper is probably the 'Vilsmeier' reagent $[Me_2N{=}CHOSOCl]^+Cl^-$ [241] (equation 60). Benzotrichloride in the presence of anhydrous ferric chloride was also used for replacement of carbonyl oxygen by chlorine[242] (equation 60).



(Ref. 241) (60) (Ref. 242)

Replacement of carbonyl oxygen by chlorine in amides by means of phosphorus pentachloride[244] or thionyl chloride[245] (equation 61) has considerable preparative importance. After spontaneous elimination of hydrogen chloride monosubstituted amides form imide chlorides, which can be reduced to Schiff's bases and converted to aldehydes. *N*,*N*-Dialkylamides treated with the above reagents yield via von Braun degradation alkyl chlorides[244,245] (*vide infra*).



(100%) (Ref. 245) (61)

Conversion of a carboxyl group in some acids to a trichloromethyl group by phosphorus pentachloride and thionyl chloride combined is interesting but without much practical value[246].

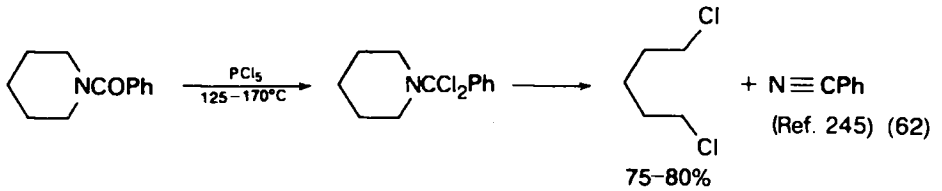
VIII. REPLACEMENT OF SULPHUR BY CHLORINE

Fairly rare examples of the replacement of sulphur by chlorine include the reaction of 2-mercaptobenzothiazole with chlorine to give 2-chlorobenzothiazole in 47% yield[247],

and the conversion of anthraquinone-α-sulphonic acid by potassium chlorate and hydrochloric acid to α-chloroanthraquinone in 87–90% yield[248].

IX. REPLACEMENT OF NITROGEN BY CHLORINE

Replacement of nitrogen by chlorine takes place in the cleavage of aziridine rings by hydrogen chloride[249] (analogous to the cleavage of epoxides), and in the cleavage of substituted amides by phosphorus pentachloride or thionyl chloride (von Braun degradation)[245] (equation 62).



(Ref. 245) (62)

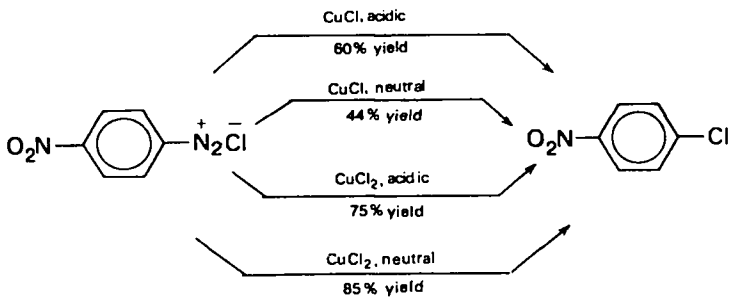
Aromatic nitro groups are replaced by chlorine at 230–250°C in dinitrobenzenes and nitrophthalic anhydrides[250].

In diazoketones, nitrogen is replaced by hydrogen and chlorine on treatment with hydrogen chloride[251,252] (equation 63) or by halogens, e.g., with bromine chloride[253].

$$PhCH_2COCHN_2 \xrightarrow{HCl} PhCH_2COCH_2Cl \quad (83-85\%)$$

(Ref. 252) (63)

By far the most important replacement of nitrogen by chlorine takes place in the reaction of aromatic diazonium salts with hydrochloric acid in the presence of copper chlorides (the Sandmeyer reaction) or copper (the Gattermann reaction). These standard procedures consisting of diazotization of aromatic amines and decomposition of the diazonium salts by heating in the presence of chloride ions provide routes to aryl chlorides with halogens in positions unsuitable for direct chlorination[254,255]. Cuprous chloride gave better yields in acidic than in neutral medium, while cupric chloride gave higher yields in neutral than in acidic medium[256] (equation 64). An elegant modification is the diazotization of amines dissolved in acetonitrile by *t*-butyl nitrite and decomposition of the diazonium salts at 65°C in the presence of cupric chloride to give 61–99% yields of aryl chlorides[257].



(Ref. 256) (64)

X. REPLACEMENT OF CARBON BY CHLORINE

Carboxyl groups can be replaced by chlorine in salts of carboxylic acids. When potassium, mercury or silver salts are treated with chlorine at elevated temperatures,

acyl hypochlorites are formed primarily and then decompose to carbon dioxide and a chloro derivatives in good to high yields (Hunsdiecker reaction)[258]. A convenient way of carrying out this reaction is to bubble chlorine into a suspension of the silver carboxylate in carbon tetrachloride or trichloroethylene. The method is especially suitable for the preparation of perfluoroalkyl chlorides[259,260] (equation 65).

$$C_5F_{11}CO_2Ag \xrightarrow{Cl_2} [C_5F_{11}COOCl] \xrightarrow{50\text{–}100^\circ C} C_5F_{11}Cl \quad \text{(71.2\%)} \qquad \text{(Ref. 260)(65)}$$

A modification which bypasses the use of elemental chlorine is based on a reaction of carboxylic acids with lead tetraacetate and lithium chloride and gives yields of 92–100% with aliphatic and alicyclic acids[261].

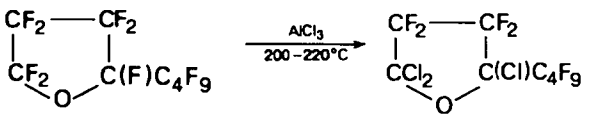
Another example of replacement of carbon by chlorine is chlorinolysis – an intensive chlorination accompanied by a breakdown of a carbon chain. The reaction requires temperatures of 300–500°C and the end-products are stable perchloro compounds[76,77,262]: carbon tetrachloride, hexachloroethane, tetrachloroethylene, hexachloro-1,3-butadiene and hexachlorocyclopentadiene (equation 66).

$$CH_3CCl{=}CHCH_2Cl \xrightarrow[475^\circ C]{Cl_2} CCl_2{=}CCl{-}CCl{=}CCl_2 + C_2Cl_6 \quad \text{(76.5\%)} \qquad \text{(Ref. 262) (66)}$$

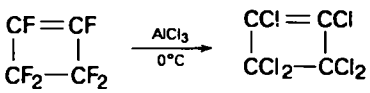
XI. REPLACEMENT OF HALOGENS BY CHLORINE

Substitution of chlorine for other halogens in organic compounds is hardly ever a preparative method. It is usually an undesirable side reaction. But if there is a necessity to replace halogens by chlorine, then lithium chloride can be used to convert bromides to chlorides in refluxing acetone[263] or in dimethylformamide at 100°C. For example, 5-chlorofural was obtained from 5-bromofural in 74% yield[264].

Aluminium chloride replaced fluorine atoms α to oxygen in perfluoro ethers at 200–220°C[265] (equation 67) and all fluorine atoms in hexafluorocyclobutene at 0°C[266] (equation 68).



(51%) (Ref. 265) (67)



(77%) (Ref. 266) (68)

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FORMATION OF CARBON–BROMINE BONDS

I. INTRODUCTION

Reactions of organic compounds with bromine resemble those of chlorine fairly closely[1–3]. However, distinct differences are due to the different thermochemistry of the two elements. The bond dissociation energy of bromine (46 kcal mol^{-1}) is lower by 12 kcal mol^{-1} than that of chlorine. Addition of bromine across double bonds is less exothermic than that of chlorine ($\Delta H = -22.5$ kcal mol^{-1} compared to -35.8 kcal mol^{-1}), replacement of hydrogen by bromine is accompanied by heat evolution of only 8.5 kcal mol^{-1} (-25 kcal mol^{-1} for chlorine), and the activation energy of this reaction is 18 kcal mol^{-1} (4 kcal mol^{-1} for chlorine).

Reactions of bromine with organic compounds are, therefore, less energetic, slower, and more selective than those of chlorine. While chlorine dominates industrial chemistry because it is cheaper than bromine, bromine's domain is the laboratory since liquid bromine is handled more conveniently than gaseous chlorine (it is easier to release a frozen stopper of a bottle of bromine than to release a frozen valve of a tank of chlorine). Moreover, brominated compounds are on the average 50–260 times as reactive in many reactions as the corresponding chlorinated derivatives, which is an advantage since the halogen compounds are usually intermediates for further synthetic reactions.

II. MOST COMMON BROMINATING AGENTS

Bromine is a heavy brown liquid, boiling at 58.8°C and having a relative density of 3.12 at 20°C. Its solubility in water at 20°C is 3.5% (bromine water). It is immiscible with phosphoric and sulphuric acid. Sulphuric acid is used for drying bromine. The critical temperature of bromine is 315°C and its critical pressure is 102 atm. It is extremely corrosive to metals, eats up cork stoppers, and damages rubber stoppers and rubber and plasticized poly(vinyl chloride) tubing. It is extremely toxic and irritates mucous membranes in the eyes and nose even in small concentrations. Handling (measuring, weighing, transfer) should be done under hoods.

Bromine adds avidly across double and triple bonds and replaces hydrogen on sp^3 carbon by a free radical process and on aromatic carbon by an ionic process. It also replaces carboxylic groups and some other elements or groups.

Hydrogen bromide (bond dissociation energy 88 kcal mol^{-1}) is a colourless gas, available in steel cylinders. Its boiling point is -66.8°C, its critical temperature is 89.8°C and its critical pressure is 84.5 atm. It dissolves in acetic acid (41% at 11°C) and in water. Aqueous hydrogen bromide – hydrobromic acid – contains 69% of hydrogen bromide when saturated at 0°C and 66.6% at 25°C. Azeotropic hydrobromic acid contains 47.8% of hydrogen bromide and boils at 126°C.

Hydrogen bromide adds to multiple bonds, replaces hydroxylic groups in alcohols by bromine, and cleaves ethers and esters to form bromo derivatives. Replacement of a diazonium group is usually carried out by hydrobromic acid and requires catalysis by copper or its compounds.

Hypobromous acid is obtained by treatment of 'bromine water' with mercuric oxide[4] or silver phosphate[5] to remove hydrogen bromide present in the mixture. It is used for adding bromine and hydroxyl groups across multiple bonds, and for bromination of aromatic compounds in the rings.

Alkali hypobromites are prepared in dilute aqueous solutions by adding bromine to cooled solutions of sodium or potassium hydroxides at 0°C[6,7]. Their applications are in replacement of acetylenic hydrogen by bromine and in bromination of ketones and aromatic rings.

Alkyl hypobromites are obtained by treating a solution of bromine in alcohols with calcium carbonate and silver nitrate[8]. Acyl hypobromites are obtained by treatment of

silver carboxylates with bromine[9]. They are used to add bromine and the rest of the molecule to double bonds and to substitute bromine for hydrogen in aromatic rings.

Iodine bromide, commercially available or prepared by adding a slight excess of bromine to iodine and evaporating the bromine after the reaction[10], is a good source of bromine cation suitable for addition to multiple bonds and for the replacement of aromatic hydrogens.

N-Bromo compounds result from the action of bromine on amides or imides. Some of them, such as *N*-bromoacetamide[11] and *N*-bromosuccinimide[12], are commercially available. They tend to decompose and liberate bromine at room temperature and are best stored in refrigerators. A general laboratory procedure for their preparation is the treatment of the parent compounds with bromine in the presence of alkali hydroxides or metal oxides. In this way, the above two compounds were prepared, as were 1,3-dibromohydantoin[13], 1,3-dibromo-2,4,5-imidazolidinetrione[13], *N*-bromophthalimide[14] and *N*,*N*-dibromobenzenesulphonamide[15].

Numerous reactions can be accomplished by *N*-bromo compounds under various conditions: addition of bromine and hydroxyl across multiple bonds (in aqueous medium) and substitution of bromine for hydrogen in reactive aromatic compounds, in positions α to double bonds and aromatic rings, and in positions α to carbonyl groups.

Phosphorus tribromide (liquid) and phosphorus pentabromide (solid) are commercially available and are used for the replacement of alcoholic hydroxyl groups by bromine. The latter compound also substitutes bromine for hydroxyl groups in acids and oxygen in carbonyl groups. Organic derivatives of pentavalent phosphorus, such as triphenoxyphosphorus dibromide, prepared from triphenyl phosphite and bromine[16], and other compounds[17], are used for replacement of hydroxyl groups by bromine in sensitive compounds, such as unsaturated alcohols.

Mild brominating agents used for the bromination of sensitive compounds such as unsaturated alcohols and reactive aromatic and heterocyclic systems include dioxane dibromide, $C_4H_8O_2Br_2$, which is prepared by adding an equimolecular amount of bromine to dioxane[18], and pyridinium perbromide, $C_5H_5\overset{+}{N}HB\bar{r}_3$, which is prepared by mixing equimolecular solutions of bromine in acetic acid with pyridinium bromide in the same solvent[19]. 'Tribromphenolbrom' (2,4,4,6-tetrabromo-2,5-cyclohexadiene-1-one) is a selective agent for bromination of aromatic amines in *para* positions[20], as is cupric bromide for α-bromination of carbonyl compounds. Metathetical halogen exchange is accomplished by calcium bromide and aluminium bromide.

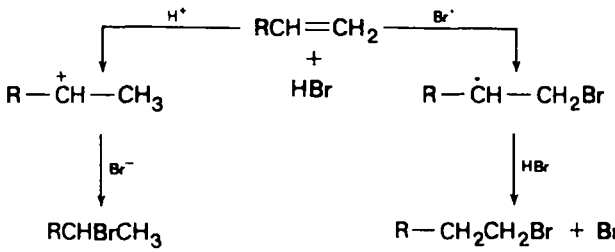
Most important physical properties and applications of the most common brominating agents are listed in Table 1.

III. ADDITION OF HYDROGEN BROMIDE ACROSS MULTIPLE BONDS

Addition of hydrogen bromide across double and triple bonds is a very complicated reaction, and its outcome depends on many factors. The addition of hydrogen chloride takes place via the ionic addition of a proton to the carbon of higher electron density, according to Markovnikov's rule. Hydrogen bromide, on the other hand, may react in the same way (route A), or else via a free radical mechanism which results in just the opposite direction of addition – anti-Markovnikov (route B) (equation 1).

The interpretation of the duality of the mechanism is as follows. In route A the attacking species is a proton which joins the carbon to produce the more stable carbonium ion; in route B the attacking species is a bromine atom (radical) which joins the carbon to produce the more stable free radical, which then reacts with a molecule of hydrogen bromide and generates a bromine radical which perpetuates the reaction. Mechanism A is favoured by Lewis acid catalysts, by polar solvents and by high

Route A Route B

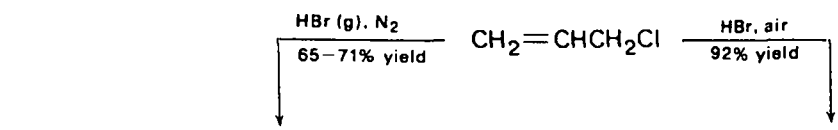


(1)

concentrations; mechanism B is enhanced by irradiation, by low concentrations in non-polar solvents, and especially by peroxides. In the latter case, peroxides may be present in the unsaturated substrate since olefins frequently form peroxides in contact with air, especially when exposed to light; or they may be added on purpose (dibenzoyl peroxide, ascaridole (1,4-peroxido-*p*-menth-2-ene) and others) if the free radical addition is desirable. On the other hand, if the free radical reaction of an olefin with hydrogen peroxide is undesirable, care must be taken to remove peroxides which might be present in the olefin, or to suppress their effect by adding antioxidants such as hydroquinone and thiophenols, and to avoid access of air to the reaction mixture. A few examples (equations 2–4) show the results of the addition of hydrogen bromide under different conditions[21–23].

$$C_3H_7CHBrCH_3 \xleftarrow{HBr,\ AcOH} C_3H_7CH{=}CH_2 \xrightarrow[Ascaridole]{HBr,\ C_5H_{12}} C_3H_7CH_2CH_2Br \quad (2)$$

(84%) (81%) (Ref. 21)



(Ref. 22) (3)

(90%) (10%)

$$CF_2BrCH_2CH_3 \xleftarrow[20°C]{HBr,\ AlBr_3} CF_2{=}CHCH_3 \xrightarrow{HBr,\ h\nu} CHF_2CHBrCH_3$$

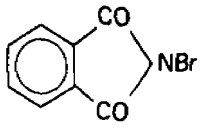
(53%) (93%) (Ref. 23) (4)

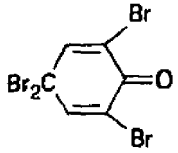
The difference in the results of the addition of hydrogen bromide across multiple bonds is referred to as the 'peroxide effect' and is unique to hydrogen bromide. Neither hydrogen chloride nor hydrogen iodide are subject to the effects of peroxides on the regiospecificity of the addition.

Addition of hydrogen bromide to 1,3-butadiene gives a mixture in which the product of 1,4-addition (1-bromo-2-butene) predominates strongly over that of 1,2-addition (3-bromo-1-butene)[24]. The composition of the mixture of both isomers is affected by the presence or absence of peroxides[24] (equation 5).

Additions of hydrogen bromide to unsaturated alcohols are complicated by concomitant replacement of the hydroxyl group, and additions to unsaturated ethers by cleavage of the ether bond. In the reactions of hydrogen bromide with α,β-unsaturated aldehydes, ketones, and acids and their derivatives, bromine is bonded almost exclusively to the β-carbon[25,26].

TABLE 1. Most common brominating agents

Reagent	Molecular weight	Melting point, °C	Boiling point, °C	Density[a]	Applications: Addition	Replacement of: H	O	N	C	Hal
Br_2[b]	159.81	−7.3	58.8	3.12/20°C	•	*			*	
HBr[c]	80.91	−86	−67	2.17	*		*	*		
HOBr	97.91	Only dilute solutions in H_2O			*	*				
KOBr	119.01	Only dilute solutions in H_2O				*				
AcNHBr	137.98	106–108			*	*				
$CCl_3CONHBr$ (NBS)	240.39	124–125			*	*				
$(CH_2CO)_2NBr$ (NBS)	117.98	176–177			*	*				
	226.02	206–207			*	*				
										

$POBr_3$	286.65	56	193	2.82					*		
PBr_5	430.45	106 dec.							*		
$SOBr_2$	207.87	−50	138 58–60/40	2.68					*		
LiBr	86.85										*
CuBr	143.45										*
$CuBr_2$	223.35						*				*
$MgBr_2$	184.11										*
$CaBr_2$	199.89										*
$AlBr_3$	266.69	97.5	263.3	2.64/10°C							*
$C_4H_8O_2Br_2$	247.91	60–61			*	*					
$C_5H_5NHBr_3$	319.82	132–134				*					
Ph_3PBr_2	422.08								*		
$(PhO)_3PBr_2$	470.08								*		
$(PhO)_3\overset{+}{P}MeBr^-$	405.21								*		
	409.69					*	•				

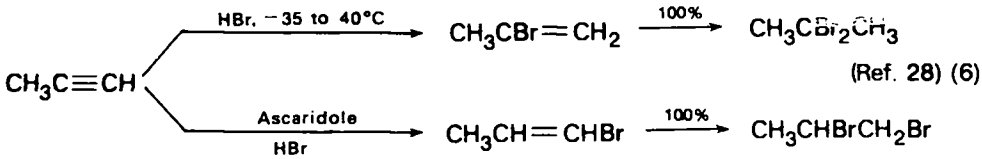
[a] Temperatures following a solidus are those at which density was evaluated.
[b] Critical temperature 302°C.
[c] Critical temperature 90°C.

$$CH_2{=}CH{-}CH{=}CH_2 \xrightarrow[65\%\ \text{yield}]{HBr,\ -78^\circ C} CH_3CHBrCH{=}CH_2 + CH_3CH{=}CHCH_2Br$$

(Ref. 24) (5)

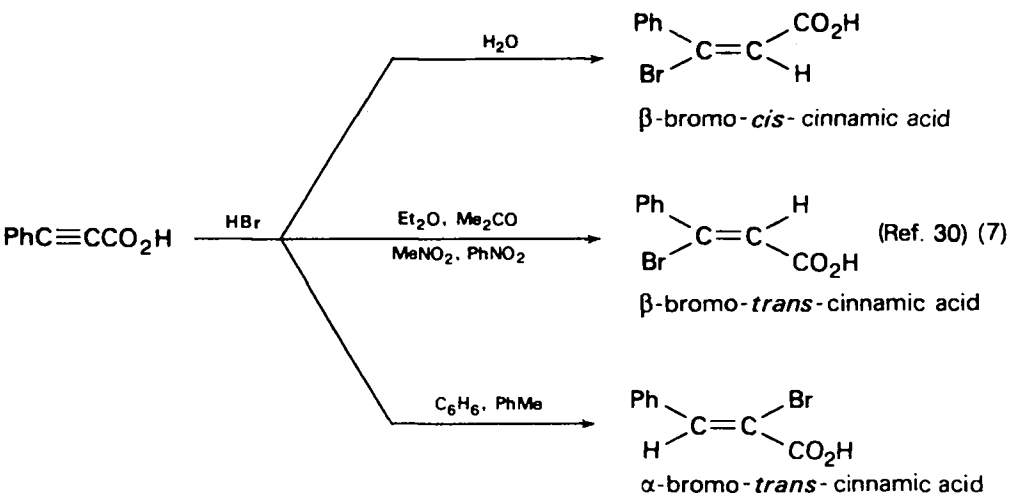
In presence of	1,2-addition product	1,4-addition product
Ascaridole	59%	41%
Diphenylamine	90%	10%

The peroxide effect also affects the addition of hydrogen bromide to acetylenes. Not only does the presence or absence of peroxides influence the addition of the first molecule of hydrogen bromide[27] but also that of the second one, so that the absence of peroxides favours formation of geminal dibromides, whereas the presence of peroxides favours that of vicinal dibromides[28] (equation 6).



(Ref. 28) (6)

From the stereochemical point of view, the addition of hydrogen bromide does not always give sterically uniform *trans* products. Propiolic acid afforded a mixture of 21% *cis* and 79% *trans* isomers of bromoacrylic acid[29]. The stereoselectivity and sometimes even the regioselectivity can be affected by solvents[30] (equation 7).



(Ref. 30) (7)

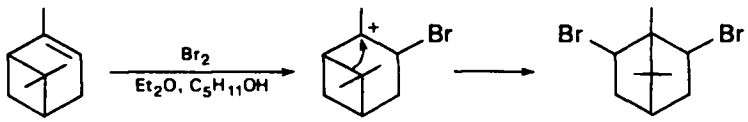
IV. ADDITION OF BROMINE ACROSS MULTIPLE BONDS AND TO AROMATIC SYSTEMS

Addition of bromine to alkenes is a fast exothermic reaction which takes place in the dark and frequently gives quantitative yields. It is often used for titration of alkenes and for conversion of alkenes to vicinal dibromides for isolation and purification purposes.

The reaction follows an ionic pathway: positively polarized bromine (or its complex) attacks the double bond and forms a cyclic bromonium intermediate which is opened

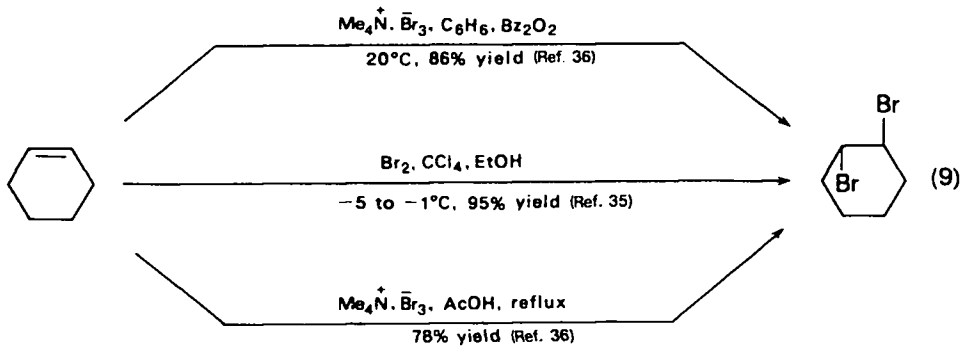
by a bromide ion from the opposite side. The addition of bromine is enhanced by Lewis acids (iodine, ferric chloride, etc.) and by high electron density at the double bond, and results in *trans* (*anti*) addition.

The reactivity of an alkene towards the addition of bromine is affected by the nature of the substituents linked to the double bond: electron-releasing groups increase the reactivity and electron-withdrawing groups decrease it. The rate of addition of bromine to alkenes of different electron density may differ over three to four orders of magnitude[31,32]. The ionic nature of the addition of bromine to alkenes is manifested by rearrangements which are due to the temporary existence of a carbonium ion intermediate[33] (equation 8), and by partial addition of acetoxy anions if the reaction



(56%) (Ref. 33) (8)

is carried out in acetic acid[34]. The *anti* addition is documented by obtaining *trans*-1,2-dibromocyclohexane from cyclohexene[35,36] (equation 9) and D,L-2,3-dibromobutane from *cis*-2-butene and *meso*-2,3-dibromobutene from *trans*-2-butene[37] (configuration assigned originally to 2-butenes was wrong).

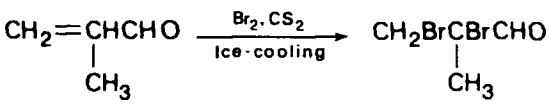


(9)

Fluorinated alkenes react with bromine fast enough and quantitatively. Chlorotrifluoroethylene bubbled through bromine until the bromine colour vanishes gives 1,2-dibromo-1-chlorotrifluoroethane[38]. Both *syn* and *anti* addition was reported with some fluoroolefins[39]. Some perfluorocycloalkenes react very slowly[40,41].

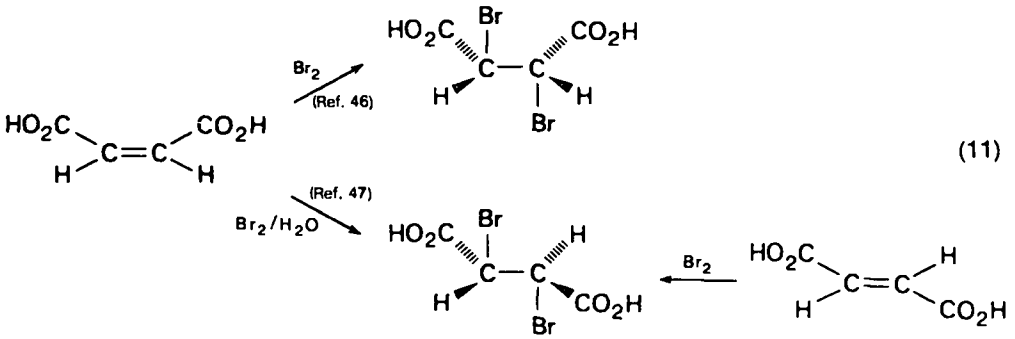
Unsaturated alcohols and their esters add bromine across the double bonds, usually without any side reactions, provided that gentle conditions (room temperature and solution of bromine in non-polar solvents) are used[42,43]. Trimethylsilyl ethers of enols add bromine and eliminate trimethylsilyl bromide to give α-bromocarbonyl compounds (equation 31).

α,β-Unsaturated carbonyl compounds add bromine at low temperatures[44] (equation 10) but eliminate hydrogen bromide easily, giving α-bromo-α,β-unsaturated aldehydes and ketones.

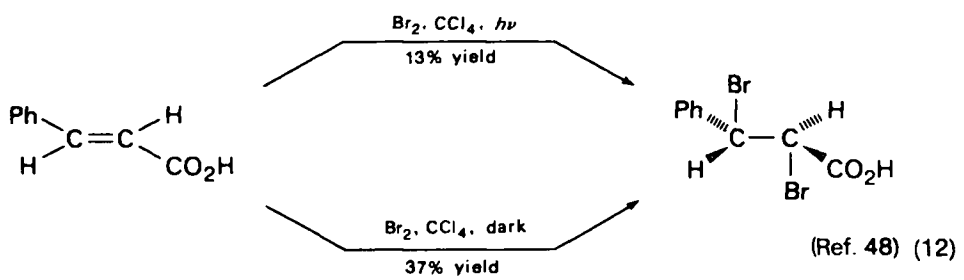


73% (Ref. 44) (10)

α,β-Unsaturated carboxylic acids and their esters give α,β-dibromo derivatives very easily at temperatures of 5–10°C[45]. Stabilization by hydroquinone is necessary to prevent polymerization. Irradiation enhances the addition but also the elimination of hydrogen bromide to give α-bromo-α,β-unsaturated derivatives. The addition of bromine to maleic and fumaric acid gives products of *trans* addition[46], but not without exceptions[47] (equation 11). Quite a few cases of *syn* addition of bromine across double bonds have been recorded[47,48] (equations 11,12).



(11)



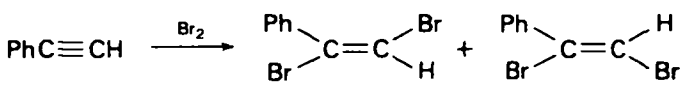
(Ref. 48) (12)

α,β-Unsaturated nitriles add bromine[49] but tend to eliminate hydrogen bromide at higher temperatures to give α-bromo-α,β-unsaturated nitriles[50] (equation 13).

$$CH_2{=}CHCN \xrightarrow[80-150°C]{CuBr_2,\ DMF} [CH_2BrCHBrCN] \longrightarrow CH_2{=}CBrCN \quad \text{(Ref. 50) (13)}$$

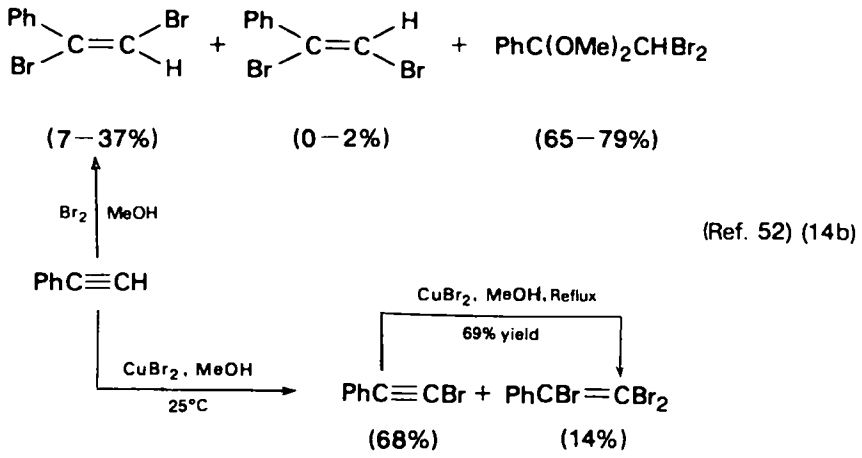
Acetylenes react with bromine and brominating agents, giving predominantly *trans*-dibromoalkenes together with the *cis* isomers[51] and some other by-products[52] (equation 14).

Addition of bromine to benzene and naphthalene occurs under irradiation but lacks in practical importance. On the other hand, in anthracene[53] and phenanthrene[54] addition of bromine takes place spontaneously, producing 9,10-dibromo-9,10-dihydro



(Ref. 51) (14a)

Solvent	Proportion of *trans* product	Proportion of *cis* product
$CHCl_3$	82%	18%
AcOH	70%	30%
AcOH + LiBr	97%	3%



(Ref. 52) (14b)

compounds at low temperatures[53,54]. These compounds eliminate hydrogen bromide and give fully aromatic 9-bromo derivatives (see Section VII). Similar disposition for adding bromine was found with hexahelicene[55].

V. ADDITION OF BROMINE AND OTHER ELEMENTS OR GROUPS ACROSS DOUBLE BONDS

Addition of bromine and fluorine across double and triple bonds has great preparative significance for the synthesis of fluoro compounds and is, therefore, discussed earlier in the chapter in the part dealing with the formation of carbon–fluorine bonds.

Applications of the addition of other mixed halogens are less frequent, mainly because such compounds are not always readily available or have to be prepared by mixing the halogens. A viable method for the addition of chlorine and bromine is treatment of an unsaturated compound with *N*-bromoacetamide in a solution of dry hydrogen chloride in chloroform[56].

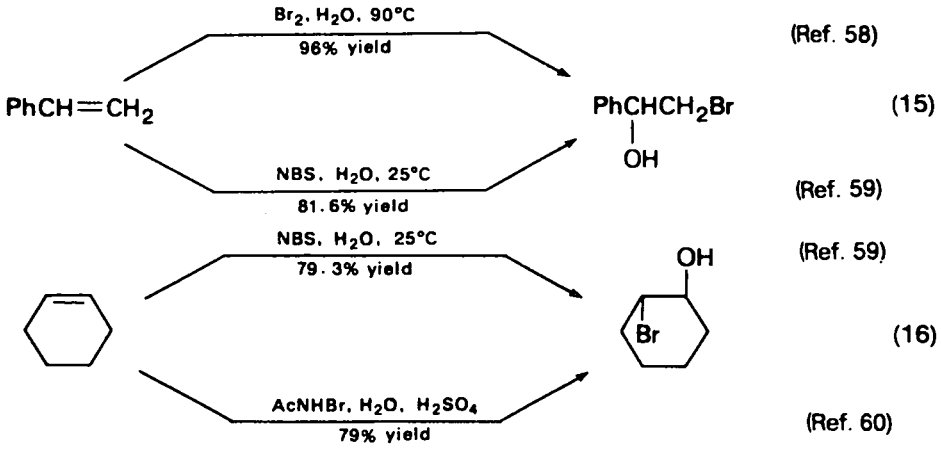
Since the rate of addition of iodine bromide across double bonds is three orders of magnitude faster than that of iodine, iodine bromide (prepared *in situ* by mixing equimolar amounts of the elements in acetic acid) is eminently suited for analytical determination of unsaturation by titration (Hanus' iodine number)[57].

Preparative applications of iodine bromide will be discussed later in the chapter in the part dealing with formation of carbon–iodine bonds.

Addition of bromine and hydroxyl is used frequently for the synthesis of bromohydrins and is effected by treatment of unsaturated compounds with hypobromous acid (either ready-made or prepared *in situ* from bromine and water)[58] or with *N*-bromo compounds in aqueous medium[59,60] (equations 15 and 16).

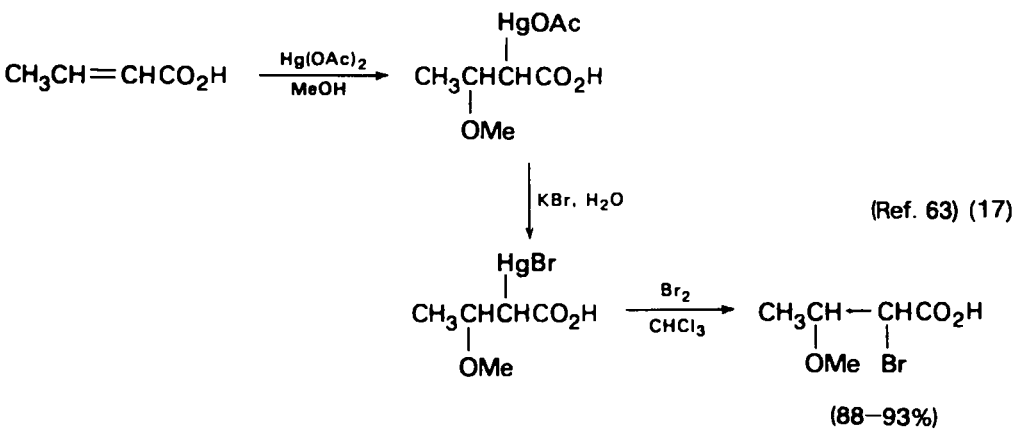
The regiospecificity is determined by the electrophilic nature of bromine, which gives Markovnikov-type addition. Since the addition takes place by a stepwise mechanism, the components add in a *trans* (*anti*) mode.

Bromine and an alkoxyl group are added to double bonds in good to high yields with the same regio- and stereospecificity as bromine and a hydroxyl group, by using bromine[8] or *N*-bromoacetamide[61] or other *N*-bromo compounds[15,62] in alcohols. A



(Ref. 58) (15) (Ref. 59) (Ref. 59) (16) (Ref. 60)

somewhat different method is alkoxybromination via organomercuric compounds[63], exemplified in equation (17). If the initial addition of mercuric acetate is carried out in acetone rather than in alcohol, bromohydrins are obtained[64].



(Ref. 63) (17)

(88–93%)

Bromine and an acyloxy group add to a double bond by means of acyl hypobromite prepared *in situ* from silver carboxylates and bromine at low temperatures (−20 to −10°C)[65]. Otherwise, decarboxylation takes place (equation 76).

VI. REPLACEMENT OF HYDROGEN BY BROMINE IN ALKANES, CYCLOALKANES, ALKENES AND ALKYNES

Like replacement of hydrogen in the above compounds by chlorine, replacement by bromine is a free radical process requiring initiation by heat or irradiation. The reaction is exothermic ($\Delta H = -8$ to -14 kcal mol^{-1}) but has a high activation energy (18 kcal mol^{-1}). It is, therefore, much slower than chlorination. On the other hand, bromination is much more selective as far as the replacement of different types of hydrogen atoms is concerned. At 300°C, the relative rates of replacement of primary:secondary:tertiary hydrogen are 1:80:1600. A distribution of isomers in the bromination of propane is shown in equation (18)[66].

The position of the second and third bromine in the bromination of bromopropanes is influenced by catalysts such as iron, ferric bromide and aluminium bromide[67]. A

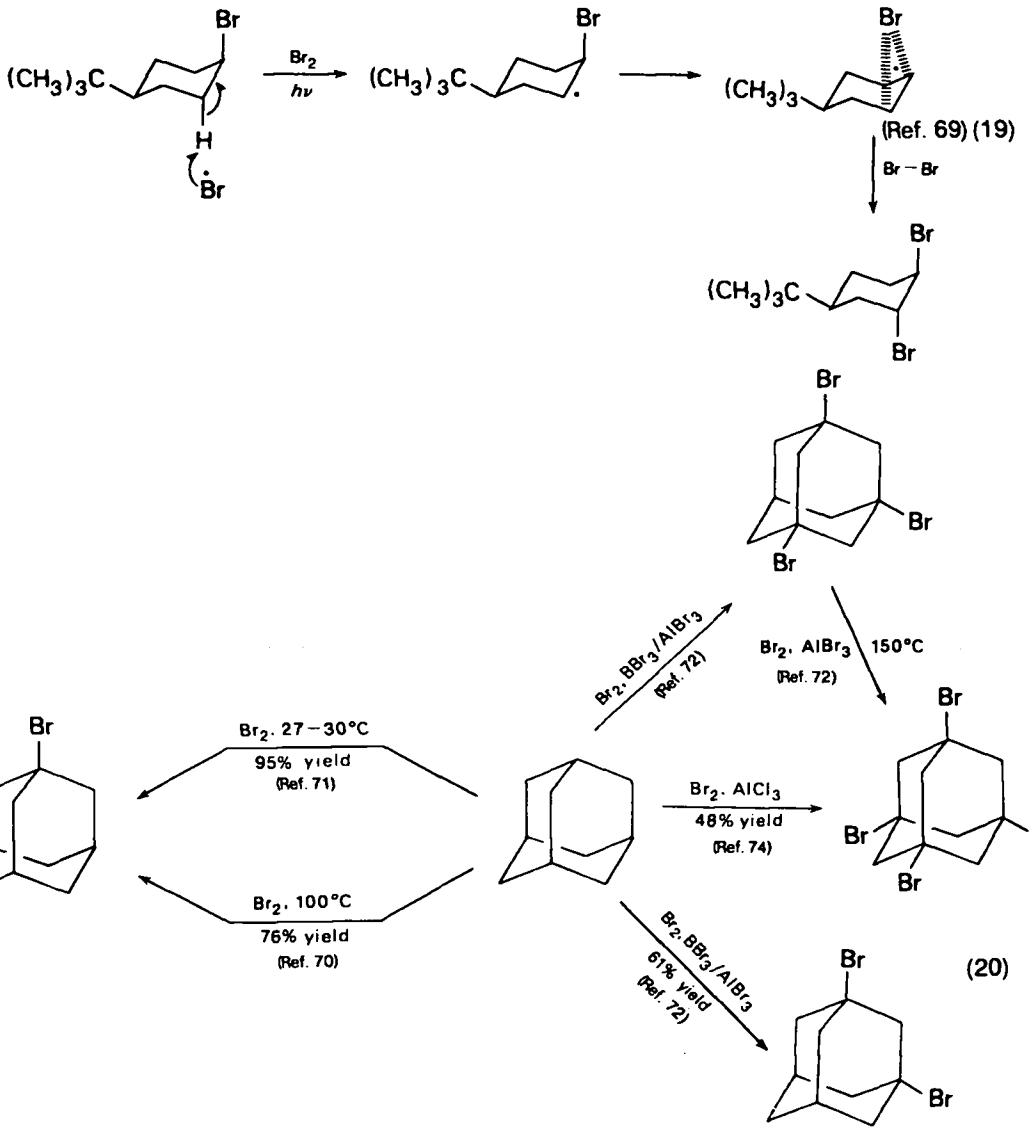
$$CH_3CH_2CH_3 \xrightarrow[330°C]{Br_2} \underset{(7.8\%)}{CH_3CH_2CH_2Br} + \underset{(82.2\%)}{CH_3CHBrCH_3} + \underset{(3.0\%)}{CH_3CHBrCH_2Br}$$

(eight times excess over Br_2)

(Ref. 66) (18)

$$+ \underset{(1.5\%)}{CH_3CBr_2CH_3} + \underset{(0.5\%)}{CH_2BrCH_2CH_2Br} + \underset{(2.5\%)}{C_3H_4Br_4}$$

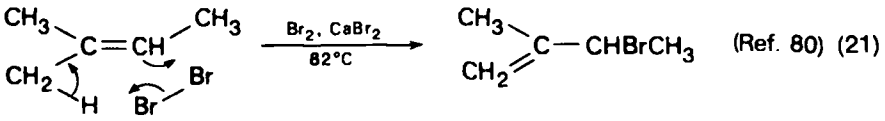
strong preference for the formation of vicinal dibromides is rationalized by assuming a bridged intermediate containing a three-membered ring with bromine[68,69] (equation 19). Mono- and polybromination of cycloalkanes can be best exemplified on adamantane[70–74] (equation 20).



Bromination of alkanes and cycloalkanes was also accomplished with special brominating agents like *N*-bromo-bis(trimethylsilyl)amine[75], *N*,*N*-dibromobenzenesulphonamide[76] or trichloromethanesulphonyl bromide[77]. These compounds are sources of bromine atoms (radicals), particularly in the presence of peroxides[76,77].

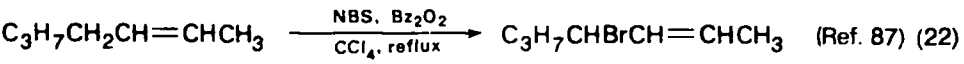
Bromination of halogenated alkanes and cycloalkanes sometimes requires strong catalysts and/or high temperatures. 1-Chloro-2,2,2-trifluoroethane was brominated to 1-bromo-1-chloro-2,2,2-trifluoroethane at 500°C[78] and, on refluxing with an excess of bromine and an equimolar amount of aluminium bromide, 2-chloroadamantane gave 67% yield of 1,3,5,7-tetrabromoadamantane[79].

Alkenes and bromine usually combine at low and moderate temperatures to form vicinal dibromides by addition of bromine across the double bond. However, some branched alkenes form substitution products by replacement of hydrogen by bromine in a position α to the double bond. 2-Methyl-2-butene gives mainly 3-bromo-2-methyl-1-butene with bromine at 82°C[80], most probably by an 'ene' reaction (equation 21). Propene gives predominantly 1,2-dibromopropane on bromination in the vapour phase at temperatures below 200°C, whereas allyl bromide is produced in 65% yield above 300°C[81].



(Ref. 80) (21)

Replacement of a hydrogen in a position α to the double bond by bromine ('allylic bromination') is accomplished conveniently by selective brominating agents such as *N*-bromosuccinimide[82–85], *N*-bromophthalimide[85], *N*-bromo-*t*-butylamine[86], *N*,*N*-dibromobenzenesulphonamide[76] and others. This reaction of alkenes and cycloalkenes, especially with *N*-bromosuccinimide, was developed into a general procedure (equation 22); an alkene dissolved in carbon tetrachloride is refluxed with *N*-bromosuccinimide (heavier than carbon tetrachloride) until the by-product – succinimide, which is lighter than the solvent – floats on the top of the liquid.

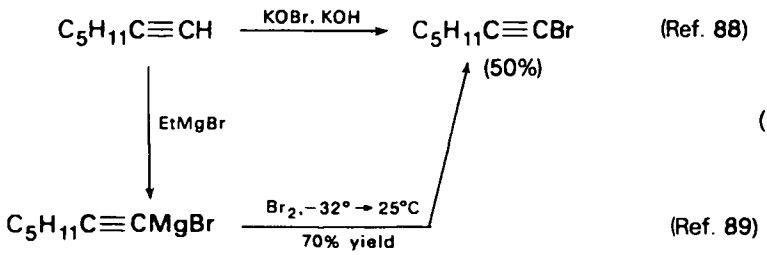


(Ref. 87) (22)

Since the reaction is enhanced by irradiation and in particular by peroxides[83,87] (which help to achieve replacement even of tertiary and benzylic hydrogens) it was believed that the substitution takes place by a free radical mechanism. However, it is now assumed that the selectivity of *N*-bromosuccinimide brominations is caused by bromine generated *in situ* in very low concentrations[84]. Be it as it may, this method gained immense popularity for allylic bromination of many unsaturated compounds containing various functional groups and is very useful in preparing intermediates in syntheses of steroids and other natural products.

Substitution of bromine for acetylenic hydrogen in alkynes cannot be accomplished directly by bromine since this would add across the triple bond to form dibromo or tetrabromo compounds. One way in which to replace the acetylenic hydrogen by bromine is to use alkali hypobromite in alkaline solutions[88], another is to treat the bromomagnesium alkyne with an insufficient amount of bromine at low temperature[89] (equation 23).

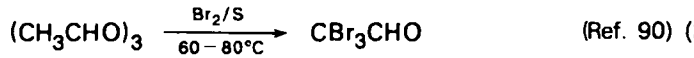
Terminal bromoacetylenes are very unstable and some, including dibromoacetylene, explode in contact with air.

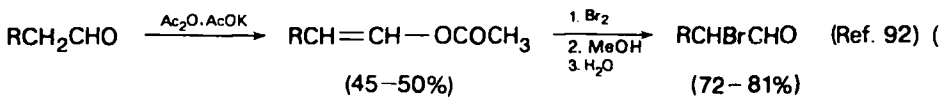


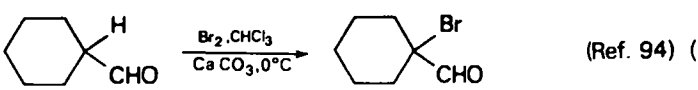
VII. REPLACEMENT OF HYDROGEN BY BROMINE IN FUNCTIONAL DERIVATIVES AT SATURATED (sp^3) CARBON (EXCEPT SIDE CHAINS IN AROMATIC SYSTEMS)

Bromination of alcohols is a complex reaction in which oxidation as well as dehydration precedes the formation of bromo derivatives. Bromination of both alcohols and ethers lacks, with a few exceptions, practical applications.

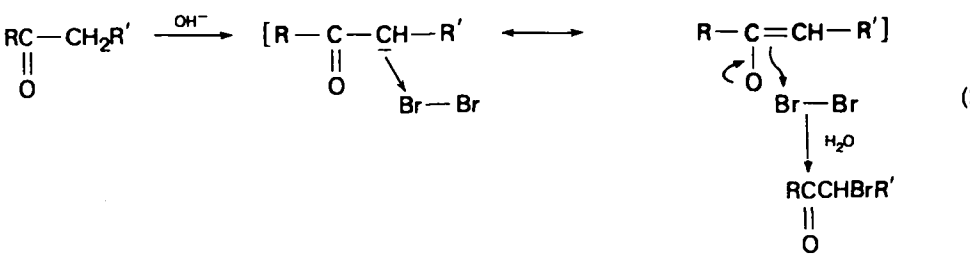
Reaction of bromine with lower aliphatic aldehydes may be accompanied by side reactions. It is of advantage to prepare α-brominated aldehydes by bromination of their trimers[90] (equation 24), their enol ethers[91], or their enol esters[92,93] (equation 25). Bromination of formylcyclohexane gave a high yield of 1-bromo-1-formylcyclohexane[94] (equation 26).



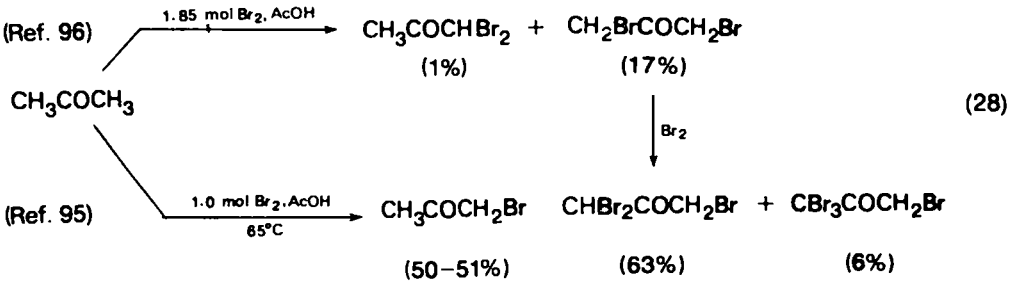




Like aldehydes, ketones are also brominated exclusively in positions α to the carbonyl group. The reason for this is that the bromination, a base- or acid-catalysed reaction, takes place at the keto–enol system (equation 27).



Bromination of acetone in acetic acid (1:1 ratio) gives 50% yield of bromoacetone[95] with some polybrominated by-products. If higher ratios of bromine to acetone are used (1.85:1), asymmetric as well as symmetric dibromoacetone is obtained[96] (equation 28). Its further bromination affords tri- and tetrabromoacetone.

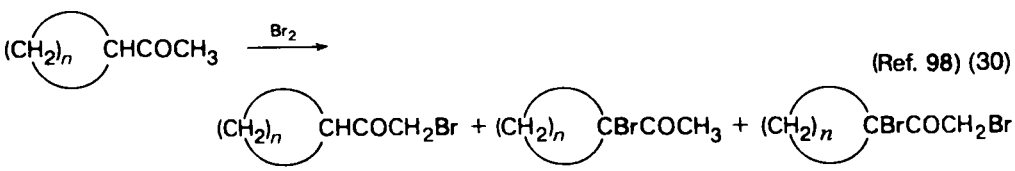


2-Butanone is brominated in both α-positions; the yield of 3-bromobutanone is highest with bromine and potassium chlorate in aqueous medium[97,98] (equation 29).

$$CH_3COCH_2CH_3 \xrightarrow{Br_2} BrCH_2COCH_2CH_3 + CH_3COCHBrCH_3 \quad \text{(Ref. 98) (29)}$$

Reaction conditions	Proportion of 1-bromobutanone	Proportion of 3-bromobutanone
Br_2, $KClO_3$, H_2O, 50 → 35–40°C	28%	72%
Br_2, CCl_4	13%	87%
Br_2, MeOH	70%	30%

The regiospecificity of bromination of non-symmetrical ketones is strongly influenced by the solvent used (equation 29). Whereas brominations in carbon tetrachloride give predominantly isomers resulting from replacement of secondary or tertiary hydrogens, and relatively larger amounts of dibrominated products, methanol as the solvent or co-solvent favours monobromination in the methyl group[98]. Examples of the solvent effect on the product distribution are given in equation (30), where the amount of the dibromide is expressed as a percentage of the sum of both monobromides.



n	Solvent	Yields 1	2	3
4	CCl_4	0%	100%	10%
4	MeOH	85%	15%	4%
5	CCl_4	40%	60%	23%
5	MeOH	100%	0%	0%

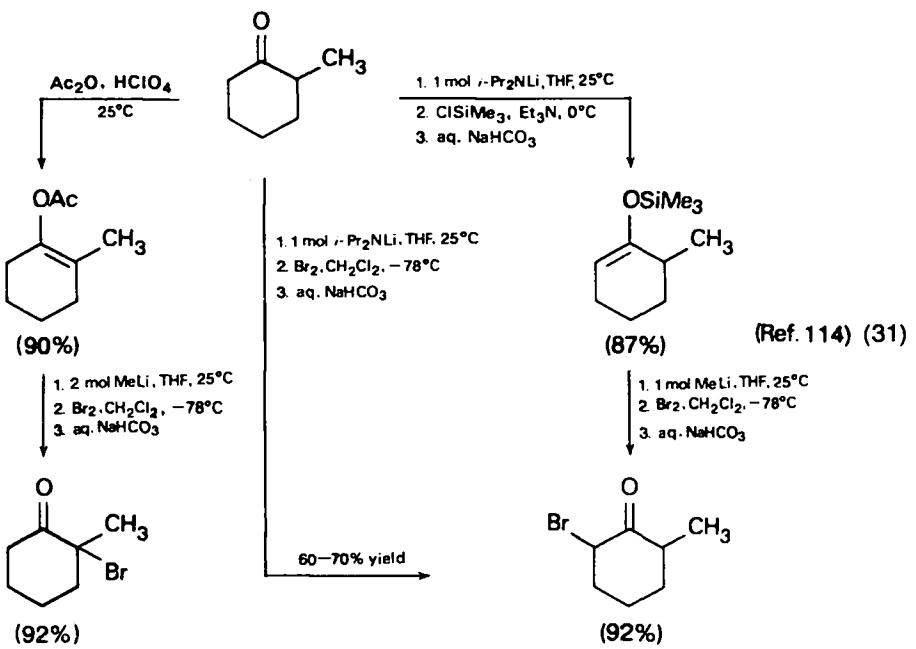
Regiospecificity in the bromination of benzyl methyl ketone with cupric bromide is affected by reaction conditions but replacement of methylene hydrogen predominates[99].

Cupric bromide is a reagent of choice for bromination of such ketones which contain functions such as double bonds or reactive benzene rings which could be affected by bromine. Thus, 3β-hydroxyandrost-5-ene-17-one gave 16α-bromo-3β-hydroxy-

androst-5-ene-17-one[100] in 45% yield, and acetophenones with phenolic groups in the ring were brominated in high yields exclusively in the methyl group[101,102].

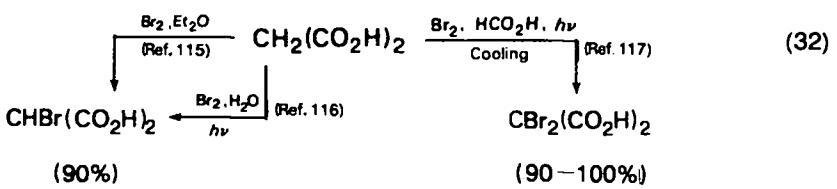
Bromination of ketones has been accomplished, generally in good to high yields, using a whole host of more or less exotic reagents such as dioxane dibromide[103,104], 'tribromophenolbrom' (2,4,4,6-tetrabromo-2,5-cyclohexadien-1-one)[105], 5,5-dibromo-2,2-dimethyl-1,3-dioxolane-4,6-dione[106], *N,N*-dimethylbromocyanoacetamide[107], pyridinium tribromide[108], trimethylbenzylammonium tribromide[109], trimethylanilinium tribromide[110], and β-carboxyethyltriphenylphosphonium tribromide[111]. However, most of them do not offer conspicuous advantages over bromine or cupric bromide.

On the other hand, both aldehydes and ketones can be brominated in good to high yields if they are converted to enol acetates or to trimethylsilyl enol ethers and treated with bromine[112–114] or *N*-bromoacetamide[113]. An elegant method for the bromination of non-symmetrical ketones with high regiospecificity is by treatment of lithium enolates prepared from the ketones and lithium diisopropylamide with bromine[114] (equation 31).



Bromination of saturated carboxylic acids and their derivatives is much more regiospecific than chlorination. Chlorine enters into almost any place in the carbon chain, and predominantly into the β-position. Bromine almost always replaces hydrogen atoms on the α-carbon.

The easiest bromination is that of malonic acid, which yields, according to the reaction conditions, monobromo-[115,116] or dibromomalonic acid[117] (equation 32).

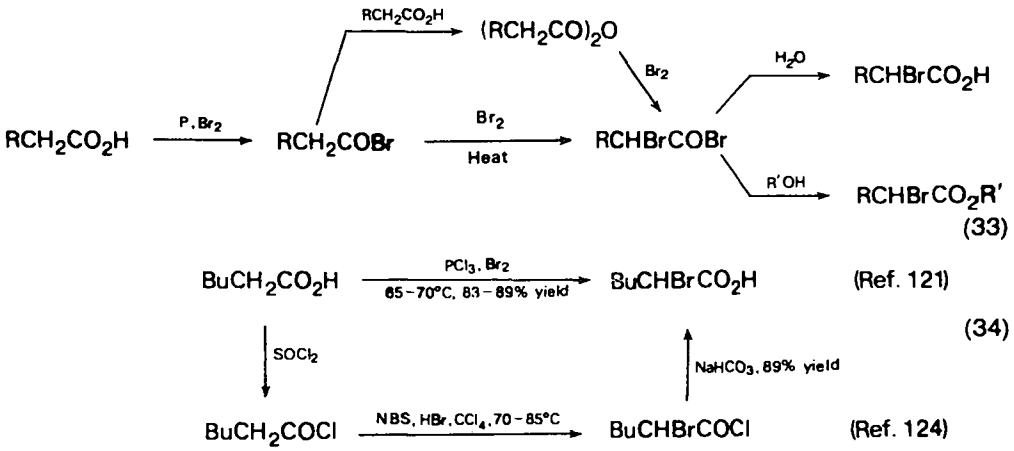


(32)

Similarly, alkylmalonic acids form monobromoalkylmalonic acids[118]. If the bromination is followed by heating, decarboxylation takes place to yield α-brominated acids[117,118].

Bromination of acetic acid takes place at higher temperatures and is usually carried out in the presence of catalysts, most frequently phosphorus[119]. Dibromo- and tribromoacetic acids require high temperatures[120] and sometimes elevated pressures.

The function of phosphorus, which is first converted by bromine to phosphorus pentabromide, is to transform the acid into its bromide or possibly its anhydride (equation 33), which is halogenated exclusively in the α-position and is easier to halogenate than the free acid (Hell–Volhard–Zelinsky method). The same effect is achieved by phosphorus trichloride[121] or tribromide (equation 34). The amount of phosphorus may be either catalytic[119] or stoicheiometric. In the latter case, the primary product of bromination is α-bromoacyl bromide which, depending on the work-up, can give α-bromoacid or its ester[38].

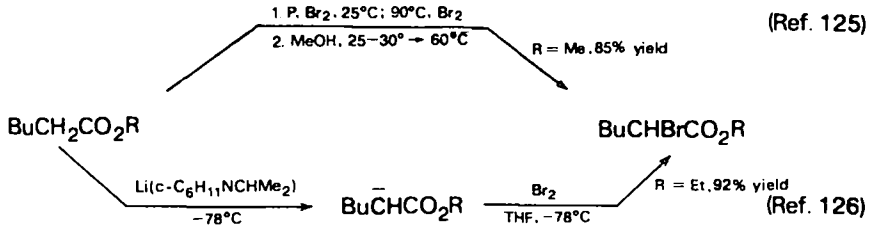


Bromination of acids via their anhydrides, which are prepared *in situ*, takes place when the carboxylic acids are brominated in polyphosphoric acid as a solvent. Cyclohexanecarboxylic acid was, thus, converted at 120°C to 1-bromocyclohexanecarboxylic acid in 76.5% yield[122].

All the above reactions require heating at fairly high temperatures. Some more gentle methods are available for α-bromination of acyl chlorides and esters. To prepare monobromoadipic acid, adipic acid is converted by thionyl chloride to its dichloride, and this is brominated with 1 mol of bromine to α-bromoadipyl dichloride. Hydrolysis of the dichloride with formic acid gives 61% of α-bromoadipic acid[116]. Bromination of acyl chlorides can also be accomplished by *N*-bromosuccinimide[123,124] (equation 34).

Bromination of esters is not easy and is accompanied by cleavage to acyl bromides. A special procedure in which the reaction mixture after the bromination is treated with the same alcohol whose ester was brominated affords 48–85% yield of α-bromoester[125] (equation 35).

The most gentle method for the synthesis of α-bromoesters is the conversion of the ester to its carbanion using dialkyllithium amide at −78°C, and the subsequent reaction with bromine in tetrahydrofuran at the same temperature[126] (equation 35). For unsaturated acids which could add bromine to the double bond, diethyl dibromomalonate was used for the bromination of the carbanions[127]. With esters containing fluorine the yields were not satisfactory[38].



Bromination of nitriles requires catalysts like phosphorus tribromide[128], or can be accomplished with phosphorus pentabromide as the brominating agent[129]. On the other hand, malonic acid dinitrile is readily monobrominated in aqueous medium[130]. Dibromomalonic acid dinitrile[131] is itself a brominating agent[132] (equation 36).

$$CH_2(CN)_2 \xrightarrow{Br_2} CBr_2(CN)_2 \xrightarrow[EtOH,\,reflux]{CH_2(CN)_2} CHBr(CN)_2 \quad \text{(Refs. 131, 132)} \quad (36)$$

(60%)

Acyl amides are easily brominated on the nitrogen atom, giving *N*-bromoamides, themselves selective brominating agents. A special reagent, acetyl hypobromite[133], gives very high yields of *N*-bromoacyl amides.

In alkyl sulphoxides, bromine replaces hydrogen next to the sulphur atom; thus, ethyl phenyl sulphoxide and bromine reacted in acetonitrile–pyridine solution at −40–25°C to give 76% yield of 1-bromoethyl phenyl sulphoxide[134].

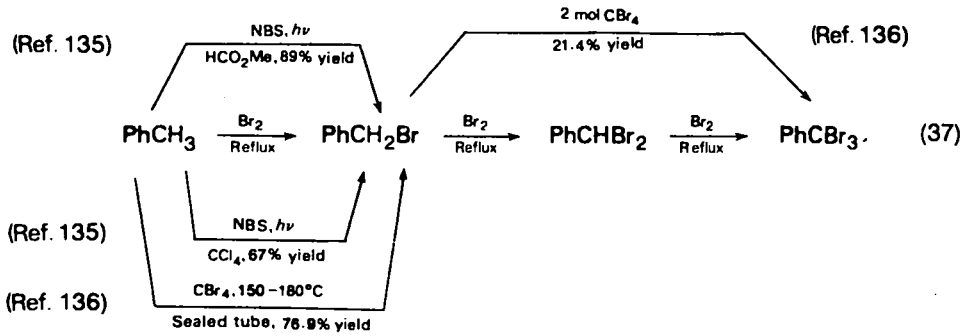
VIII. REPLACEMENT OF HYDROGEN BY BROMINE IN AROMATIC SYSTEMS AND THEIR SIDE CHAINS

Bromination of aromatic compounds in their rings is an electrophilic substitution which obeys the same rules which are described in the corresponding paragraphs on chlorination earlier in this chapter.

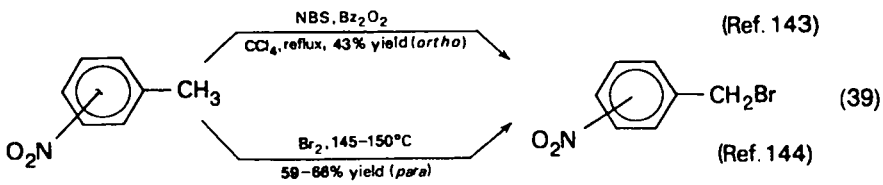
Benzene is brominated in the presence of a catalytic amount of iron to give, depending on the amount of bromine used, various proportions of bromobenzene and *p*-dibromobenzene. Separation of both products is achieved by steam-distillation and purification of bromobenzene by distillation and of *p*-dibromobenzene by crystallization. Laboratory procedure can be found in almost any organic chemistry laboratory manual.

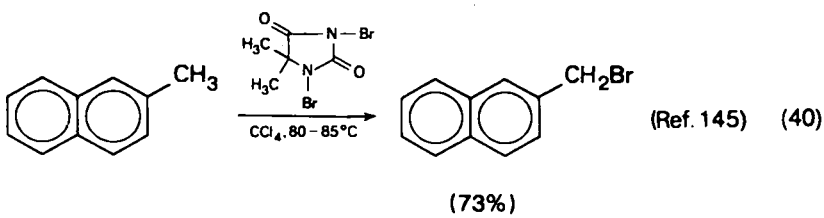
Benzene homologues either undergo bromination in the ring or in their side chains. The side-chain bromination is a free radical process which requires initiation by irradiation, by heat (usually both), or by peroxides. Ring bromination has to be catalysed by Lewis acids such as aluminium or ferric bromide (or iron), antimony halides, iodine and others. In this way, it is possible to direct bromine into the desired positions. Moreover, some brominating reagents are suitable just for one and not the other type of bromination.

Toluene is brominated in the side chain by adding bromine to boiling toluene, best with simultaneous irradiation. Depending on the amount of bromine used, benzyl bromide, benzal bromide or benzotribromide (the two last-mentioned ones at higher temperatures only) can be obtained in good yields. Benzyl bromide was also obtained by bromination of toluene with *N*-bromosuccinimide in the presence of benzoyl peroxide[135], or with carbon tetrabromide in sealed tubes[136] (equation 37). Under similar conditions, xylenes and higher homologues of benzene and their ring-substituted derivatives are brominated in their side chains exclusively, always in



the position α to the aromatic ring: *p*-bromotoluene[137], *o*-xylene[138], ethylbenzene[139], γ-bromopropylbenzene (to α-γ-dibromopropylbenzene[140]), prehnitene (to 2,3,6-trimethylbenzyl bromide[141]), phthalide[142], *o*-[143] and *p*-nitrotoluene[144], and homologues of naphthalene[145,146] (equations 38–40).

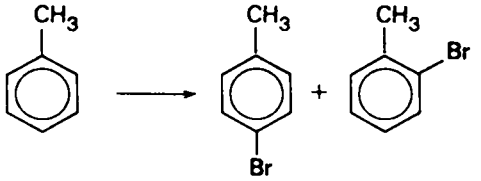




Bromination of toluene in the ring results always in a mixture of *o*- and *p*-bromotoluenes, which are difficult to separate and purify. Some brominating reagents give more *p*-bromotoluene and less *o*-bromotoluene than others[147,148] (equation 41) but the best way to prepare pure isomers is by Sandmeyer or Gattermann reaction of diazotized toluidines.

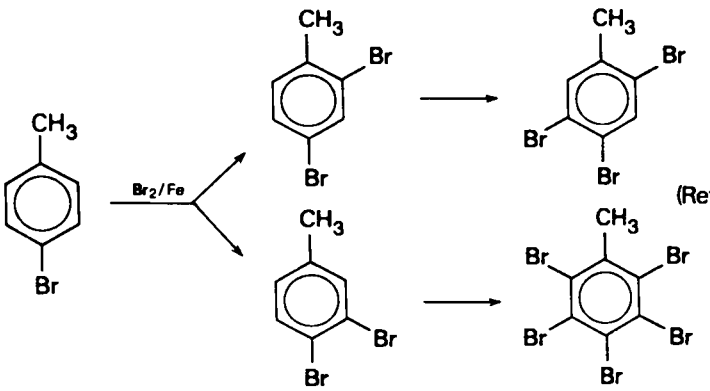
Higher homologues of benzene were ring-brominated with bromine alone[149], with bromine and thallium triacetate[148], and exceptionally even with bromine under irradiation (in the case of *t*-butylbenzene which does not have benzylic hydrogens to be replaced under the free radical conditions[150]).

Bromination of halogenated aromatic compounds gives, depending on the reaction conditions, monobromo and polybromo derivatives. Fluorobenzene was brominated predominantly to *p*-bromofluorobenzene[151]. In benzotrifluoride bromine enters at the *meta* position[152]. Brominated toluenes afford different isomeric dibromotoluenes, tribromotoluene, and ultimately pentabromotoluene[153] (equation 42).



(Refs. 147, 148) (41)

Reaction conditions	Proportion of *para* product, %	Proportion of *ortho* product, %
$CuBr_2$	60	40
Br_2, $Tl(OAc)_3$, 0°C	60	8



(Ref. 153) (42)

Polybromination of benzene homologues with side chains branched at the α-position gives hexabromobenzene under vigorous conditions (undiluted bromine, iron or aluminium catalyst)[154]. Under similarly forcing conditions even tetrafluoro- and pentafluorobenzene were fully brominated (in 20–60% fuming sulphuric acid) in yields around 80%[155,156].

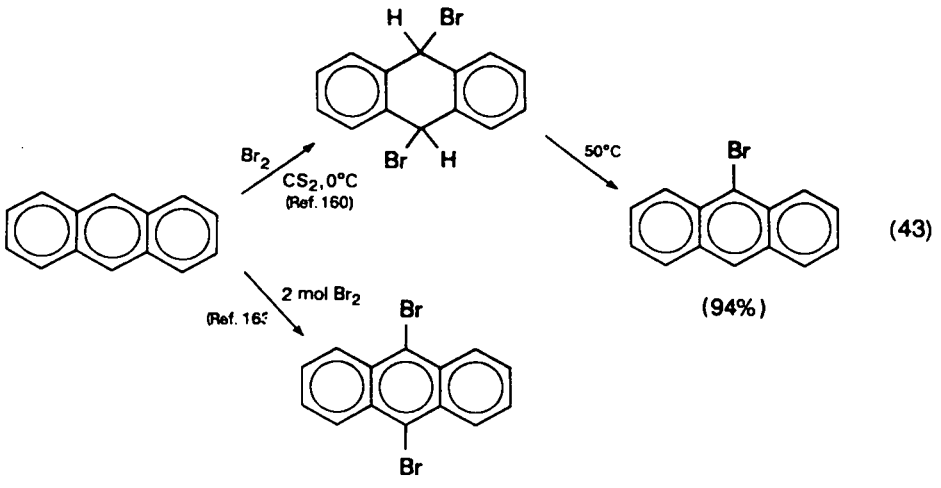
Polynuclear aromatic hydrocarbons are brominated more readily than benzene. Naphthalene, for example, gives exclusively 1-bromonaphthalene on bromination even without a catalyst[157]. Further bromination gives 1,4- and 1,5-dibromonaphthalenes[158]. Fluorene gave 2-bromofluorene on bromination with *N*-bromosuccinimide[159].

Anthracene and phenanthrene, under mild conditions, add bromine at the 9,10-positions and form 9,10-dibromo-9,10-dihydro derivatives[160,161], which on heating lose hydrogen bromide and give 9-bromo substituted compounds in high yields[160–162]; with two molecules of bromine, 9,10-dibromoanthracene was obtained[163] (equation 43). Pyrene treated with bromine in carbon tetrachloride at room temperature afforded 78–86% of 3-bromopyrene[164].

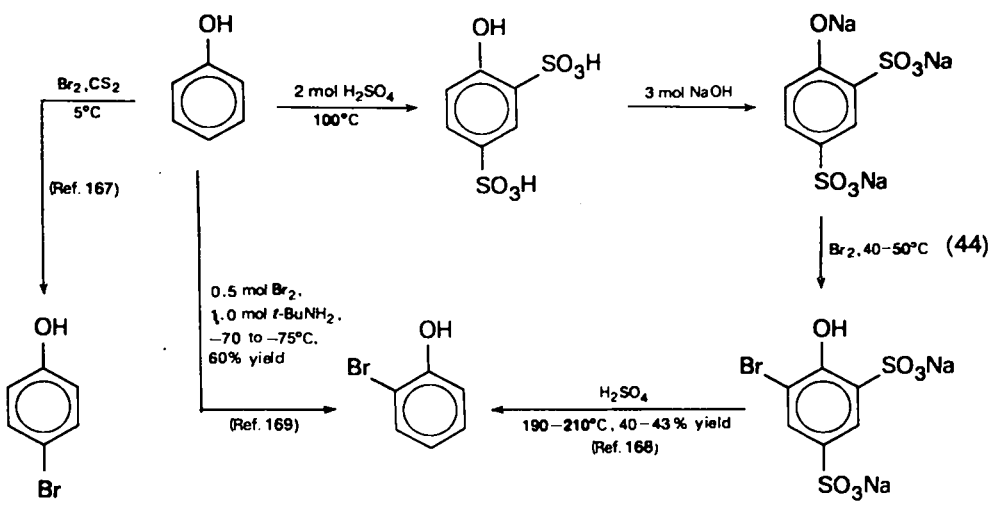
Highly condensed aromatic polynuclear hydrocarbons, e.g. coronene[165] and hexahelicene[55,166], give monobromo and dibromo derivatives.

Phenols are very reactive and are brominated under mild conditions without catalysts. Phenol itself gives almost exclusively *p*-bromophenol at low temperatures[167]; special methods are necessary for the preparation of pure *o*-bromophenol[168,169] or 2,6-dibromophenol[169] (equation 44).

An excess of bromine converts phenol into 2,4-dibromophenol, 2,4,6-tribromophenol, and ultimately to the so-called 'tribromophenolbrom',



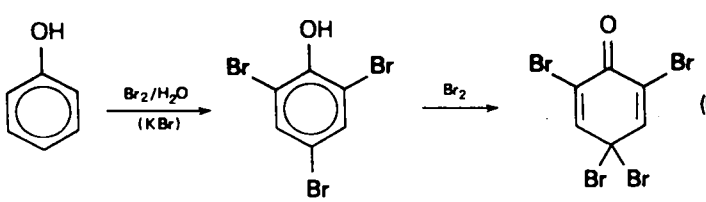
(43)



(44)

2,4,4,6-tetrabromo-2,5-cyclohexadiene-1-one, a compound capable of acting as a brominating agent[170] (equation 45). Homologous phenols behave similarly[171].

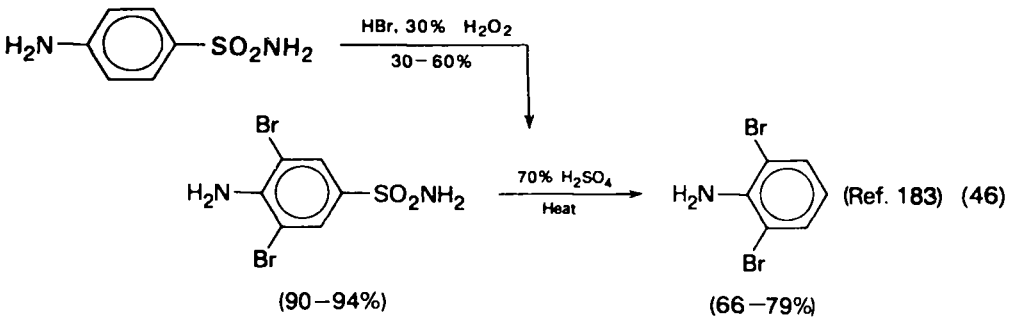
Under different reaction conditions, bromine can be introduced into position 2, position 4 or both in the phenolic ring of oestrone, oestradiol and oestriol in 78–90% yields[172].



(Ref. 170) (45)

Like phenols, phenol ethers are brominated at low temperatures and without catalysts. Under such conditions the hydrogen bromide evolved in the reaction does not cleave the ether bond. Anisole gave *p*-bromoanisole in 83% yield[173]. In the presence of aluminium bromide, diphenyl ether gave perbromodiphenyl ether[174]. Some special reaction conditions were used for bromination of anisole and its homologues and derivatives: bromine in the presence of antimony pentachloride[175], bromine in the presence of thallium triacetate[176], and *N*-bromosuccinimide with irradiation[177]. Esters of phenols suffer probably partial cleavage by hydrogen bromide as their yields are not very high: on heating with bromine in acetic acid 2-acetoxybiphenyl gave 51% of 2-acetoxy-5-bromobiphenyl[178]. Benzoates of nitrophenols are brominated preferentially in the ring of the acid[179].

Aromatic amines are very reactive. Aniline affords *p*-bromoaniline and 2,4,6-tribromoaniline[180]; its *N*-alkyl derivatives behave similarly[181]. Acetanilide is brominated considerably more slowly[182] and requires more energetic conditions, especially for polybromination. With bromine in acetic acid at 50–55°C, aceto-*p*-toluidide gave 60–67% yield of *o*-bromoaceto-*p*-toluidide[182]. Sulphanilic acid and sulphanilamide were brominated in both positions *ortho* to the amino group by hydrogen bromide and potassium bromate or 30% hydrogen peroxide[183] (equation 46). In this way, 2,6-dibromoaniline can be prepared after hydrolytic removal of the sulphonyl group[183].



(Ref. 183) (46)

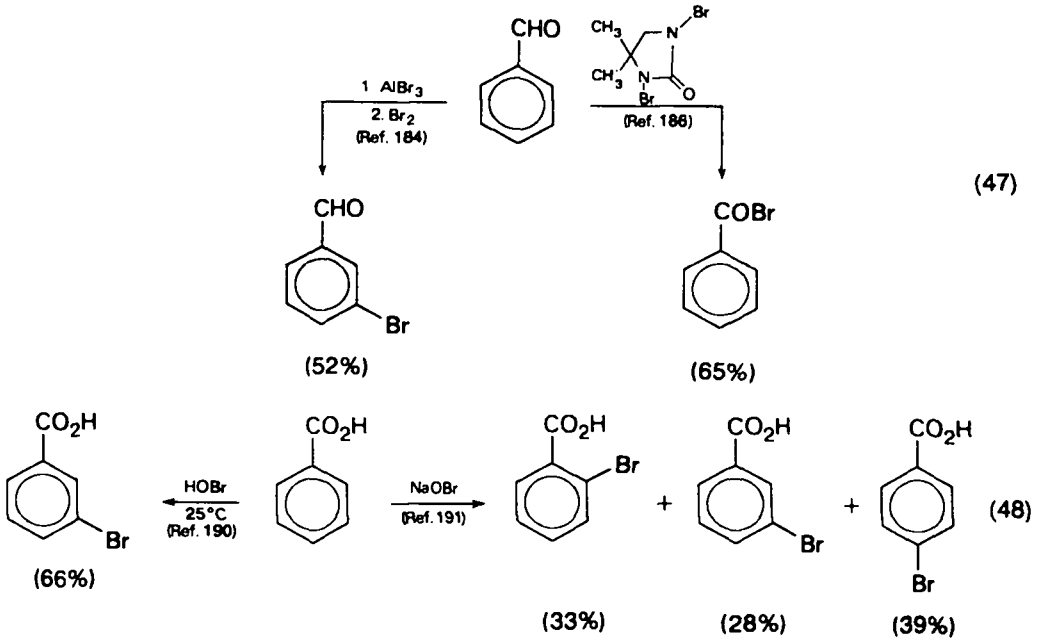
Aromatic aldehydes and ketones are brominated in positions *meta* to the carbonyl groups and only under rather vigorous conditions. Benzaldehyde gave 52% yield of *m*-bromobenzaldehyde after it was first converted to a molecular complex with aluminium bromide ('swamping catalyst' procedure)[184] (equation 47). Under the same conditions terephthalic dialdehyde afforded terephthalyl dibromide[185]. Benzaldehyde and its nitro derivative were converted to the corresponding benzoyl bromides by 1,3-dibromo-5,5-dimethylhydantoin[186,187] (equation 47).

Acetophenone[188], propiophenone[189], and methyl acetophenones[189] were brominated in 63–75% yields in positions *meta* to the carbonyl group using an excess of aluminium bromide and bromine.

Bromination of aromatic acids requires vigorous conditions or special reagents. *m*-Bromobenzoic acid was obtained by bromination with hypobromous acid[190]. When alkaline hypobromite was used, a mixture of all three isomeric bromobenzoic acids was obtained[191] (equation 48).

Terephthalic acid was brominated with bromine in fuming sulphuric acid (10–30% SO_3) at 70–100°C to give quantitative yields of tetrabromoterephthalic acid[192].

The presence of activating substituents such as hydroxyl or amino groups facilitates bromination of hydroxybenzoic and aminobenzoic acids considerably. On reaction with hydrogen bromide and hydrogen peroxide salicylic acid yielded 5-bromo- and

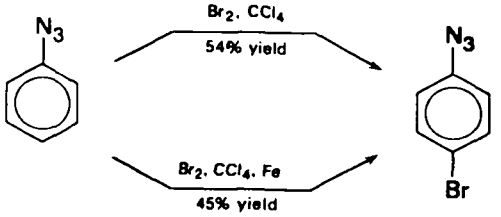


3,5-dibromosalicylic acids in high yields[193]. *m*-Aminobenzoic acid was transformed with bromine in aqueous hydrochloric acid at 0°C into 3-amino-2,4,6-tribromobenzoic acid in good yield[194].

Nitro compounds are brominated in positions *meta* to the nitro groups under rather vigorous conditions. Nitrobenzene affords *m*-bromonitrobenzene in yields of 60–75% on bromination in the presence of iron at 135–145°C[195], while for analogous bromination of *p*-nitrotoluene to 2-bromo-4-nitrotoluene a temperature of 75–80°C was sufficient[196].

As in the case of aromatic carboxylic acids, activating substituents facilitate bromination of nitrated benzene rings considerably. Thus, *p*-nitrophenol was brominated in both *ortho* positions with bromine in acetic acid at 85°C to give 2,6-dibromo-4-nitrophenol in 96–98% yield[197], and *m*-nitroaniline gave 2,4,6-tribromo-3-nitro-aniline in 90% yield[180].

Azidobenzene afforded *p*-bromoazidobenzene in 54% yield (equation 49), and 2-azidonaphthalene gave 2-azido-1-bromonaphthalene in 57% yield[198].

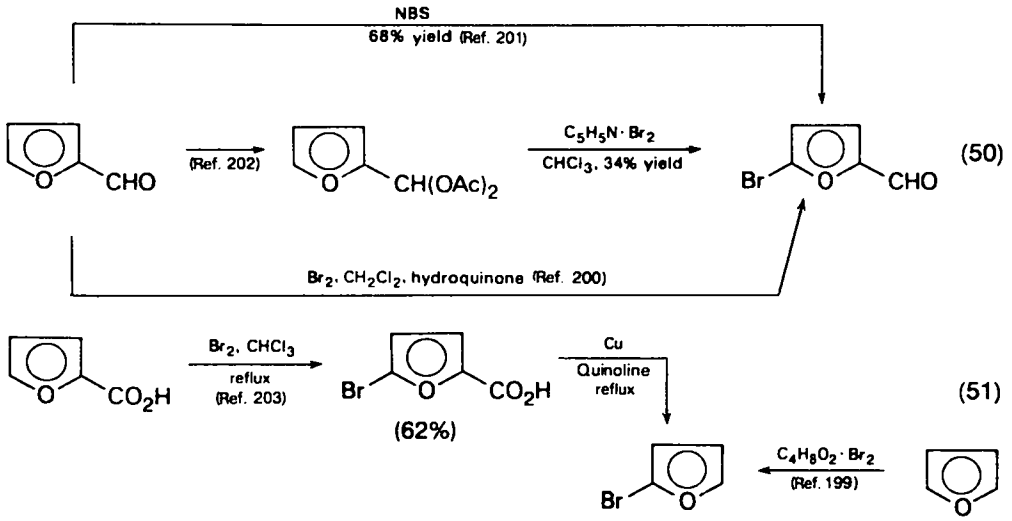


(Ref. 198) (49)

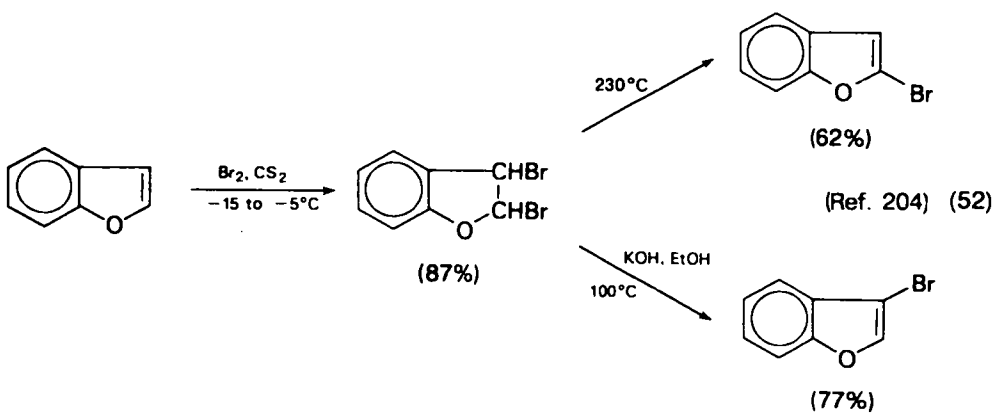
IX. REPLACEMENT OF HYDROGEN BY BROMINE IN AROMATIC HETEROCYCLES

Five-membered heterocycles containing oxygen, sulphur or nitrogen react with bromine very readily. Furan has a tendency to add bromine and is easily cleaved by

hydrogen bromide so that special brominating agents such as dioxane dibromide must be used[199]. Since electron-withdrawing substituents decrease the sensitivity of the furan ring, furan-2-carboxaldehyde[200,201] and its derivatives[202] and furan-2-carboxylic acid[203] can be brominated without difficulties (equations 50 and 51). An easy

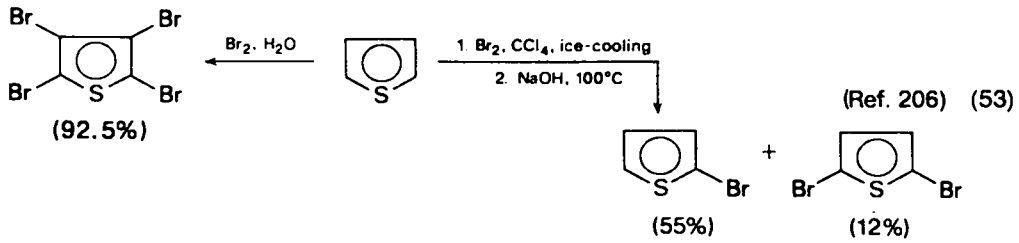


decarboxylation of brominated furan-2-carboxylic acid by heating with copper in quinoline provides a bypass to the synthesis of brominated furans. Bromination takes place preferentially at the position α to oxygen. Only if this position is occupied does β-bromination occur. Benzofuran adds one molecule of bromine in the cold giving 2,3-dibromobenzofuran, which gives 2-bromo- or 3-bromobenzofuran depending on the reaction conditions[204] (equation 52).



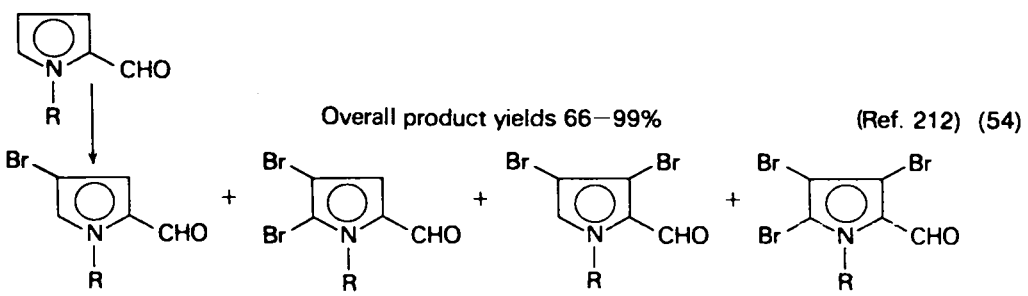
Bromination of thiophene does not present any problems. Depending on the amount of bromine used and on the solvent, 2-bromo-[205], 2,5-dibromo-[205], or tetrabromothiophene[206] can be prepared (equation 53).

Successful bromination of thiophene and its 2- and 3-alkyl homologues in 80–95% yields was accomplished by treatment with *N*-bromosuccinimide alone[207], while in the presence of benzoyl peroxide side chain bromination took place in 3-methylthiophene[208].



Bromination of 2-acetylthiophene[209] in the presence of a large excess of aluminium chloride gave 66% of 4-bromo- and 13.7% of 4,5-dibromo-2-acetylthiophene. A similar mixture was also obtained by bromination using *N*-bromosuccinimide[210]. When higher 2-thienyl alkyl ketones were treated with bromine and a large excess of aluminium chloride, they gave 43–63% yields of 4-bromo-2-thienyl alkyl ketones[211]. With a smaller amount of aluminium chloride, bromination took place in the α-position of the alkyl group in 42.6–94.5% yields[211].

Pyrrole itself is very reactive toward bromine and gives tetrabromopyrrole easily. Its derivatives with electron-withdrawing substituents such as aldehydes, ketones, acids and their esters allow more or less selective bromination in different positions of the ring, depending on the reagents and reaction conditions. With a large excess of aluminium chloride added to pyrrole-2-carboxaldehyde and *N*-methylpyrrole-2-carboxaldehyde ('swamping catalyst') these compounds gave predominantly 4-bromopyrrole-2-carboxaldehyde and 4-bromo-*N*-methylpyrrole-2-carboxaldehyde, respectively. The distribution of isomeric dibromo and tribromo derivatives depends on the ratio of bromine to the substrate and on the substrate[212] (equation 54).



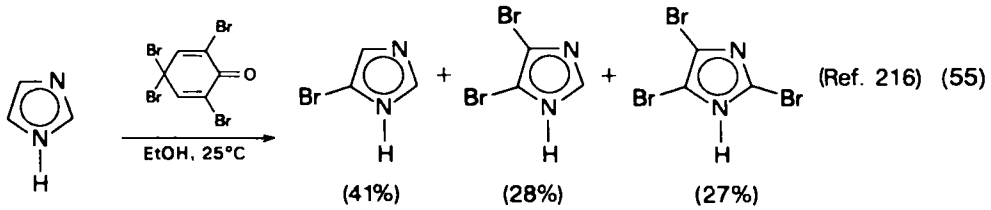
R	Reaction conditions	Proportions of yields, %			
		4-bromo	4,5-dibromo	3,4-dibromo	2,3,4-tribromo
H	1 mol Br_2	100	—	—	—
H	2 mol Br_2	—	55	45	—
H	3 mol Br_2	—	3	2	95
CH_3	1 mol Br_2	90	—	10	—
CH_3	2 mol Br_2	—	6	67	27
CH_3	3 mol Br_2	3	2	7	88

When treated with 1 mol of bromine in carbon tetrachloride at 0 or 28°C, pyrrole-2-carboxaldehyde gave predominantly the 4-bromo and small amounts of the 5-bromo derivatives. At 70°C almost equal amounts of 4-bromo- and 5-bromo- and a small amount of 4,5-dibromopyrrole-2-carboxaldehyde are formed[213]. With 2 mol of

bromine, the 4,5-dibromopyrrole-2-carboxaldehyde was obtained almost exclusively[213]. Different proportions of 4-bromo-, 5-bromo-, 4,5-dibromo-, and exceptionally even of tribromo derivatives were obtained by brominating methyl pyrrole-2-carboxylate with various brominating agents. The 4-bromo derivative is the most favoured one in most cases[213].

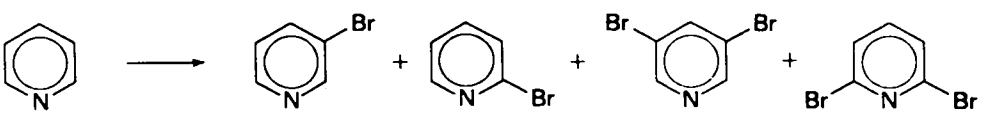
Bromination of 3-acetylpyrrole and methylpyrrole-3-carboxylate gave 5-bromo derivatives in 52–63% yields[214].

Imidazole was brominated very easily to give 78% yield of tribromoimidazole[215]. Better selectivity was obtained when 2,4,4,6-tetrabromo-2,5-cyclohexadien-1-one was used as the brominating agent[216] (equation 55).



(Ref. 216) (55)

Lack of reactivity of the pyridine ring towards electrophilic substitution makes bromination of pyridine very difficult. Elevated temperatures are needed for the introduction of bromine into β-positions, and very high temperatures (500°C) or special reagents for α- and γ-substitution[217]. Bromination of pyridine hydrochloride at 212–215°C afforded 34–42.5% of 3-bromo- and 19–35% of 3,5-dibromopyridine[218]. A method producing 3-bromopyridine in 86% yield is based on heating pyridine with bromine and 65% oleum at 130°C in sealed tubes[219]. A mixture of 17% of 3-bromo- and 22.7% of 2-bromopyridine was obtained by heating pyridine, bromine and carbon tetrabromide in the vapour phase at 450°C[220], whereas treatment of pyridine at 375–450°C with bromine chloride made *in situ* gave 75% of 2-bromopyridine, 21% of 2-chloropyridine, 2% of 3-bromopyridine, and 1.5% of 2,6-dibromopyridine[220]. Another procedure for the synthesis of predominantly 2-bromopyridine (46%) with smaller amounts of 2,6-dibromopyridine (17%) is by high temperature, vapour-phase reaction at 500°C[221]. The bromination of pyridine is exemplified in equation (56).



(56)

Reaction conditions	Yield, %			
	3-bromo	2-bromo	3,5-dibromo	2,6-dibromo
HCl, $HgCl_2$ followed by Br_2, 212–215°C	34–42.5	—	19–35	—
Br_2, 65% oleum, 130°C, sealed tube	86	—	—	—
Br_2, 450°C	17	22.7	—	—
Br_2, 500°C	—	46	—	17
BrCl, 375–450°C	—	75	—	1.5

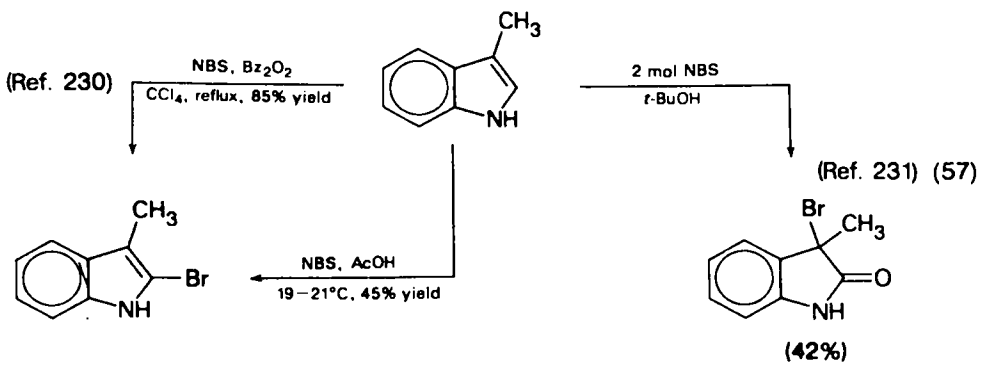
Methylpyridines were converted to monobromo and dibromo derivatives in yields up to 50% by heating with bromine and 65% fuming sulphuric acid at temperatures of 80°C[222].

Pyridine oxide is not only easier to brominate than pyridine, but it also undergoes electrophilic attack in positions different from those in pyridine, viz. the 2 and 4 positions[223]. This information is contrary to that given in a later work, which reports bromination of pyridine oxide in acetic anhydride at position 3, of quinoline oxide at positions 3 and 6, and of isoquinoline oxide at position 4[224].

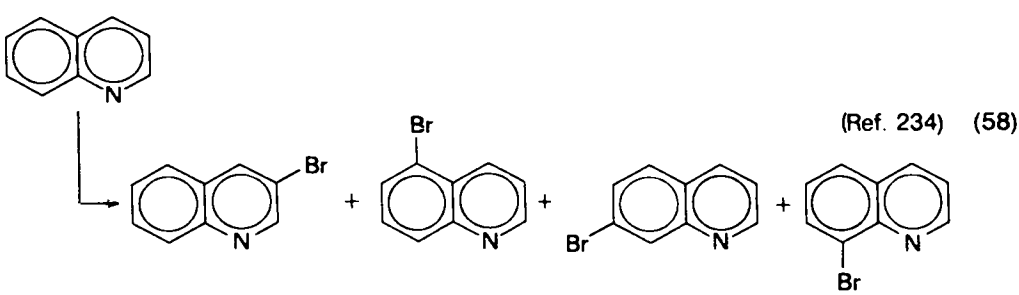
Pyridine derivatives carrying activating substituents exhibit considerably more facile bromination of the ring and orient the bromine into *ortho* and *para* positions with respect to themselves. 3-Hydroxypyridine-*N*-oxide gave 2-bromo and 2,4,6-tribromo-3-hydroxypyridine-*N*-oxide with bromine in aqueous medium[225], 2-aminopyridine gave 62–67% yield of 2-amino-5-bromopyridine with bromine in acetic acid[226], and 3-aminopyridine gave 67% of 2-bromo- and 14% of 2,6-dibromo-3-aminopyridine with 2,4,4,6-tetrabromo-2,5-cyclohexadien-1-one[227].

Pyrimidines were brominated with *N*-bromosuccinimide in acetic acid in position 5[228] while 5-methyl-2,4,6-trichloropyrimidine with the same reagent in the presence of benzoyl peroxide was brominated in the side chain in 95% yield[229].

Indole afforded 3-bromoindole in 60% yield on treatment with dioxane perbromide[199]; 3-methylindole yielded 85% of 2-bromo-3-methylindole on treatment with *N*-bromosuccinimide in the presence of benzoyl peroxide[230], and 42% of 3-bromo-3-methyloxindole with *N*-bromosuccinimide in *t*-butyl alcohol[231] (equation 57). Bromine in acetic acid converted ethyl indole-2-carboxylate into its 3-bromo derivative[232].



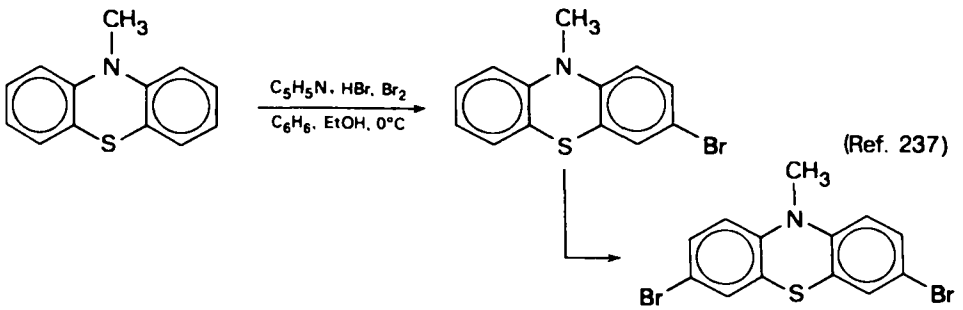
Quinoline was brominated with bromine in pyridine and carbon tetrachloride to 3-bromoquinoline in 82% yield[233]. Under different conditions a whole host of bromoquinolines was obtained[234], some of which are shown in equation (58).



Reaction conditions	Yields, %			
	3-bromo product	5-bromo product	7-bromo product	8-bromo product
Br_2, $(CH_2Br)_2$, 135°C	11,2	—	45.2	—
Br_2, C_5H_5N, CCl_4, 75°C	24.2	15.4	→	21.7
HCl; Br_2, $PhNO_2$, 180°C	97.6	—	—	—

Quinoline-*N*-oxide heated with bromine and thallium acetate in acetic acid at 50°C afforded 65.8% yield of 4-bromoquinoline-*N*-oxide[235], while refluxing of quinoline-*N*-oxide with bromine and sodium acetate in acetic anhydride gave 60% yield of 3,6-dibromoquinoline-*N*-oxide[236].

Bromination of 10-methylphenothiazine with pyridinium perbromide yielded 3-bromo- and 3,7-dibromo-10-methylphenothiazine[237] (equation 59).



(Ref. 237) (59)

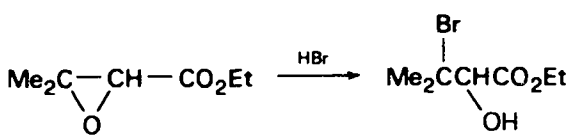
X. REPLACEMENT OF OXYGEN BY BROMINE

A carbon–bromine bond is formed in the cleavage of ethers (epoxides), esters, lactones and sulpho esters, and by replacement of hydroxyl groups in alcohols.

A. Cleavage of Ethers (Epoxides)

Epoxides (oxiranes) react with hydrogen bromide under mild conditions to form vicinal bromoalcohols – bromohydrins[238]. The reaction is a stereospecific S_N2 displacement with inversion. A *cis* epoxide gives a *threo* racemate and a *trans* epoxide gives an *erythro* racemate, or a *meso* form if the epoxide is symmetrical[239].

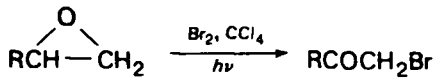
Glycidic esters are opened by hydrogen bromide to give β-bromo-α-hydroxy esters[240] (equation 60). Many examples of the cleavage of epoxides to bromohydrins are found in steroids[241].



(Ref. 240) (60)

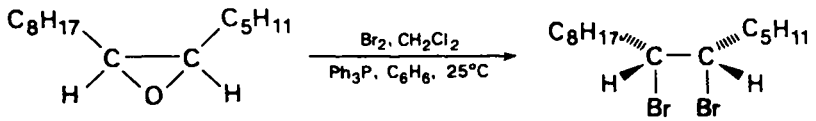
Epoxides can also be opened with bromine to give α-bromoketones in high yields[242] (equation 61).

Treatment of epoxides with triphenylphosphine dibromide gives vicinal dibromides with double inversion; *cis* epoxides give *erythro* dibromides, and *trans* epoxides give mixtures of *threo* and *erythro* dibromides[243] (equation 62).



(Ref. 242) (61)

R	Yield, %
C_4H_9	87
C_5H_{11}	87
C_6H_{13}	90
$C_{10}H_{21}$	85



(Ref. 243) (62)

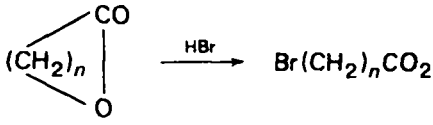
(85%)

Aliphatic ethers were successfully cleaved with boron tribromide in good yields[244], but this reaction has minimal practical application. On the other hand, cleavage of tetrahydrofuran with 50% hydrobromic acid in sulphuric acid gives 1,4-dibromobutane in 82–88% yield[245]. In alkyl aryl ethers the fission takes place in such a way as to give phenols and alkyl bromides[246]. In certain heterocyclic ethers, e.g. 2-methoxy- or 4-methoxyquinolines, bromine became attached to the aromatic ring – a useful method for the synthesis of 2-bromo- and 4-bromoquinolines[247].

B. Cleavage of Esters, Lactones and Sulpho Esters

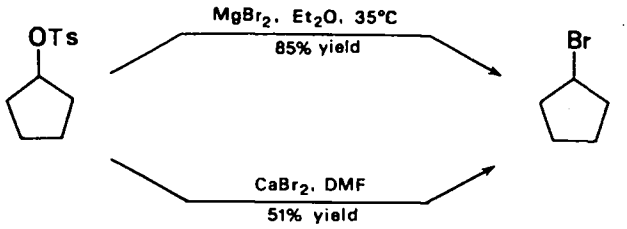
Esters are converted to acids and the corresponding bromides by hydrogen bromide. In carbohydrate chemistry, this reaction is used to convert hexoses via their pentaacetates to tetraacetylbromohexoses[248]. An interesting cleavage of esters, giving 28–73% yields of alcohols, was achieved by α,α-dibromodimethyl ether in the presence of anhydrous zinc bromide[249].

Cleavage of lactones – which are obtainable from cyclic ketones by the Baeyer–Villiger reaction – is a good preparative method for ω-bromocarboxylic acids[250] (equation 63).



(Ref. 250) (63)

Very useful preparation of alkyl bromides is via the reaction of alkyl methanesulphonates[251], benzenesulphonates, or most frequently *p*-toluenesulphonates[251,252], with sodium[252], lithium[253], magnesium[251], calcium[254] or pyridinium bromide[255]. In the majority of cases the reaction is an S_N2 displacement with inversion of configuration when applicable (equation 64), and does not involve rearrangements[254] – an advantage compared to the displacement of hydroxyl groups by using hydrogen bromide. It is applicable to all types of sulphonates, including allylic and acetylenic ones[251], takes place usually under mild conditions, and gives good to excellent yields of the bromides.



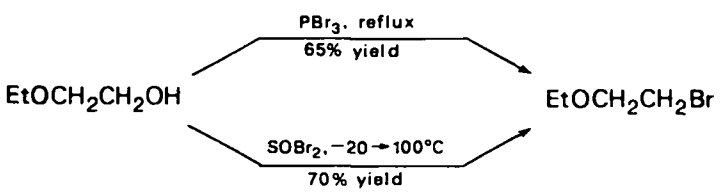
C. Replacement of Hydroxyl in Alcohols

Alcoholic hydroxyl groups are easily replaced by bromine on treatment of alcohols with hydrogen bromide. Since the reaction, especially with secondary and tertiary alcohols, follows an S_N1 pathway, rearrangement during the carbonium ion stage may occur. This disadvantage can be avoided if, instead of hydrogen bromide, phosphorus tribromide is used to transform alcohols into alkyl bromides. The first reaction step is conversion of the alcohol to a phosphite ester which is cleaved, in an S_N2 reaction, by the hydrogen bromide formed in the reaction. Thus, the replacement of the hydroxyl may take place without rearrangement: With phosphorus pentachloride, inversion of configuration was observed. Alcohols can be also converted to bromides by trimethylsilyl bromide via trimethylsilyl ethers, and by triphenylphosphine dibromides and similar reagents. These can replace even phenolic hydroxyls by bromine.

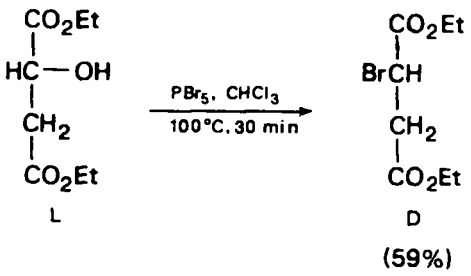
In order to convert alcohols into alkyl bromides, the alcohols are treated with gaseous hydrogen bromide[256] or its solution in water[257] or acetic acid[258] at temperatures depending on the nature of the alcohol. The reaction is catalysed by sulphuric acid which, simultaneously with hydrogen bromide, can be generated *in situ* by an elegant method based on the introduction of sulphur dioxide into a mixture of the alcohol, bromine and ice[259]. In this way, isoamyl alcohol was transformed into isoamyl bromide and allyl alcohol into allyl bromide in 90–95% yields, respectively[259] (equation 65). Some alcohols, and especially glycols, require anhydrous hydrogen bromide and heating at higher temperature. For instance, 1,10-dibromodecane was obtained in 90% yield by passing hydrogen bromide through molten decamethylene glycol at 95–100°C[256].

$$CH_2{=}CHCH_2OH \xrightarrow[\text{Ice}]{Br_2,\ SO_2} CH_2{=}CHCH_2Br \quad \text{(95\%)} \qquad \text{(Ref. 259)} \quad (65)$$

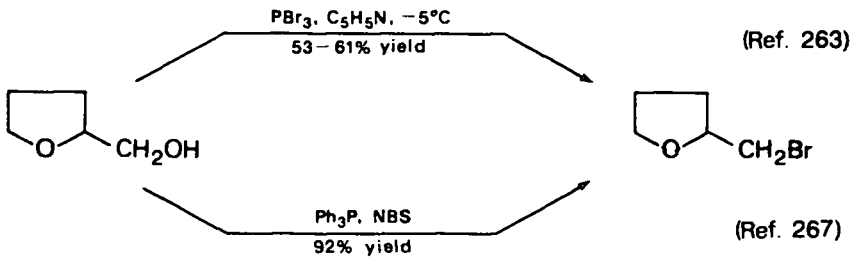
Reaction of alcohols with phosphorus tribromide gives good to high yields of alkyl bromides (equation 66) and is especially suitable for the synthesis of bromides which could suffer rearrangements or side reactions with hydrogen bromide, such as addition across the multiple bond or cleavage of an ether bond[260–263].



Instead of phosphorus tribromide, phosphorus oxybromide[264] and phosphorus pentabromide[265] were used for replacement of hydroxyl groups (equation 67). Since



(Ref. 265) (67)



(Ref. 263)

(68)

(Ref. 267)

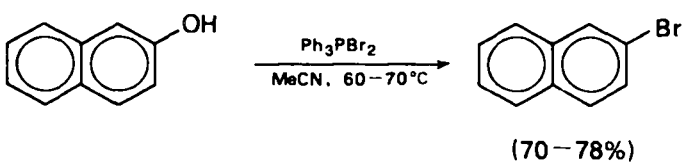
phosphorus pentabromide is a crystalline solid which is difficult to handle, phosphorus tribromide finds much more frequent application.

Replacement of hydroxyl groups by bromine was further achieved by treatment of alcohols with triphenylphosphine and bromine[266] or *N*-bromosuccinimide in dimethylformamide[267,268] (equation 68). Yields of 70–85% were obtained when substituting bromine for primary hydroxyl groups in carbohydrates. Good yields were obtained on treatment of alcohols with reagents prepared from triphenyl phosphite and bromine[16].

Unlike thionyl chloride, thionyl bromide is not nearly as popular for the preparation of alkyl halides from alcohols, although it offers a very simple and clean-cut procedure and good yields[269,270] (equation 66). A relatively new reagent transforming alcohols into bromides with inversion of configuration, when applicable, is dimethylbromosulphonium bromide[271].

Trimethylsilyl bromide[272] or trimethylsilyl chloride in the presence of lithium bromide[273] will convert alcohols first to trimethylsilyl ethers which are cleaved by the hydrogen bromide generated during the reaction. Yields obtained are impressive (91–100%)[272].

Triphenylphosphine dibromide can not only replace alcoholic hydroxyl groups[274] but also hydroxyl groups bonded to aromatic rings[275,276] (a reaction difficult to achieve with other reagents) (equation 69).

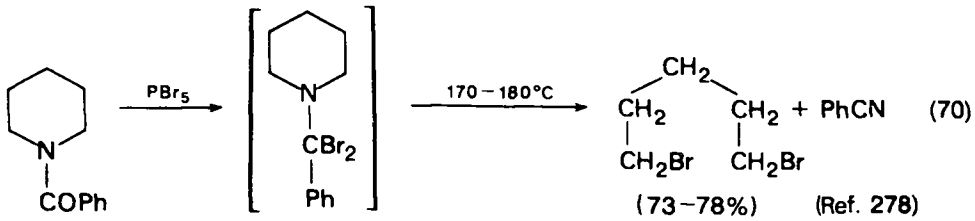


(Ref. 276) (69)

XI. REPLACEMENT OF NITROGEN BY BROMINE

When *N*-alkyl-substituted amides are treated with phosphorus pentabromide they undergo fission of the carbon–nitrogen bond and give bromoalkanes and nitriles.

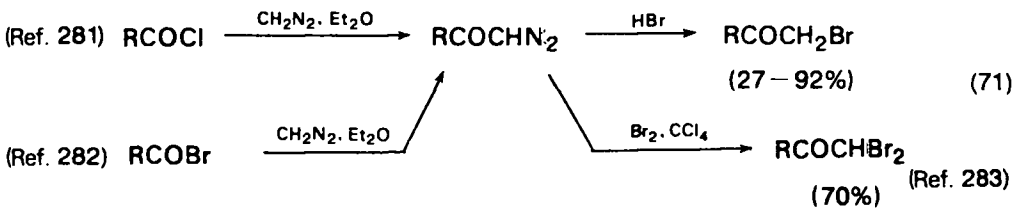
N-Benzoylpyrrolidine yielded 70% of 1,4-dibromobutane by this procedure[277], and *N*-benzoylpiperidine yielded 1,5-dibromopentane[278] (equation 70).



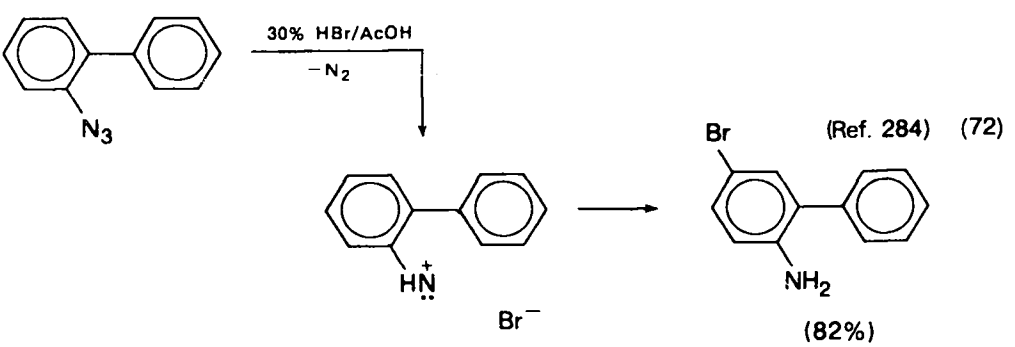
In a similar reaction of ε-caprolactam with phosphorus pentabromide and bromine, replacement of nitrogen by bromine and fission of the lactam ring was accompanied by α-bromination to give α,ω-dibromocaproic acid in 90% yield[279].

Replacement of a nitro group in nitrobenzene and other aromatic nitro compounds lacks practical application, but replacement of the nitro group in 1-nitroadamantane accompanied by bromination at position 3 by means of bromine and aluminium bromide is claimed to be a useful way to synthesize 1,3-dibromoadamantane, which is formed in 26–30% yield[280].

Aliphatic diazo compounds react with hydrogen bromide to give monobromo compounds, and with bromine to give *gem*-dibromo compounds (after elimination of nitrogen). This reaction is frequently used for the synthesis of monobromo-[281,282] or dibromomethyl[283] ketones from diazomethyl ketones prepared from diazomethane and acyl chlorides[281], or, better still, acyl bromides[282] (equation 71).



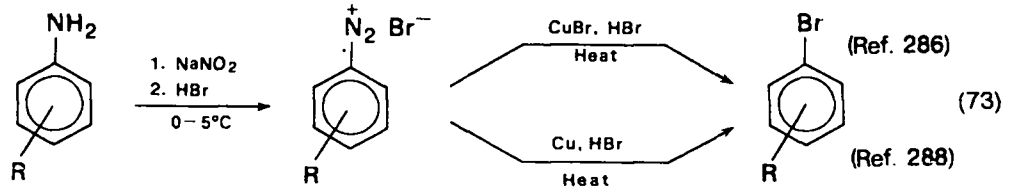
Azides are similarly decomposed by hydrogen bromide with the elimination of nitrogen. Thus, 2-azidobiphenyl was converted to 2-amino-5-bromobiphenyl[284] (equation 72).



Aliphatic amino compounds can be transformed into bromo compounds by treatment with nitrosyl bromide, usually prepared *in situ* from bromine and nitrous oxide[285]. The reaction was used for the preparation of α-bromoacids from α-amino

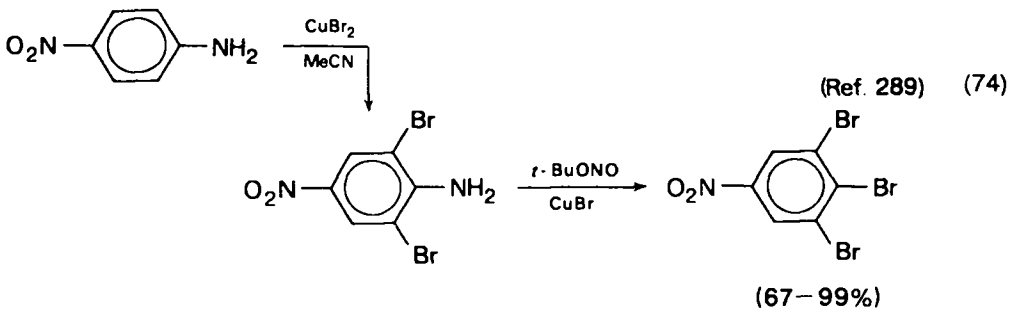
acids or their derivatives. The replacement occurred with retention of configuration: natural asparagine (–) was converted to (–)-bromoaspartic acid and its β-amide[285].

Of much greater importance is the replacement of diazotized amino groups by bromine in the aromatic series. The reaction is accomplished by catalytic decomposition of aromatic diazonium salts by hydrogen bromide in the presence of cuprous bromide or elemental copper. The former reaction is named after Sandmeyer, the latter after Gattermann. Both reactions are very general and applicable to a wide variety of aromatic amines. The conditions of diazotization and decomposition may vary depending on individual amino compounds, and so can the yields of the bromo compounds. A general procedure is diazotization of the aromatic amine with one equivalent of sodium nitrite and at least two and a half or three equivalents of sulphuric acid or, better still, 40–48% hydrobromic acid (not hydrochloric acid) under cooling. This is followed by decomposition of the solution by warming in the presence of at least one equivalent of hydrobromic acid and half an equivalent of cuprous bromide prepared by reduction of cupric sulphate with sodium sulphite[286] or metallic copper[287] in the presence of sodium bromide (equation 73). Metallic copper may be substituted for cuprous bromide[288].



(73)

A very interesting combination of electrophilic bromination and replacement of the amino group was achieved when primary aromatic amines were treated with cupric bromide and *t*-butyl nitrite in anhydrous acetonitrile. The following sequence of reactions resulted in 67–99% yields[289] (equation 74).

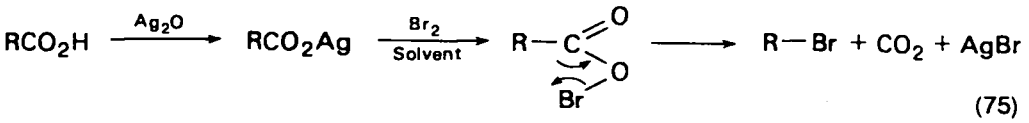


(74)

XII. REPLACEMENT OF CARBON BY BROMINE

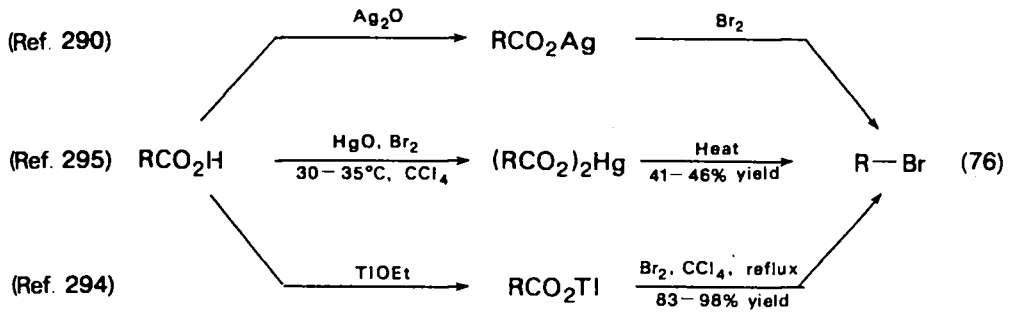
Heating of metal salts of carboxylic acids with bromine results in the replacement of the carboxyl group by bromine (Hunsdiecker's reaction). The reaction proceeds through an intermediate – acyl hypobromite – which eliminates carbon dioxide and forms a bromo compound[290–292]. The reaction is best carried out by refluxing the silver salts with bromine in carbon tetrachloride[291] or trichloroethylene, which gave better yields[293] (equation 75).

Instead of ready-made silver salts[290–293] or thallium salts[294] free carboxylic acid can be heated with bromine in carbon tetrachloride or tetrachloroethane in the presence of



(75)

mercuric oxide[295,296]. The reaction is very useful for the preparation of aliphatic and especially perfluoro aliphatic bromo compounds[292] in 40–99% yields (equation 76).

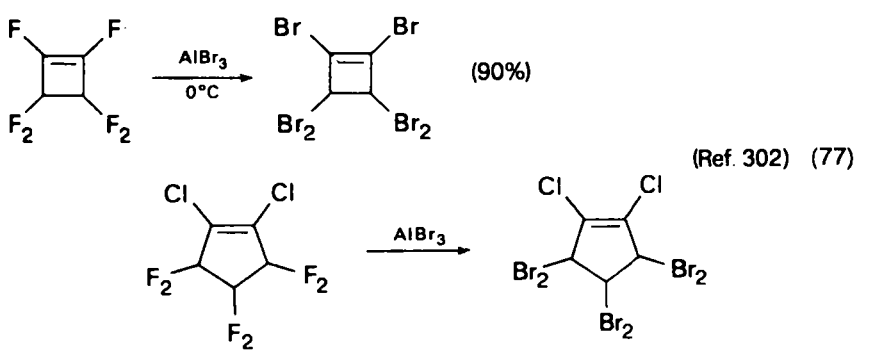


In cyclopropane, the carbon–carbon bond is cleaved by bromine at room temperature, especially under irradiation, giving 1,3-dibromopropane and 1-bromopropane[297]. Similar fission occurs with 1-methyl-3-phenyl- and 1-cyclohexyl-2-phenylcyclopropane[298].

XIII. REPLACEMENT OF OTHER ELEMENTS BY BROMINE

Elemental bromine cleaves bonds between carbon and boron and between carbon and silicon. Triphenylboron gave 84% bromobenzene[299], and 1-trimethylsilylindene gave a 66% yield of 1-bromoindene[300].

Other halogens can be replaced by bromine by means of metal bromides, although such reactions usually lack practical applications. In 4-chloro-2-butyn-1-ol, chlorine was replaced by bromine by refluxing in methanol with sodium bromide[301], and in perfluorocyclobutene and 1,2-dichloroperfluorocyclopentene the fluorines were replaced by bromines by applying aluminium bromide at 0°C[302] (equation 77).



A general method of replacing other halogens by bromine is a reaction of bromine with Grignard reagents prepared from alkyl chlorides or alkyl and aryl iodides. Examples of such a metathetical exchange are shown in equation (78).

$$RCl \xrightarrow[Et_2O]{Mg} RMgCl \xrightarrow[Et_2O]{Br_2} RBr$$

$$ArI \xrightarrow[Et_2O]{Mg} ArMgI \xrightarrow[Et_2O]{Br_2} ArBr \qquad (78)$$

XIV. REFERENCES

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FORMATION OF CARBON–IODINE BONDS

I. INTRODUCTION

Iodine is the Cinderella among its sister halogens. It is more expensive and less reactive than bromine, its compounds are less stable and tend to decompose, and their reactivity, hardly by one order of magnitude higher than that of the corresponding bromine compounds, does not offset the above-mentioned disadvantages. Consequently, applications of iodine and its compounds are fairly limited.

A few thermodynamic data may help to clarify the differences between iodine and bromine. The bond dissociation energy of iodine (36 kcal mol^{-1}) is lower by 10 kcal mol^{-1} than that of bromine. Addition of iodine across double bonds is still exothermic ($\Delta H = -15.5$ kcal mol^{-1}, compared to -22.5 kcal mol^{-1} for bromine), but replacement of hydrogen by iodine at sp^3 carbon is endothermic ($\Delta H = +6.1$ kcal mol^{-1} compared with -8.5 kcal mol^{-1} for bromine), and the activation energy is more than 33 kcal mol^{-1}.

For these reasons direct substitution iodination of saturated compounds is impractical. To make it thermodynamically feasible, the reaction temperature would

have to be raised so much that the reverse reaction, reduction of an iodo compound by hydrogen iodide, would predominate, not to mention the fact that the organic material might decompose entirely.

Similar obstacles are encountered in additions of iodine to double bonds: vicinal diiodides sometimes spontaneously eliminate iodine and regenerate olefins. Thus, the practical uses of iodination shrink to the replacement of hydrogen by iodine in aromatic compounds, of oxygen in ethers and alcohols, of a diazonium group in aromatics, of the carboxyl group in carboxylic acids, and of halogens (transhalogenation).

The most thorough treatment of the iodination of organic compounds is published in *Houben-Weyl's Methoden der organischen Chemie*[1]. Technological aspects are discussed in Kirk and Othmer's *Encyclopedia of Chemical Technology*[2], and theoretical aspects in Patai's *Chemistry of the Carbon–Halogen Bond*[3].

II. MOST COMMON IODINATING AGENTS

Iodine, I_2, is a solid consisting of dark violet plates or scales with metallic lustre. Iodine sublimes easily, forming violet vapours. It is practically insoluble in water (solubility at 20°C is 0.3 g l^{-1}) but dissolves readily in aqueous solutions of sodium or potassium iodides: 15.9 g of iodine in 1l of 0.12 N solution, and 420 g in 1l of 1.9 N solution of potassium iodide. Its solutions in polar solvents (ether, ethanol, acetic acid) are brown, and in non-polar solvents (heptane, benzene, chloroform, carbon tetrachloride and carbon disulphide) are violet. The solubilities of iodine in grams per 100 g of the solvent at the temperatures listed are as follows: heptane, 1.70 at 25°C and 4.20 at 50°C; benzene, 14.09 at 25°C and 25.51 at 50°C; chloroform, 2.63 at 20°C and 11.03 at 62°C; carbon tetrachloride, 2.60 at 35°C and 11.72 at 78°C; carbon disulphide, 14.62 at 20°C and 26.75 at 42°C; ether, 26.1 at 0°C; ethanol (anhydrous), 23.0 at 15°C; acetic acid (anhydrous), 3.16 at 25°C[1].

In aqueous alkali hydroxides, iodine dissolves with the formation of iodides and hypoiodites which disproportionate to iodides and iodates, especially at higher temperatures.

Iodine reacts with alkenes and acetylenes to give vicinal di- and tetraiodides, respectively, replaces hydrogen in aromatic rings, and replaces carboxylic groups in metal salts of carboxylic acids.

Hydrogen iodide is a colourless gas available in steel cylinders. It dissociates at higher temperatures to hydrogen and iodine. It forms aqueous solutions containing 90% of hydrogen iodide at 0°C, 70% at room temperature (fuming hydroiodic acid, density 1.97–2.0), and 56.7% (azeotropic hydroiodic acid, density 1.70, b.p. 126.5°C). The acidity of hydroiodic acid is considerably higher than that of hydrobromic and hydrochloric acid.

Hydrogen iodide adds across multiple bonds, replaces alcoholic hydroxyl groups by iodine, cleaves ethers to alkyl iodides, and replaces diazonium groups by iodine.

Iodine monochloride (commercially available) is a red-brown liquid or a black-brown solid. It decomposes above 100°C to iodine cation and chloride ion. It can chlorinate at temperatures higher than about 200°C. At lower temperatures iodine monochloride is a reactive iodinating agent used especially for addition across multiple bonds (Wijs' iodine number).

Iodine monobromide (commercially available) may be prepared by mixing the elements and removing excess bromine by passing carbon dioxide through the product at 50°C. Iodine monobromide dissociates into iodine and bromine ions and acts both as an iodinating as well as a brominating agent. It is suitable for addition across double bonds – Hanus' iodine number.

Both the aforementioned mixed halogen iodides are much more reactive in the additions to alkenes than iodine. The relative rates at 25°C in solutions in acetic acid are 1.0 for iodine, 3×10^3 for iodine bromide, and 10^5 for iodine chloride[4].

Other sources of positive iodine, such as hypoiodous acid (HOI), alkali hypoiodites (KOI), alkyl hypoiodites (ROI) and acyl hypoiodites (RCOI), are so unstable that they are prepared *in situ* from iodine in water, in alkaline hydroxides, in alcohols in the presence of mercuric oxide, or from iodine and silver carboxylates, respectively.

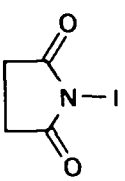
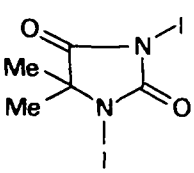
Similarly, phosphorus triiodide is prepared from the elements in the presence of the alcohols which are to be converted to the alkyl iodides. The more stable triphenylphosphite diiodide, $(PhO)_3PI_2$ (diiodotriphenoxyphosphorane)[5], and methyl triphenoxyphosphonium iodide[6], $(PhO)_3P^+MeI^-$, are prepared from their components under anhydrous conditions in essentially quantitative yields and are used for conversion of alcohols to alkyl iodides.

The important iodinating agents *N*-iodosuccinimide[7] and 1,3-diiodo-5,5-dimethyl hydantoin[8] are prepared from iodine and silver succinimide[7] and iodine and disodium-5,5-dimethylhydantoin, respectively.

In contrast to the analogous N-chloro and N-bromo compounds, N-iodo compounds accomplish neither allylic nor benzylic iodination. They are used mainly for electrophilic iodination of aromatic compounds.

Physical properties and applications of the most common iodinating agents are listed in Table 1.

TABLE 1. Most common iodinating agents

Reagent	Molecular weight	Melting point, °C	Boiling point, °C	Density[a]	Applications: Addition	Replacement of: H	O	N	C	Hal
I_2	126.90	113.6	185	4.93/20°C	*	*			*	
HI	127.91	−50.8	−35.4[b]		*		*			
ICl	162.36	13.9 (β) 27.2 (α)	97	3.10/29°C	*	*				
IBr	206.81	40°	116d.	4.42	*	*				
	224.98	200–201			*	*				
	379.92	192–195			*	*				
PI_3	411.69	61					*			
$(PhO)_3\overset{+}{P}Me\bar{I}$	452.23	146					*			
NaI	149.92	651		3.67				*		*
KI	166.02	680		3.12				*		

[a]Temperatures following the solidus indicate temperatures at which densities were evaluated, in degrees Celsius.

[b]Critical temperature, 151°C, critical pressure 82 atm.

III. ADDITION OF HYDROGEN IODIDE ACROSS MULTIPLE BONDS

Addition of hydrogen iodide across multiple bonds is accomplished by treating the unsaturated compounds with concentrated hydroiodic acid (gaseous hydrogen iodide or its solution in acetic acid are used only exceptionally). The hydroiodic acid can be prepared *in situ* from alkali iodides and phosphoric acid[9]. The addition takes place according to Markovnikov's rule, a proton joining the carbon of higher electron density. Peroxides do not affect the direction of addition since they are reduced by hydrogen iodide. Propene gives isopropyl iodide[10,11], cyclohexene yields 90% of iodocyclohexane[9] and 1-bromopropene gives a mixture of both possible isomers[11] (equation 1). α-Methylcrotonic acid affords exclusively the β-iodo compound[12] (equation 2).

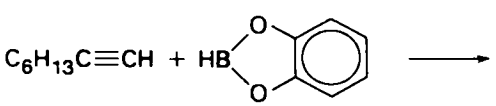
$$CHBr{=}CHCH_3 \xrightarrow{HI} \underset{(27\%)}{CHBrICH_2CH_3} + \underset{(49\%)}{CH_2BrCHICH_3} \quad \text{(Ref. 11)} \quad (1)$$

$$CH_3CH{=}C(CH_3)CO_2H \xrightarrow{HI,\ CHCl_3} CH_3CHIC(CH_3)CO_2H \quad \text{(Ref. 12)} \quad (2)$$

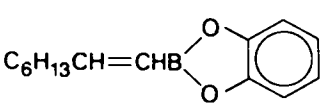
Isomer	Yield, %
Z	44.5
E	74.0

Since the addition of hydrogen iodide is an electrophilic reaction proceeding through a carbonium ion, rearrangements occur[13].

Reaction of acetylenic compounds with one molecule of hydrogen iodide leads to iodoalkenes or their derivatives. Addition of hydrogen iodide to phenylpropiolic acid gave a mixture of *cis* and *trans*-β-iodocinnamic acid[14]. An indirect method of adding hydrogen iodide to acetylenes, with anti-Markovnikov regiospecificity, is a reaction of an acetylene with a borane followed by treatment with iodine[15] (equation 3).



(Ref. 15)

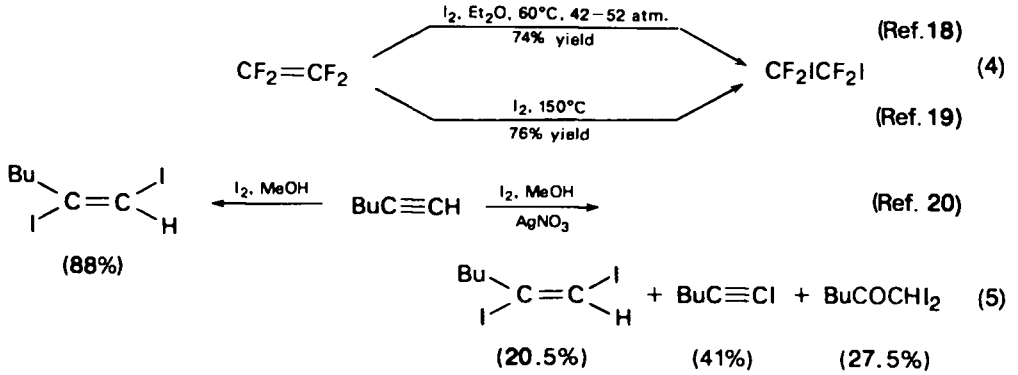


$$\xrightarrow[3.\ I_2,\ Et_2O]{1.\ H_2O,\ 25°C;\ 2.\ NaOH,\ 0°C} C_6H_{13}CH{=}CHI \quad (3)$$

(71%)

IV. ADDITION OF IODINE ACROSS MULTIPLE BONDS

Addition of iodine across double bonds gives vicinal diiodo compounds[16]. The reaction is reversible: vicinal diiodides may eliminate iodine especially at higher temperatures, and give alkenes. In fact, the reaction of vicinal dibromo compounds with sodium iodide in water or acetone solution gives the alkene as the main product[17]. It is, therefore, somewhat surprising that addition of iodine to tetrafluoroethylene takes place only at higher temperatures[18,19] (equation 4). Acetylenes combine with iodine to form vicinal *trans*-diiodoolefins[20] together with other compounds (equation 5).



V. ADDITION OF IODINE AND OTHER ELEMENTS OR GROUPS ACROSS DOUBLE BONDS

Addition of iodine and fluorine across a double bond is accomplished by treatment of an alkene with *N*-iodosuccinimide in anhydrous hydrogen fluoride[21], nd is an important method for the synthesis of fluoro compounds (p. 1032).

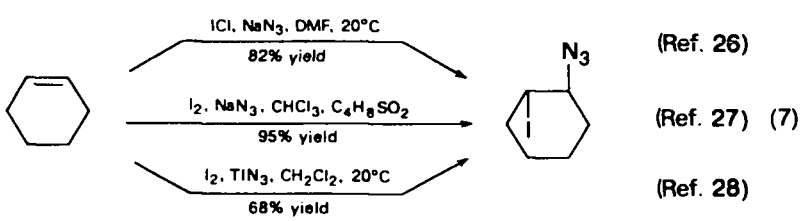
Iodine and chlorine are added using iodine monochloride. With non-symmetrical alkenes the addition is not regiospecific, and the direction of addition depends on the reaction conditions[22,23] (equation 6).

Reaction conditions	Proportion of A, %	Proportion of B, %
−8 to −5°C, glass	98	2
25–30°C, Monel metal	70	30
40–50°C, $FeCl_3$	34	66

Since the rate of addition of iodine monochloride to alkenes is about five orders of magnitude greater than that of iodine[4], iodine monochloride is used for analytical determination of double bonds in unsaturated compounds, especially fats, by determination of the 'iodine number' (according to Wijs)[24].

Iodine monobromide was used for similar purposes (Hanus' iodine number). It is only a thousand times as reactive as iodine bromide, but is prepared more conveniently[25].

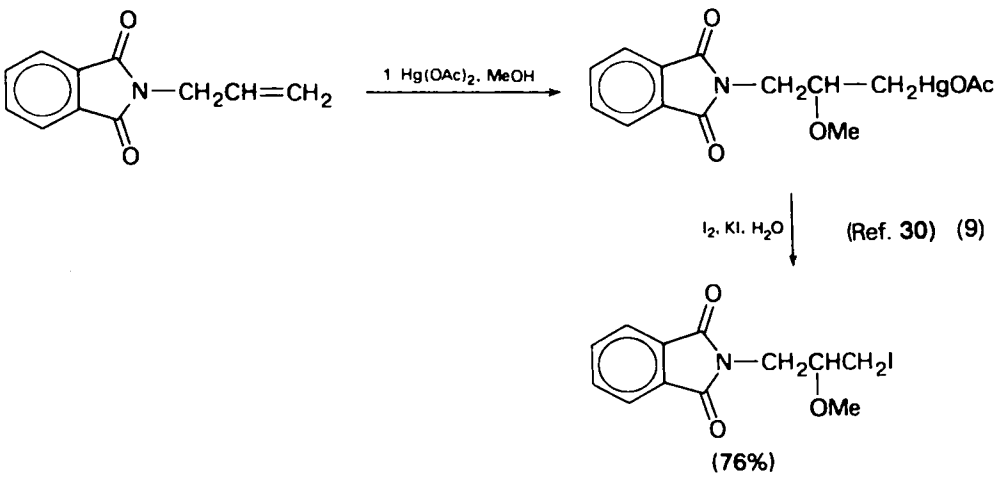
Trans addition of iodine and an azido group to form vicinal iodoazides was accomplished by treating an alkene with iodine chloride and sodium azide in acetonitrile or dimethylformamide[26], or with iodine and thallium azide[27] or sodium azide[28] (equation 7).



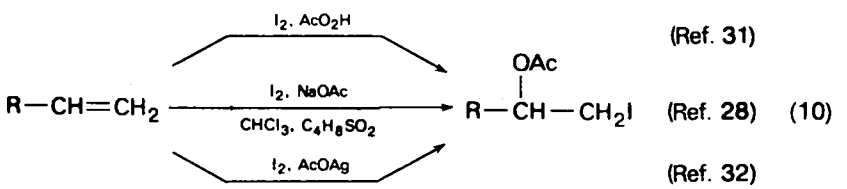
Addition of iodine and a hydroxyl group takes place in a *trans* mode when an alkene is treated with iodine in an aqueous medium[29] (equation 8). Hydrogen peroxide helps recycling of the iodine by oxidizing the hydroiodic acid produced as a by-product[29]. Iodine adds to the carbon of higher electron density.

$$C_3H_7CH{=}CH_2 \xrightarrow[2.\ H_2O_2,\ Me_2CO]{1.\ I_2,\ H_2O} C_3H_7CH(OH)CH_2I \quad (85\%) \qquad \text{(Ref. 29)} \quad (8)$$

Iodine and methoxyl were added to an alkene using a mercuration–iodination procedure in methanolic medium[30] (equation 9).



A reaction of an alkene with iodine and peroxyacetic acid[31] or with sodium acetate[28] or silver acetate[32] results in the formation of an iodohydrin acetate in 54–80% yield (equation 10).



VI. REPLACEMENT OF HYDROGEN BY IODINE IN NON-AROMATIC COMPOUNDS

Replacement of hydrogen by iodine in alkanes and cycloalkanes is all but unknown for reasons explained in Section I. In methyl ketones, however, alkali hypoiodites replace all three hydrogens by iodine, probably via the enolates formed in the basic medium. The 1,1,1-triiodoketones are degraded by the alkaline medium to an acid having one less carbon, and to iodoform[33].

Since iodoform, a yellow crystalline solid, is easily identifiable by its smell and melting point, iodination with alkali hypoiodites is used as an analytical test for methyl ketones or their progenitors (Lieben test)[33]. With the advent of NMR, the iodoform test became less significant.

Introduction of iodine into positions α to the anhydride group in acetic anhydride[34] or α to the carboxyl in saturated aliphatic acids may proceed through intermediate enols[35] (equation 11).

$$(CH_3CO)_2O \xrightarrow[\text{75\% yield (Ref. 34)}]{I_2, H_2SO_4, HNO_3, 50-60^\circ C} CH_2ICO_2H \xleftarrow[\text{79.4 - 100\% yield (Ref. 35)}]{I_2, ClSO_3H, CH_2ClCH_2Cl} CH_3CO_2H \quad (11)$$

Acetylenic hydrogen was replaced by iodine when 1-heptyne was treated first with sodamide in liquid ammonia and then with iodine[36] (equation 12).

$$C_5H_{11}C{\equiv}CH \xrightarrow[\text{30\% yield}]{NH_3, I_2, 20^\circ C, \text{autoclave}} C_5H_{11}C{\equiv}CI \quad \text{(Ref. 36)} \quad (12)$$

$$C_5H_{11}C{\equiv}CH \xrightarrow[\text{6\% yield}]{Na, NH_3; I_2, -33^\circ C} C_5H_{11}C{\equiv}CI$$

VII. REPLACEMENT OF HYDROGEN BY IODINE IN AROMATIC SYSTEMS

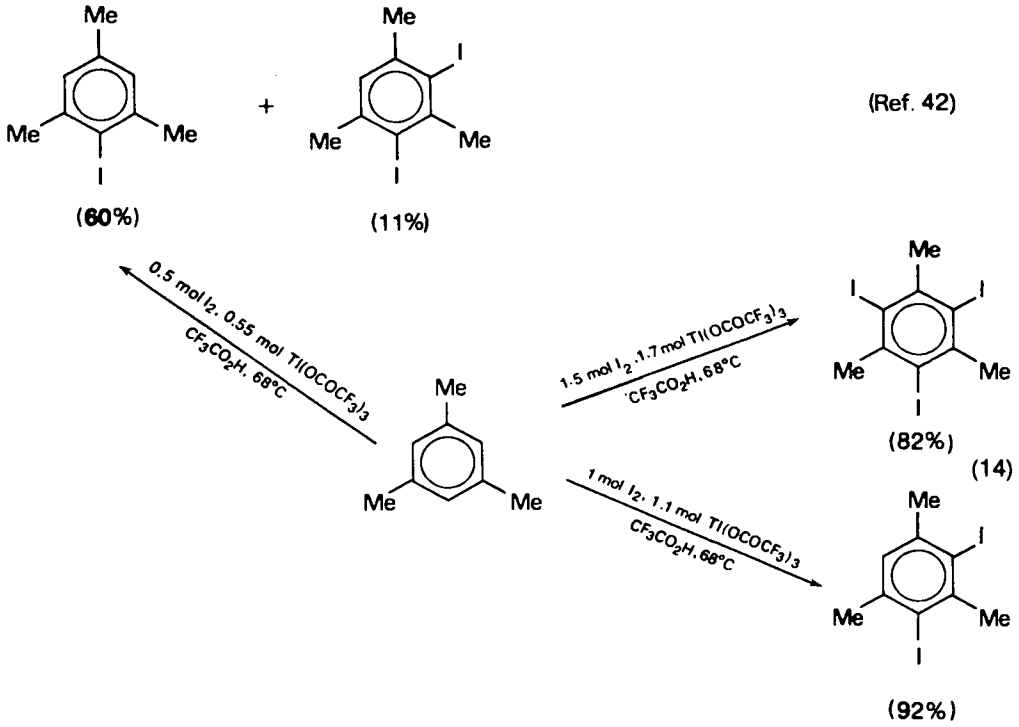
In contrast to hydrogens at saturated carbon (sp^3), aromatic hydrogens are replaced by iodine relatively easily, even in compounds carrying deactivating substituents. Since iodination is reversible, hydrogen iodide generated in the reaction tends to reduce the iodo compound to the starting material. It must, therefore, be removed from the reaction as soon as it is formed. This can be achieved by its neutralization with sodium bicarbonate, calcium carbonate or mercuric oxide, or by precipitation of the insoluble silver iodide with silver sulphate or other silver salts. In the ideal situation, hydrogen iodide can be reoxidized to iodine by fuming sulphuric acid (oleum), nitric acid, iodic acid, hydrogen peroxide, alkali persulphate, organic peroxy acids and other oxidizing agents. As an example, iodination of benzene is shown in equation (13)[37–42].

$$C_6H_6 \longrightarrow C_6H_5I \quad (13)$$

Reaction conditions	Yield, %	Ref.
I_2, H_2SO_4, Ag_2SO_4	75–80	37
I_2, HNO_3, 50°C	86–87	38
I_2, $Na_2S_2O_8$, AcOH, reflux	70	39
I_2, AcO_2H, H_2SO_4, 70°C	77.3	40
I_2, CF_3SO_3Ag	100	41
I_2, $Tl(OCOCF_3)_3$	89	42

In some cases, the iodinating agent is not iodine but acetyl hypoiodite formed from iodine and peroxyacetic acid[40], or trifluoromethanesulphonyl hypoiodite formed from iodine and silver trifluoromethanesulphonate[41]. In the case of thallium tris(trifluoroacetate), the iodo compound is formed by iodination of an organothallium compound, $C_6H_5Tl(OCOCF_3)_2$[42].

The reaction conditions illustrated in equation (13) are applicable to most aromatic compounds having alkyl groups or substituents attached to the benzene rings. Depending on the nature of such substituents, milder or harsher conditions must be applied. Strongly deactivated tetrafluorobenzene[43] and pentafluorobenzene[44] were successfully iodinated in strong fuming sulphuric acid to diiodo- and monoiodoperfluorobenzenes in 81% and 71% yields, respectively.



Homologues of benzene were converted to monoiodo compounds by iodine and peroxyacetic acid in the presence or absence of sulphuric acid[40]. Polyiodination of benzene and its homologues was achieved by iodine and thallium tris(trifluoroacetate) in trifluoroacetic acid as the best solvent[42] (equation 14).

In iodination of biphenyl, diphenylmethane and 1,2-diphenylethane, acetyl hypoiodite prepared *in situ* from iodine and peroxyacetic acid gave predominantly *p*-iodo derivatives[45].

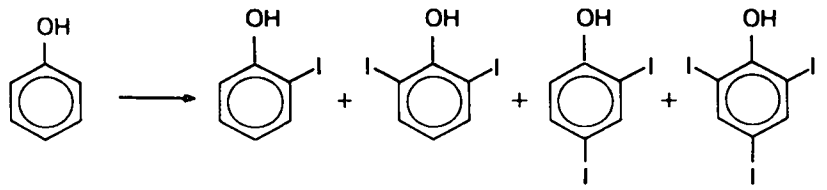
Phenols are iodinated very easily, especially in the presence of ammonia or alkalis when the iodinated species are the phenoxide ions. As a consequence of the highly activated ring, polyiodination in positions *ortho* and *para* to the hydroxyl group usually results. Some regioselectivity for predominance of *ortho* iodination was achieved when thallium(I) acetate and iodine were used[46] (equation 15).

Otherwise, if *o*- or *p*-monoiodophenols are to be prepared, indirect introduction of iodine by iodination of phenol-mercurials (equation 46) or by Sandmeyer or Gattermann reactions is more suitable (p. 1156). Iodination of phenol(s) was also achieved by other iodinating agents such as iodine chloride[47], *N*-iodomorpholine hydroiodide[48] and 1,3-diiodo-5,5-dimethylhydantoin[49] (equation 16).

Phenol ethers are iodinated with iodine[50,51] (equation 17) or with iodine chloride[52] or with iodine and silver trifluoromethanesulphonate[41] in good to excellent yields and under mild conditions.

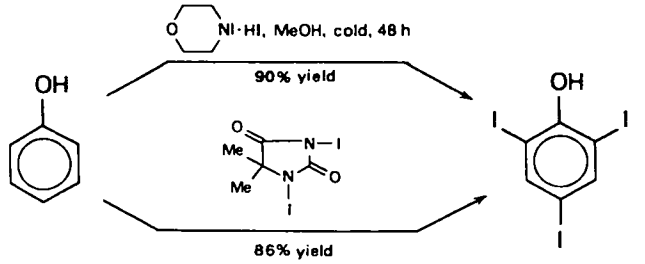
Under various conditions, aniline was iodinated to *p*-iodoaniline[53], 2,4-diiodoaniline[54] or 2,4,6-triiodoaniline[54] (equation 18). The triiodoaniline was also obtained from aniline and 1,3-diiodo-5,5-dimethylhydantoin, which, in addition, iodinated acetanilide to *p*-iodoacetanilide in 75% yield[49].

Iodination of aromatic rings occurs readily and gives good yields even if deactivating

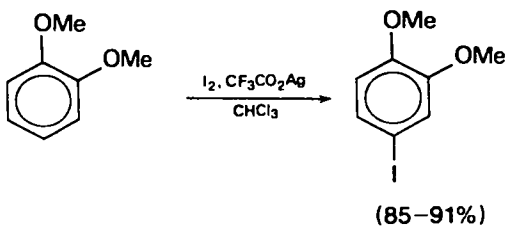


(Ref. 46) (15)

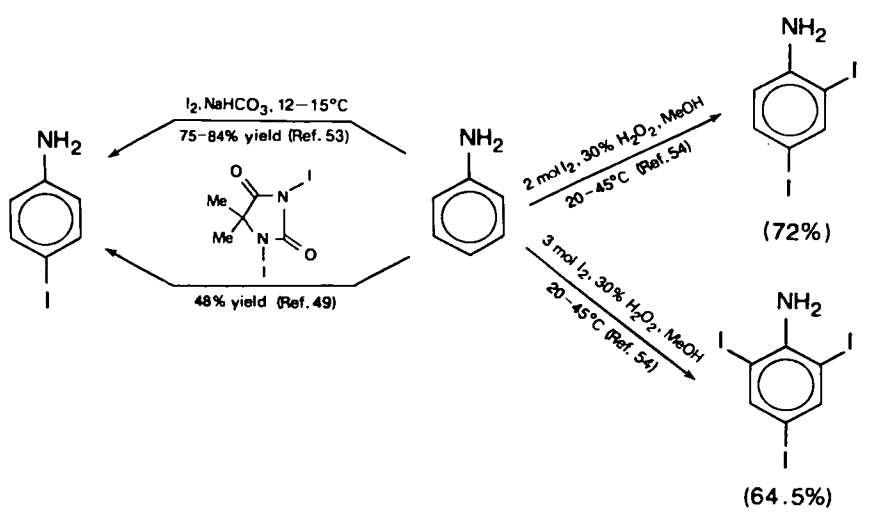
Reaction conditions	Proportion of product, %			
	2-Iodo-phenol	2,6-Diiodo-phenol	2,4-Diiodo-phenol	2,4,6-Triiodo-phenol
1 mol I_2, 1.2 mol TlOAc, AcOH, 20°C	83	17	—	—
3 mol I_2, 3.6 mol TlOAc, AcOH, 20°C	—	7	7	86



(Ref. 48) (16) (Ref. 49)

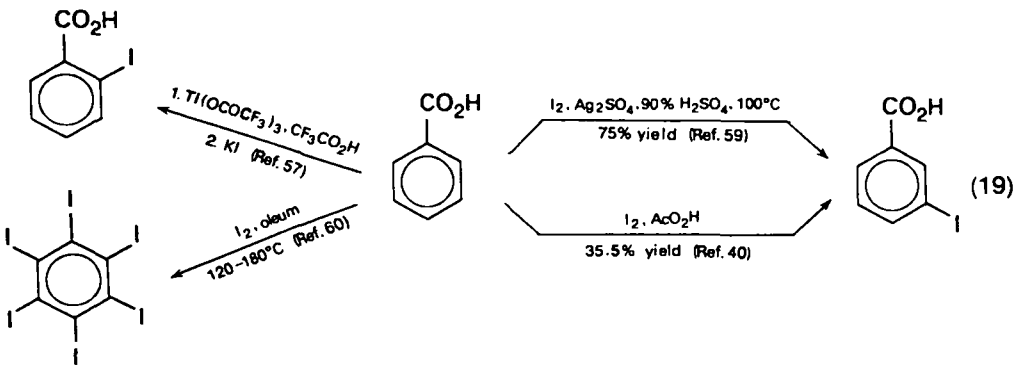


(Ref. 51) (17)



(18)

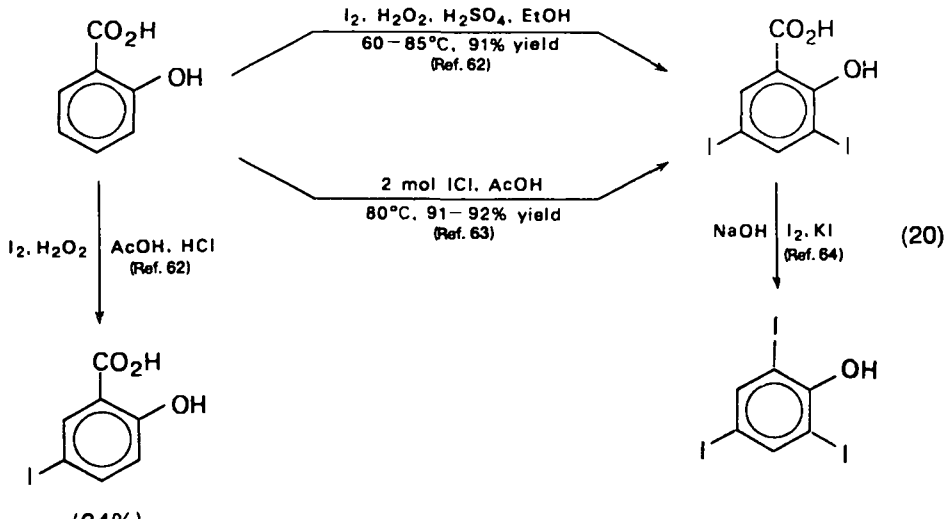
substituents are bonded to the ring. Benzotrifluoride afforded quantitative yield of *m*-iodobenzotrifluoride on treatment with iodine and silver trifluoromethanesulphonate[41]; fluorenone gave 41% yield of 2-iodofluorenone and 58% yield of 2,7-diiodofluorenone on treatment with *N*-iodosuccinimide in 90% sulphuric acid[55]; 10,10-dimethylanthrone gave 1-iodo-10,10-dimethylanthrone with iodine and thallium tris(trifluoroacetate)[56]; and benzoic acid gave *o*-iodo-[57,58] or *m*-iodobenzoic acid[40,59], depending on the reagents used (equation 19). Iodination of benzoic acid in fuming sulphuric acid gave hexaiodobenzene[60] (equation 19). Phthalic anhydride yielded 80–82% of tetraiodophthalic anhydride on heating with iodine in oleum[61]. Under such extreme conditions the carboxyl group is frequently replaced by iodine[60], as is also shown in equation (19).



(19)

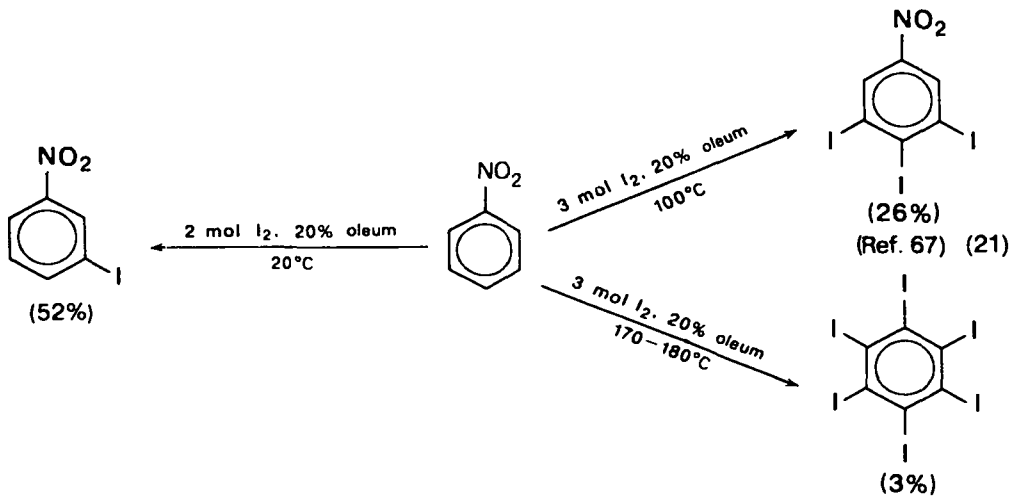
The presence of activating substituents in benzoic acid makes iodination very easy, and replacement of the carboxyl group by iodine takes place even under mild conditions. Salicylic acid gave 5-iodo-[62] and 3,5-diiodosalicylic[62,63] acids and even 2,4,6-triiodophenol[64] (equation 20). Anthranilic acid was iodinated with iodine monochloride in 88–90% yield to 5-iodoanthranilic acid[65], and in 91% yield to 2,4,6-triiodoaniline[66].

Polyiodinated aromatic carboxylic acids are useful radio-opaque compounds, so that direct iodination is a welcome method for their synthesis which otherwise would be very tedious.



(20)

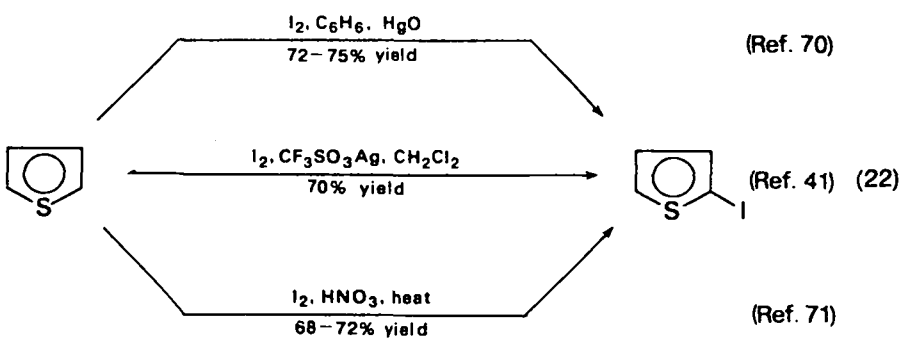
Nitrobenzene was iodinated, under fairly vigorous conditions, to *m*-iodonitrobenzene[67], to 3,4,5-triiodonitrobenzene[67] and even to hexaiodobenzene[67] (equation 21).



p-Nitroaniline and iodine monochloride afforded 2,6-diiodo-4-nitroaniline in 56–64% yield[68].

VIII. REPLACEMENT OF HYDROGEN BY IODINE IN AROMATIC HETEROCYCLES

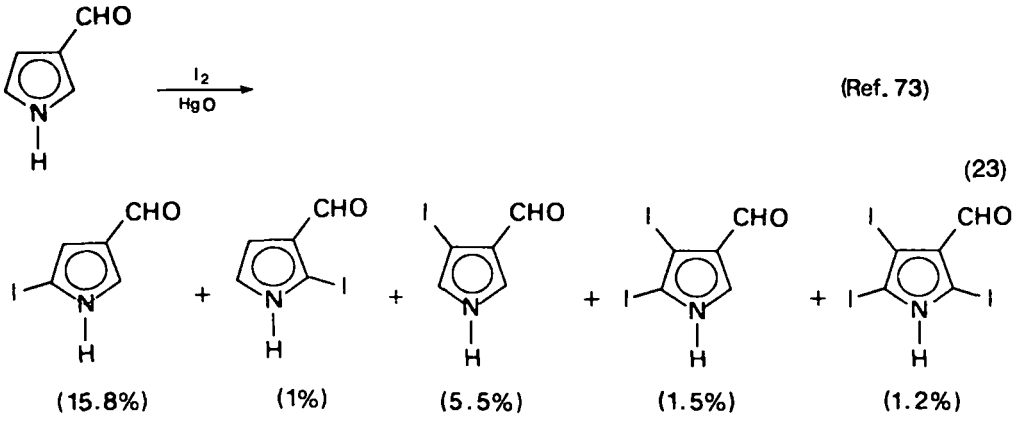
Direct iodination of furan itself has not been reported. However, iodine and dimethyl sulphoxide gave, via an addition product, 5-iodo-2[2′-quinoxalinyl]furan from 2-[2′-furyl]quinoxaline in 94% yield[69]. Iodination of thiophene occurs at mild conditions to give 2-iodothiophene[41,70,71] (equation 22).



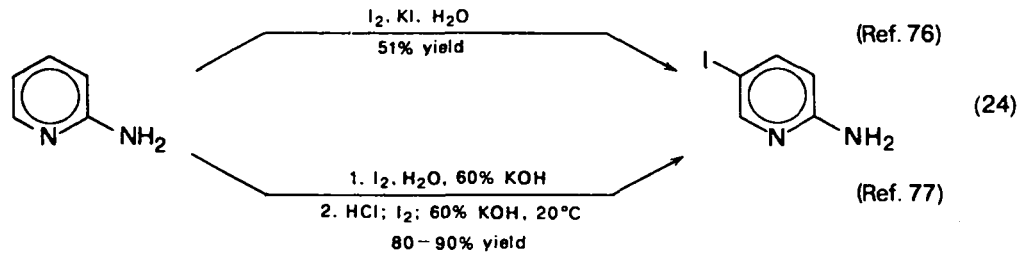
Using iodine and 10% hydrogen peroxide in ethanol–acetic acid solution, pyrrole is converted under very mild conditions to 2,3,4,5-tetraiodopyrrole in 80% yield[72].

Pyrrole-2-carboxaldehyde and pyrrole-3-carboxaldehyde were iodinated in the presence of mercuric oxide or iodic acid to many mono-, di- and triiodo compounds[73] (equation 23).

Pyrazole gave 98% yield of 4-iodopyrazole on refluxing with iodine, potassium iodide and sodium acetate in water[74].



Iodination of pyridine itself with iodine was not accomplished. However, 3-iodopyridine was obtained by decarboxylation of 3-iodopyridine-2,6-dicarboxylic acid, prepared by oxidation of 3-iodo-2,6-dimethylpyridine which resulted from heating 2,6-lutidine with iodine and 30% oleum at 200–210°C[75]. In contrast to such harsh treatment, 2-aminopyridine was iodinated to 2-amino-5-iodopyridine under very gentle conditions[76,77] (equation 24).



Refluxing 8-hydroxyquinoline with ethanolic solution of iodine and 25% aqueous hydrogen peroxide afforded 89% yield of 5,7-diiodo-8-hydroxyquinoline[78].

IX. REPLACEMENT OF OXYGEN BY IODINE

The most important reactions involving cleavage of carbon–oxygen bonds by iodo compounds are transformations of ethers to alkyl iodides, of epoxides to iodohydrins, and of alcohols and their sulpho esters to alkyl iodides.

A. Cleavage of Ethers (Epoxides)

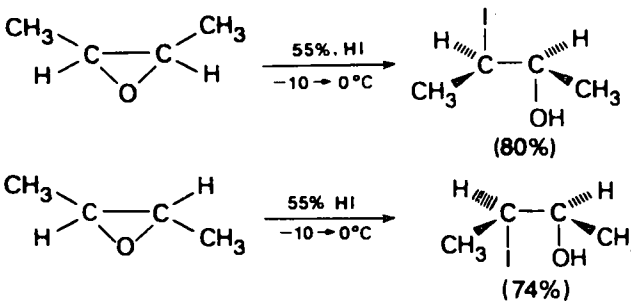
Of all hydrogen halides, hydrogen iodide is the most suitable for cleavage of ethers. Aliphatic ethers give alkyl iodides[79] and alkyl aryl ethers give alkyl iodides and phenols[80]. The former reaction has few applications since alkyl iodides can be prepared more conveniently from alcohols than from the less accessible ethers. Although the latter reaction also has only limited preparative importance[80] (e.g. equation 25), it is used for quantitative determination of aromatic methoxy groups[81].

Cleavage of tetrahydrofuran with anhydrous gaseous hydrogen iodide or, better still, hydrogen iodide developed *in situ* gives high yields of 1,4-diiodobutane[82] (equation 26).

$$PhO(CH_2)_6CO_2H \xrightarrow[160-170°C]{57\%\ HI} PhOH + I(CH_2)_6CO_2H \quad (70\%) \quad \text{(Ref. 80)} \quad (25)$$

$$\xrightarrow[\text{Reflux}]{KI,\ H_3PO_4} I(CH_2)_4I \quad (92-96\%) \quad \text{(Ref. 82)} \quad (26)$$

Epoxides (oxiranes) are cleaved stereospecifically by azeotropic hydroiodic acid under very gentle conditions: *cis* oxides give *threo* iodohydrins and *trans* oxides *erythro* isomers[83] (equation 27).



(80%) (Ref. 83) (27)

(74%)

A steroidal epoxide was opened to a *trans* iodohydrin by azeotropic hydroiodic acid[84]. Sometimes hydrogen iodide does not cleave the epoxides but reduces them to unsaturated compounds[85].

B. Cleavage of Alkyl Sulphonates

Treatment of alkyl methanesulphonates or, much more frequently, *p*-toluenesulphonates (tosylates) with sodium iodide in acetone or magnesium iodide in ether developed into a general procedure for the synthesis of alkyl iodides[86] (equation 28). The reaction is usually carried out by refluxing or heating in sealed

$$CH{\equiv}C(CH_2)_nCH_2OTs \xrightarrow[20°C]{NaI,\ Me_2CO} CH{\equiv}C(CH_2)_nCH_2I \quad \text{(Ref. 86)} \quad (28)$$

n	Yield %
1	64
2	70

vessels, but some tosylates give good yields of alkyl iodides even at room temperature[87]. This method is a by-pass of the conversion of alcohols to alkyl iodides since alkyl tosylates are prepared from alcohols very easily and are transformed into alkyl iodides without using hydrogen iodide or phosphorus iodide, both of which could affect other functions in the molecules[87].

Conversion of alkyl tosylates to alkyl iodides is an S_N2 displacement in most cases and takes place without rearrangements and with complete inversion of configuration in high yields[88] (equation 29): β-tosylates of steroidal alcohols gave α-iodosteroids[88].

Replacement of the tosyl group by iodine is frequently used in carbohydrate chemistry[89].

$$(+)\text{—}C_6H_{13}CHMeOTs \xrightarrow[20°C]{MgI_2,\ Et_2O} (-)\text{—}C_6H_{13}CHMeI \quad \text{(Ref. 88)} \quad (29)$$

(94%)

C. Replacement of Hydroxyl in Alcohols

Alcohols distilled or refluxed with azeotropic (57%) hydroiodic acid give good to high yields of alkyl iodides[90]. With higher alcohols and glycols fuming hydroiodic acid (density = 1.94) must be used[91] (equation 31). Alternatively, the alcohols can be treated with anhydrous hydrogen iodide prepared *in situ* from potassium iodide and phosphoric acid[92,93] (equations 30, 31).

$$ROH \xrightarrow[100-120°C,\ 3-5\ h]{KI,\ 95\%\ H_3PO_4} RI \quad \text{(Ref. 93)} \quad (30)$$

R	Yield, %
n-Pr	95
i-Bu	88
t-Bu	77.9

$$HOCH_2(CH_2)_8CH_2OH \xrightarrow[100\%\ \text{excess, reflux}]{HI\ (\text{density } 1.94)} ICH_2(CH_2)_8CH_2I \quad \text{(Ref. 91)}$$

(88.5%)

$$HOCH_2(CH_2)_4OH \xrightarrow[100°C]{KI,\ H_3PO_4} ICH_2(CH_2)_4CH_2I \quad \text{(Ref. 92)} \quad (31)$$

(95.3%)

The replacement of hydroxyl groups by iodine can also be achieved by treatment of alcohols with phosphorus triiodide, which is always prepared *in situ* from white or, more frequently, red phosphorus and iodine. The reaction is carried out by heating the alcohol with phosphorus and iodine[94] (equation 32) or, with volatile alcohols, by refluxing alcohol and phosphorus in a special apparatus which provides for gradual flushing of iodine into the reaction flask by condensed alcohol[95]. In this way, lower aliphatic iodides were prepared in 90–95% yields[95].

$$C_{16}H_{33}OH \xrightarrow[145-150°C]{P,\ I_2} C_{16}H_{33}I \quad \text{(Ref. 94)} \quad (32)$$

(78%)

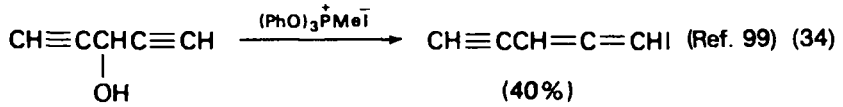
Because of the reducing properties of hydrogen iodide, glycerol can be converted to isopropyl iodide if it is heated with phosphorus and iodine in the presence of water, which generates hydrogen iodide[96], or to allyl iodide under anhydrous conditions[97] (equation 33).

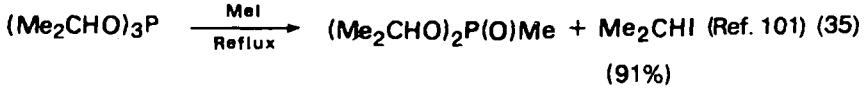
$$\text{(Ref. 96)} \quad \xrightarrow[\text{Distillation}]{P,\ I_2,\ H_2O} \quad CH_3CHICH_3$$

$$CH_2(OH)\text{—}CH(OH)\text{—}CH_2(OH) \quad \text{(Ref. 97)}$$

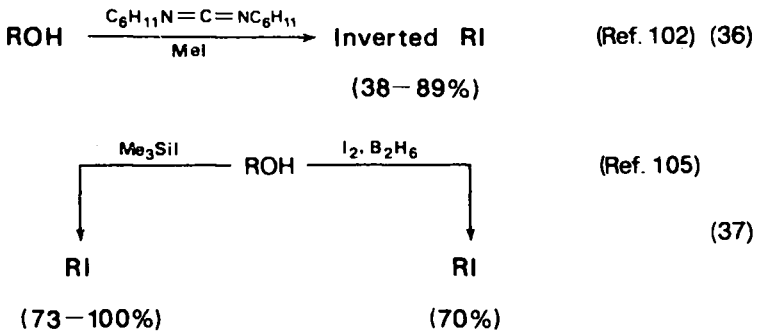
$$\xrightarrow[\text{Distillation}]{P,\ I_2} \quad CH_2{=}CHCH_2I \quad (33)$$

An elegant method for the synthesis of alkyl iodides is the reaction of alcohols with diiodotriphenoxyphosphorane, $(PhO)_3PI_2$[98], or with methyltriphenoxyphosphonium iodide[6,99] (equation 34), or with methyl iodide and triphenyl[100] or triisopropyl[101] phosphite (equation 35). This modification is especially suited for sensitive and reactive alcohols. However, propargylic alcohols undergo rearrangement[99].





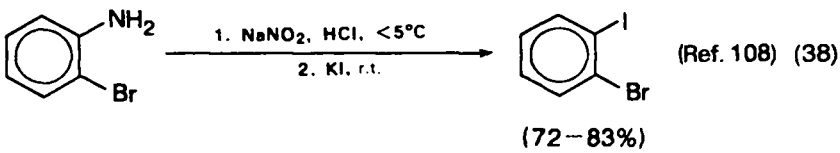
Other ways of converting alcohols to alkyl iodides are by their reaction with dicyclohexylcarbodiimide and methyl iodide[102,103] (equation 36), with trimethylsilyl iodide[104] (equation 37) and with diborane and iodine[105] (equation 37).

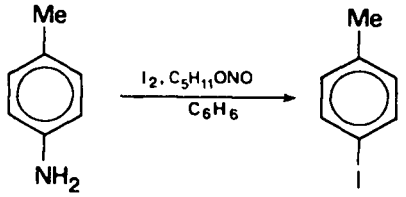


X. REPLACEMENT OF NITROGEN BY IODINE

Aliphatic diazo compounds form geminal diiodides on treatment with iodine[106]; trifluorodiazoethane afforded 1,1-diiodo-2,2,2-trifluoroethane in 87% yield[106].

The most useful replacement of nitrogen by iodine takes place when aromatic diazonium compounds are treated with sodium or potassium iodide. In contrast to the analogous reactions leading to chlorides or bromides, the reaction of the diazonium salts with iodides does not require catalysis by copper or its compounds. Just treatment or heating of the aqueous solutions of diazotized amines with an aqueous solution of alkali iodide results in the replacement of the original amino group by iodine[107–110] (equations 38, 39).





(Ref. 109) (39)

(49–60%)

XI. REPLACEMENT OF CARBOXYL BY IODINE

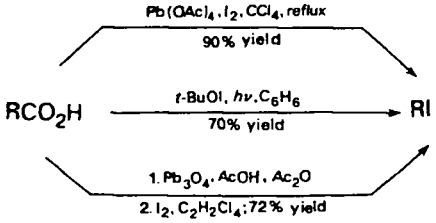
Energetic iodination of aromatic carboxylic acids such as benzoic and terephthalic acid, and especially salicylic and anthranilic acid, resulted in decarboxylation and replacement of carboxyl by iodine[64,66] (equation 20).

More systematic replacement of a carboxyl group by iodine takes place during the heating of silver salts of carboxylic acids with iodine (Hunsdiecker's reaction) and leads to alkyl or aryl iodides in good yields. Intermediates are acyl hypoiodites and triacyloxyiodine, $I(OCOR)_3$[111]. This method has a great value for the synthesis of iodo derivatives inaccessible by other methods, e.g. perfluoroalkyl iodides[112,113] (equation 40).

$$AgOCO(CF_2)_4COOAg \xrightarrow[100-150°C]{2\ mol\ I_2} I(CF_2)_4I \quad \text{(Ref. 112)} \quad (40)$$

(64%)

Similar decarboxylative iodination was achieved by decomposition by iodine of lead salts prepared *in situ* from carboxylic acids and lead tetraacetate[114], or lead oxide (Pb_3O_4) in acetic acid and anhydride[115], or by treatment of free carboxylic acids with *t*-butylhypoiodite under irradiation[114] (equation 41).



(Ref. 114)

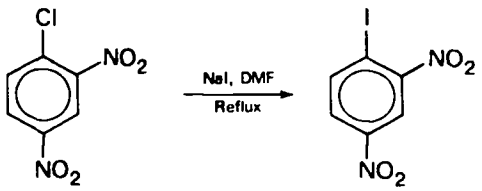
(Ref. 114) (41)

(Ref. 115)

XII. REPLACEMENT OF HALOGENS BY IODINE

As in the case of organic fluorides, 'transhalogenation' is very useful for the synthesis of organic iodides. It is based on halogen–iodine interchange and is usually effected by refluxing an alkyl halide (or sufficiently reactive aryl halide) with sodium iodide in acetone (Finkelstein reaction) or other solvents[116–119] (equations 42, 43). Since the solubility of sodium iodide in acetone is much greater than that of sodium bromide or sodium chloride, the bromide and chloride will precipitate from acetone and will thus shift the equilibrium towards the formation of the organic iodide. Both acetone and sodium iodide must be dry – commercial sodium iodide is not hygroscopic but contains some water even if declared pure[120]. A convenient way of drying sodium iodide is to heat the finely ground material in a flask in a steam bath under reduced pressure, or, in

$$Cl(CH_2)_6Cl \xrightarrow[\text{Reflux}]{NaI,\ Me_2CO} I(CH_2)_6I \quad (50\%) \qquad \text{(Ref. 116)} \quad (42)$$



(65–71%) (Ref. 117) (43)

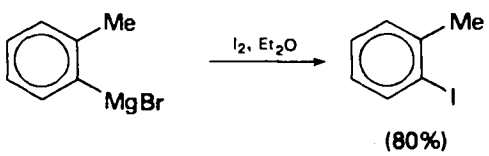
small amounts, to heat the crude iodide in a test tube attached to an aspirator until no more water condenses on the walls of the test tube[120].

Conversion of organic bromides and especially chlorides to iodides is usually done in order to increase their reactivity in nucleophilic displacements. Such a transhalogenation can be accomplished *in situ*, by adding a small amount of dry sodium iodide (0.1 or 0.05 mol equivalent) to a reaction mixture containing a nucleophile (e.g. a sodium derivative of a carbanion) and alkyl bromide or chloride. The amount does not have to be stoicheiometric since the sodium iodide is recycled by the alkylation of the organic iodide with the sodium salt of the nucleophile.

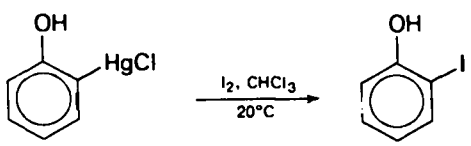
$$RCl \xrightarrow{NaI} RI \xrightarrow{NaCH(CO_2R)_2} RCH(CO_2R)_2 + NaI \qquad (44)$$

XIII. REPLACEMENT OF METAL BY IODINE

An infallible method for the replacement of a halogen by iodine is reaction of iodine with an organometallic compound prepared from an organic halide and lithium or alkyl lithium[121], magnesium[122,123], or mercury[124,125]. Such metathesis takes place under mild conditions, usually in boiling ether, and gives good yields of iodo compounds (equations 45, 46).



(80%) (Ref. 123) (45)



(63%) (Ref. 124) (46)

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HALOGENATION TABLES*

I. INTRODUCTION

Halogenation and other methods of preparation of halogen derivatives include an enormous number of reactions and reagents available for introducing halogens into organic products and intermediates. The Halogenation Tables is an attempt to correlate starting materials, products and halogenating agents to facilitate an orientation in this field of chemistry and to show what reactions are suitable for a specific purpose. Isolated and exceptional cases are omitted, but most common types of organic compounds and halogenating agents are included. A critical evaluation of the individual applications are shown in different markings: ⊕ means most common use, + means applicable, and (+) means of limited or rare application. The tables are based on the monographs listed at the end, on original literature references, and on the authors' experiences.

II. EXPLANATION OF SYMBOLS

RH	aliphatic and alicyclic hydrocarbons and saturated hydrocarbon chains far enough from functional groups
C=C	alkenes, cycloalkenes and their functional derivatives
C=C—CH	allylic systems
C≡C	acetylenes and their derivatives
C≡CH	terminal acetylenes and their derivatives
ArH	aromatic hydrocarbons and aromatic heterocyclics and their derivatives having at least one hydrogen in the aromatic ring
ArCH	benzylic systems
RX	halogen derivatives other than those of the reacting halogen
ROH	alcohols and exceptionally phenols
RCHOR	ethers having at least one hydrogen next to oxygen
ROR′	ethers, aliphatic and aliphatic–aromatic
ArCHO	aromatic aldehydes
CHO, —CO—	aldehydes, ketones
CHCHO, CHCOR	aldehydes and ketones having at least one α-hydrogen
$COCH_3$	methyl ketones (in haloform reaction)
CO_2H, RCO_2H	carboxylic acids
$CHCO_2H$	carboxylic acids having at least one α-hydrogen
CHCZ, CHCN	acyl halides, esters and nitriles having at least one α-hydrogen
CONH	primary or secondary amides

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CONHR	secondary amides and their tautomers —C(OH)=N— in heterocycles
$CONR_2$	tertiary amides
RSH, RSSR	mercaptans, thiophenols and disulfides
RSO_2H	sulfinic acids
RSO_3H, $ArSO_3H$	sulfonic acids, aromatic sulfonic acids
$ROSO_2R'$	alkyl sulfonates
SO_2NH	primary or secondary sulfonamides
$ArNO_2$	aromatic nitro compounds
CHN_2	aliphatic diazo compounds, especially diazoketones
ArN_2^+	aromatic diazonium compounds
C=NOH	oximes, especially ketoximes
RNH	primary and secondary amines
C—C	carbon–carbon bond cleavage (halogenolysis)
P, S, I	tertiary phosphines, sulfides and aryl iodides (conversion to high-valency states of P, S, I)

III. FLUORINATION

Starting compound:	RH	C=C	C=C	C=C	C≡C	C≡C	ArH	ArH	RX	CHX_2 CX_3	ROH	—CHO —CO—	$COCH_2$	CO_2H	COCl	$CONH_2$	$ROSO_2R'$	SO_2Cl	CHN_2	ArN_2^+	C—C	P S I
Product:	RF	CF—CF	CH—CF	CX—CF[a]	CF_2—CF_2	$(CH{=}CF)$ CH_2—CF_2	ArH + 6F[b]	ArF	RF	$CHXF_2$, CHF_2 CXF_2, CF_3	RF	$-CHF_2$ $-CF_2$	COCHF	CF_3	COF	CONHF	RF	SO_2F	CH_2F CHFX	ArF	CF + FC	PF_2[c] SF_2[c] IF_2[c]
F_2 or electrolysis in HF	⊕	⊕			(+)		⊕	(+)	(+)	+						⊕						
FCl[d]				⊕																		
FBr[d]				⊕															+			
FI[d]				⊕																		
$FClO_3$			⊕			⊕			(+)	⊕	(+)		⊕[e]						⊕			
HF[f]									(+)		+			⊕[g]								⊕
SF_4										⊕		⊕										
SeF_4, MoF_6																						
NOF, NO_2F				⊕																		
AsF_3, SbF_3, SbF_3Cl_2										⊕												
SbF_5		(+)					(+)		(+)	⊕												
SiF_4, Na_2SiF_6										⊕									(+)			
HBF_4, $NaBF_4$																			⊕			
AgF, HgF		[i]							⊕													
HgF_2									⊕	⊕												

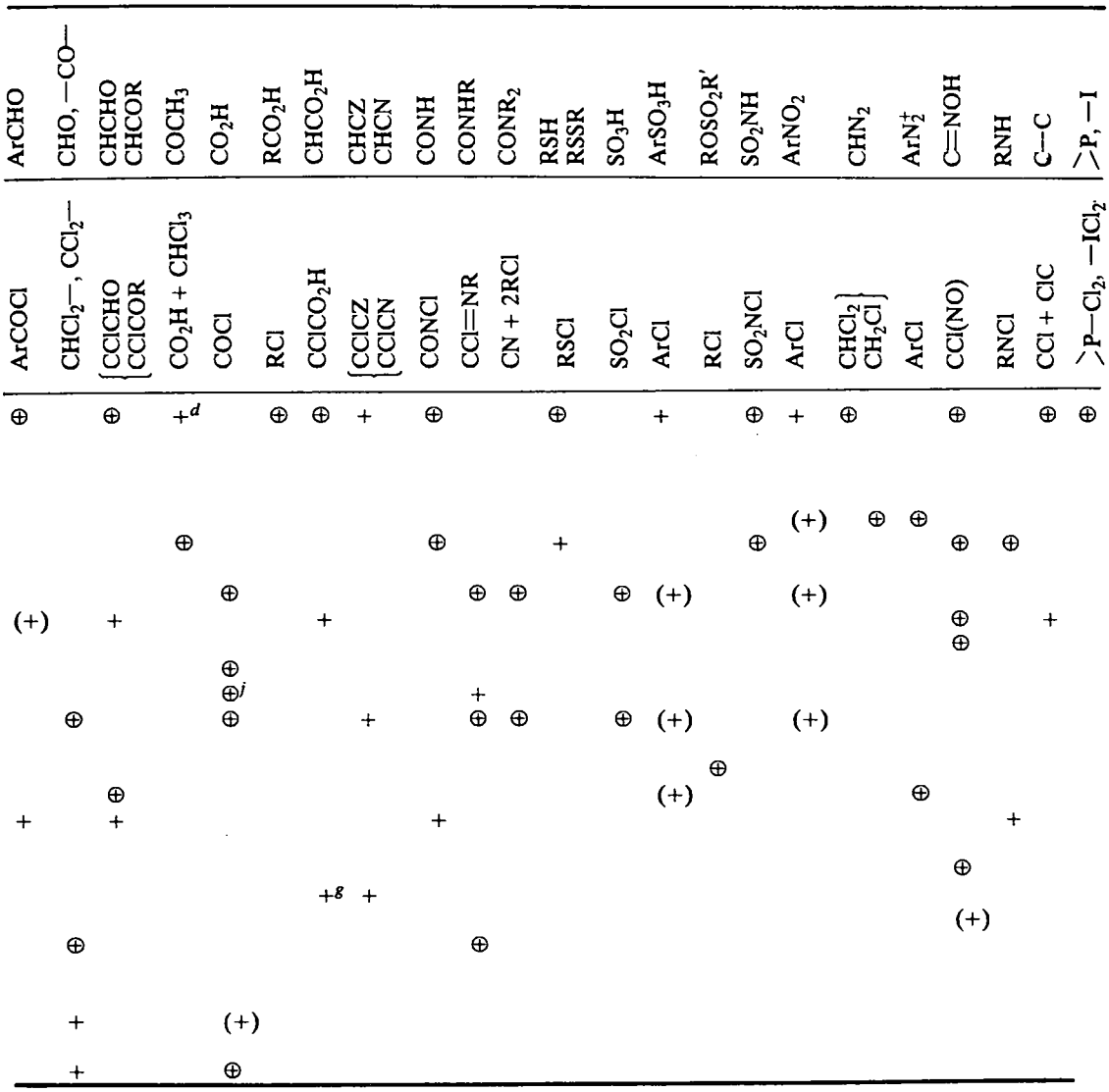
AgF_2, CoF_3 (MnF_3, CeF_4, BiF_5)	⊕	⊕				⊕		(+)	⊕									
LiF, NaF, KHF_2, TlF														⊕			+	
KF (RbF, CsF)			⊕[i]	+[k]				⊕[l]	⊕					⊕		⊕	⊕	
XeF_2	⊕	⊕					⊕											
$ArIF_2$		⊕					(+)											
$ArSF_3$											⊕		⊕					
Et_2NSF_3										⊕	⊕							
Ph_3PF_2, Ph_2PF_3										⊕								
Et_2NCF_2CHClF										⊕								
$PbF_2(OAc)_2$		⊕																
CF_3OF	⊕			⊕			⊕											
COF_2, COClF										+								

[a] X = Cl, Br, I. In reaction with NOF and NO_2F, X = NO or NO_2. In reaction with CF_3OF, X = OCF_3.
[b] Addition of six fluorines to aromatics and halogenated aromatics with partial and/or total replacement of hydrogens or halogens by fluorine.
[c] High-valency fluorides of phosphorus, sulfur and iodine.
[d] Prepared *in situ* from hydrogen fluoride and *N*-chloro, *N*-bromo-, and *N*-iodo amides, respectively; from fluorine tribromide and bromine, or iodine pentafluoride and iodine, respectively.
[e] Replacement of hydrogens in enol ethers, enamines, and in β-dicarbonyl and β-dicarboxyl compounds only.
[f] Frequently in the presence of catalysts: antimony chlorides in liquid phase, and ferric or chromic salts in vapour phase reactions.
[g] Preparation of $ArIF_2$ from ArIO.
[h] Intermediate RCOF can be isolated if limited amount of sulfur tetrafluoride is used.
[i] Silver fluoride in the presence of hydrogen fluoride.
[j] In the presence of proton donors such as formamide.
[k] In the presence of iodine, X = I.
[l] KF also replaces aromatic halogens activated for nucleophilic displacement and halogen atoms in aromatic polyhalogen compounds.

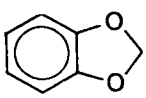
IV. CHLORINATION

Starting compound:	RH	C=C	C=C	C=C	C=C	C=C—CH	C≡C	C≡C	C≡C	C≡CH	ArH	ArH	ArCH	RX[a]	ROH	RCHOR	ROR'
Product:	RCl	CCl—CCl	CH—CCl	C(OH)—CCl	CY—CCl[b]	C=C—CCl	CCl=CCl / CCl_2—CCl_2	CH=CCl / CH_2—CCl_2	$CO—CCl_2$	C≡CCl	ArH.6Cl	ArCl	ArCCl	RCl	RCl	RCClOR	RCl[c]
Cl_2	⊕	⊕		⊕[d]	⊕[e]	⊕	⊕			+[f]	⊕[g]	⊕	⊕	(+)		⊕	
ClF[h]					⊕												
ClBr					⊕												
ClI					⊕												
HCl			⊕					⊕						(+)	⊕[i]		+
HOCl, NaOCl				⊕		(+)			⊕	⊕		+					
S_2Cl_2, SCl_2	(+)				+										(+)		
$SOCl_2$												(+)	(+)		⊕		+
SO_2Cl_2	+[g]	+										+	+[g]				
NOCl		+			⊕												
PCl_3					+										⊕		
$POCl_3$															⊕		
PCl_5		(+)										⊕	(+)		⊕[k]	+	
$AlCl_3$														⊕			
LiCl																	
CuCl, $CuCl_2$												(+)		+			
ROCl[l]				⊕	⊕	+[g]						+					
RNHCl	(+)									(+)							
RCONHCl[m]				(+)[d]		+						(+)					
$(CH_2CO)_2NCl$	+[g]	(+)			+[e]	(+)						(+)	⊕[g]				
RSO_2NNaCl												(+)					
Ph_3PCl_2[n], $(RO)_3PCl_2$															⊕		
$ArICl_2$		+										(+)				(+)	
$CHCl_2OCH_3$, $PhCCl_3$															+		+
RCOCl, $COCl_2$, $(COCl)_2$																	(+)

[a] X = F, Br, I.
[b] Y = F, Br, I, OR, S, N, P.
[c] Including chlorohydrins by cleavage of oxides.
[d] In the presence of water and/or alkalis.
[e] In the presence of alcohols or acids, Y = OR or OCOR, respectively.
[f] By reaction of alkali acetylides or acetylenic organometallics.
[g] In the presence of peroxides or under ultraviolet irradiation.
[h] Generated *in situ* from anhydrous hydrogen fluoride and alkyl hypochlorite, *N*-chloroamides or *N*-chlorosuccinimide.



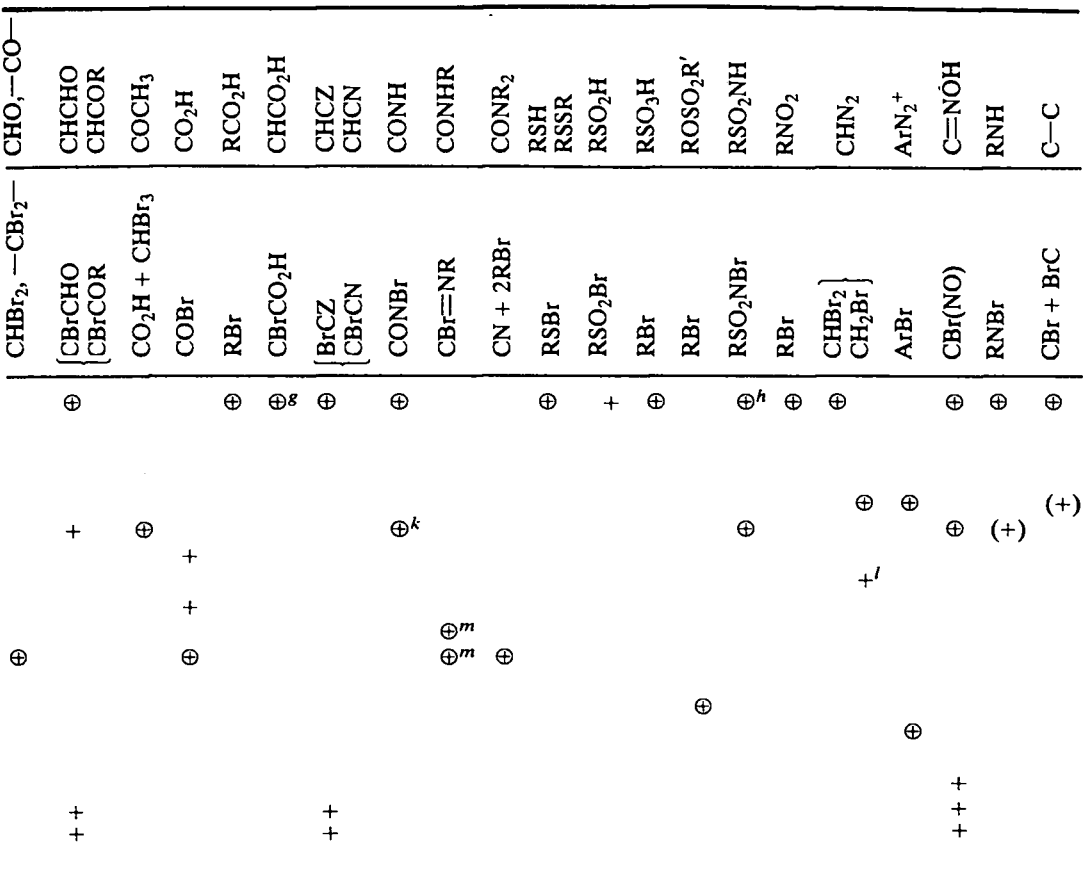
[i] Especially in the presence of anhydrous $ZnCl_2$ (Lucas' reagent).
[j] Only from salts.
[k] Also phenolic hydroxyl can be replaced.
[l] Also prepared *in situ* from chlorine and alcohols.
[m] *N*-Chloroacetamide, *N*,2,4-trichloroacetanilide, *N*-chlorourea, *N*,*N*-dichloro-5,5-dimethylhydantoin, *N*-chlorosaccharin, etc.

[n] Also  PCl_3, $(PhO)_3\dot{P}MeCl^-$, $(PhO)_3\dot{P}(CH_2Ph)\,Cl^-$, $Ph_3P{\cdot}CCl_4$, $(Me_2N)_3P{\cdot}CCl_4$.

V. BROMINATION

Starting compound:	RH	C=C	C=C	C=C	C=C	C=C—CH	C≡C	C≡C	C≡C	C≡CH	ArH	ArH	ArCH	RX^a	ROH	CHOR	ROR'	RCHO
Product:	RBr	CBr—CBr	CH—CBr	C(OH)—CBr	$CY—CBr^b$	C=C—CBr	CBr=CBr $CBr_2—CBr_2$	CH=CBr $CH_2—CBr_2$	$CO—CBr_2$	C≡CBr	ArH + 6Br	ArBr	ArCBr	RBr	RBr	CBrOR	RBr	RCOBr
Br_2	⊕	⊕		⊕[c]	⊕[d]	⊕	⊕			+[e]	⊕[f]	⊕	⊕	⊕		⊕		⊕
BrF[i]					⊕													
BrCl					⊕							⊕						
BrI					⊕							(+)						
HBr			⊕					⊕						+	⊕		⊕[j]	
HOBr, NaOBr				⊕					⊕	⊕		+						
$SOBr_2$															+			
NOBr																		
PBr_3															⊕			
$POBr_3$																		
PBr_5															⊕			
$AlBr_3$														⊕			(+)[n]	
LiBr, KBr, $CaBr_2$														⊕				
CuBr, $CuBr_2$																		
ROBr												(+)						
RCONHBr				⊕[c]	⊕[o]	+[p]						(+)	+[p]					
$(CH_2CO)_2NBr$ (NBS)				⊕[c]		⊕[p]						(+)	⊕[p]		+[q]			
Ph_3PBr_2, $(RO)_3PBr_2$															⊕		+	
CBr_4												(+)						
RCOBr															(+)			

[a] X = F, Cl, I.
[b] Y = F, Cl, I, OR, OCOR.
[c] In the presence of water.
[d] In the presence of methanol, Y = OMe.
[e] Reaction with acetylenic organometallics.
[f] Under ultraviolet irradiation.
[g] In the presence of phosphorus or phosphorus tribromide.
[h] In the presence of alkalis or mercuric oxide.



[i] Generated *in situ* from hydrogen fluoride and *N*-bromoamides, or from bromine trifluoride and bromine.
[j] Including cleavage of oxides to bromohydrins.
[k] Alkali hypobromite prepared *in situ* from alkalis and bromine.
[l] Direct replacement of primary amino group without isolation of diazo compound.
[m] Also in tautomers —C(OH)=N— (in heterocycles).
[n] Also boron bromide cleaves the ethers to alkyl bromides.
[o] In the presence of alcohols (Y = OR), in the presence of acids (Y = OCOR).
[p] Presence of peroxides is sometimes necessary.
[q] *N*-Bromosuccinimide + triphenylphosphine.

VI. IODINATION

Starting compound:	Product:	I_2	IF	ICl	IBr	HI
C=C	Cl—Cl	⊕				⊕
C=C	CH—Cl					
C=C	C(OH)—Cl	$+^c$				
C=C	CX—Cl[b]	$\oplus^p$	$\oplus^i$	⊕	⊕	
C≡C	Cl=Cl Cl_2—Cl_2	⊕				
C≡C	CH=Cl CH_2—Cl_2					⊕
C≡CH	C≡Cl	$\oplus^a$				
ArH	ArI	$\oplus^f$		⊕		
RY[a]	RI					$+^r$
ROH	RI					⊕
ROR′	RI					⊕
CHO, —CO—	CHI_2, —Cl_2—	$+^g$				
CHCOR CHCHO	ClCOR ClCHO	$\oplus^f$				
$COCH_3$	CO_2H + CHI_3	$\oplus^h$				
CO_2H	COI					
RCO_2H	RI	⊕				
$CHCO_2H$	$ClCO_2H$	$+^f$		+	+	
CONH	CONI	⊕				
$ROSO_2R'$	RI					
CHN_2	CH_2I CHI_2	⊕				⊕
ArN_2^+	ArI					+

NaOI, KOI			⊕	+				⊕				
S_2I_2				(+)								
PI_3					⊕				+			
AlI_3					+							
NaI, KI				⊕							⊕	⊕
RCO_2I	+[k]		(+)	+								
$(CH_2CO)_2NI$ (NIS)							+					
$(PhO)_3PI_2$												
$(PhO)_3PMeI$					⊕							

[a] Y = Cl, Br.
[b] X = F, Cl, Br.
[c] In the presence of water and mercuric oxide (hypoiodous acid *in situ*).
[d] In the presence of mercuric oxide and alcohol (X = OR).
[e] From acetylenic organometallics.
[f] Presence of oxidizing agents such as HIO_3, H_2O_2, etc., is necessary.
[g] From hydrazones of aldehydes and ketones.
[h] In the presence of alkali.
[i] From hydrogen fluoride and *N*-iodosuccinimide.
[j] Only with very reactive halogen derivatives such as acyl chlorides, α-chloroethers, etc.
[k] Acyl hypoiodite, generated *in situ* from silver carboxylate and iodine; X = OCOR.

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CHAPTER **23**

Alkene-forming eliminations involving the carbon-halogen bond

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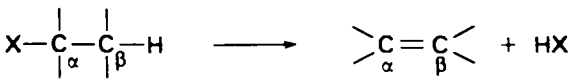
I. INTRODUCTION

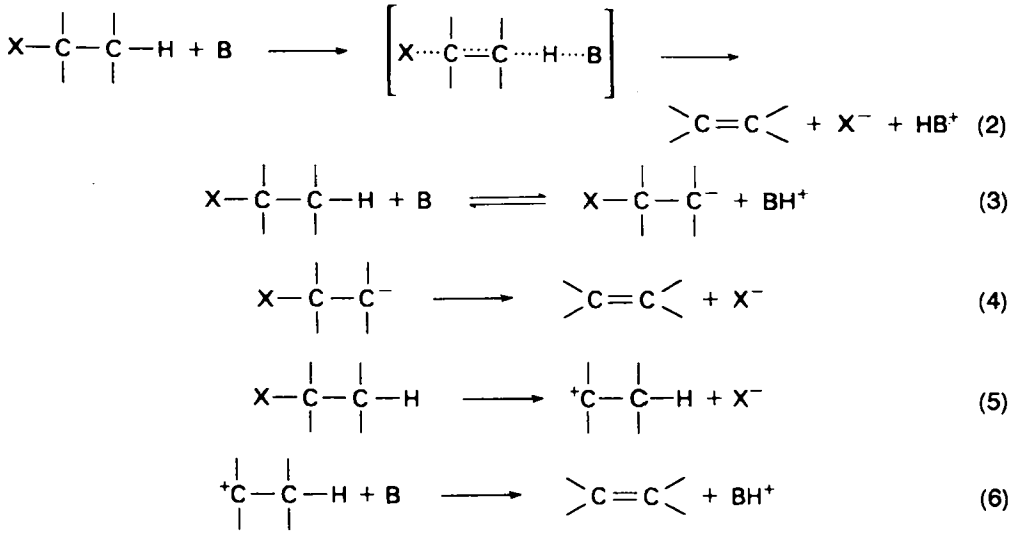
One of the most important reactions of alkyl halides involving the carbon–halogen bond is certainly the loss of one molecule of hydrogen halide in an elimination process. Of the different types of eliminations, the β- or 1,2-eliminations leading to alkenes (equation 1) are certainly those which have attracted most interest. These processes are usually promoted by bases, but can also occur under solvolytic conditions or in the absence of solvent (pyrolytic eliminations).



(1)

Since the fundamental work by Hanhart and Ingold[1], the mechanistic aspects of β-eliminations have been continuously and intensively investigated by numerous research groups and the impressive number of review articles which have appeared in the last decade[2–21], in addition to an excellent and comprehensive book[22], clearly show that the interest in these reactions is still alive and is not going to decline in the near future.

This continuous interest is probably related to the fact that β-eliminations, despite their apparent simplicity, exhibit a great deal of mechanistic complexity, representing a challenge to which a large number of workers have responded during more than half a century. Accordingly, in a β-elimination, two bonds are broken and two new bonds are formed, thus originating a large number of mechanistic possibilities ranging from a concerted reaction, where bond formation and bond breaking take place in a single step (*E*2 mechanism, equation 2), to stepwise reactions involving either the formation of a carbanion (*E*1cB mechanism, equations 3 and 4), or the formation of a carbonium ion (*E*1 mechanism, equations 5 and 6) as reaction intermediates, to say nothing for the moment of the further differentiations which can occur in each of the above mechanisms (*vide infra*).



Moreover, β-eliminations can and do exhibit dramatic changes in the stereochemical outcome as well as in the relative proportions of positional and geometrical isomeric olefins depending on the substrate structure and reaction conditions. Knowledge of the factors which determine these changes, and the understanding of the interplay between the stereochemistry, orientation and reaction mechanism, is of both theoretical and practical importance.

The mechanistic features of β-eliminations have been reviewed in this same series quite recently[11,18]. However, a new assessment of the subject appears warranted in view of the significant developments which have taken place in the last few years, allowing several long-standing problems to be resolved or to be seen in a new perspective.

This review will be dedicated mainly to a discussion of these recent developments, limiting the background as much as possible. The focus will be, of course, on eliminations from alkyl halides. However, eliminations involving other leaving groups will also be considered wherever necessary for comparison purposes and also for better defining the scope of the mechanistic conclusions.

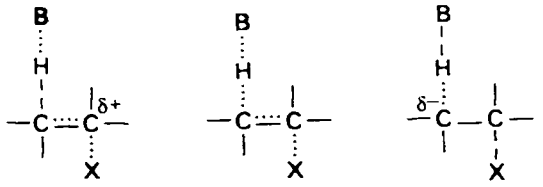
II. *E2* REACTIONS

A. The Structure of the Transition State

1. *The E1-like–E1cB-like spectrum*

In an *E*2 reaction, the breaking of the C_β—H bond occurs together with the breaking of the C_α—X bond (X = leaving group) and the formation of the double bond between C_α and C_β (equation 1).

However, it was realized long ago[1,23] that, in these reactions, the breaking and the formation of the various bonds need not be synchronous. This led to the theory of the 'variable *E*2 transition state' which, in its comprehensive formulation[24], considers a spectrum of transition states (Scheme 1, B = base), from the *E*1-like to the *E*1cB-like. In the middle of the spectrum there is a central structure exhibiting equal extents of C_β—H and C_α—X bond breaking and consequently no charge at either C_α or

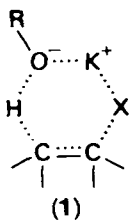


SCHEME 1

C_β. In these structures, bonds indicated with dashed lines are stronger than those indicated with dotted lines.

Whereas there is overwhelming evidence supporting the existence of the centre–right portion of this spectrum[25] that is utilized by the great majority of eliminations promoted by alkoxides and other strong bases (by far the most important class of β-elimination reactions), clear support for an $E1$-like transition state is lacking[26,27]. However, examples of eliminations with a reactivity pattern compatible with such a transition state have recently been reported[28,29].

The spectrum of Scheme 1 is generally considered to hold also for $E2$ eliminations with *syn* stereochemistry. However, when the *syn* elimination is promoted by an ion-paired base or higher ionic aggregates (associated base) a cyclic transition state (**1**) has been suggested[30,31], in which an interaction between the positive counterion and the leaving group is possible.



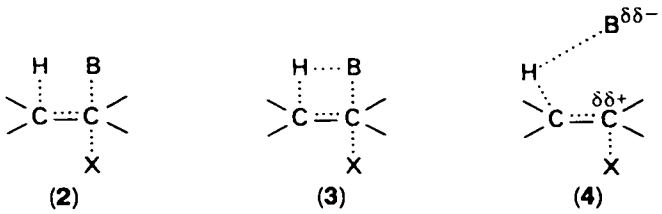
(**1**)

2. *Transition states for eliminations promoted by weak bases*

Winstein and Parker and their associates[32] have expressed the view that the $E1$-like–$E1$cB-like spectrum cannot account for the behaviour of β-eliminations from secondary and tertiary alkyl derivatives with a good leaving group, promoted by weak bases of high carbon nucleophilicity (especially bromide and chloride in dipolar aprotic solvents and thiolate in alcoholic solvents). These reactions are often significantly faster than the more common β-eliminations promoted by the much stronger alkoxide bases and, moreover, present quite distinct features concerning stereochemistry, orientation and structural effects (*vide infra*).

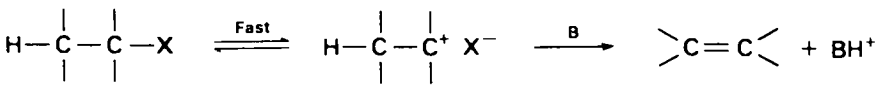
According to Winstein and Parker, the behaviour of weak base-induced eliminations can be much better rationalized by assuming that these reactions take place via transition state **2** or transition state **3**, involving a partial covalent interaction between the base and C_α and a well developed double bond. They named these reactions $E2C$ to distinguish them from those occurring via transition states in the right–centre portion of Scheme 1, which are designated $E2H$. Winstein and Parker also suggested that there may be a gradual shift from the $E2C$ to the $E2H$ transition state as the base becomes stronger, as the substrate acidity increases, or as the leaving group becomes poorer.

More recently, McLennan[13,33] has suggested that the interaction between the base and C_α might be mainly electrostatic in nature, thus leading to the transition state structure **4**. This idea is in agreement with α-deuterium isotope effect data, which have



consistently indicated an insignificant covalent interaction between the base and C_α in the transition state of weak base-promoted eliminations[34].

The *E*2C hypothesis has been the object of much controversy and has not yet won general acceptance. The major criticism has come from Bunnett and coworkers[35], who have long contended that eliminations promoted by halides and thiolates can be conveniently discussed within the framework of the theory of the 'variable *E*2 transition state'[28,35b]. Another hypothesis is that these eliminations might take place by an $(E2)_{ip}$ mechanism involving a slow base attack on a rapidly formed tight ion pair (Scheme 2)[6,36].



SCHEME 2

In several articles and reviews, the relative merits of the *E*2C transition state and of the alternative mechanistic possibilities have been thoroughly discussed[6,13,28,34b,c,36]. However, no definitive conclusion is possible at present since each of the suggested mechanisms can explain most, but *not all* of the experimental facts concerning eliminations induced by weak bases. Perhaps transition state **4** has some advantage in this respect since it incorporates features belonging to the *E*2 and *E*2C hypotheses. Accordingly, as reasonably pointed out by Ford and Hauri[37], 'Since major objections to all three mechanisms, *E*2C, *E*2 and $(E2)_{ip}$, can be raised, a compromise between them comes closest to fitting all the data available'.

In the following discussion, these reactions will always be indicated as 'eliminations promoted by weak bases'. In all other cases, it is intended that we are dealing with the more common eliminations induced by alkoxides and other strong bases.

B. Structural Effects on the *E*2 Transition State

Since there is a close relationship between the transition state structure of a bimolecular elimination and the outcome of the reaction itself, with particular regard to stereochemistry and orientation[35b], considerable effort has been made to obtain information on the effects exerted by structural changes in the base and in the substrate on the transition state geometry of an *E*2 reaction. The determination of the reaction constant ρ, the primary and secondary deuterium isotope effects, the leaving group effect and the Brönsted coefficient β are the most common tools used to determine the transition state character of an *E*2 reaction.

The interpretation in this respect of primary deuterium kinetic isotope effect has been particularly discussed in these years. The Melander and Westheimer picture of a k_H/k_D maximum corresponding to a transition state in which the proton is half transferred to the base, whereas smaller values are expected when the hydrogen is either less or more than half transferred in the transition state[38], has been challenged by Bell and his associates, who have preferred to ascribe variations in k_H/k_D values to tunnelling[39]. However, the data available so far do not appear to give experimental support to this hypothesis even if it is recognized that tunnelling can significantly influence the value of the deuterium kinetic isotope effect[40].

Other factors which can affect k_H/k_D are the non-linearity of the transition state and the coupling between the hydrogen and the heavy atom motions[41]. Both these factors act in the direction to depress k_H/k_D. Several studies concerning calculation of hydrogen and heavy atom kinetic isotope effect in elimination reactions are available[41a,d,e,42].

Recently, it has been suggested that useful indications on the $E2$ transition state structure can also be obtained by measuring the activation volume[43]. Another recent proposal is that the determination of the ρ value in the elimination from substituted arenesulphonates is a very sensitive probe of the carbon-leaving group bond-breaking in the transition state[44].

The theoretical aspects of the problem have also been investigated and some predictions are now possible, at least for eliminations occurring via transition states in the $E1$-like–$E1$cB-like spectrum. We will first give an outline of this theoretical approach and then examine the experimental results.

1. *Theoretical predictions*

The More O'Ferrall potential energy diagram[45] and the Winey and Thornton hypotheses[46] provide a convenient framework for the discussion of structural effects on elimination reactions occurring via transition states in the $E1$-like–$E1$cB-like spectrum. According to these suggestions, structural changes modify the transition state geometry through the operation of effects on those vibration modes of the transition state which are involved in the structural change itself, parallel and perpendicular to the reaction coordinate. The former, parallel effects, are in the direction opposite to that of the force exerted by the structural change; the latter, perpendicular effects, are in the same direction as this force. If, for example, the leaving group effect is considered, we have the situations depicted in Figure 1, for a central and an $E1$cB-like transition state. In the former case (Figure 1, line a), any normal mode involving a change in the C_α—X bond (X = leaving group) is increased along the reaction coordinate and decreased in the direction perpendicular to it by a change to a poorer leaving group. The resultant effect is a transition state with more carbanionic character, a higher degree of C_β—H bond rupture and little change in the degree of C_α—X bond breaking. With an $E1$cB-like transition state (Figure 1, line b) only perpendicular effects have to be considered (parallel vibration does not involve C_α—X motion) and a change to a poorer leaving group will cause a transition state with less C_α—X bond breaking, more carbonium ion character and little change in the extent of C_β—H bond breaking.

Predictions concerning other structural effects can easily be made following the same reasoning. The results are reported in Table 1. It should be noted that in these predictions perpendicular and parallel effects are considered approximately equal in magnitude, which might not always be a valid assumption[47] since the nature of the effects depends on the curvature of the energy surface at the saddle point. In this respect it is interesting to note that information on the energy and curvature of the energy surface can be obtained by determining the changes in the structure–reactivity parameters (e.g. ρ and β) with changes in the structure of the reactants[48].

Another limitation of the treatment is that the possible role of the steric requirements of the base is not considered[49].

2. *Effect of the leaving group*

It has long been known that in the eliminations from 2-arylethyl halides, the carbanionic character of the transition state increases as the leaving group becomes poorer, i.e. in the order I < Br < Cl < F[50]. Even if less complete data are available,

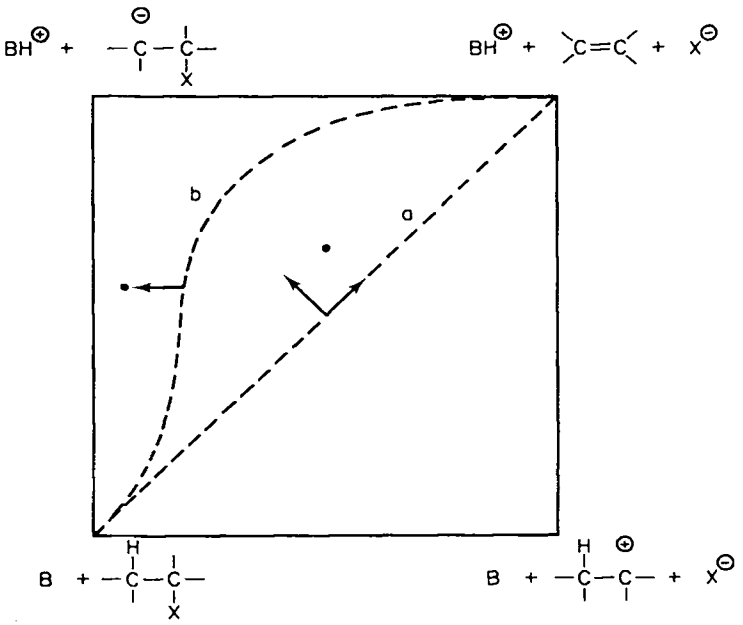


FIGURE 1. Changes in transition state geometry caused by change to a poorer leaving group evaluated by a schematic potential energy diagram (contour lines omitted) for β-elimination reactions B + H—C—C—X → BH^+ + C=C + X^-. Approximate reaction coordinates for processes occurring via central and *E*lcB-like transition states are indicated by the dashed lines a and b, respectively. The arrows give the direction of parallel (along the reaction coordinate) and perpendicular effects. The position of the unperturbed transition state is at the origin of the arrow(s). The new position, resulting from a change to a poorer leaving group, is indicated by the dot.

TABLE 1. Theoretical predictions of the effects of structural changes on the geometry of the transition state of *E*2 reactions[a]

Structural modification	Effect on the structure of	
	the central transition state	the *E*1cB-like transition state
Change to a poorer leaving group	Longer C_β—H, more carbanion character at C_β, little change in C_α—X	Shorter C_α—X, more carbanion character at C_β, little change in C_β—H
Change to a stronger base	Shorter C_α—X, more carbanion character at C_β, little change in C_β—H	Shorter C_β—H, less carbanion character at C_β, little change in C_α—X
Electron-withdrawing substituents at C_β	Longer C_β—H, shorter C_α—X, more carbanion character at C_β	Shorter C_β—H, shorter C_α—X, little change in carbanion or carbonium ion character
Electron-donating substituents at C_α	Shorter C_β—H, longer C_α—X, less carbanion character at C_β or more carbanion character at C_α	Little change in C_β—H, longer C_α—X, less carbanion character at C_α

[a]According to Winey and Thornton hypothesis[46].

there is little doubt that the extent of C—H bond breaking also increases in that order[46]. Since a central $E2$ transition state is reasonable for the eliminations from 2-phenylethyl iodide, these results fit in nicely with the theoretical predictions in Table 1.

The same situation almost certainly pertains for the eliminations from non-activated alkyl halides, as an increase in the proportion of the least substituted olefin in the order I < Br < Cl < F has been observed[51,52]. This suggests an increase in the same order in the carbanionic character of the transition state.

Still in line with theoretical predictions, when highly carbanionic transition states are dealt with, the effect of changing the leaving group is somewhat different from that observed before. Thus, on going from fluoride to trimethylammonium leaving group, no substantial change in the extent of C—H stretching in the transition state is observed[46].

Interestingly, in the EtONa-promoted eliminations from 2-phenylethyldimethylanilinium salts substituted in the leaving group, the nitrogen isotope effect decreases steadily as the leaving group becomes poorer[47]. This result is somewhat at odds with the theory that predicts such an outcome only for reactions utilizing highly carbanionic transition states. Since this should not be the case, at least in some of the eliminations from anilinium salts, it has been suggested that perpendicular effects might prevail on the parallel ones, thus leading to the observed results.

3. *Substituent effects at C_β and C_α*

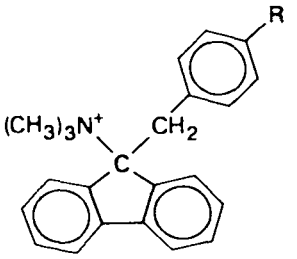
a. Substituents at C_β. Information in this respect comes mainly from studies concerning the reactions of 2-arylethyl derivatives. By introducing groups in the ring, the electronic effect of the β-substituent is modified whereas steric effects remain constant.

In the eliminations from 2,2-diaryl-1,1-dichloroethanes in MeOH–MeONa[53,54], and from 2-arylethyltrimethylammonium ions in EtONa–EtOH[55], an increase in the electron withdrawing power of the β-substituent increases the value of the primary deuterium isotope effect and decreases the leaving group isotope effect, thus suggesting a decrease in the extent of both C—H and C—X bond breaking in the transition state. In the reactions of ammonium salts, the decrease in the degree of C—X bond rupture is also indicated by the values of the α-^{14}C isotope effect, which becomes smaller as the substituent becomes more electron withdrawing[56]. These results are nicely in line with theoretical predictions, as the above reactions should be characterized by a highly carbanionic transition state.

Interestingly, theoretical calculations of kinetic isotope effect in the eliminations from *para*-substituted 2-phenylethyltrimethylammonium ions give values of β-deuterium and ^{15}N isotope effect quite close to those experimentally observed and suggest that the transition states of the various *para* substituents lie in a line parallel to the central $E2$ diagonal in the More O'Ferrall diagram[42a]. It would seem, therefore, that the amount of negative charge which accumulates on C_β in the transition state does not depend on the substituent, but is primarily a function of the leaving group as predicted by Thornton rules for an $E1cB$-like transition state.

Unlike the above results, in the eliminations from 9-(4-R-benzyl)fluorene-9-trimethylammonium ions (**5**), the primary deuterium isotope effect and the nitrogen isotope effect increase as the electron withdrawing power of the R substituent increases[57,58]. This result, which is in striking contrast with the theory, has been attributed to an effect of steric crowding in the transition state of the reaction.

As the electron withdrawing power of the β-substituent is increased, a more or less strong increase in the primary deuterium isotope effect has been observed in the



(5)

eliminations from 1-chloro-1-phenyl-2-arylethanes[59], 2-arylethyl bromides[60–63] and 2-arylethyldimethylsulphonium ions[63] in different base–solvent systems, which would indicate a decrease in the degree of C—H bond stretching in the transition state. Since these reactions should utilize a transition state close to the central one, the observed results would not seem to be in line with theoretical predictions. However, it should be noted that in several cases differences in the k_H/k_D values are barely outside experimental error. Moreover, conclusions based exclusively on the values of deuterium isotope effect are often quite uncertain due to the double valued nature of this effect and the possible complications caused by tunnelling.

A decrease in the extent of C—Cl bond breaking and no substantial change in the degree of C—H bond breaking as the β-substituent becomes more electron withdrawing, are indicated for the eliminations from 2-arylethyl chlorides, by measurements of β-deuterium and β-^{14}C isotope effects[56].

b. Substituents at C_α. In the reactions of 1-arylethyltrimethylammonium ions promoted by EtONa in EtOH[64] and by *t*-BuOK in *t*-BuOH[65], a change in the electronic effect of the α-substituent modifies the transition state geometry much in the same way as β-substituents do in the eliminations from 2-arylethyltrimethylammonium ions. Accordingly, an increase in the electron withdrawing power of the α-substituent appears to produce a transition state with a lower degree of C—H bond breaking.

A different result is observed in the eliminations from 1-arylethyl chlorides induced by *t*-BuOK in *t*-BuOH—DMSO, where measurements of the β-^{14}C isotope effect suggest that the same structural change as above now causes an increase in the degree of C—H bond rupture[66]. This result is in agreement with the theory since the reactions of 1-arylethyl chlorides should utilize a near-centre transition state.

4. Effect of the base

The problem of the base-dependence of the transition state structure of an alkene-forming *E*2 reaction has recently been reviewed[20]. Only a summary of the main conclusions will be reported here.

a. Strength of the base. There is now quite convincing evidence that an increase in base strength leads to an increase in the carbanionic character of the transition state of a concerted elimination reaction. As shown by the data for ρ and the deuterium isotope effect reported in Table 2 for the eliminations from 2-arylethyl bromides[67] and 2-arylethyltrimethylammonium ions[68] this conclusion is independent of the transition state character. The main contribution to this shift is given by a decrease in the extent of carbon–leaving group bond breaking in the transition state of the reaction with the stronger base since the stretching of the C_β—H bond appears little affected.

The rules of Table 1 predict the observed result *only* for reaction occurring via a central *E*2 transition state. With *E*1cB-like reactions (such as that of

TABLE 2. Base-dependence of the transition state structure in some elimination reactions of 2-arylethyl derivatives in DMF

Substrate	Base (pK_a)[a]	ρ[b]	k_H/k_D[c]	k_{Br}/k_{Cl}[d]
$ArCH_2CH_2Br$	C_6H_5ONa (18)	2.64[e]	7.6[f]	120
	4-ClC_6H_4ONa (16.7)		7.8[f]	
	4-$NO_2C_6H_4ONa$ (10.8)	1.84[e]	9.0[f]	
	2,6-(t-Bu)$_2C_6H_3ONa$ (17, 27)	2.44[g]	9.0[g]	146
$ArCH_2CH_2N^+(CH_3)_3$[h]	C_6H_5ONa (18)	4.25	2.8	
	3-$NO_2C_6H_4ONa$ (14.4)	3.81	2.3	

[a] pK_a of the conjugated acid in DMSO (personal communication by Prof. F. G. Bordwell).
[b] From the elimination rates of ring-substituted phenylethyl derivatives.
[c] $PhCH_2CH_2X/PhCD_2CH_2X$ rate ratio.
[d] $PhCH_2CH_2Br/PhCH_2CH_2Cl$ rate ratio at 30°C.
[e] At 0°C[67a].
[f] At 21°C[67b].
[g] At 0°C[70].
[h] All data at 55°C[68].

trimethylammonium salts) the opposite result would have been expected, namely a decrease in the carbanionic character of the transition state as the base becomes stronger. Tentatively, it may be suggested that perpendicular effects cannot be excluded from consideration, even in the case of reactions utilizing a highly carbanionic transition state.

In contrast to previous conclusions, neither the deuterium isotope effect, nor the ρ value are significantly influenced by changes in base strength in the *syn* eliminations of HCl from *trans*-2,3-dichloro-2,3-dihydrobenzofuran promoted by phenoxides[69]. However, recent studies on these systems have suggested that these substrates could react by an *E*1cB mechanism (Section III.C.2).

b. Steric requirements of the base. In Table 2, the comparison of the ρ and leaving group effect values for the eliminations promoted by phenoxide ions with those for the eliminations induced by 2,6-di-*t*-butylphenoxide ions[70] suggests that the steric requirements of the base do not significantly influence the structure of the *E*2 transition state. This conclusion contrasts with some theoretical predictions[49] and with the finding that the eliminations promoted by 2,6-di-*t*-butylphenoxide exhibit geometrical and positional orientations which are quite different from those displayed by bases of minor size[14].

The deuterium isotope effect values also suggest a similar extent of C—H bond breaking in the transition state of the reactions of the two phenoxides. However, McLennan has recently performed theoretical calculations suggesting that the comparison of k_H/k_D values for a tight (reaction with phenoxide) and a loose (reaction with 2,6-di-*t*-butylphenoxide) transition state could be of little significance[71]. Nevertheless, in view of the similar ρ and k_H/k_D values noted above, it seems difficult to envisage substantial differences in the C—H bond stretching for the transition states of the two eliminations.

c. State of association of the base. In the last decade, one of the most significant developments concerning the study of elimination reactions has been the recognition that the main features of an elimination promoted by tight ion pairs or higher ionic aggregates (associated base) can be substantially different from those of the corresponding reaction induced by solvated ions or solvent separated ion pairs (dissociated base)[14]. The role of base association can be investigated by studying reactions promoted by *t*-BuOK in *t*-BuOH in the absence and in the presence of a

TABLE 3. Effect of base association on the transition state structure of some elimination reactions promoted by *t*-BuOK in *t*-BuOH[20]

Substrates	18-Crown 6-ether	ρ	k_H/k_D[a]	k_{Br}/k_{Cl}[b]
2-Arylethyl bromides[c]	Absent	2.53	8.1	23
	Present	2.77	8.0	19
1-Phenyl-2-arylethyl chlorides[d]	Absent	2.20	7.9	41.9
	Present	3.40	8.0	28.8
trans-2-Arylcyclopentyl tosylates[e]	Absent	2.3	2.0	
	Present	3.2	3.0	

[a]Rate ratio between the unsubstituted substrate and its β-deuterated analogue.
[b]$C_6H_5CH_2CH_2Br$:$C_6H_5CH_2CH_2Cl$ or $C_6H_5CHBrCH_2C_6H_5$:$C_6H_5CHClCH_2C_6H_5$ rate ratio.
[c]At 30°C[72].
[d]At 30°C[73].
[e]At 50°C[74].

potassium-complexing crown ether. In *t*-BuOH, a solvent of low dielectric constant, *t*-BuOK is strongly associated, but, in the presence of the crown ether, dissociation of ion pairs and ionic aggregates occur.

The effect of base association on the transition state geometry of an *E*2 reaction is illustrated by the data reported in Table 3 concerning the *anti* eliminations from 2-arylethyl bromides[72] and 1-phenyl-2-arylethyl chlorides[73] and the *syn* eliminations from *trans*-2-arylcyclopentyl tosylates[74]. It can be noted that on going from associated to dissociated *t*-BuOK, the transition state structure for the eliminations from 1-phenyl-2-arylethyl chlorides and *trans*-2-arylcyclopentyl tosylates undergoes a shift towards the *E*1cB-like extreme, whereas the extent of C—H bond breaking remains practically unchanged. This is expected because dissociated *t*-BuOK should be a much stronger base than associated *t*-BuOK, as is also shown by its much greater reactivity. Again in line with the theoretical predictions, the degree of carbon–halogen bond breaking in the transition state of the reactions of 1-phenyl-2-arylethyl chlorides is smaller with the more strongly dissociated base[73].

Remarkably different behaviours are exhibited by the eliminations from 2-arylethyl bromides, which undergo no significant change in the transition state geometry as the base association is changed, although a strong rate enhancement is observed. No explanation for this intriguing result is available at present. Results not in line with the predictions reported in Table 1 have also been obtained in the eliminations from *trans*-2,3-dibromo-2,3-dihydrobenzofuran[75]. In this case, an increase in base association decreases both the deuterium kinetic isotope effect and the carbanionic character of the transition state. However, as we have already mentioned, the eliminations from this system probably take place via an *E*1cB mechanism (see Section III.C.2).

d. Solvation of the base. Eliminations promoted by OH^- in water and by alkoxides in the corresponding alcohols are accelerated to a large extent by the progressive additions of DMSO. The phenomenon can be reasonably ascribed, at least for the most part, to an increase in medium basicity due to the lower solvating power of DMSO towards anions compared with the hydroxylic solvents.

In the reactions of 2-arylethyl bromides with *t*-BuOK in *t*-BuOH–DMSO[72b] and with OH^- in H_2O–DMSO[62], however, the rate enhancements caused by the increase in DMSO concentration are not accompanied by significant changes in the transition

state structure, a result which parallels the already observed insensitivity of the transition state of these reactions to changes in base association.

With charged substrates, however, different results are obtained. In the eliminations from 2-phenylethyldimethylsulphonium and 2-arylethyltrimethylammonium ions promoted by OH^- in DMSO–H_2O, the primary deuterium istotope effect, k_H/k_D, increases up to a maximum value and then decreases as the DMSO content in the solvent mixture is increased[40a,b,76,77]. The result has been interpreted as an indication that the degree of proton transfer in the transition state of these reactions steadily decreases from a situation in which the proton is more than 50% transferred to the base to a situation in which it is less than 50% transferred.

However it is very intriguing that, when the reactions of 2-(*p*-acetylphenyl)ethyldimethylsulphonium bromide are considered, an increase in DMSO concentration causes only a slight increase in the k_H/k_D value, without any evidence of a maximum[78]. Moreover, in the EtO^--induced elimination from 1-arylethyltrimethylammonium ions in EtOH–DMSO the k_H/k_D values are insensitive to solvent composition[65], and in the reactions of 1,1-diphenyl-2,2-dichloroethanes promoted by MeONa in DMSO–MeOH k_H/k_D decreases as the DMSO concentration is increased[52].

No explanation for these contrasting behaviours is available at present, but it clearly appears that a change in the transition state structure from more to less than 50% of proton transfer to the base, as the composition of DMSO–ROH mixture is changed, is not a general phenomenon.

It should also be noted, however, that according to recent work changes in k_H/k_D with changes in solvent composition could not show any correlation with the solvent effect on the overall free energy of the reaction, but depend on alteration in the extent of the solvent involvement in the reaction itself[79]. In this case the interpretation of the experimental results in terms of the Melander and Westeimer model[38] would not be possible.

Results consistent with expectation (lower degree of C—X bond breaking in the transition state as the DMSO concentration and thereby the medium basicity is increased) have been obtained by measuring the leaving group isotope effect in the eliminations from 2-phenylethyldimethylsulphonium[80], 2-phenylethyltrimethylammonium ions[77] and 1,2-diphenyl-2,2-dichloroethane[54]. It can be recalled that the former two reactions behave differently than the latter with respect to the solvent influence on the deuterium kinetic isotope effect values.

C. Positional and Geometrical Orientation

1. General

The problem of orientation arises when isomeric olefins can be formed from a given substrate. More specifically, *positional orientation* is concerned with the relative proportion of isomeric olefins differing in the position of the double bond; *geometrical orientation* refers to the relative amounts of *trans* and *cis* isomers. For historical reasons, we also speak of Saytzeff orientation when the orientation of the double bond formation is towards the more substituted β carbon, and of Hofmann orientation when it is towards the less substituted β carbon.

The factors affecting olefin proportions in *E*2 reactions have been intensively studied and are still attracting considerable interest. Our understanding of this problem has progressed significantly in the last few years, thanks mainly to the recognition that eliminations can exhibit a *syn–anti* dichotomy[5] and that different ionic forms of the base (associated and dissociated, see Section II.B.4.b) can operate

simultaneously in the elimination process and lead to different orientation results. Following this discovery, most of the efforts have been directed towards the study of reactions in which individual stereochemical processes promoted by homogeneous base forms can be examined and this has resulted in much more significant results than those obtained in the past.

In the next sections, we will examine the factors which play a role with respect to the orientation of *E*2 reactions, with the main focus on the most recent results. Many reviews are available with respect to the earlier discussion[9,11,12,22,24,35b,81–83].

2. *Effect of base strength*

a. Positional orientation. The predominant role of base strength rather than of base size in determining positional orientation in *anti* dehydrohalogenations from 2-butyl halides has been conclusively demonstrated by Bartsch and coworkers[84,85]. Using a dipolar aprotic solvent (DMSO) in which the active species is the dissociated form of the base, these workers observed a gradual increase in the proportion of 1-butene from 2-iodobutane by increasing the base strength of a series of oxyanions including phenoxides, alkoxides and benzoates[84]. Some results are reported in Table 4. More significantly, plots of the free energy differences between transition states for the formation of terminal and internal olefins versus the pK_a of the base were found to exhibit a satisfactory linearity over a variation in base strength of 20 pK_a units.

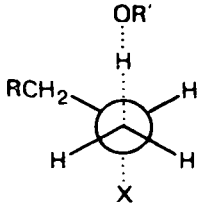
This observation can reasonably be explained by considering that, as already seen in Section II.B.4.a, an increase in base strength increases the carbanion character of the transition state of the elimination reaction. Saytzeff orientation is thus made more difficult by the increase in the unfavourable interactions between the electron-donating alkyl group and the partial negative charge present on C_β.

The steric requirements of the base can play a role only with very hindered bases such as 2,6-di-*t*-butylphenoxide, tricyclohexylmethoxide and tri-2-norbornylmethoxide[86], which exhibit deviations from the above linear free energy relationship. These bases form more 1-butene than anticipated by their basicity, which is in agreement with previous suggestions[87,88] that steric interactions between the base and the substrate should be less important in the transition state leading to the terminal olefin (**6**) than in that leading to the internal olefin (**7**).

TABLE 4. Positional orientation in the eliminations from 2-iodobutane promoted by different bases in DMSO at 50°C[84]

Base	pK_a	1-Butene, %
$C_6H_5CO_2K$	11.0[a]	7.2
$4\text{-}NO_2C_6H_4OK$	10.78[b]	7.5
C_6H_5OK	18.03[b]	11.4
$2,6\text{-}(t\text{-}Bu)_2C_6H_3OK$	17.27[b]	19.2
MeONa	29.0[c]	17.0
EtONa	29.8[c]	17.1
t-BuOK	32.2[c]	20.7

[a]C. D. Ritchie, in *Solute–Solvent Interactions*, (Ed. J. F. Coetzee and C. D. Ritchie) Marcel Dekker, New York (1969), p. 230.
[b]Personal communication by Prof. F. G. Bordwell.
[c]W. N. Olmstead, Z. Margolin and F. G. Bordwell, *J. Org. Chem.*, **45**, 3295 (1980).



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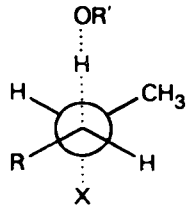

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The onset of steric effects on positional orientation, however, depends to some extent on the structure of the alkyl group on the β carbon. Thus, with 4-methyl-2-pentyl iodide, potassium *t*-butoxide also deviates from the free energy correlation[86]. The steric requirements of oxyanion bases appear to increase in the order *t*-butoxide < tricyclohexylmethoxide < tri-2-norbornylmethoxide.

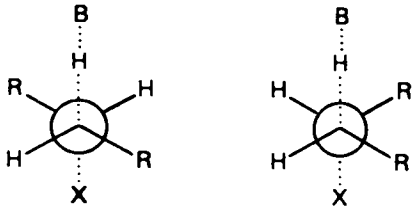
Results similar to those of the oxyanion bases have been observed with nitrogen bases (anilides) and carbon bases (methides)[85]. The sensitivity of orientation to base strength depends on the nature of the basic atom, decreasing in the order O > N > C.

The eliminations promoted by weak bases exhibit a Saytzeff orientation which is much more marked than that observed in the eliminations promoted by oxyanions or other strong bases[32a,b,89,90]. For example, 2-pentyl bromide reacts with bromide ions in acetone to give 98% 2-pentene whereas it yields 77% and 89% 2-pentene with EtOK in EtOH and with F^- in acetone, respectively. The phenomenon, which can have preparative interest, has been considered to support the view that the eliminations promoted by weak bases occur by an olefin-like *E*2C transition state (**2**) (Section II.A) since the Saytzeff product is more stable than the Hofmann one. However, a factor other than the difference in olefin stability must be operating, since the Saytzeff/Hofmann product ratio is sometimes larger than the thermodynamically controlled product ratio[32b]. It has been suggested that this additional factor is the size and the branching of the groups bonded at the β carbon which, among other things, could interfere with the approach of the base at C_α[13].

b. Geometrical orientation. The influence of the nature of the base on geometrical orientation is generally less important than that on positional orientation, as is shown by the observation that with 2-halobutanes and 2-halopentanes in DMSO, the *trans* : *cis* 2-alkene ratio is neither influenced by base strength, nor by its steric requirements[84–86, 89–91]. This point is convincingly illustrated by the finding that an average *trans* : *cis* 2-butene ratio of 3.31 ± 0.14 can be calculated for the reaction of 2-iodobutane with 18 bases covering a range of 20 pK_a units and encompassing extremely different steric situations.

This finding is surprising since a stronger base should produce a more carbanion-like transition state with a less developed double bond, thereby reducing the role of eclipsing effects between the R groups, which are certainly among the most important factors determining the difference in energy between the transition states **8** and **9** leading to the *trans* and *cis* olefins, respectively. Clearly the use of *trans*:*cis* ratios as a criterion for judging the degree of double bond formation at the transition state of an *E*2 reaction does not seem possible in this case.

In some instances, small but significant changes in geometrical orientation are produced by changes in base strength with substrates other than 2-halobutanes and 2-halopentanes. No general trend can be observed, however, and the interpretation of these results is not simple. Thus, in the eliminations from 4-methyl-2-pentyl iodide in DMSO, very similar *trans*:*cis* 4-methyl-2-pentene ratios are observed with *p*-nitrophenoxide, phenoxide, and 2,6-di-*t*-butylphenoxide ions, which would again



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indicate an insignificant role of both steric and base strength effects[86]. In contrast, the *trans*:*cis* ratio decreases from 37.1 to 15.1 as the base is changed from potassium *t*-butoxide to potassium tri-2-norbornylmethoxide, suggesting the operation of steric effects as the two alkoxides have similar base strength. Accordingly, steric effects should decrease the *trans*:*cis* ratio since in the transition state leading to the *cis* olefin (**9**) a bulky base can orient itself towards the side where there are only hydrogen atoms, thus avoiding the steric interactions with the alkyl groups.

In the reactions of 4-heptyl bromide and, to a lesser extent, in those of 2- and 3-pentyl bromides, slightly different *trans*:*cis* ratios are observed when diastereoisomeric alkoxides are employed[92]. This is certainly a steric effect since the diastereoisomeric bases should have the same base strength.

With bulky and asymmetric leaving groups, e.g. the tosylate group, the sensitivity of geometrical orientation to the steric requirements of the base should be much higher than those observed with alkyl halides. Accordingly, a significant decrease in the *trans*:*cis* 2-alkene ratio has been found in the reactions of 2-alkyl tosylates as the base is changed from phenoxide to 2,6-di-*t*-butylphenoxide[86].

In dipolar aprotic solvents, eliminations promoted by weak bases exhibit *trans*:*cis* ratios similar to or lower than those observed in reactions induced by strong oxyanion bases[89,90]. However, owing to uncertainties bound to the use of the *trans*:*cis* ratio as a valuable criterion for the determination of the transition state geometry, we feel that no conclusion can be drawn from these findings with respect to the controversial mechanism of these eliminations.

3. *Effect of base association*

It has long been known that in the eliminations from alkyl halides and other substrates with neutral leaving groups, a substantial increase in the proportion of the terminal olefin accompanied by a decrease in the *trans*:*cis* 2-alkene ratio takes place as the solvent–base system is changed from CH_3OH–CH_3OK or C_2H_5OH–C_2H_5OK to either *t*-BuOH–*t*-BuOK or Et_3COH–Et_3COK[51,93–97]. (Interestingly, it has recently been discovered that positional orientation can be profoundly modified by tunnelling, which is more important in the formation of the Hofmann olefin[98]. However, the differences observed between EtOK–EtOH and *t*-BuOK–*t*-BuOH still remain when the data are corrected for the tunnelling contribution.) In contrast, when alkoxides are used in dipolar aprotic solvents, this concomitant change in positional and geometrical orientation is not observed[90] Moreover, with either *t*-BuOK or Et_3COK, the proportion of the terminal olefin decreases and the *trans*:*cis* 2-alkene ratio increases on going from a low polar to a dipolar aprotic solvent. Some representative data are in Table 5. Finally, in a low polar solvent, *trans*:*cis* values lower than unity are frequently observed, especially with tosylates, but in some cases even with halides[99].

These findings can be rationalized satisfactorily by considering that in alcohols of low polarity, such as *t*-BuOH or Et_3COH, the elimination is promoted by the

TABLE 5. Orientation in some eliminations from 2-iodobutane at 50°C[97]

Base–solvent	1-Butene, %	*trans*:*cis* ratio for 2-butene
EtOK–EtOH	11.7	3.25
t-BuOK–*t*-BuOH	34	2.17
Et_3COK–Et_3COH	49.3	1.50
t-BuOK–DMSO	20.7	2.99
Et_3COK–DMSO	20.9	3.13
EtONa–DMSO	17.1	3.32

associated base, whereas in dipolar aprotic solvents, or in the more polar alcohols (EtOH or MeOH), it is the dissociated form of the base which is the main reacting species[14] (see also Section II.B.4.b). The main evidence which supports this interpretation is as follows:

(i) The difference in orientation between the elimination promoted by *t*-BuOK in *t*-BuOH and *t*-BuOK in DMSO practically disappears when the former reaction is carried out in the presence of a crown ether. The same result is obtained when potassium is replaced by a tetralkylammonium ion as the positive counterion. Under these conditions, both in DMSO and in *t*-BuOH, the main reacting species should be the dissociated form of the base.

(ii) Eliminations promoted either by *t*-BuOK in *t*-BuOH or by Et_3COK in Et_3COH exhibit very similar orientation to that observed when these bases are used in low polar aprotic solvents such as toluene and benzene. Clearly, in all these cases, the elimination is promoted by the associated base.

(iii) Both positional and geometrical orientation in the elimination promoted by *t*-BuOK in low polar solvents depend on base concentration in agreement with a competition between associated and dissociated base species in equilibrium with one another. (However, alternative explanations for this phenomenon are available[72a,100].) Data which illustrate these points are collected in Table 6.

The reasons for the different orientations exhibited by the associated and the dissociated bases have been the object of discussion. Indeed, the observation that more terminal alkene and lower *trans*:*cis* ratios are obtained with the former than with the latter is not consistent with a simple basicity effect. As the dissociated base is much stronger than the associated one, an opposite effect in the positional orientation would have been predicted (see preceding section).

TABLE 6. Orientation in some eliminations from 2-bromobutane at 50°C[88]

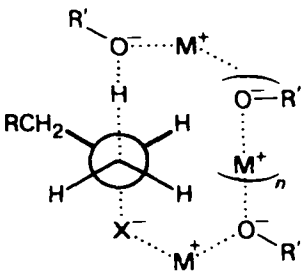
Base–Solvent	1-Butene, %	*trans*:*cis* ratio for 2-butene
t-BuOK (0.1 M)–*t*-BuOH	37.7	1.86
t-BuOK (0.5 M)–*t*-BuOH	44.1	1.66
t-BuOK (1 M)–*t*-BuOH	49.8	1.47
t-BuOK (0.5 M)–*t*-BuOH–18C6[a]	32.5	2.93
t-BuOK (0.5 M)–DMSO	30.6	3.16
t-BuON(Pr-*n*)$_4$	31.3	2.99

[a]18C6 = dicyclohexyl-18-crown-6 ether.

Bartsch and coworkers have suggested that the associated base, more probably an ionic aggregate than an ion pair, has much larger steric requirements than those of the dissociated base (*clump aggregate model*) in any case, sufficient to cause the onset of base steric effect even with a 2-butyl derivative. We have already mentioned that a steric interaction between the base and the substrate leads to a smaller *trans*:*cis* ratio and to a greater proportion of terminal alkene.

In an alternative explanation[7,99,101,102], emphasis is instead put on the possible coordination of the cation of the associated base with the partially charged leaving group in the transition state of the reaction. This interaction is considered particularly important in solvents of poor solvating capacity.

If the base is an aggregate of ion pairs (e.g. *t*-BuOK in benzene), the transition states for the formation of the isomeric olefins can be depicted as in structures **10–12** (*belt aggregate model*)[7,101].



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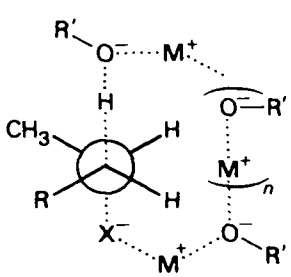

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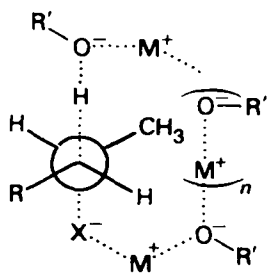

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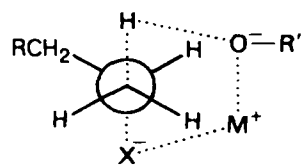
The steric interaction between the base and the substrate is expected to be stronger in the transition state **12** leading to the *trans* 2-alkene, where either the methyl or the R group has to interact with the ionic aggregate, than in **10** and **11**. Consequently, the observed increases in the *trans*:*cis* ratio and in the 1-alkene:2-alkene ratio as we move from the dissociated to the associated base are accounted for.

A variation of the belt aggregate model (transition states **13–15**) has been suggested for the cases (e.g. t-BuOK in *t*-BuOH) in which the associated base exists mainly as a monomeric ion pair[99,102]. However, these transition states involve a marked departure



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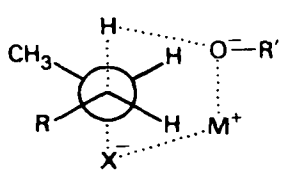

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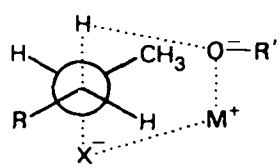
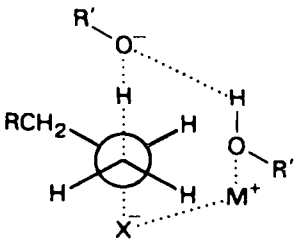


(15)

from the linear arrangement usually assumed for the base, hydrogen, and C_β in the *E*2 transition state, which has raised the question of its consistency with the values of deuterium kinetic isotope effect usually observed in elimination reactions promoted by associated bases[99,103]. This problem has been overcome by Zàvada and coworkers who, very recently, in consideration of the propensity of *t*-BuOK to form a strong solvate with one molecule of *t*-BuOH, have replaced structures **13–15** with structures **16–18** in which a solvent molecule is introduced between the two paired ions[104]. In transition states **16–18**, the approach of the base to the proton is linear.

Choice between these hypotheses is quite difficult. However, it has been observed that even exceedingly bulky dissociated bases fail to match the orientation exhibited



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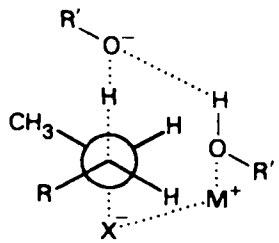

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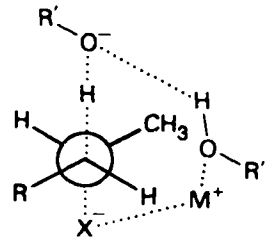


(18)

by the associated base[85,91,97]. For example, 2-iodobutane reacts with the extremely sterically hindered base, lithium *cis*-2,6-dimethylpiperidide in diglyme, in the presence of a crown ether, to give 17.2% of 1-butene and a *trans*:*cis* 2-butene ratio of 3.2. However, with *t*-BuOK in *t*-BuOH 34% of 1-butene and a *trans*:*cis* ratio of 2.17 are obtained[91]. Moreover, very recent work has shown that the elimination rates for the formation of the *trans*-olefin from a series of alkyl tosylates show a sensitivity to the size of the alkyl group bonded to C_α which is much the same with both associated and dissociated bases[105].

These findings cast doubt on the idea of an associated base with much larger steric requirements than those of a dissociated base and indirectly lend strong support to the hypothesis of attractive interactions between the associated base and the substrate. Aside from the possible rationalizations of the phenomenon, it is useful to note that control of base association by a crown ether[106] or the use of self-solvating bases[107] has provided very effective reagents for the performance of clean bimolecular 1,2-eliminations.

Interestingly, with β-phenyl-activated substrates, the effects of base association on geometrical orientation are opposite to those described above[108–110]. With these substrates, the *trans*:*cis* ratios are larger with the associated than with the dissociated base (Table 7). A tentative explanation for this finding has invoked attractive interaction between the counterion of an associated base with the β-aryl group in the transition state leading to the *trans* olefin[21]. With β-vinyl-activated alkyl halides the situation is intermediate between those observed with unactivated and β-phenyl-activated substrates[21].

TABLE 7. Geometrical orientation in some eliminations from 1-phenyl-2-X-propanes at 60°C

	trans:*cis* ratio for 2-methylstyrene in different base-solvent systems		
X	EtONa–EtOH[108]	*t*-BuOK–*t*-BuOH[109,110]	*t*-BuOK–*t*-BuOH–crown ether[109,10]
I	28.3	74.5	28.5
Br	24.7	78.5	30
Cl	25.0	72	45
F	112.4		

4. *Effect of the leaving group*

In the eliminations from alkyl halides, both positional and geometrical orientations are affected by the nature of the halogen. The relative amount of terminal olefin increases in the order I < Br < Cl < F[51,52,111–113] whereas the *trans*:*cis* 2-alkene ratio decreases in the order I > Br > Cl > F[51,52,111–113], although an order Cl > Br > I has been reported in the eliminations from 2-butyl halides with EtONa in EtOH[114]. The

TABLE 8. Positional and geometrical orientation in some *anti* elimination reactions from 2-X-hexanes with MeONa in MeOH at 100°C[51]

X	2-hexene:1-hexene	*trans*:*cis* ratio for 2-hexene
I	4.2	3.6
Br	2.6	3.0
Cl	2.0	2.9
F	0.43	2.3
OTs[a]	1.9	1.9
$\dot{N}(CH_3)_3$[b]	0.039	0.28

[a]At 59.5°C. [b]With *n*-BuOK in *n*-BuOH at 85°C[115]

phenomenon is so marked that 2-alkyl fluorides exhibit Hofmann orientation in all solvent–base combinations. Some data are reported in Table 8, where results for the tosylate and trimethylammonium leaving group are also included.

These observations can reasonably be explained by the effects that the different halogens exert on the position of the *E*2 transition state in the spectrum of Scheme 1. The carbanionic character of the transition state increases in the order I < Br < Cl < F (Section II.B.2) and a parallel increase in the relative proportion of the Hofmann olefin and a parallel decrease in the *trans*:*cis* ratio are expected.

It has also been suggested that hydrogen bonding to the leaving group can affect orientation in an elimination reaction since, in the reactions of 2-decyl halides with potassium cresolate in DMSO, the proportion of the isomeric olefins is slightly influenced by the presence of *p*-cresol[116].

The steric requirements of the halogens are not of significant importance with respect to geometrical and positional orientation. Accordingly, a plot of log (2-alkene:1-alkene ratio) against reactivity in different base–solvent systems (MeONa–MeOH[112], *t*-BuOK–*t*-BuOH[51], *t*-BuOK–DMSO[52]) is satisfactorily linear.

Of the neutral leaving groups other than halides, phenylsulphonyl and benzenesulphonate groups deviate from the above correlation in the direction of smaller 2-alkene:1-alkene ratios. Probably, steric effects are also operating in this case since the steric repulsion between the leaving group and the alkyl groups is smaller in the transition state leading to the terminal alkene than in those forming the internal olefins[87].

It is quite likely also that, in the eliminations from ammonium salts, the marked Hofmann orientation and the low *trans*:*cis* ratios generally observed are related to the large steric requirements of the trimethylammonium group and to its poor leaving ability (see also Section II.D.3.a).

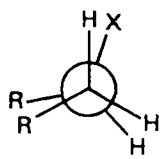
In the eliminations from β-phenyl-activated substrates, geometrical orientation, as positional orientation, responds to leaving group effects differently from the reactions of unactivated alkyl halides. Accordingly, in the reactions of 1-phenyl-2-halogenopropanes, the *trans*:*cis* 1-phenylpropene ratio changes in the order I ≃ Br ≃ Cl < F, the maximum value being observed with fluorine as the leaving group[108,109]. The data are presented in Table 7. It has been suggested that, in phenyl-activated systems, the *trans*:*cis* ratio is determined not only by the eclipsing effects as they are felt in the terminal olefin, but also by the fact that the phenyl group can conjugate with the partial negative charge developing on the β carbon much better in the transition state leading to the *trans* olefin than in that leading to the *cis* olefin. By this conjugative effect, an increase in the carbanionic character of the transition state would promote an increase in the *trans*:*cis* ratio, i.e. a result opposite to that caused by

TABLE 9. Geometrical orientation in the *syn* elimination from 2-decyl halides promoted by *t*-BuOK in benzene and DMSO[99]

	trans:*cis* ratio for 5-decene	
Halogen	Benzene	DMSO
F	21.5	2.5
Cl	7.1	2.5
Br	6.7	2.2

eclipsing effects. Thus, the very high *trans*:*cis* ratio observed with fluorine as the leaving group can be explained by assuming that in the strongly carbanionic transition state of the reactions of the fluoro derivative, the conjugative effect is the dominating one. With the other halogens, the two opposite effects match each other, or nearly so, and the *trans*:*cis* ratio is little affected by the nature of the leaving group.

Zàvada and coworkers have been able to determine the influence of the leaving group on the geometrical orientation of a *syn* elimination from 2-decyl halides in different base–solvent systems[99]. It has been found that the *trans*:*cis* ratio increases approximately in the order Br < Cl < F, opposite to that generally observed in *anti* eliminations (Table 9). On the other hand, in a *syn* elimination, the differences in the energies of the transition states leading to the *cis* and *trans* olefins (**19** and **20**, respectively) are expected to increase as the transition state moves from a 'central' structure resembling the olefin, to an *E*1cB-like structure resembling the reactant.



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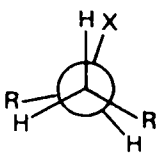


(20)

5. *Effect of the alkyl structure*

With substrates of the type RCH_2CHXCH_3 or $RCH_2CX(CH_3)_2$, an increase in the size of the R group generally increases the relative proportion of the Hofmann olefin[86,89,96,114,117]. Some data are presented in Table 10. Either steric or inductive effects can explain the phenomenon but the distinction between these two effects is generally difficult since the size and the electron releasing power of the alkyl groups increase simultaneously. Moreover, the relative weight of the two effects certainly depends on the steric requirements of the base and the leaving group and on the structure of the transition state.

It is probable that with linear R groups, inductive effects are generally more important than steric effects; accordingly, with *t*-BuOK in *t*-BuOH, the latter appears to become operative only when R is $CH(CH_3)_2$ or a larger group[86]. In contrast, the use of free energy relationships would suggest that the effect of alkyl substitution in elimination reactions can be accounted for *entirely* by steric effects[118].

In eliminations promoted by weak bases, the situation is reversed: there is a substantial increase in the proportion of the terminal olefin when the size of the R group at C_β is increased[32a,89]. Possible explanations of this finding have already been mentioned (Section II.C.2).

TABLE 10. Orientation in the eliminations from $RCH_2CHBrCH_3$ promoted by EtOK in EtOH[89]

R	1-Alkene, %	*trans*:*cis* ratio for 2-alkene
CH_3[a]	18	3.2
CH_2CH_3[b]	23	3.9
$CH(CH_3)_2$[b]	34	12

[a]At 50°C.
[b]At 60°C.

An increase in the size of alkyl groups at C_α and C_β can cause a significant increase in the values of *trans*:*cis* 2-alkene ratios[86,89]. Thus, whereas in the reaction of 2-butyl iodide the value of the *trans*:*cis* ratio is *c*. 3 with a great variety of bases in DMSO, the values range from 15 to 37 with 4-methyl-2-pentyl iodide[86]. Simple lengthening of the chain has a lesser effect: 2-decyl iodide and 5-decyl bromide exhibit similar *trans*:*cis* ratios[99,113].

Eclipsing effects certainly play a role in this respect, but other effects have to be operating too as the *trans*:*cis* ratio has been found to exceed the thermodynamically controlled equilibrium ratio of the isomeric olefins in the eliminations from 4-methyl-2-pentyl and from 2-methyl-3-pentyl derivatives[89]. Another intriguing observation has been that the former system exhibits a larger *trans*:*cis* ratio than the latter in spite of the fact that both systems afford the same geometrical isomers[89].

It has been suggested that the departing leaving group may interfere with the free rotation of the alkyl group at C_α in the transition state. It follows that it is possible to raise the energy of those conformations which minimize eclipsing effects in the *cis* olefin, thus giving higher *trans*:*cis* ratios than those in the equilibrium mixture. Since this effect should be sensitive to the size of the alkyl group, it would also explain the different *trans*:*cis* ratios in the 2-methyl-3-pentyl system ($R_\alpha = CH(CH_3)_2$, $R_\beta = CH_3$) and 4-methyl-2-pentyl system ($R_\alpha = CH_3$, $R_\beta = CH(CH_3)_2$)[89,119].

However, the interaction of R_β and the leaving group must also be important, otherwise it would be difficult to explain the increase in the *trans*:*cis* ratio observed on going from butyl ($R_\alpha = CH_3$, $R_\beta = CH_2CH_3$) to 4-methyl-2-pentyl ($R_\alpha = CH_3$, $R_\beta = CH(CH_3)_2$) derivatives.

Interestingly, branching at C_α and C_β is less important with tosylate than with halogens as the leaving groups[86]. However, the tosylate group is asymmetric and in the transition state leading to the *cis* olefin it can orient itself away from the side where there are alkyl groups[120]. Thus, there is, in this case, a factor that tends to decrease the *trans*:*cis* ratio as the size of the alkyl group is increased.

D. Stereochemistry

1. General

*E*2 elimination reactions have long been considered to take place almost exclusively via an *anti* periplanar transition state, the *syn* route becoming operative only in those particular situations in which the *anti* arrangement was disfavoured by geometrical constraint (e.g. cyclopentyl derivatives and bicyclic systems).

This belief was based on the available experimental evidence and supported by theoretical arguments[121]; the most common of these is certainly that the bonding

electrons of the carbon–hydrogen bond are performing a backside displacement of the leaving group, as it occurs in S_N2 reactions[122].

However, in the second half of the 1960s, the fundamental work by Sicher and coworkers clearly showed, first in medium rings[31,123–127] and then in acyclic systems[128–130], that a *syn* pathway of elimination can successfully compete with the *anti* one, especially when highly branched alkoxides (e.g. *t*-BuOK) in low polarity solvents (*t*-BuOH or, better, benzene) are used. It has been discovered that the *syn* route is much more important in the formation of *trans* olefins than in that of *cis* olefins, the *syn* pathway to a *cis* olefin requiring a transition state in which the alkyl groups on the α and β carbons are eclipsed. In many cases a true dichotomy of mechanisms is observed, the *trans* olefin being exclusively formed by a *syn* route, the *cis* olefin by an *anti* route (*anti–syn* dichotomy).

That the *syn* eliminations could no longer be considered to be rare processes was further confirmed by the observation that in the eliminations from small ring cycloalkylammonium salts (with the exception of the cyclohexyl derivatives) a significant proportion of the *syn* pathway also contributed to the overall process[131].

In the light of these fundamental developments, most of the research has subsequently dealt with the important problem of determining the structural factors which play a role in the *anti–syn* competition and their relative importance. We will now outline some of the main conclusions of this research; for further details the reader is referred to the exhaustive and authoritative review by Bartsch and Zàvada which has appeared very recently[21].

2. *Effect of the base*

a. Ion pairing and base association. In the study of the stereochemistry of the *E*2 reactions from neutral substrates, one of the most significant achievements has certainly been the recognition of the fundamental role exerted in this respect by ion pairing of the base or, more generally, by its state of association[31,126,132,133]. There is now overwhelming evidence that an associated base enhances strongly the relative proportion of the *syn* route, whereas the reverse takes place when the base is present as solvent-separated ions (dissociated base). This evidence can be summarized as follows.

First, a drastic increase in the relative proportion of the *syn* elimination is generally observed when the polarity of the solvent is decreased[99,130,134–136], as is clearly illustrated by the data of Table 11 for 5-decyl halides and tosylates[99].

Secondly, in solvents of low polarity (e.g. *t*-BuOH and benzene) the contribution of the *syn* route can be drastically decreased by the addition of a crown ether which is

TABLE 11. Contribution of the *syn* and *anti* routes in the elimination 5-X-decane → 5-decene promoted by *t*-BuOK in benzene and DMSO[99]

	Percentage of *syn* (overall)	
X	Benzene	DMSO
F	76.4	12.6
Cl	40.6	6.6
Br	17.0	3.0
OTs	16.0	4.2
$\dot{N}(CH_3)_3$	84.2	75.9

able to convert intimate ion pairs and ionic aggregates (associated base) into solvent-separated ions (dissociated base)[135,137–140]. For example, we can mention the significant observation that the *trans*:*cis* ratio in the reaction of cyclodecyl bromide with *t*-BuOK in benzene decreases from 55 to 0.12 after the addition of 18-cyclohexyl-6-crown ether. The *trans* olefin is mainly formed via the *syn* route, the *cis* olefin via the *anti* route[135].

Thirdly, the relative weights of *anti* and *syn* pathways is influenced by the nature of the alkoxide base cation, the cations favouring ion pairing also favouring *syn* elimination[127]. Thus, *t*-BuONa is more effective than *t*-BuOK and PhOLi more effective than PhOK in promoting *syn* elimination from hexyl tosylates[141,142].

Finally, it has been shown that the *syn*:*anti* ratio can be increased simply by increasing the base concentration, an effect which should enhance the relative proportion of the associated base with respect to the dissociated one[132].

The high favourable effect that ion association exerts on the *syn* route in the elimination from alkyl halides and tosylates has been reasonably explained by the simultaneous coordination of the associated alkali metal cation with the oxyanion and the leaving group in the cyclic transition state **1**. Coordination of the base counterion with the leaving group is also possible in the transition state for the *anti* elimination (Section II.C.3), where the intervention of higher ionic aggregates than those involved in *syn* elimination has been suggested by kinetic studies[101,143]. However this coordination is clearly less important than in the *syn* process.

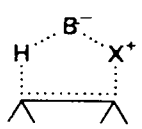
Kinetic studies have shown that ion pairing of the base decreases the rates of both *anti* and *syn* eliminations, the former being more affected than the latter[75,144]. Thus, the increased tendency towards a *syn* stereochemistry under ion pairing conditions, is not due to a favourable effect of base association on the *syn* pathway, but rather to the fact that base association disfavours the *syn* route less than the *anti* one.

The involvement of the associated base is of negligible importance in the eliminations from ammonium salts (Table 11). In this case, the dissociated form of the base is the predominant active species in both polar and non-polar solvents, because in the latter metathesis occurs between the quaternary ammonium salt and the associated alkoxide (equation 7).

$$RN^+(CH_3)_3 + X^- + RO^-M^+ \rightleftharpoons M^+X^- + RN^+(CH_3)_3 + RO^- \qquad (7)$$

The equilibrium (equation 7) should be shifted towards the right since the association between M^+ and X^- is stronger than that between M^+ and RO^- and weak interactions are expected between the bulky ammonium ion and RO^-.

In the reactions of ammonium ions with phenoxides in DMSO–*t*-BuOH, free ions are more effective than ion pairs in promoting *syn* eliminations[145] in agreement with the proposal[126] that the transition state for the *syn* eliminations from ammonium ions should have the structure depicted in **21** with the anion simultaneously coordinating



(21)

the proton and the positively charged leaving group. The association present in **21** should be stronger as the polarity of the solvent decreases, and this might explain the decrease in the proportion of *syn* elimination also observed with the ammonium salts as the solvent polarity is decreased[99,126,130,146].

A very special effect of base association with an unusually strong leaving group–cation interaction has been suggested by Caubere and coworkers to explain the observation that the 'complex base', $NaNH_2$–*t*-BuONa, displays a surprisingly high propensity to perform *syn* eliminations[147]. For example, 60% of 1-bromocyclohexene is formed from *trans*-1,2-dibromocyclohexane and 'complex base' in tetrahydrofuran, certainly via a *syn* route. No trace of this product is obtained when either *t*-BuONa or $NaNH_2$ were used separately.

Furthermore, when the 'complex base' is made to react with *trans*-1-bromo-2-fluorocyclohexane or with *trans*-1-chloro-2-fluorocyclohexane only the formation of 1-bromo- and 1-chlorocyclohexene, respectively is observed[148], thus showing that preferential *syn* elimination of HF has taken place in both cases. It has been suggested that the strength of the interaction between the leaving group and the base counterion (which is much stronger with the more electronegative fluorine) is the dominant factor determining the relative leaving group ability of the halogens. For other factors which can promote preferential loss of fluorine from vicinal chlorofluorides see Section III.C.2.

b. Base strength. Unequivocal information on the effect of base strength is available only for eliminations from ammonium salts[146b,126].

In the reactions of cycloalkyltrimethylammonium ions the proportion of *syn* elimination is much larger with CH_3OK than with PhOK (a weaker base) in a variety of solvents. This is a base strength effect since the steric requirements of the two bases are quite similar and differences in the extent of ion pairing should make CH_3OK less effective than PhOK in promoting the *syn* pathway[126]. An increase in the medium basicity also increases the extent of *syn* elimination from 3-hexyltrimethylammonium ions[114]. With neutral substrates, two bases of different strength in the same solvent also differ in the extent of ion pairing and the distinction between ion pairing and basicity effects is difficult since both act in the same direction.

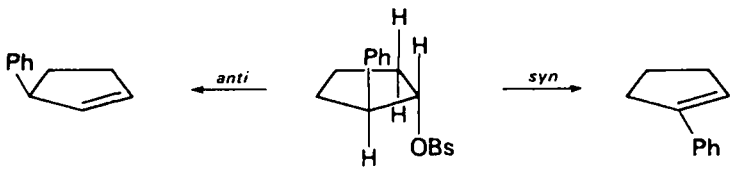
The rationalization of the base strength effect on the *anti–syn* competition has been the object of discussion[5,99,126,145], mainly because of the uncertainty which has long existed on the actual role of the base strength with respect to the transition state structure of *E*2 reactions. Now it seems clear that an increase in base strength leads to a more carbanionic transition state with both neutral and charged substrates (Section II.B.4.a). With a stronger base, therefore, the transition state is more reactant-like than with a weaker base and has more negative charge at C_β. Both conditions should act in the direction of favouring the *syn* route; accordingly, a reactant-like transition state should reduce the stereoelectronic constraint favouring the *anti* route, whereas the view that *E*1cB-like transition states favour the *syn* pathway, the expulsion of the leaving group requiring inversion of configuration at the β carbon, is supported by recent calculations[149].

It should be noted, however, that the increase in the relative proportions of *syn* elimination with the increase in base strength could simply be due to the fact that the *syn* process is more sensitive than the *anti* one to this factor. Accordingly, *syn* eliminations utilize more carbanionic transition states with a larger degree of C—H bond breaking than those of *anti* eliminations, as shown by the ρ and kinetic isotope effect values determined in cases in which direct comparison of the two processes has been possible. It seems plausible, therefore, to expect that the rate of *syn* eliminations is more sensitive to the base strength effect than that of *anti* eliminations.

In consideration of the fact that the *anti* → *trans* route can be disfavoured by an effect of steric hindrance to the base approach (*vide infra*), an increase in the steric requirements of the base should increase the proportion of *syn* elimination. Indeed, it has been found that in benzene a change from MeOK to *t*-BuOK leads to an enhanced proportion of the *syn* route[126]. However, the base strength is also changed and it is not possible to assess the relative contribution of steric and base strength effects.

Still more difficult to interpret is the general finding (for both neutral and charged substrates) that when working with alkoxide in the conjugate alcohol branching of the alkoxide produces an increased extent of *syn* elimination[30,115,125,127,130,134,136,141,142,150–153]. Probably, the phenomenon is due more to a decrease in the solvent polarity which, as noted above, should favour the *syn* route, than to a change in basicity of the medium.

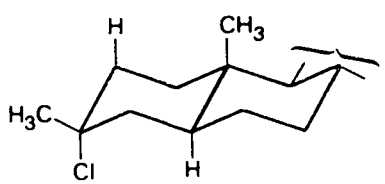
In the reactions promoted by weak bases, an almost exclusive *anti* stereochemistry is generally observed[32a,c,154]. Interestingly, the propensity for the *anti* pathway is, in these reactions, stronger than in the eliminations promoted by strong bases. An example is presented in Scheme 3[32c]. It has been suggested that these observations are evidence in favour of the *E*2C mechanism (Section II.A.2) for weak base-promoted eliminations. Indeed, the interaction between the base and C_α, in the transition state of these reactions, should help to expel the leaving group (structures **2–4**), thereby introducing a further factor which favours an approach of the base *anti* to the leaving group.



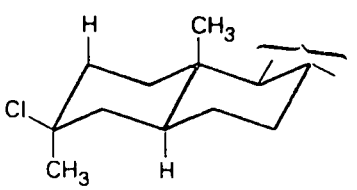
SCHEME 3

However, it should be noted that in Scheme 3 a great part of the propensity to undergo a *syn* elimination in *t*-BuOK–*t*-BuOH is due to a base association effect as only 30% of this route is observed in the presence of a crown ether[74]. Moreover, the difference in the propensity towards the *syn* pathway between weak base-promoted and strong base-promoted eliminations results from the comparison between unactivated *anti* eliminations and phenyl-activated *syn* eliminations. Thus, with the strong base, the elimination towards the phenyl group (*syn* pathway) could be much more favoured than with the weak base only because the former reaction utilizes a more carbanionic transition state than the second, being thus more strongly influenced by the electronic effect of the phenyl group.

Another noteworthy feature of weak base-promoted eliminations from cyclohexyl derivatives is that of the two possible *anti* routes, the *anti* diaxial route is favoured over the *anti* diequatorial one to a lesser extent than with strong bases[32a,c]. However, the differences are not large enough to imply substantially different transition states for the two reactions. Moreover, different leaving groups (halides and tosylates) are often compared and variations in the energy of the ground state conformations might also play a role. In this respect, it has been observed that in the eliminations from the 3-chloro-3-methyl-5α-cholestanes **22** and **23** promoted by *t*-BuOK in *t*-BuOH the



(22)



(23)

difference in reactivity between the compound with axial chlorine and that with equatorial chlorine is only 1.7 at 100°[155]. It has been suggested that the elimination in the compound with equatorial chlorine is an anticoplanar process with a skew-boat conformation.

3. *Effect of the leaving group*

In the eliminations from alkyl halides, the proportion of the *syn* route increases in the order Br < Cl < F, as shown by the data reported in Table 11, where the results for the trimethylammonium and the tosylate leaving group are also reported for comparison. It can be noted that a solvent of low polarity is essential for the occurrence of a substantial amount of *syn* elimination from alkyl halides. In the polar solvent DMSO the percentage of *syn* elimination is very low. The reason for this phenomenon has been discussed in the preceding section.

The data in Table 11 give the overall contribution of the *syn* route, but it should be noted that in benzene such a contribution is much larger in the formation of the *trans* olefin than in the formation of the *cis* olefin with all the leaving groups. In particular, with F and $\overset{+}{N}(CH_3)_3$, a *syn–anti* dichotomy is observed as the *trans* and *cis* olefins are almost entirely formed via the *syn* and the *anti* routes, respectively[99,156]. In DMSO this behaviour is exhibited only by the trimethylammonium group.

Since ammonium ions are the compounds which usually show the greatest preference for *syn* eliminations a fundamental role in this respect had been attributed to the bulkiness of the leaving group. However, the data of Table 11 clearly show that this factor cannot be the only one favouring a *syn* stereochemistry. Accordingly, among the alkyl halides, the greatest propensity for the *syn* elimination is shown by the compound possessing the smallest leaving group. It is noteworthy that in benzene, the extent of *syn* elimination observed with 5-decyl fluoride is quite close to that observed with 5-decyltrimethylammonium ion. Likewise, the reaction of 3-hexyl fluoride to give 3-hexene promoted by *t*-BuOK in *t*-BuOH exhibits *c.* 68% of *syn* elimination[141], which compares with 80% *syn* elimination observed for the corresponding reaction of 3-hexyltrimethylammonium iodide[115].

The *anti–syn* competition appears, therefore, to be strongly influenced by the polar characteristics of the leaving group, the propensity for the *syn* route increasing with the electronegativity of the leaving group (Br < Cl < F in the alkyl halides series). This trend can be reasonably explained by the theory of the variable *E*2 transition state; accordingly, the carbanion character of the transition state increases in the order Br < Cl < F (Section II.B.2) and, as a consequence, *syn* elimination has more chance to compete with the *anti* one.

The high proclivity of ammonium salts for *syn* elimination is also in line with this explanation as the eliminations from these compounds generally utilize a highly carbanionic transition state[50]. As we will see later, however, steric effects are also very important in this case.

4. *Effect of the alkyl structure*

a. Open-chain compounds. With unbranched 2-alkyl halides, *syn* elimination makes little or no contribution to the overall elimination process. Thus, 2-butyl bromide reacts by an *anti* route in a variety of base–solvent systems, including *t*-BuOK–*t*-BuOH[157].

No data for 2-alkyl fluorides that should exhibit the maximum tendency towards *syn* elimination are available. However, the geometrical orientation observed in some eliminations from 2-decyl fluoride suggests that this compound should predominantly,

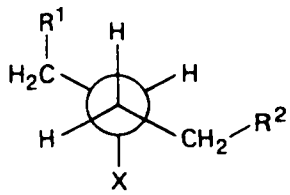
if not exclusively, react by an *anti* route[113]. A strong propensity for an *anti* elimination is also exhibited by 2-alkyl tosylates and trimethylammonium ions[21].

Branching of the alkyl moiety increases the propensity for *syn* elimination. Thus, whereas 2-decyl halides react by an *anti* stereochemistry[113], substantial contributions of the *syn* pathway have been observed with 5-decyl halides[99], as shown in Table 11.

The tendency towards *syn* elimination is also lower if the process leads to a trisubstituted olefin instead of to a disubstituted olefin[5,21]. In the former case, eclipsing interaction between two alkyl groups cannot be avoided, whatever the geometrical isomer formed.

More detailed studies concerning the effect of alkyl structure upon the *anti–syn* competition have been carried out with alkyl tosylates and onium salts. It seems interesting to report here the main conclusions of these studies even though it is recognized that their extension to the case of alkyl halides is doubtful.

In the reactions of 2- and 3-hexyltrimethylammonium ions and 2- and 3-hexyl tosylates, the proportion of the *syn* route leading to the *trans* olefin (*syn* → *trans* route) increases in the order 2-hexyl → *trans*-2-hexene < 3-hexyl → *trans*-2-hexene < 3-hexyl → *trans*-3-hexene[115,142,152], thus indicating that substituents at β' and γ carbon atoms play an important role in promoting *syn* stereochemistry. It has been suggested that both the β' and γ substituents (the former more than the latter) hinder the approach of the base at the hydrogen in the conformation required for an *anti* elimination to the *trans* olefin (structure **24**, R^1 and R^2 are the β' and γ substituents respectively), thereby indirectly favouring the *syn* pathway (conformation **25**) where the proton is easily acessible to the base.



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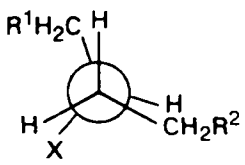

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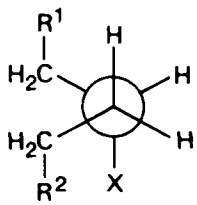


(26)

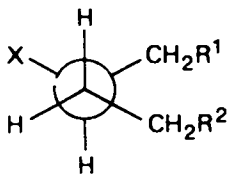
The system could be forced to assume conformation **24** in the *anti* elimination process to reduce the repulsions between the bulky leaving group and the R^1 and R^2 groups[115]. Recently, however, it has been suggested that such a repulsion might be an effect of the hydrocarbon-like ends of the alkyl chain and the leaving group with its partial charge[142]. Thus a bulky leaving group would not be necessary to favour conformation **24** for the elimination transition state.

Steric hindrance to the base approach should be less important in the *anti* pathway to the *cis* olefin (conformation **26**) where the proton can be approached from the side where only hydrogen atoms are placed. This hypothesis would also rationalize the observation that the *cis* olefin is formed nearly exclusively by an *anti* stereochemistry and the low *trans*:*cis* ratios generally found in the *anti* eliminations from alkyltrimethylammonium ions.

Kinetic investigations[142,153] have shown, however, that the increase in the proportions of *syn* elimination with an increase in the size of β' groups observed for tosylates and ammonium ions could have a different origin. With tosylates, the above increase is due mainly to a decrease in the rate of the *anti* → *trans* path, whereas the rate of the *syn* → *trans* route is little affected, in full agreement with previous reasonings[142]. With ammonium salts, however, substitution significantly increases the

rate of the *syn* → *trans* pathway, whereas it has little influence on the rate of the *anti* → *trans* route[153].

It has been suggested[153] that the increase in the rate of the *syn* → *trans* route with the size of the group on the β' carbon observed for ammonium salts is due to a relief of ground state strain which occurs in going from the more favoured ground state conformation **27**, where the alkyl groups are forced into a *gauche* relationship by the exceedingly high steric requirement of the ammonium group, to the conformation **25**, leading to the *trans* olefin via a *syn* route. Of course, the steric relief will increase by increasing the size of R^1, thus accounting for the observed rate-enhancing effect.



(27)

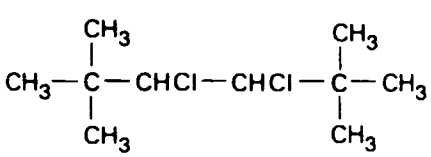
An analogous relief of ground state strain, again related to the interaction between the two alkyl groups, is also suggested in the *anti* → *trans* elimination process which involves conversion of **27** into **24**. However, in **24**, R^1 also exerts an effect of steric hindrance to the base approach (*vide supra*) which, evidently, offsets partially the rate-enhancing effect resulting from the relief of ground state strain.

It has also been suggested that, in ammonium salts, lengthening of the alkyl chain might lead to a steric inhibition of solvation of the positively charged centre, which is more important in the ground state than in the overall neutral transition state. Since the phenomenon should be more marked in the *syn* than in the *anti* transition state, it would account for the effects discussed above[142]. However, the threshold of steric complexity needed for a significant hindrance to the solvation of the trimethylammonium group is higher than that present in the investigated systems[153].

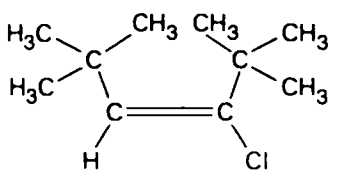
Comparable studies involving alkyl fluorides would certainly be of great interest for a definitive asset of the role of steric effect in the *anti–syn* competition.

Compounds which are β-halogen- and β-aryl-activated generally show a much lower propensity to react by an *anti* route than the unactivated ones. For example, *meso*- and *d,l*-4,5-dichlorooctane exhibit complete *anti* stereochemistry in *t*-BuOK–benzene[101], whereas in this base–solvent system a significant proportion of the eliminations from 5-decyl chloride takes place by a *syn* route (Table 11). Likewise, *meso*- and *d,l*-2,3-dibromobutane react via an *anti* route even under heterogeneous conditions[158].

Substantial *syn* elimination can be observed in some eliminations from



(28)



(28a)

meso-3,4-dichloro-2,2,5,5-tetramethylhexane (**28**) promoted by *t*-BuOK in low polar solvents[159]. However, with this compound, the *anti* process should be disfavoured as it leads to the thermodynamically less stable *cis* olefin **28a**.

The observation that a β-halogen or a β-aryl substituent favours the *anti* elimination is somewhat surprising as the introduction of an electron-withdrawing substituent at the β-carbon should increase (or leave practically unaffected) the carbanion character of the transition state (Table 1). Thus, if an effect on the elimination stereochemistry had to be expected, this was an effect of increasing the proportion of the *syn* route, contrary to that observed. In the case of ammonium salts which exhibit a similar trend with respect to the effect of phenyl substituent on the reaction stereochemistry, it has been suggested that, in the presence of a rigid phenyl group, the selective hindrance to the base approach which favours *syn* elimination does not arise[160]. However, it is doubtful that this explanation can be used for the halogeno derivatives.

b. Cyclic compounds. In four-membered rings, the *syn* coplanar alignment of hydrogen and leaving group is much easier than the *anti* one. Thus, it is not surprising that qualitative observations on the behaviour of *cis*- and *trans*-1,2-dibromocyclobutane suggest only a very small preference for the *anti* pathway[161]. Likewise, the *anti* elimination from *cis*-2-phenylcyclobutyl tosylate promoted by *t*-BuOK in *t*-BuOH is only 2.5 times faster than the *syn* elimination from the *trans* isomer[162]. In line with the discussion of leaving group effect on the stereochemistry of *E*2 reactions, the *syn* pathway is the predominant one in some eliminations from cyclobutyltrimethylammonium ions[131,163].

In the cyclopentyl derivatives, both the *anti* and *syn* periplanar arrangements of hydrogen and leaving group are attainable without much difficulty, and with halogen or tosylate as the leaving group the *anti* route is favoured over the *syn* one to an extent slightly larger than that observed with cyclobutane derivatives. Thus, in the eliminations from *trans*-1,2-dibromocyclopentane, unactivated *anti* elimination competes with the bromine-activated *syn* eliminations better than in the corresponding reaction of *trans*-1,2-dibromocyclobutane[161]. Again, the proportion of *syn* elimination can be very high in the case of the reactions of cyclopentyltrimethylammonium salts (but, in any case, lower than with cyclobutyltrimethylammonium salts) especially when a geminal dimethyl group is present in the cyclopentane moiety[131,163–165].

In the cyclohexane system a strong preference for an *anti* stereochemistry is generally observed regardless of the leaving group as the chair conformation of this ring is well suited to an *anti* diaxial, but not to a *syn* periplanar alignment of hydrogen and leaving group. However, we have previously seen (Section II.D.1.a) that *syn* elimination from vicinal cyclohexyl dihalides is possible under very special experimental conditions.

With medium rings, the propensity for a *syn* pathway in the elimination leading to the *trans* olefin is generally greater than that observed in acyclic systems. Halides conform to this behaviour, as is shown by the observation that *syn* elimination appears to be operating either largely or exclusively in the formation of the *trans* olefin in medium ring cycloalkyl bromides[127]. The extent of *syn* elimination depends on the ring size, the maximum value (*c.* 90% with *t*-BuOK in benzene) being obtained with 10–12-membered rings.

Likewise, *trans*-1,2-dibromo- and *trans*-1,2-dichlorocyclodecane exhibit a strong tendency towards *syn* elimination in various base–solvent systems[134].

The reasons for the high propensity of medium ring compounds to undergo *syn* eliminations, forming the less stable *trans* olefin, are quite well understood. They lie mainly in the steric shielding towards the base approach of the hydrogen atom *anti* to the leaving group, which is located in an intra-annular position[5,126].

III. *E*1cB ELIMINATIONS

A. The *E*1cB Mechanisms

For stepwise eliminations involving a carbanion intermediate (Scheme 4) several mechanistic variants are possible, depending on the rate of formation and reprotonation of the carbanion and on the rate of its decomposition to alkene[6].

$$SH + B \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} S^- + BH^+$$

$$S^- \xrightarrow{k_2} \text{alkene}$$

SCHEME 4

When the condition $k_{-1} \ll k_1 \gg k_2$ prevails, the substrate SH is entirely converted to the carbanion and the rate of alkene formation equals the rate of decomposition of the carbanion itself. This mechanism is generally called the $(E1)_{anion}$ mechanism. It was also dubbed by Rappoport, who first recognized it[166], the *E*1cB mechanism of the second type. The main features of this mechanism are: (a) overall first-order reaction, (b) a primary deuterium isotope effect, $k_H/k_D = 1$; (c) a rate increase by electron-releasing β substituents; (d) hydrogen isotope exchange with the solvent.

The $(E1)_{anion}$ mechanism requires substrates with a very acidic β-hydrogen and a sluggish leaving group. Many examples of this mechanism have been found[167], but none of these concerns halogens as leaving groups. In some cases, conversion of S^- to alkene involves the species BH^+ in a bimolecular process. The name *E*2cB for this variant of the $(E1)_{anion}$ mechanism has been suggested[167]. When $k_1 \ll k_{-1} \gg k_2$, the carbanion is reversibly formed in steady state concentration. This mechanism is named the $(E1cB)_R$ mechanism (R stands for reversible). The rate law is

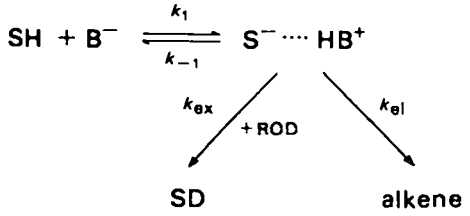
$$k_{obs} = \frac{k_1 k_2[B][SH]}{k_{-1}[BH^+]}$$

and reactions occurring by this mechanism should exhibit (a) a rate-retarding effect by BH^+; (b) a primary deuterium isotope effect, $k_H/k_D = 1$; (c) hydrogen isotope exchange with the solvent; (d) a leaving group isotope effect or element effect; (e) a rate increase by electron-withdrawing β substituents.

When $k_2 \gg k_{-1}$, the formation of the carbanion is irreversible and we have the $(E1cB)_I$ mechanism (I stands for irreversible). A second-order reaction, first order in both the base and the substrate, is observed and no hydrogen isotope exchange with the solvent is expected. Morover, an $(E1cB)_I$ reaction should exhibit a substantial primary hydrogen isotope effect but no leaving group isotope effect. Electron-withdrawing β substituents should increase the reaction rate.

Borderline behaviour between those pertaining to the $(E1cB)_R$ and $(E1cB)_I$ reactions is observed when k_2 is comparable in magnitude to k_{-1}. If this situation arises, a mechanistic cross-over between the two mechanisms can be induced by changing the reaction conditions (*vide infra*).

Finally, if the carbanion formed is tightly solvated (e.g. via hydrogen bonding) or ion paired (in reactions with neutral bases), the mechanism is called the $(E1cB)_{ip}$ mechanism. The carbanion can also return to reactants without undergoing exchange with the solvent (internal return) and Scheme 4 has to be modified to give Scheme 5 (ROD = deuterated solvent).



SCHEME 5

In the $(E1cB)_{ip}$ mechanism, clean second-order reactions are observed as the rate is no longer retarded by BH^+, even if the carbanion is reversibly formed. Moreover, hydrogen isotope exchange with the bulk solvent takes place only if the rate of exchange of the solvated carbanion is larger than the rate of loss of the leaving group ($k_{ex} > k_{el}$). If $k_{el} < k_{-1}$, no primary hydrogen isotope effect should be observed, but substantial leaving group isotope effects or element effects are expected.

The distinction between the different $E1cB$ mechanisms is frequently much more difficult than it would appear by the observation that each of these mechanisms exhibits one or more characteristic features. The real problem is that very often the recognition of these features is experimentally troublesome, if not impossible. For example, the determination of the leaving group isotope effect is not only an experimental problem of considerable complexity, but it can be carried out only with particular leaving groups. Moreover, when the reaction is promoted by the conjugate base of the solvent, it is by no means possible to test whether the rate is retarded by BH^+.

In the borderline region between the $(E1cB)_R$ and the $(E1cB)_I$ mechanism mechanistic conclusions are, sometimes, easier. Thus, the observation that in buffered solution an increase in buffer concentration causes a change from general to specific base catalysis (buffer saturation kinetics) is a strong indication of a mechanistic cross-over from a $(E1cB)_I$ to an $(E1cB)_R$ mechanism. An inverse solvent isotope effect should be also observed in situations where both k_2 and k_{-1} (scheme 4) contribute to the overall elimination rate[168].

Of course, it is also very difficult to distinguish between the concerted $E2$ mechanism and the stepwise $E1cB$ mechanism. Particularly challenging is the distinction of the $E2$ mechanism from the $(E1cB)_{ip}$ and the $(E1cB)_I$ ones. Detailed discussions on this problem are available[11,15,169] and recently it has been suggested that the activation volume might provide a convenient measure of the $E2$–$E1cB$ character in elimination reactions[43].

To simplify the discussion, we will regroup $E1cB$ eliminations according to the mechanistic variants they are supposed to follow. In this context, we will also deal briefly with the criteria used for the mechanistic attribution.

B. Reactions Involving Reversibly Formed Carbanions

Even if a formal objection has been raised[170], it is generally accepted[171] that the occurrence of hydrogen isotope exchange between the substrate and the solvent accompanying elimination (especially if the exchange is faster than elimination) provides strong evidence for an $(E1cB)_R$ mechanism. The operation of this mechanism is also strongly suggested by the observation of specific base catalysis when the reactions can be carried out in buffered solutions. Another significant piece of evidence supporting the $(E1cB)_R$ mechanism is a primary hydrogen isotope effect of unity, which, however, does not allow us to distinguish this mechanism from the

$(E1cB)_{ip}$ one if $k_{el} \ll k_{-1}$ in the latter. Other mechanistic criteria will be discussed in the following sections.

The most favourable conditions for the occurrence of an $(E1cB)_R$ mechanism are: a poor leaving group, a product olefin not much more stable than the reactants (the return of the carbanion to the reactants has, thus, more chance to be faster or at least to compete with the leaving group loss) and a rather stable carbanion.

1. *Halides as leaving groups*

Since $(E1cB)_R$ and $(E1cB)_{ip}$ mechanisms require a relatively poor leaving group most of the examples of these mechanisms in the reactions of halogen compounds involve fluorides, especially trifluoromethyl derivatives. Fluorine is the poorest leaving group among the halogens and, moreover, its nucleofugal ability from various environments decreases in the following order[172a]: $CHF_2 \gg CF_2OR > CF_2CF_3 \gg CF_3$.

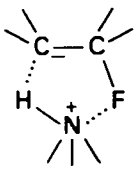
Exchange rates much faster than rates of β-elimination, suggesting an $(E1cB)_R$ mechanism, were first observed by Hine and coworkers in the HF eliminations from CF_3CHCl_2 and $CH_3OCF_2CHCl_2$[173]. More recent examples of substantial exchange accompanying elimination include $C_6H_5CHClCF_3$[174], $C_6H_5CH(CF_3)_2$[172b], and $(p\text{-}NO_2C_6H_4)_2CHCF_3$[175].

For the HF eliminations from $C_6H_5CHClCF_3$ and $C_6H_5CH(CF_3)_2$ promoted by EtONa in EtOH, it has been observed that both the elimination and the exchange exhibit a negligible primary hydrogen isotope effect[172b,174]. Since the absence of a primary isotope effect in the exchange reaction is diagnostic of extensive internal return from a solvated carbanion[176], it has been reasonably suggested that the eliminations from these substrates take place by the $(E1cB)_{ip}$ mechanism (Scheme 5)[172b,174]. Since the exchange is faster than elimination in both cases, the condition $k_{ex} > k_{el}$ must hold for the two hydrogen-bonded carbanions.

Conclusive evidence for the operation of an $(E1cB)_{ip}$ mechanism with $k_{ex} < k_{el}$ has also been obtained in the HF eliminations from (2-phenylsulphonyl)ethyl fluoride, (**29**, X=F)[177] and 2-fluoro-2-(phenylthio)ethylphenyl sulphone[178] (**30**) promoted by

$C_6H_5SO_2CH_2CH_2X$ (**29**) $\qquad$ $C_6H_5SO_2CH_2CHFSC_6H_5$ (**30**)

triethylamine in benzene or acetonitrile. In these reactions, no H–D exchange was observed when the deuterated compounds were allowed to react in the presence of triethylammonium chloride, nor was the reaction rate decreased. However, primary deuterium isotope effect values of unity or very close to unity were measured. It was also observed that eliminations from **30** followed an exclusive *syn* pathway, which was explained by suggesting an interaction between the fluorine atom and the positively charged nitrogen as depicted in structure **31**.



(**31**)

Very interestingly, it has also been pointed out[174,179,180] that an $(E1cB)_{ip}$ reaction with $k_{el} > k_{ex}$ and k_{el} competing with k_{-1} could exhibit the behaviour hitherto

considered to be peculiar to concerted eliminations. Thus, the results obtained in the HCl eliminations from $C_6H_5CHClCF_2Cl$ promoted by EtONa in EtOH (no H–D exchange; $k_H/k_D = 3$ at 0°C; rate much faster than in the HF elimination from $C_6H_5CHClCF_3$) have been interpreted in terms of an $(E1cB)_{ip}$ mechanism on the basis of the following evidence: (a) elimination from $ArCHClCF_2Cl$ exhibits the same β value as elimination from $ArCHClCF_3$ to which an $(E1cB)_{ip}$ mechanism has been convincingly assigned (*vide supra*); (b) the k_H/k_D values are temperature independent, the deuterated and the protonated compounds exhibit nearly equal energies of activation, whereas $A_H/A_D > 2.4$; (c) the chloro: fluoro leaving group effect (10^5) is too high for a concerted process. These behaviours do not seem compatible with a single step reaction, whereas they may be consistent with an $(E1cB)_{ip}$ mechanism, provided that a competition is established between internal return and loss of chlorine. Anomalous Arrhenius parameters have also been found in the eliminations from p-$ClC_6H_4CHClCF_2Cl$, $C_6H_5CHBrCF_2Br$, $C_6H_5CHBrCH_2Br$ and $C_6H_{11}CHBrCF_2Br$[179].

Koch and Dahlberg[180a] have further observed that while anomalous Arrhenius parameters are suggestive of a two-step process involving moderate internal return, this mechanistic possibility may also be, in principle, compatible with normal Arrhenius behaviour, or it may even produce a temperature dependence of kinetic isotope effect similar to that expected for reactions exhibiting quantum mechanical tunnelling. As a consequence, the distinction between the $(E1cB)_{ip}$ and the $E2$ mechanisms would become a formidable task, requiring the development and application of new mechanistic criteria. In the absence of these criteria, it could not even be excluded that the scope of the $(E1cB)_{ip}$ mechanism is much wider than originally thought, also including systems usually considered to be *bona fide* examples of the operation of the $E2$ mechanism.

Koch and Dahlberg[180a] have also suggested that one of these criteria is provided by the determination of the leaving group or β-carbon isotope effect in the elimination from a given compound and its deuterated counterpart. Identical values should be obtained for single step reactions, whereas different values are expected for a stepwise reaction with moderate internal return since the extent of internal return should be less with the deuterated compound. When this criterion has been applied to the eliminations from $C_6H_5CH(CH_3)CH_2X$(X = Cl, I) and $C_6H_5CHClCH_2Cl$, the experimental results have suggested an E2 mechanism in the former case and a stepwise mechanism in the latter[180b].

In a search for new mechanistic criteria of simpler application, Koch and coworkers have also proposed that internal return might be detected by measuring the reactivity difference between alkoxide-promoted elimination in t-BuOH and EtOH[181]. Since the t-BuOK–t-BuOH/EtOK–EtOH reactivity ratio usually ranges from 0.3 to 50 for reactions which almost certainly proceed by an $E2$ mechanism[182], it has been suggested that significantly higher values, say 200 or more, might indicate the operation of a stepwise mechanism as less internal return should occur in t-BuOH than in EtOH, probably owing to the lesser protonating capacity of the former solvent, which is also a weaker acid[183]. By this criterion, a stepwise mechanism has been suggested for the eliminations from $C_6H_5CH_2CF_3$, $C_6H_5CH_2CHF_2$, $C_6H_5CH_2CF_2Cl$ and $C_6H_5CH_2CF_2CF_3$[181].

Clearly, the observations by Koch and coworkers are of great interest since they might put the mechanistic aspects of elimination reactions in an entirely new light. However, we feel that further theoretical and experimental work is necessary before firm conclusions can be drawn. There is no doubt that some of Koch's results cannot be easily fitted in with a single step mechanism, but we feel that this alone cannot be sufficient proof in favour of the $(E1cB)_{ip}$ mechanism. On the other hand, it should be

noted that this mechanistic scheme can also experience some difficulty in rationalizing the observed results. For example, the $(E1cB)_{ip}$ mechanism is accommodated to the findings obtained in the eliminations from $C_6H_5CHClCF_3$ and $C_6H_5CHClCF_2Cl$ by assuming a drastically different interplay of k_{el} and k_{-1} in the two systems. It is, however, puzzling that this difference causes substantially different k_H/k_D values for the two reactions, whereas identical ρ values are observed.

Finally, an $(E1cB)_R$ mechanism has also been observed in the reactions of some halogenoketones[184]. Convincing evidence in this respect comes from the observation of specific base catalysis.

2. *Other leaving groups*

For reasons already mentioned, the chances for the observation of an $(E1cB)_R$ mechanism increase when leaving groups which are poorer than halides are involved. For example, the operation of this mechanism has been convincingly demonstrated (by detection of hydrogen isotope exchange and/or observation of isotope effect values of unity) by Stirling and coworkers for numerous β-phenylsulphonyl- and β-cyano-activated ethyl derivatives (**29** and **32**) with a quite sluggish leaving group such as C_6H_5O, $C_6H_5SO_2$, C_6H_5S and 'onium groups[185–188].

$$NCCH_2CH_2X$$

(32)

Interestingly, the reversible nature of these reactions has been exploited to obtain a scale of leaving group ability from a carbanion[185,189–191]. Owing to the activation of these systems a very wide range of leaving groups (most of them not known to depart as anions in simple eliminations and substitutions) encompassing a range of *c.* 10^{14} in reactivity has been examined. It has been observed that the leaving group ability does not correlate with the pK_a of the conjugate acid of the leaving group (unless a homogeneous series is considered) nor with the leaving group nucleophilicity.

Other interesting examples of reactions involving a reversibly formed carbanion can be found in the alkene-forming eliminations from 9-fluorenylmethanol[192], 9-methoxymethylfluorene[193], 1-methoxyacenapthene[194] p-$NO_2C_6H_4CH_2CH_2SCH_2CO_2^-$[195], $C_6H_5OCH_2CH_2COCO_2H$[196], $C_6H_5OCH_2CH_2COCH_3$[197], and also in the sulphene formation from $C_6H_5CH_2SO_2OAr$[198]. For several of these systems, support for a stepwise mechanism of elimination is also given by the observation of specific base catalysis at high buffer concentrations (buffer saturation kinetics) which clearly indicates a mechanistic cross-over from the $(E1cB)_I$ to the $(E1cB)_R$ mechanism.

C. Reactions Involving Irreversibly Formed Carbanions

The absence of a leaving group isotope effect is certainly the most significant evidence supporting the irreversible formation of a carbanion in an elimination process. In the absence of leaving group isotope effect measurements, or when these measurements are not possible, the observation of little or no sensitivity of the elimination rate to the nature of the leaving group is also frequently used as an indication in favour of an $(E1cB)_I$ mechanism.

When possible, the reliability of the latter approach can also be enhanced by taking into account the small effect that the leaving group may exert on the elimination rate through its influence on the carbanion stability. To this purpose, the elimination rate is compared with the ionization rate, evaluated by a Taft plot for the ionization of non-eliminating compounds of the same series. If the calculated rate of ionization and the observed rate of elimination are very similar, an $(E1cB)_I$ mechanism is suggested;

if the latter is much faster than the former (by at least one or two orders of magnitude, in view of the approximations involved in the calculation), an $E2$ mechanism is much more probable. Recently, however, this approach has been criticized. Details of this criticism will be reported in the following sections.

Finally, when buffer saturation kinetics are observed, an $(E\text{cB})_\text{I}$ mechanism is clearly indicated at the lower buffer concentrations, where the reaction exhibits general base catalysis.

In systems which can form a stable carbanion, a relatively good leaving group should favour the operation of an $(E1\text{cB})_\text{I}$ mechanism as, in this case, the loss of the leaving group from the carbanion has a better probability of being faster than carbanion reprotonation. Thus, there are numerous examples of reactions suggested to occur by an irreversibly formed carbanion which involve halides as leaving groups. It should be anticipated, however, that a substantial part of the mechanistic attribution has to be considered only as tentative since the distinction between $(E1\text{cB})_\text{I}$ and $E2$ reactions is often extremely difficult.

1. 2,2-Diarylethyl derivatives

A reaction which almost certainly occurs by an $(E1\text{cB})_\text{I}$ mechanism is the HCl elimination from 1,1-bis(*p*-nitrophenyl-2,2-dichloroethane (**33**) promoted by MeONa in MeOH[54,199]. Accordingly, this reaction exhibits a negligible k^{35}/k^{37} chlorine isotope effect. Interestingly, with less electron-withdrawing ring substituents than the *p*-NO_2 group, a small but significant chlorine isotope effect is observed and this has suggested a mechanistic cross-over at the $E1\text{cB}$–$E2$ borderline induced by the electronic effect of the β substituent.

An $(E1\text{cB})_\text{I}$ mechanism has also been suggested by McLennan and Wong[200] for the alkoxide-promoted eliminations from DDT (**34**) on the basis of the following

$(p\text{-}NO_2C_6H_4)_2CHCHCl_2$ $(p\text{-}ClC_6H_4)_2CHCCl_3$

(33) **(34)**

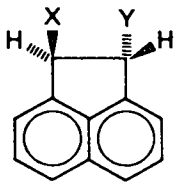
evidence: (a) the rates of elimination from Ar_2CHCCl_3 fit the Brönsted plot established for the ionization of fluorene derivatives and are correlated by the basicity function H_M for MeONa solutions in MeOH, with slope identical to that observed for the ionization reactions of fluorenes; (b) the values of primary deuterium isotope effect decrease in going from MeONa–MeOH to *t*-BuOK–BuOH, contrary to that which usually occurs in processes which presumably take place by the $E2$ mechanism; (c) the primary isotope effect for eliminations from DDT, promoted by bases of different strength in MeOH, reaches a maximum value with the base (namely PhO^-) which has the same pK_a value as that which was estimated for DDT ($\Delta pK_a \simeq 0$), as expected for a proton transfer reaction uncoupled to the departure of the leaving group.

However, serious doubts as to the validity of this mechanistic attribution have been raised very recently by Fry and coworkers[201], who have found a substantial α-^{14}C isotope effect in the eliminations from DDT and other Ar_2CHCCl_3 derivatives promoted by MeONa in MeOH. This finding clearly shows that bonding changes are taking place at the α carbon in the rate-determining step and therefore suggests an $E2$ mechanism. On the other hand, the evidence (c) above is invalid as McLennan has reported[202] that it was based on an incorrect estimation of the pK_a value for DDT. (It was, however, also concluded that a maximum isotope effect at $\Delta pK = 0$ is not a necessary condition for a simple proton transfer process[202].) An $E2$ mechanism seems probable also for the weak base-induced eliminations from DDT in aprotic solvents[203,204].

2. *1,2-Dihalogenoacenaphthenes and 2,3-dihalogeno-2,3-dihydrobenzofurans*

Very recently an $(E1cB)_I$ mechanism has been suggested for the *syn* eliminations from *trans*-1,2-dihalogenoacenaphthenes (**35–38**) promoted by *t*-BuOK in *t*-BuOH[205]. It has been observed that **35** (loss of HBr) and **36** (loss of HCl) react at practically the same rate and that **37** (loss of HF) is slightly more reactive (*c.* threefold) than both **35** and **36**. Thus the order of leaving group ability is F > Cl ≈ Br. Since fluorine is lost from **37** at a rate twice as fast as either bromine from **35** or chlorine from **36**, even in the presence of 18-crown-6 ether, the observed order of leaving group ability cannot be attributed to a preferential interaction between fluorine (the most electronegative halogen) and the metal counterion of the associated base, as suggested for the eliminations induced by complex bases (Section II.D.1.a). Clearly, whereas this order is certainly incompatible with a significant degree of breaking of the carbon–halogen bond in the transition state of the reaction, it points strongly to the operation of an $(E1cB)_I$ mechanism. Probably, the slightly larger reactivity of fluorine as a leaving group might reflect a greater ability of this halogen to stabilize a carbanion when acting from the β-position. Little information is available, however, on the relative ability of β-halogens to stabilize a carbanion. On the basis of σ^* values for the CH_2X group, an order F > Cl > Br is predicted. However, a reverse order Cl > F can be assumed from data concerning nucleophilic vinylic substitutions[206]. It is probable that different factors acting in opposite directions (e.g. the electronegativity and the polarizability of the halogens) play a role in this respect and that the relative weight of these factors depends on the particular system under consideration. For further considerations on the effect of β-substituents on the carbanion stability, see also Section III.C.4.

The difluoro compound **38** was found to be much less reactive (by *c.* 10^4-fold) than **37** (loss of HF) and this was considered to be in line with the well known much greater ability of an α-chlorine atom to stabilize a carbanion with respect to an α-fluorine atom[207].

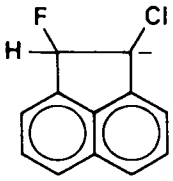


(35) X = Br, Y = Cl

(36) X = Y = Cl

(37) X = Cl, Y = F

(38) X = Y = F



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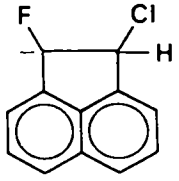
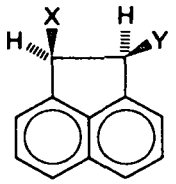


(40)

Another interesting observation was that only HF is eliminated from **37**. Clearly, of the two carbanions **39** and **40** which can be derived from **37**, the former, where the negative charge is stabilized by an α-chlorine, is practically the sole carbanion formed. Thus, only fluorine is lost in the eliminations from **37**.

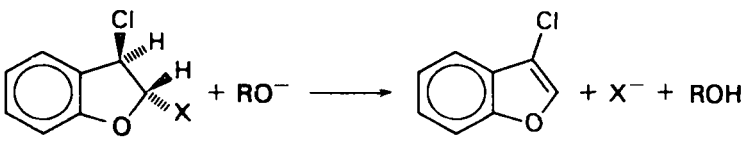
Anti elimination of HCl from **41** is significantly faster (*c.* 35-fold) than HF elimination from **42**[208]. This substantial leaving group effect suggests an *E*2 mechanism or, less probably, an $(E1cB)_R$ mechanism for the *anti* eliminations from dihalogenoacenaphthenes. It would thus appear that the reaction stereochemistry plays a fundamental role with respect to the elimination mechanism.



(41) X = Y = Cl

(42) X = Cl, Y = F

The kinetic data for the *syn* eliminations of HX from *trans*-2-X-3-chloro-2,3-dihydrobenzofurans (**43**) (X = Cl, Br, F) to give **44** promoted by *t*-BuOK in *t*-BuOH and EtOK in EtOH[208] are reported in Table 12. In *t*-BuOK–*t*-BuOH, the relative leaving group reactivity Br: Cl: F is 3.9:1:8.2, which suggests an $(E1cB)_I$ mechanism at least for the reaction of **44** (X = Cl) and **44** (X = F). However, this attribution probably holds also for **44** (X = Br) since all three halogeno derivatives exhibit a very similar value of the primary deuterium isotope effect, thus suggesting that the breaking of the C—H and C—X bonds are substantially uncoupled in the transition state.



(43) (44)

Interestingly, in EtOK–EtOH, the relative leaving group reactivity Br:Cl:F is 8:1:0.45, which could also be compatible with an *E*2 mechanism involving a very low degree of C—X bond breaking at the transition state. In agreement with the *E*2 mechanism, the value of the primary isotope effect is significantly influenced by the nature of the leaving group, k_H/k_D decreasing in the order Br > Cl > F, as expected for a concerted reaction.

However, the possibility cannot be excluded that in EtOH–EtOK the mechanism is still stepwise, involving the formation of a partially reversible carbanion for **44** (X = F) and, to a lesser extent, for **44** (X = Cl) (k_{-1} competes with k_2 in Scheme 4). A k_{-1} value higher in EtOH than in *t*-BuOH is in agreement with previous considerations. Moreover, it is quite reasonable to expect that the k_2/k_{-1} ratio will decrease as the breaking of the leaving group becomes more difficult, thus accounting for the observed

TABLE 12. Kinetic data for the elimination from 2-X-3-chloro-2,3-dihydrobenzofurans promoted by *t*-BuOK in *t*-BuOH and EtOK in EtOH at 30°C[208]

	t-BuOK–*t*-BuOH		EtOK–EtOH	
X	k_H, l m^{-1} s^{-1}	k_H/k_D[a]	k_H, l m^{-1} s^{-1}	k_H/k_D[a]
Br	1.87	2.9	1.22×10^{-2}	4.4
Cl	0.48	3.0	1.52×10^{-3}	2.6
F	3.96	3.1	6.93×10^{-4}	1.7

[a]Rate ratio between 2-X-3-chloro-2,3-dihydrobenzofuran and 2-X-3-chloro-3-deuterio-2,3-dihydrobenzofuran.

trend in the k_H/k_D values. However, since no isotopic exchange with the solvent is observed the intermediate should be a hydrogen-bonded carbanion, $(E1cB)_{ip}$ mechanism.

3. 2-Arylsulphonylethyl derivatives

In both the anti and the syn eliminations from 2-phenylsulphonylcyclohexyl halides and arylsulphonates promoted by OH^-, the leaving group effects (k_{Br}/k_{Cl}) are small (e.g. the bromo:chloro leaving group effect is *c.* 4 in the *syn* elimination)[209]. This finding has been considered indicative of a mechanism involving an irreversibly formed carbanion. The $(E1cB)_I$ mechanism is also supported by the observation that the *anti* and *syn* eliminations (from *cis* and *trans*-2-arylsulphonylcyclohexyl derivatives, respectively) exhibit a very similar ρ value. It has also been suggested that the intermediate carbanion is highly solvated since the rate of elimination is much greater than the calculated rate of isotopic exchange (Scheme 5, $k_{el} > k_{-1} > k_{ex}$).

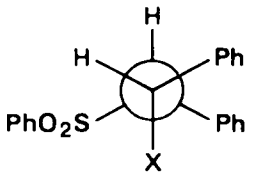
Comparison of ionization rates obtained by Taft plots with the rates of elimination from 2-phenylsulphonylethyl halides (**29**) promoted by EtO^- in EtOH has led to the suggestion that the mechanism is $(E1cB)_I$ for **29** (X = Cl, F) as the elimination rate is very similar to the calculated ionization rate. It is probably *E*2 for **29** (X = Br, I), which instead exhibit a rate of elimination greater than that of ionization[186]. However, the primary deuterium isotope effects for the four halides are significantly different[177,186], decreasing in the order I > Br > Cl > F. This observation would indicate a variable coupling of C—H and C—X bond breaking in the transition state and would also point to the operation of an *E*2 mechanism also for the reaction of **29** (X = Cl) at least. In this respect, it is interesting to note that **29** (X = F) exhibits a k_H/k_D value identical to those observed in the eliminations from **29** (X = OAc), **29** (X = OMs) and **29** (X = OTs), which are all supposed to take place by an $(E1cB)_I$ mechanism on the basis of the ionization plots[186].

The introduction of an α- and β-phenyl group into **29** (X = Br) and **29** (X = Cl) to give the α- and β-phenyl halogenosulphones **45** and **46**, respectively, causes a very similar effect on the elimination rate to that observed in the ionization of model systems with poor leaving groups[186]. An $(E1cB)_I$ mechanism for the reactions of **45** and **46** (X = Cl, Br) seems indicated, and it is also supported, in the case of the α-phenyl derivative, by the matching of the elimination rate with the calculated rate of ionization.

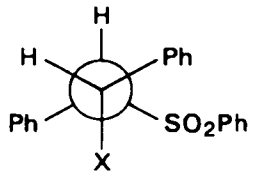
$C_6H_5SO_2CH_2CHXC_6H_5$ **(45)** $C_6H_5SO_2CH(C_6H_5)CH_2X$ **(46)**

Likewise, an $(E1cB)_I$ mechanism seems the most probable for the MeONa-promoted eliminations from *erythro*- and *threo*-1,2-diphenyl-2-*p*-tosylsulphonylethyl bromides and chlorides[210,211], **47** and **48** (X = Cl, Br), respectively. Very low k_{Br}/k_{Cl} values (*c.* 2) are observed and the primary deuterium isotope effect for the bromo compounds are not much different from those for the corresponding chloro compounds[210]. Moreover, the difference in reactivity between the *erythro* and *threo* isomers is similar to that observed between the corresponding isomers of 1,2-diphenyl-2-phenoxyethylphenyl sulphone, **47** and **48** (X = OC_6H_5) in detritiation reactions[211].

Interestingly, the eliminations from **47** (X = Cl, Br) occur by an *anti* stereochemistry, whereas for the *threo* isomers **48** (X = Cl, Br) the elimination stereochemistry can be either exclusively *anti* (e.g. with CH_3CO_2Na in $(CH_3)_2SO$) or exclusively *syn* (e.g. with *t*-BuOK in *t*-BuOH)[212]. The way that these results can be

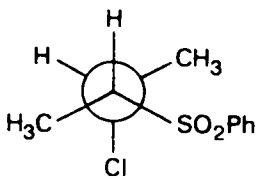


(47)



(48)

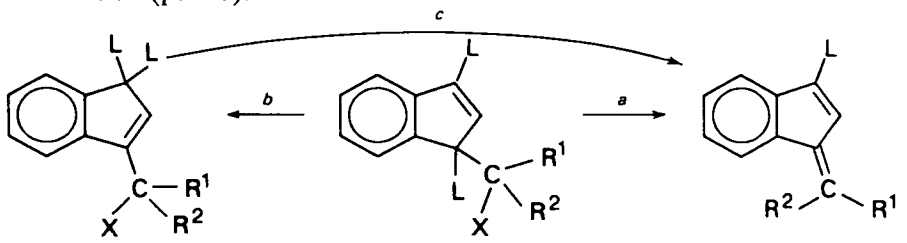
accommodated to the $(E1cB)_I$ mechanism has been discussed in detail[21,212]. An $(E1cB)_I$ mechanism has been suggested also for the amine-promoted eliminations from **49**, which present a predominantly *syn* stereochemistry[213].



(49)

4. *Indene derivatives*

The base-induced reactions of the indene derivatives **50** and **51** (*erythro* and *threo*) (L = H or D) give a very complex pattern of results. Elimination of LX and/or 1,3-proton (or 1,3-deuteron) transfer are possible (equation 8, paths *a* and *b* respectively). Moreover, the rearrangement products can undergo a true 1,4-elimination (path *c*).



(8)

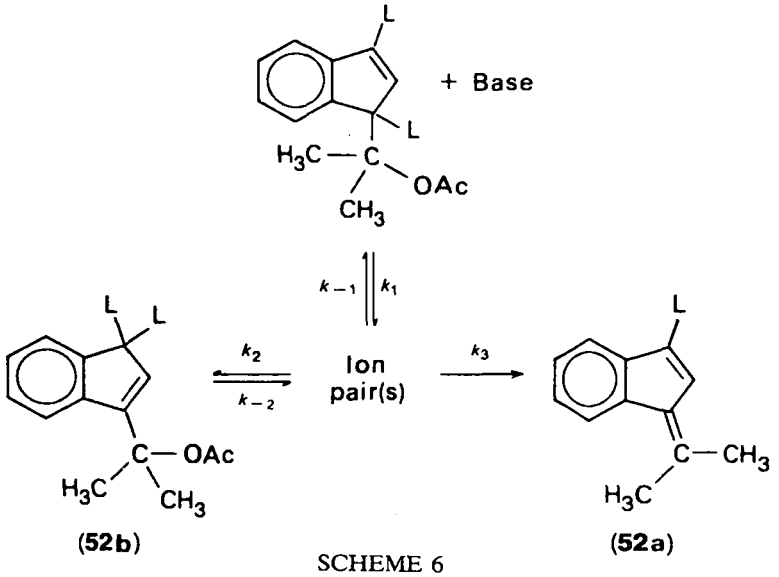
(**50**) $R^1 = R^2 = CH_3$

(**51**) $R^1 = H \quad R^2 = CH_3$

These reactions have been investigated in great detail by Ahlberg and coworkers who, in several cases, have been able to study paths *a*, *b* and *c* simultaneously and to determine the reaction rate and the deuterium isotope effect of each of the three processes. The results obtained, which are reported in a series of papers[214–219], have led to the suggestion that the 1,2-eliminations from **50** (X = OAc), **50** (X = Cl) and **51** (X = OAc) promoted by MeONa in MeOH are stepwise reactions involving an irreversibly formed intermediate, presumably a carbanion (reactions with MeONa) or ion-paired carbanions (reactions with amines).

The main evidence in this respect derives from the observation that, in the reactions of **50** (X = OAc) and **51** (X = OAc) with amines, where 1,2-elimination competes with a 1,3-proton transfer reaction, the latter reaction, which is substantially

intramolecular, exhibits an unusually large deuterium isotope effect. For example, a k_H/k_D value as large as 39 has been found in the reaction of the *threo* isomer of **51** (X = OAc) with quinuclidine[219]. In contrast, relatively low deuterium isotope effects have been observed in the 1,2-elimination reactions. This finding strongly suggests that 1,2-elimination and 1,3-proton transfer are coupled through at least one irreversibly formed common intermediate (ion-paired carbanion) as described in Scheme 6 for the specific case of **50** (X = OAc).



(52b) **(52a)**

SCHEME 6

Accordingly, in this scheme, the slow formation of the ion pair, which is characterized by a substantial isotope effect, is followed by two competing processes with different isotope effects. The conversion of the ion pair to the 1,2-elimination product (**52a**) should not be sensitive to isotopic substitution, whereas the collapse to the rearrangement product (**52b**) should exhibit a significant isotope effect. As a consequence, the isotope effect for the overall reaction which proceeds via the competing process with the largest isotope effect (the 1,3-proton transfer) should be amplified as observed. The other overall reaction (the 1,2-elimination) is instead expected to exhibit an attenuated isotope effect, again in line with experimental findings.

That 1,3-proton transfer and 1,2-elimination share a common intermediate is also indicated by the observation that when reactions of **50** (X = OAc, Cl, OMe, Me) either with amines or with MeONa are compared, the total rate (elimination plus proton transfer) has been found to increase on going, for example, from **50** (X = OAc) to **50** (X = Cl), whereas the rate of 1,3-proton transfer decreases[218].

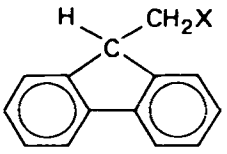
Interestingly, it has also been noted that the rate of elimination from **50** (X = Cl) is greater than that from **50** (X = OAc). Thus, if previous mechanistic attributions are correct, it would result that a stepwise mechanism involving an irreversibly formed carbanion is compatible with a significant leaving group effect[218]. To rationalize this observation, it has been proposed that partial breaking of the C—X bond also occurs in the $(E1cB)_I$ mechanism, presumably because a hyperconjugative interaction between the carbanionic centre and the electron-attracting leaving group takes place. This suggestion is of great interest since it would provide a unifying view of the interaction mechanisms in *E*2 and *E*1cB reactions. Another consequence of this

suggestion is that it raises some doubt on the value of the Taft equation (which considers polar effects only) as a means of calculating the rate of proton abstraction reactions from substrates of the type H—C—C—X, where X is an electron-withdrawing group, and thereby on the validity of the comparison between ionization and elimination rates as a mechanistic criterion.

Thibbin has further pursued these ideas and has proposed that the Taft equation should be replaced by the free energy relationship reported in equation (9), where σ^* is the polar substituent constant of CH_2X and L is the leaving group ability of X[220].

$$\log(k/k_0) = \rho^*\sigma^* + lL \tag{9}$$

The parameter l measures the sensitivity of the reaction system to changes in L. The L values for various substituents have been determined by using the HX eliminations from 9-(X-methyl)fluorenes, **53**, assumed to occur via an $(E1cB)_I$ mechanism, as reference reactions ($l = 1$). The use of this equation supports the mechanistic assignments for the indene derivatives and also suggests an $(E1cB)_I$ mechanism for the eliminations from 2-phenylsulphonylethyl halides, including chlorides and bromides.



(53)

Even if this approach is very interesting, it should be noted that the assumption of an $(E1cB)_I$ mechanism for the eliminations from 9-(X-methyl)fluorenes, e.g. **53** (X = Cl, Br), which exhibit a greater rate than that predicted by the Taft plot, is arbitrary. In fact, these deviations were previously used by More O'Ferrall to assign an $E2$ mechanism to these systems[221]. Moreover, the observation of linear plots when equation (9) is applied to the reactions of indene and 2-phenylsulphonylethyl derivatives only indicates that the deviations from the Taft plots in these reactions are proportional to those observed in the eliminations from 9-(X-methyl)fluorenes. Interpretations of this phenomenon other than those provided by Thibbin could be envisaged.

Finally, this suggestion does not account for the absence of a leaving group effect in the elimination from the dihalogenoacenaphthenes (Section III.C.2) and for the lack of a chlorine isotope effect in the eliminations from **33** (Section III.C.1).

5. *Other systems*

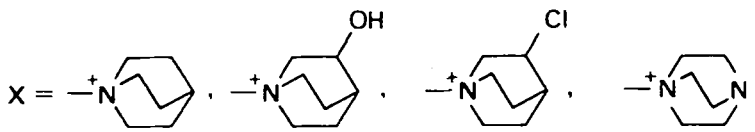
In the eliminations from β-cyanoethyl derivatives ($NCCH_2CH_2X$), the comparison of the rate of elimination with the predicted ionization rate suggests an $(E1cB)_I$ mechanism when X is Cl, OTs OMs and OAc[186].

With β-benzoylethyl derivatives ($C_6H_5COCH_2CH_2X$) the same criterion indicates an $(E1cB)_I$ mechanism for X = Cl, SPh, OPh and SO_2Ph[186].

A stepwise mechanism has been convincingly suggested for the base-promoted elimination from *N*-(2-*p*-nitrophenylethyl)quinuclidinium ions (**54**) in aqueous solutions[168,222] on the basis of a considerable body of evidence: (a) buffer saturation kinetics were observed; (b) isotope exchange at C_β occurs concurrent with elimination; (c) a very large inverse solvent isotope effect was measured, using data at very early reaction times (prior to significant exchange). The magnitude of this effect increases by increasing buffer concentration.

$p\text{-}NO_2C_6H_4CH_2CH_2X$

(54)



The buffer saturation and the variable solvent isotope effect clearly indicate a change from an $(E1cB)_I$ to an $(E1cB)_R$ mechanism as the buffer concentration is increased.

The same mechanism also holds when eliminations were carried out in DMSO–H_2O. In the mixed solvent one of the main pieces of evidence was that, under conditions where general base catalysis is observed, the Brönsted β value was found to be independent of the nature of the leaving group[222b].

Since the eliminations from 2-arylethylquinuclidinium ions with *para* substituents different from the NO_2 group appear to follow an $E2$ mechanism[222], these reactions represent another example of a mechanistic cross-over from a concerted to a stepwise mechanism induced by changing the electron withdrawing power of the β-substituent.

A low sensitivity of the elimination rate to the nature of the leaving group, supporting an $(E1cB)_I$ mechanism, has also been observed in the elimination of ArOH from $CH_3COCH_2CH_2OAr$[197] and $(CH_3)_3CSCOCH_2CH_2OAr$[223] and in the eliminations of $ArCO_2H$ from $(CH_3)_3CSCOCH_2CH_2OCOAr$[223].

Another interesting case is the HCl elimination from $C_6H_5COCH_2CHClC_6H_5$, which is catalysed not only by base, but also by acid[224]. A rate-controlling, acid-catalysed enolization, followed by loss of chloride ion from the enol or its anion, has been suggested. In neutral or basic media the results (general base catalysis) are consistent with either an $E2$ or an $(E1cB)_I$ mechanism.

IV. *E*1 ELIMINATIONS

A. General

The most suitable conditions for the operation of the $E1$ mechanism (equations 5 and 6) are a substrate prone to form a relatively stable carbonium ion, a good leaving group and an ionizing solvent of low nucleophilicity. Generally, solvolytic eliminations from tertiary and secondary halides and tosylates are discussed in terms of an $E1$ mechanism of elimination utilizing the framework provided by the Winstein ion pair mechanism for sequential ionization–dissociation (Scheme 7)[225], according to which an intimate ion pair (**55**) and solvent-separated ion pair (**56**) are formed *en route* to the dissociated ion.

$$RX \rightleftharpoons \underset{(55)}{R^+ X^-} \rightleftharpoons \underset{(56)}{R^+ \,\|\, X^-} \rightleftharpoons R^+ + X^-$$

SCHEME 7

Solvent attack can take place at any stage of the ionization–dissociation process, leading to both elimination ($E1$ reaction) and substitution products (S_N1 reaction). In addition, olefins can also be formed by attack of the leaving group X^- on R^+. This process most probably occurs at the stage of the intimate ion pair. Thus, elimination

and substitution products could derive, in some cases, from different intermediates; for example, the former from an intimate ion pair, the latter from a solvent-separated ion pair[226].

However, it is necessary to point out that whereas Scheme 7 has met general acceptance for the solvolytic reactions of tertiary derivatives, it has raised some controversy with respect to its application to the solvolysis of secondary alkyl derivatives[227,228]. Since secondary substrates exhibit less tendency to ionize than the tertiary ones and are more susceptible to nucleophilic attack, it has been suggested that in solvents of relatively good nucleophilicity, the former could undergo a solvent attack on the undissociated substrate and form the products directly or via a nucleophilically solvated ion pair[227]. It is clear that, in the former case, the solvolytic elimination would simply be an $E2$ process.

B. Stereochemistry

In spite of the fact that $E1$ eliminations involve proton loss from a carbocation, these reactions can exhibit substantial stereospecifity, ranging from predominantly *anti* to predominantly *syn* stereochemistry.

Generally, an *anti* alignment of the β-proton and the leaving group in the starting material should be favoured since it allows the β-proton to provide considerable assistance to the ionization process, either by a hyperconjugative effect[229,230] or by neighbouring group participation[231,232], which will be much more important when tertiary β-hydrogens are involved. Moreover, in the carbocation formed this arrangement provides the most efficient orbital overlap for the formation of the double bond.

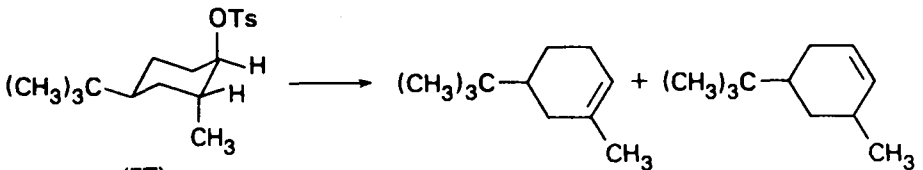
The stereochemical requirements of $E1$ eliminations are, however, much less stringent than those of $E2$ eliminations. Thus, in the former reactions the *syn* pathway frequently competes with the *anti* one and can even become predominant when the proton loss occurs at the stage of the intimate ion pair.

This situation was nicely illustrated long ago by the data of Skell and Hall concerning solvolytic eliminations from 2-butyl tosylates[233]. The stereochemistry of these eliminations was predominantly *anti* in relatively strong dissociating solvents (80% aqueous ethanol and acetamide), but became predominantly *syn* in the less dissociating solvents nitrobenzene and acetic acid, where it is probable that the leaving group plays an important role in the abstraction process at the intimate ion pair stage. However, it should be noted that, in contrast to this hypothesis, neither the fraction of elimination nor the percentage of the *syn* route in the elimination process depends on the nature of the leaving group in the acetolysis of 2-butyl derivatives[234] (Table 13). It has been suggested, therefore, that these reactions are not $E1$ eliminations, but more probably $E2$ reactions, with an $E1$-like transition state, promoted by the solvent (acetic acid). In an $E1$-like transition state, the stereoelectronic requirements which favour an *anti* stereochemistry for the $E2$ reaction should be strongly reduced, and this would explain the predominantly *syn* elimination observed. However, since the transition state structure of an $E2$ reaction is expected to change with the nature of the leaving group, it also seems difficult to fit this explanation with the absence of a leaving group effect on the reaction stereochemistry.

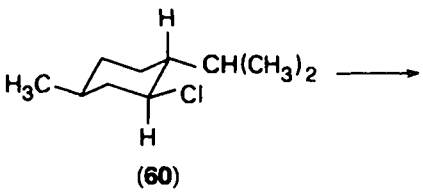
In the solvolysis of *cis* and *trans*-4-*t*-butylcyclohexyl brosylates in aqueous ethanol, the olefin-forming step involves the loss of the hydrogen *trans* to the leaving group[231,235]. In other cyclohexyl derivatives, *syn* elimination is also possible and can prevail over the *anti* one when with the former a more alkylated alkene is obtained. Thus, in the acetolysis of *cis*-4-*t*-butyl-*trans*-2-methylcyclohexyl tosylate (**57**), the olefin **58** (*syn* elimination) represents 41% of the total reaction product as compared with 26% of the olefin **59**[236].

TABLE 13. Fraction of elimination and percentage of *syn* route in the 2-butene formation from *threo*-3-deutero-2-X-butane in acetic acid[234]

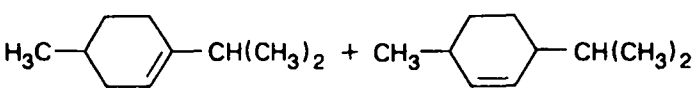
X	Elimination yield, %	Percentage of *syn* route, %
Cl	42	69
Br	46	68
I	42	
OTs	44	72



Likewise, in the eliminations from menthyl chloride (**60**) olefins **61** and **62** are obtained in a 2:1 ratio[237].



(**60**)



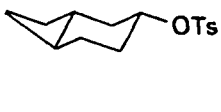
(**61**) (**62**)

Since hydride shifts can occur under unimolecular conditions, both **58** and **61** could derive, at least in part, from a route actually involving hydrogen migration to form a tertiary carbocation. This possibility, however, has been shown to play only a minor role in the reaction of menthyl chloride[237].

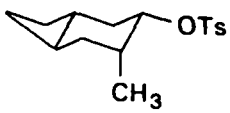
In the solvolysis of neomenthyl tosylate in aqueous trifluoroethanol and aqueous ethanol, the elimination reaction (which accounts for 75% of the products) follows a rate-determining 1,2-hydride shift from a tertiary to a secondary carbon atom. Interestingly, the migrating hydrogen is not the one involved in the elimination reaction[238].

The conformation of the leaving group (axial or equatorial) does not seem very important as both *cis*- and *trans*-4-*t*-butylcyclohexyl brosylates afford similar yields of olefin (85% with the former, which has an axial leaving group, and 67% with the latter, which has an equatorial leaving group)[231,235]. Due to the important role that β-hydrogen neighbouring group participation appears to play with respect to the ionization of these systems[231], it has been suggested that a twist-boat transition state is involved in the ionization from cyclohexyl derivatives with an equatorial leaving group[235,236,239,240].

In keeping with this suggestion, it has been found that the introduction of an axial methyl group in the 4 position of **63** to give **64** causes a great enhancement of the solvolysis rate in methanol (*c.* 100-fold) and a significant increase in the yield of the elimination product (from 40 to 65%)[241]. In contrast, if the 4-methyl group is equatorial (**65**) there is a decrease in the solvolysis rate (*c.* 10-fold) and the elimination



(**63**)

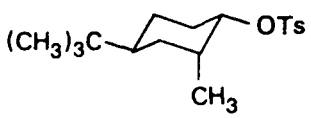


(**64**)

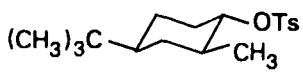
(**65**)

yield becomes negligible. The intervention of a twist-boat form in the solvolysis process can explain these observations since such a form can be more easily obtained from **64** than from **65**: in the former case the 1,3-diaxial interactions involving the methyl group are removed. Furthermore, only in the twist-boat conformation from **64** are the *β*-hydrogen and the leaving group in an approximate *anti* periplanar arrangement.

A somewhat different situation pertains when acetolysis of the tosylates **66** and **67** are compared; again the compound with the axial methyl group solvolyses at a much faster rate than that with the equatorial methyl group; however, the yield of elimination products is similar for **66** and **67**[236]. It is possible that in acetic acid the *syn* elimination is promoted by the leaving group within the ion pair and can therefore more successfully compete with the substitution reaction.



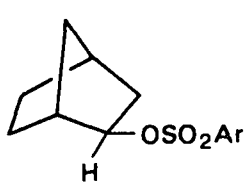
(**66**)



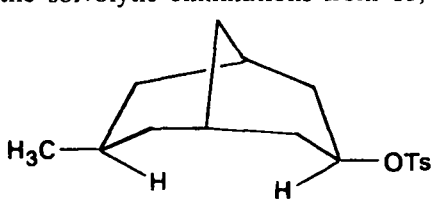
(**67**)

The stereochemistry of the solvolytic elimination from cyclopentyl brosylates has been investigated in different solvents[226,242–244]. In ethanol–water, *anti* elimination is only slightly favoured over *syn* elimination (*anti*:*syn* ratio 1.37), whereas in 97% trifluoroethanol–water and in 90% hexafluoroisopropanol–water the *syn* elimination is some four times faster than the *anti* one. On the basis of secondary deuterium kinetic isotope effect measurements it has been suggested that in the more nucleophilic solvent mixture (ethanol–water) the elimination as well as the substitution reaction takes place by solvent attack on a reversibly formed ion pair. In contrast, both in 97% trifluoroethanol–water and in 90% hexafluoroisopropanol–water the elimination is promoted by the leaving group at the stage of the intimate ion pair[226,228,242–245]. However, these conclusions have been criticized and it has been proposed that solvolysis of secondary cyclopentyl sulphonates are better described in terms of a nucleophilically solvent-assisted process[246–248].

A *syn* pathway is also followed in the solvolytic eliminations from **68**, **69**[249] and



(**68**)



(**69**)

cyclodecyl tosylates[250]. In these cases, an elimination induced by the anion has also been proposed.

C. Orientation

Solvolytic elimination generally leads to the predominant formation of the more alkylated olefin. In general this tendency is much more marked than that observed in the *E*2 eliminations which follow the Saytzeff rule[251]. An exception to this trend is, however, represented by weak base-promoted eliminations (see Section II.C.2.a).

The adherence of *E*1 eliminations to the Saytzeff orientation probably originates from the greater stability of the more alkylated olefins. That this is the case is also shown by the observation that an apparent breakdown of this rule is obtained in those cases where, owing to steric effects, the less alkylated olefin is the most stable one[251].

A deviation from the Saytzeff rule has also been observed in the eliminations from vicinally *trans*-alkylated cycloalkyl tosylates[252]. The phenomenon is probably due to the fact that, with these compounds, the formation of the Saytzeff olefin requires an elimination reaction with a *syn* stereochemistry. However, in spite of such a requirement, Saytzeff orientation is the outcome of the solvolysis from methyl chloride[237].

Orientation in a solvolytic elimination can also be significantly influenced by the leaving group. For example, Cram and Sahyun have observed that acetolysis of 2-phenyl-2-butyl chloride affords 74% of 1,2-dimethyl-1-phenylpropene (68% *trans*, 9% *cis*) whereas from 2-phenyl-2-butyl acetate the yield of the same olefin is 55% (53% *trans*, 2% *cis*)[253]. Thus the nature of the leaving group has influenced both positional and geometrical orientation.

An effect of the leaving group on the olefin proportion has also been observed in the ethanolysis of 2-pentyl and *t*-pentyl derivatives[254].

Interestingly, in the solvolysis of 2-methyl-3-pentyl tosylates, the *trans*:*cis* ratio for 4-methyl-2-pentene is much larger than that obtained in the solvolysis of 4-methyl-2-pentyl tosylates[119]. Thus, the same situation occurs that has already been observed for the *E*2 eliminations from these substrates (Section II.C.5). If the elimination occurs from an ion pair in which the leaving group can still exert a steric effect, the explanation used to rationalize this phenomenon in the *E*2 reactions could also be used in this case. It cannot be excluded, however, that the solvolytic elimination leading to 4-methyl-2-pentene involves nucleophilic assistance by the solvent.

D. *E*1–S_N1 Competition

Solvolytic processes are certainly not among the more important synthetic routes for the preparation of olefins. The main reason is that the formation of substitution products effectively competes with that of elimination products in most of the solvolytic reactions (*E*:*S* competition). The main factors which influence this competition will be the object of the following discussion.

1. Effect of the alkyl structure

Solvolysis of unbranched secondary alkyl halides generally gives very low yields of olefin[255]. With tertiary derivatives the proportion of olefin increases, and can become very large with bulky alkyl groups bound to the tertiary carbon atom. For example, 65% of olefin forms in the solvolysis of **70** in 80% aqueous ethanol[256].

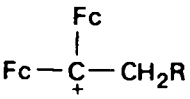
According to the Hughes and Ingold explanation, the favourable effect of branching on the elimination reaction has been ascribed to the greater stability of

$$(CH_3)_3CCH_2CH_2C(CH_3)_2Cl$$

(70)

the more substituted olefins[83]. In contrast, Brown and Fletcher preferred to call steric effects into play and argued that a heavily α-substituted carbocation would give an alkene in preference to a substitution product since the latter process involves the binding of a fourth group to the α carbon[256].

Probably, both steric and polar effects can play an important role with respect to the *E*:*S* competition. Accordingly, it is quite obvious that such a competition will depend on both the rate of proton loss from the carbocation (which should be greater the more stable is the alkene formed) and the rate of nucleophilic attack of the solvent on the carbocation (which should decrease as the α-bonded groups become bulkier). A very recent piece of evidence in this respect is the finding that the rate of water addition to the carbocation **71** (Fc = ferrocenyl) in aqueous acetonitrile can be decreased by increasing the bulkiness of the R group[257]. When R = *t*-Bu, the elimination rate also decreases, but to a much smaller extent than that of substitution.



(71)

In cyclohexyl derivatives, the *E*:*S* competition is higher when the leaving group is axial than when it is equatorial. Thus, in the methanolysis of *cis*- and *trans*-3-methylcyclohexyl tosylates, the elimination yields are 36 and 58%, respectively[252].

In 2-alkyl-substituted cyclopentyl and cyclohexyl derivatives, the *E*:*S* ratio is generally larger with the *cis* than with the *trans* isomer (*cis* rule)[4,252]. Since most of the eliminations are towards the alkyl group, the phenomenon can be rationalized on the basis of the already discussed preference for reactions with an *anti* stereochemistry. Steric factors, however, can also play a role in this respect[4]. An exception to this trend is the methanolysis of *cis*,*cis*-1-decalyl tosylate, which gives a higher proportion of olefin than that given by the *cis*,*trans* isomer[252].

2. *Effect of the leaving group*

In solvolytic reactions involving a fully dissociated carbonium ion, the *E*:*S* ratio should be independent of the leaving group. This expectation has indeed been fulfilled for reactions in water, a strongly dissociating solvent[258].

However, when the elimination takes place at the ion pair stage, the leaving group is often the proton-abstracting base and therefore can play a fundamental role in determining the *E*:*S* ratio.

It has generally been found that the more basic is the counterion in the ion pair, the larger is the *E*:*S* ratio. For example, Cocivera and Winstein[259] observed that, in ethanol or acetic acid, the olefin yield increases in going from *t*-butyldimethylsulphonium perchlorate to *t*-butyl bromide and Bunnett and Eck[260] have found that, in the methanolysis of 2,3,3-trimethyl-2-butyl halides, the olefin fraction in the products increases in the order I < Br < Cl. Similar results have been obtained in the solvolysis of *exo*-2-norbornyl arenesulphonates (**68**)[249], where electron-donating substituents in the leaving group increase the *E*:*S* ratio, and in the solvolysis of cumyl derivatives[261].

TABLE 14. Elimination:substitution (E:S) ratio in the solvolysis of some t-pentyl and 2-pentyl derivatives in ethanol[254]

Substrate[a]	E:S ratio
t-PeBr	1.75
t-PeŠMe$_2$ I$^-$	2.77
t-PeŠMe$_2$ ClO$_4^-$	0.42
2-PeBr	0.38
2-PeŠMe$_2$ I$^-$	2.5
2-PeŠMe$_2$ ClO$_4^-$	1.43

[a] t-Pe = t-pentyl; 2-Pe = 2-pentyl.

The situation can be significantly more complicated, however, since Feit and Wright have observed that in the solvolysis of t-pentyldimethylsulphonium iodide, the E:S ratio is larger than in the solvolysis of t-butyldimethylsulphonium perchlorate and t-butyl bromide[254]. With secondary alkyldimethylsulphonium salts, the E:S ratio is independent of the nature of the anion and is in each case larger than for the corresponding secondary bromide. Some data are presented in Table 14. It has been proposed that since the ion pair formed in a solvolysis is born into the solvation environment left behind by its precursor, even very subtle changes in the leaving group can influence the product distribution. The possibility of nucleophilic participation by the solvent in the solvolytic reactions of the secondary substrate, however, should also be considered.

More recently, it has also been suggested that in cases where elimination occurs at the stage of the intimate ion pair, and substitution at the stage of the solvent-separated pair, the change in the E:S ratio with the leaving group may be due to variations in the stability of the carbonium ion or the intimate ion pair[262]. Thus, the observation that in aqueous dioxane dioxane the solvolysis of PhCClBrCH$_3$ affords more olefin than that of PhCCl$_2$CH$_3$, in spite of the fact that chloride is more basic than bromide, has been rationalized by assuming that chloride ion, because of the higher charge density, stabilizes the ion pair more effectively than bromide ion. However, the reason why a more stable ion pair should exhibit a greater preference to convert itself to a solvent-separated ion pair than to undergo an elimination process is not clear.

3. *Effect of the solvent*

The role of the solvent in the E:S competition is at least twofold. It influences the relative stability of the different ionic intermediates and it can intervene directly as the reactive species in both elimination and substitution processes. Ionizing power, nucleophilicity and basicity are, therefore, the more important solvent properties which affect the relative proportion of the elimination and substitution products.

In the solvolysis of cyclopentyl brosylate in ethanol–water mixtures, products appear to be formed by a rate-determining attack of the solvent on a tight ion pair. The percentage of elimination thus increases by decreasing the fraction of the more nucleophilic ethanol in the solvent mixture (11.8% and 21.9% elimination in 100% and 70% ethanol, respectively)[242]. Trifluoroethanol is certainly less nucleophilic than ethanol: the olefin yield from cyclopentyl brosylate, in 70% trifluoroethanol–water, is 41.8%. A still larger value (76.4%) is obtained in 97% trifluoroethanol–water. The nucleophilicity and basicity of the latter mixture are so low that elimination is, in this

case, probably promoted by the leaving group within the intimate ion pair. Likewise, with *t*-butyl chloride in trifluoroethanol–water, the isobutene yield goes down from 33 to 4% when the percentage of water in the mixture passes from 1 to 60%[263].

In solvolyses where elimination takes place by a counterion attack at the ion pair stage, the solvent can also influence the *E*:*S* ratio by affecting (e.g. via hydrogen bonding) the basicity of the counterion itself. This hypothesis has been put forward to explain the observation that in the solvolysis of 2-norbornyl arenesulphonates (**68**)[249] and of the bicyclo[3.3.1]nonyl tosylate (**69**)[264] in carboxamides, the olefin yield decreases in the order dimethylacetamide > DMF > *N*-methylacetamide > *N*-methylformamide, which is the order of increasing hydrogen-bonding ability of these solvents.

No significant influence of the solvent on the *E*:*S* ratio has been observed in the solvolysis of some butyl, pentyl and hexyl derivatives in *n*-butyl, *s*-butyl and *t*-butyl alcohol[119].

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CHAPTER **24**

Structural chemistry of the carbon–halogen and carbon–pseudohalogen bonds

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I. INTRODUCTION

This article is concerned with the structural chemistry of the C—X bond where X is halogen atom or pseudohalogen group. Structural chemistry of a specific bond means the geometical parameters which define a specified bond (e.g. bond length, bond angles, torsion angles).

The knowledge of the bond length between atoms provides a qualitative, if not quantitative, measure of the bond strength. It has been established beyond doubt that the higher the bond order (for a given pair of atoms) the shorter the bond length. Variation in bond length between given pairs of atoms indicates changes in the electronic properties of the specified bond. Bond order is formally defined as one-half of the excess of electrons in bonding orbitals over those in antibonding orbitals involved in the bond formation. However, this definition will lead to bond orders of integral or half-integral numbers. The relationship between bond order and bond length (in ångstroms) was given[1] by the equation $D(n') = D(1) - 0.71 \log n'$, where $D(1)$ is the bond length for $n' = 1$. Thus, for a given bond length a number of fractional bond orders can be obtained. The C—C distances in molecules vary from 1.20 Å in alkynes to 1.33 Å in alkenes and 1.54 Å in alkanes. (Although much longer bond distances have been observed in strained molecules, the mean value is 1.54 Å.) The decrease in C—C bond length from alkanes to alkynes has been interpreted[1] in terms of increasing π-bond character. The formally single bond, such as in 1,3-butadiene, is shorter than in alkanes (1.48 Å). This shortening was attributed to an increase in π-bond character of that bond. However, the recognition[2] that the effective covalent radius of a carbon atom varies with the state of hybridization could also serve as an explanation for the shortening of that bond. The same explanation was adopted for the experimental observations of carbon–halogen bonds which vary significantly in length. In plotting values for C—H, C—C, C—Cl, C—Br and C—I bond distances against the percentage of s-character of the carbon atom hybrid orbitals, all points for a given C—X bond lie on a straight line[3], and the lines are approximately parallel. These results suggest that the bond lengths are mainly determined by the state of hybridization at the carbon atom rather than by resonance. This is in agreement with quadrupole coupling constant measurements which indicate that the C—Cl bond in vinyl chloride has little double bond character (*ca.* 5%)[4,5]. However, simple additivity of covalent radii could not be accepted, as was pointed out[6] for C—F bond length. The covalent radius of an sp^3 carbon atom is 0.77 Å while that of F is 0.72 Å; simple additivity would predict a bond distance of 1.49 Å while the observed one in CH_3F is 1.39 Å, and in CF_4 it is 1.32 Å.

The shortening of the C—F bond distance on replacement of H atoms in CH_3F by fluorine atoms necessitates some other explanation. These experimental observations led to a more general conclusion[6] that, in the absence of any marked steric effect, replacement of X in the structure, X—A—Y by an atom more electronegative than X causes the adjacent A—Y bond to become shorter. A rule was proposed[6] that atomic s-character concentrates in an orbital directed towards an electropositive substituent, or, atomic p-character concentrates in orbitals directed towards electronegative substituents.

In a recent article on the same subject[7] it was pointed out that in order to account for variations in carbon–halogen bond distance it is necessary to consider several possible effects: (i) hybridization of the carbon atom; (ii) hybridization of the halogen atom; (iii) electron delocalization of halogen lone pairs; (iv) electronegativity differences; (v) ionic character in the carbon–halogen bond; (vi) intramolecular steric effects; and (vii) intermolecular interactions in the solid state.

As has been pointed out, and will be shown in the following sections, the hybridization of the carbon atom has the major influence on the carbon–halogen bond lengths. The classification of those bonds has therefore been carried out according to the state of hybridization of the carbon atom. Within a class of compounds, other minor variations in bond lengths may be detected and attributed to the other effects stated above. Some of these effects will be mentioned in the following sections.

There are four sources for structural data: crystal structure determination by X-ray and neutron diffraction methods or electron diffraction and microwave (MW) spectra of molecules in the gaseous state. One should be aware of the differences in the definitions of bond lengths among these methods.

The bond length obtained from X-ray and electron diffraction methods is the distance between the centres of the electron densities of the bonded atoms. The bond length obtained from neutron diffraction or calculated from MW spectra is the distance between the centres of masses of the bonded atoms. The differences in the definitions suggest that comparison of data available from those methods should be made with caution. However, it was found that the differences in bond lengths, obtained from X-ray and neutron diffraction methods, are of the order of 0.01 Å for the atoms discussed in this article.

Other differences might occur in comparison of bond lengths obtained in the crystalline state (X-ray and neutron diffraction methods), where packing forces play an important role, and those obtained in the gaseous state (electron diffraction and MW spectra), where the molecules are regarded as separate individuals with no intermolecular interactions.

The main disadvantage in using electron diffraction or MW data is the fact that calculation of bond lengths can be carried out only for small molecules and therefore that the data are limited.

The best available source for structural data is that found in crystal structures obtained by X-ray diffraction methods. In the last three decades over 3000 crystal structures of compounds possessing C—X bonds have been elucidated.

In compounds in which the carbon atom is bonded to a terminal halogen atom, the bond lengths are the important and significant structural parameters while bond angles are determined by the other substituents on the carbon atom, rather than by the halogen. However, in carbon–pseudohalogen bonds, bond angles play an important role in the structural chemistry. This chapter will concentrate, therefore, on bond lengths in carbon–halogen bonds and on bond lengths and bond angles in carbon–pseudohalogen bonds. Various statistical methods have been applied in order to tabulate geometrical parameters, of which two will be mentioned. The normal probability plot[8,9], in which each observation is associated with its estimated standard deviation, leads to a weighted mean value. This procedure needs a great deal of effort when very many observations are used. It was used to calculate the mean value of the bond distance between bromine and an aromatic carbon atom[10]. The alternative method is to use as many observations as available, to plot a histogram and to calculate the unweighted mean value and the standard deviation of the population. An example illustrating the combination of the two methods is the calculation of C—Cl bond length in perchlorinated aromatic compounds[11], where a histogram is given but a weighted mean value was calculated. Although the weighted mean value is more accurate, the few examples which will be given in the following sections show that a simple averaging procedure using many observations leads to the same mean value.

There are differences in the meaning of the estimated standard deviations (e.s.d.s) calculated by the two procedures. The weighted e.s.d.s indicate the significance and accuracy of the weighted mean value, while in the other procedure one obtains the

e.s.d.s of the population which are used to make a decision regarding the adoption of a single observation for use with a class of compounds. The results which will be presented in the following sections were obtained by the following course:

(i) The data for C—X bond lengths were obtained by using the data base and program system of the Cambridge Crystallographic Data Centre[12].

(ii) The data obtained from crystal structures of organometallic compounds were eliminated to avoid inaccuracy influenced by the presence of heavy atoms.

(iii) The data used was taken only from results obtained with well refined crystal structures ($R < 0.10$).

(iv) Histograms were plotted for various types of compounds.

(v) The unweighted mean value of C—X length was calculated using the expression

$$\bar{l} = \frac{1}{N} \sum_{i=1}^{N} l_i$$

where $\bar{l}$ = calculated mean value of bond length, l_i = bond length of the ith observation, N = number of observations used in the histogram.

(vi) The standard deviation of the population was calculated using the expression $\{[(l_i - \bar{l})^2]/[N - 1]^{1/2}\}$.

(vii) Exceptional observations which deviate significantly in the histogram were eliminated and will be discussed separately.

(viii) The mean values will always be given to an accuracy of four significant figures together with the population e.s.d.s; for a single observation the experimental bond distance will be given as it is given in the literature, e.g. 1.402(26) Å means that the bond length was calculated to be 1.402 Å with an estimated standard deviation of ± 0.026 Å.

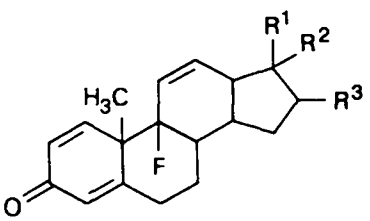
(ix) The bond distances used are not corrected for librational motion, unless otherwise specified.

II. CARBON–FLUORINE BONDS

A. Saturated Compounds

The lengths of carbon–fluorine bonds in monofluoro saturated compounds lie in the range 1.348–1.454 Å. The scatter of the bond lengths is shown in Figure 1. The mean value for 41 observation is 1.402(26) Å.

The limited number of observations does not permit classification into subgroups. However, it was found that the longer bond lengths were observed in steroids possessing the common skeleton **1**. The longest bond distance of 1.454 Å was observed in 17α,21-dipropionyloxy-9α-fluoro-16β-methylpregna-1,4,11-triene-3,20-dione[13]. The shortest bond lengths were found in aliphatic compounds in which fluorine



(1)

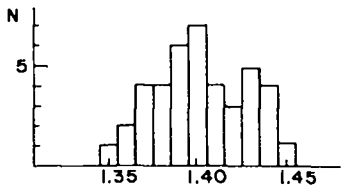
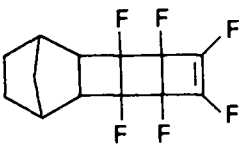
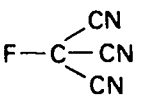


FIGURE 1. Histogram of C—F bond distances (Å) found in aliphatic compounds.

atoms are bonded to adjacent carbon atoms, such as in 3,4,5,6,7,8-hexafluoropentacyclo-[8.2.1.$0^{2,9}$.$0^{3,8}$.$0^{4,7}$] tridec-5-ene[14] **2**, where distances of 1.374(3) and 1.362(3) Å have been observed. The longer bond length of the two aliphatic C—F bonds is the one which has fewer adjacent C—F bonds. Further shortening of the C—F bond is obtained by introducing another electronegative atom or group on the same carbon atom. In fluoro(tricyano)methane[15] (**3**) a bond distance of 1.364(7) Å has been found.

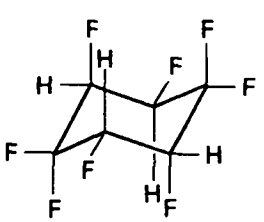


(**2**)



(**3**)

The shortening of the C—F bond is most notably exhibited in polyfluorinated molecules. The histogram given in Figure 2, based on 312 observations, shows that the mean C—F bond length in such compounds is decreased to 1.326(28) Å. However, this value seems to be shorter than expected. This shortening is a result of many observations of short distances due to large thermal vibrations observed in crystal structures of compounds possessing terminal CF_3 groups. In compounds where only two fluorine atoms are bonded to the same carbon atom a mean value of 1.347(17) Å has been obtained from 101 experimental values. The histogram for that group, given in Figure 3(a), shows no influence of high thermal vibrations. 1H*a*:2H*e*/4H*a*:5H*e*-octafluorocyclohexane[16] (**4**) serves as a nice example where two categories of C—F



(**4**)

bond exist: C—F bonds involving monofluoro-substituted C atoms and those involving difluoro-substituted C atoms. The former are significantly longer (1.383(3), and 1.374(3) Å) than the latter (1.356(3) and 1.354(3) Å). (The molecule has a centre of symmetry.) In perfluoroaliphatic compounds the whole range of scatter of bond length values is represented in the histogram. In *cis*-perfluorobicyclo[4.4.0]decan-1,6-diol[17] (**5**) the 16 C—F distances range from 1.336(7) to 1.351(7) Å. In perfluorododecahydrotetra(cyclopenta)cyclooctane[18] (**6**) the 12 independent C—F distances range between 1.310(7) Å and 1.354(6) Å.

The histogram for 196 observations of C—F bonds in aliphatic compounds where

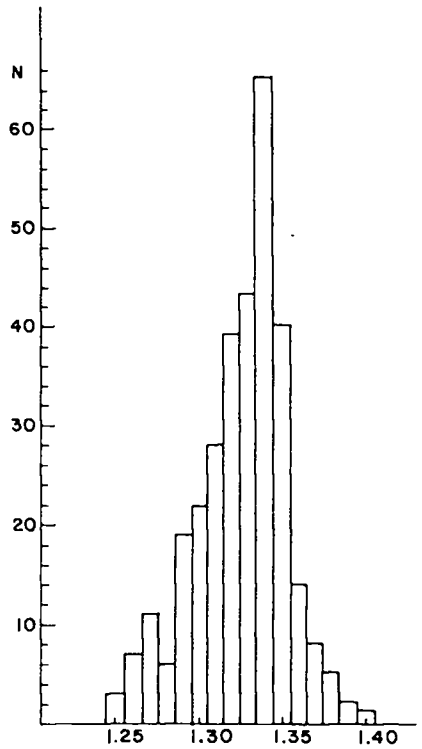
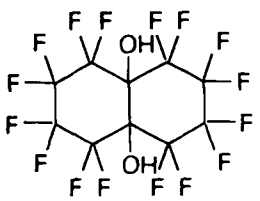
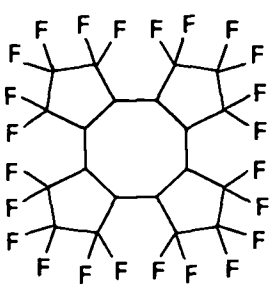


FIGURE 2. Histogram of C—F bond distances (Å) found in aliphatic compounds in which the carbon atom is polysubstituted by fluorine atoms.



(5)



(6)

the carbon atom is triply substituted by fluorine atoms is shown in Figure 3(b). The asymmetric histogram is well understood. Terminal CF_3 groups often have large thermal vibrations which cause a non-real shortening of these bonds. Therefore, the mean value of 1.314(25) Å is underestimated. Such a situation does not exist in hexakis(trifluoromethyl)benzene[19] (7), where C—F bond distances range between 1.320(4) and 1.346(4) Å (mean values 1.331(8) Å and 1.344 Å after correction for libration).

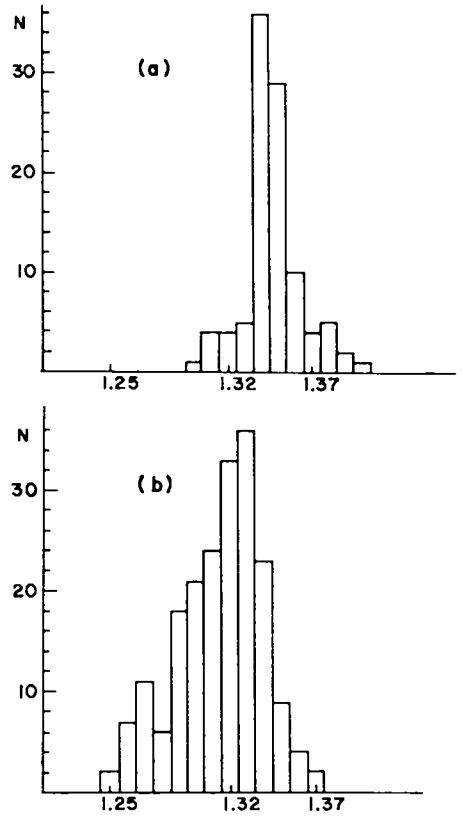
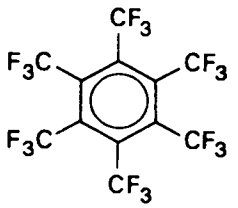
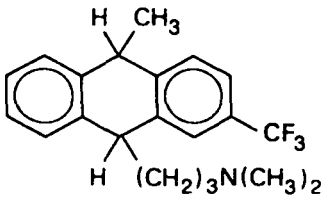


FIGURE 3. Histogram of C—F bond distances (Å) found in aliphatic compounds: (a) compounds in which two fluorine atoms are bonded to the same carbon atom; (b) compounds in which three fluorine atoms are bonded to the same carbon atom.



(7)

In (+)-*cis*-9-(3-dimethylaminopropyl)-10-methyl-2-(trifluoromethyl)-9,10-dihydroanthracene[20] (**8**) C—F bond distances range from 1.20(2) to 1.33(1) Å, but the fluorine atoms do have a large thermal vibration which causes an artificial shortening of those bonds. It seems reasonable to set the C—F bond distance in this type of compounds at a longer value of 1.324 Å. The C—F bond length found in CF_4[21] at 10 K is 1.32 Å (e.s.d. not given).



(8)

As a conclusion to the experimental facts indicated above, it is possible to assume that as the number of fluorine atoms bonded to the same carbon atom increases the carbon–fluorine bond distances tend to be shorter.

B. Aromatic Compounds

Fluorinated aromatic compounds are subdivided into two main groups: aromatic compounds possessing one or more fluorine atoms and bonded to non-adjacent carbon atoms, and aromatic compounds possessing fluorine atoms in positions *ortho* to each other.

Figure 4(a) shows a histogram for 34 observations in aromatic compounds of the first group. The C—F bond distances range between 1.33 and 1.38 Å with a mean value of 1.359(12) Å. The longest bond distance was observed in 1-{1-[4,4-bis(4-fluorophenyl)butyl]-4-piperidinyl}-5-chloro-1,3-dihydro-2*H*-benzimidazol-2-one[22] **(8a)** (1.368(9), 1.378(7) Å).

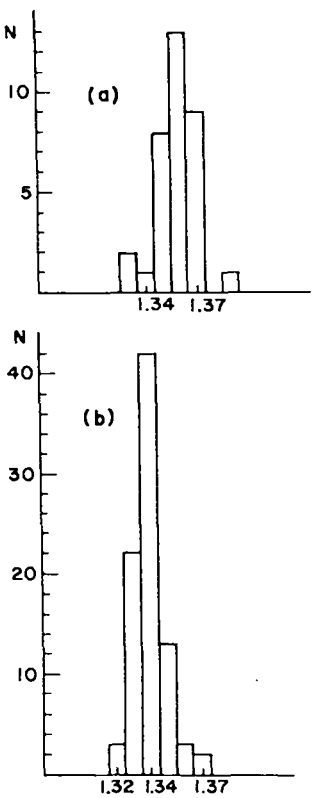
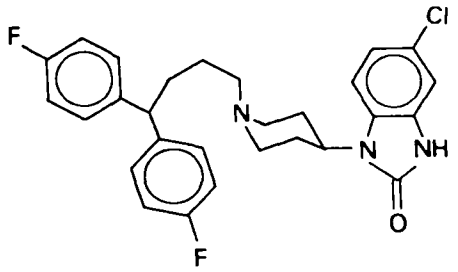
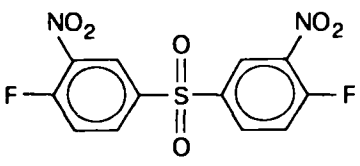


FIGURE 4. Histogram of C—F bond distances (Å) found in aromatic compounds: (a) C—F bonds in positions *meta* or *para* to each other, or monosubstituted aromatic compounds; (b) C—F bonds in positions *ortho* to each other.

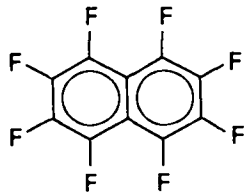


(8a)

The shortest C—F distance (1.332(4) Å) was observed in difluoro-3,3′-dinitro-4,4′-diphenyl sulphone[23] (**9**). This short bond is attributed to the effect of the strong electron-withdrawing nitro group in a position *ortho* to the C—F bond. Shortening of C—F bond lengths due to the electronegative fluorine atom bonded to an adjacent carbon atom is even more pronounced in the second group of aromatic compounds. The histogram for 85 observations in this group of compounds is shown in Figure 4(b). The mean value of the C—F bond length is 1.340(10) Å. Octafluoronaphthalene[24] (**10**) may serve as a representative example. The four independent



(9)



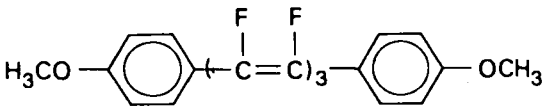
(10)

C—F bond distances range between 1.336(4) and 1.344(5) Å. Insignificantly shorter bond lengths were observed in hexafluorobenzene[25], where the C—F distances are 1.330(9) and 1.330(5) Å (not corrected for librational motion) or 1.355 and 1.357 Å (corrected for librational motion). The shortening of C—F bond distances in perfluoroaromatic compounds is an extreme example of the more general observation that as the number of C—F bonds in positions *ortho* to each other increases, the C—F bond lengths decrease. This shortening is also observed in polyfluorinated ethylenes. This further shortening is to some extent in agreement with the Bent rule[6], meaning that when a second electronegative group is added to the same carbon atom, further shortening occurs. The addition causes a compression of the density around that carbon atom and hence a shortening of adjacent bond lengths. The introduction of F atoms affects not only the adjacent C—F bond lengths; generally the other adjacent bonds are also somewhat shortened[26].

Electronic study of 12 fluorobenzenes[27] by the Pariser–Parr–Pople method led to the conclusion that variations in C—F bond lengths should be less than 0.004 Å. These results are in contradiction to the experimental values and should be clarified either by more accurate calculations or by obtaining systematic and more accurate experimental data.

C. Olefinic Compounds

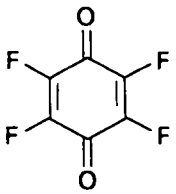
The mean value of the C(sp^2)—F bond length is 1.348(10) Å, as obtained from 28 observations. In a non-cyclic olefin such as 1,6-di(*p*-anisyl)hexafluoro-1,3,5-



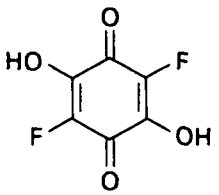
(11)

triene[28] (**11**) C—F distances are slightly longer (1.356(2)–1.359(2) Å). However, in the similar compound 1,8-diphenyloctafluoro-1,3,5,7-octatetraene[29] the distances range between 1.342(4) and 1.357(5) Å.

C—F bond lengths in quinones are similar to those in pure olefinic compounds. The shortening of the C—F bond in tetrafluoro-*p*-benzoquinone[30] (**12**) (1.330(6) and 1.339(6) Å) compared with 1.360(4) Å in fluoroanilic acid[31] (**13**) is explicable in terms of the electronegative effect of the fluorine atoms in positions *ortho* to each other.



(12)



(13)

D. Acetylenic Compounds

The C(sp)—F bond length was calculated, from microwave spectral data[32], to be 1.279(2) Å in fluoroacetylene and 1.262(2) Å in cyanogen fluoride (FCN). The shortening of the C—F bond length in the latter compound is explained in terms of resonance structures with partially charged atoms.

III. CARBON–CHLORINE BONDS

A. Saturated Compounds

The carbon–chlorine bond length in aliphatic chloro compounds as quoted by Pauling[1] is 1.767 Å, but it was based on limited data. The vast amount of data now available from X-ray crystal structure determination shows a large scatter of carbon–chlorine bond distances. The bond lengths range from 1.73 to 1.86 Å, with some exceptional examples which will be discussed.

The scattering of the data is such that we are unable to find any systematic correlation between variations in C—Cl bond distances and the various factors outlined in the introduction (Section I). However, the influence of introducing a strong electronegative atom or group on the carbon attached to the chlorine leads to a subdivision of the aliphatic chloro compounds into two main groups: aliphatic compounds with a monochloro-substituted carbon atom and aliphatic compounds with a polychloro-substituted carbon atom.

The 244 observations from the former group are shown on the histogram given in Figure 5(a). The mean value for the $C(sp^3)$—Cl bond length is 1.788(26) Å.

In (+)-cyclophosphamide[33] (**14**) the two C—Cl bond distances observed differ by 0.1 Å, being 1.81(2) and 1.92(2) Å. Karle and coworkers[33] suggest that the longer distance is to a chlorine atom which is partially dissociated from the molecule.

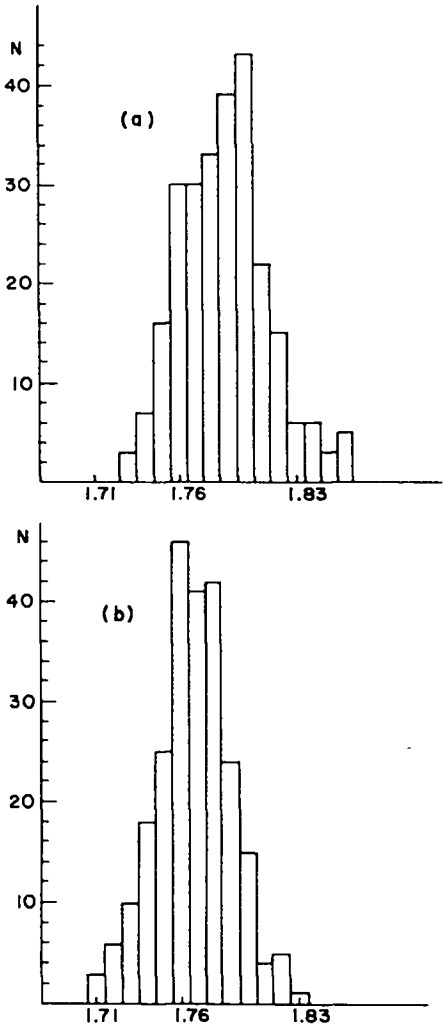
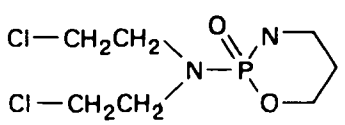
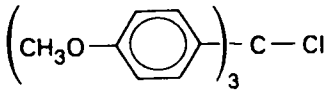


FIGURE 5. Histogram of C—Cl bond distances (Å) found in aliphatic compounds: (a) C atom is monosubstituted by Cl atom; (b) C atom is polysubstituted by Cl atoms.



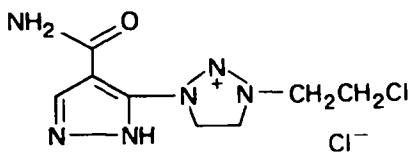
(14)

A long C—Cl bond has also been observed in molecules in which the bonded carbon atom is highly substituted by bulky groups such as in tris(*p*-methoxyphenyl)methyl chloride[34] (**15**) (1.860(8) Å).



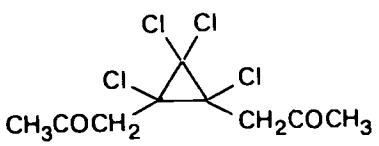
(15)

Short C(sp^3)—Cl bond distances were observed in various simple chloroparaffins, where the C—Cl bond is a terminal group of a long-chain molecule. However, in this case these atoms suffer from large thermal vibrations which cause an artificial decrease of bond lengths. That is, probably, the reason for the short bond of 1.694(7) Å which was observed in 1-(2-chloroethyl)-3-(4-carbamoylpyrazol-3-yl)-Δ^2-1,2,3-triazolinium chloride (**15a**)[35].

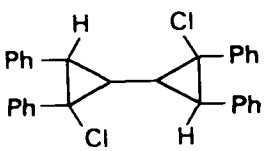


(15a)

Short distances were also observed in cyclopropane derivatives. In *cis*-1,2-diacetonyl-1,2,3,3-tetrachlorocyclopropane[36] (**16**), the bond lengths are 1.749(8) and 1.756(7) Å, but in 2,2′-dichloro-2,2′,3,3′-tetraphenylbicyclopropane[37] (**17**) the bond lengths are 1.785(5) and 1.792(5) Å.



(16)

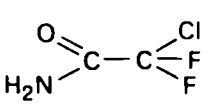


(17)

The shortening of C—Cl bonds in cyclopropane derivatives is explained by the greater s-character in the state of hybridization of the C atom, thus decreasing the distance to the chlorine atom. The noticeable lengthening of the bond in **17** compared with **16** might be a result of the introduction of bulky groups on the same carbon atom.

A histogram derived from 234 observations for the second group of aliphatic compounds is shown in Figure 5(b). The mean value of the C—Cl bond distances is 1.768(23) Å. Although the effect of introducing more electronegative atoms on the same carbon atom is less pronounced than for the C—F bonds, the shortening is significant. Some of the shorter bond lengths observed are not real, the atoms involved are in terminal groups (in most of the cases as CCl_3) which have high thermal vibrations.

An interesting example of the shortening of the C—Cl bond length due to the introduction of electronegative atoms on the same carbon atom is that of chlorodifluoroacetamide[38] (**18**). The C—Cl bond distance of 1.714(6) Å is highly affected by



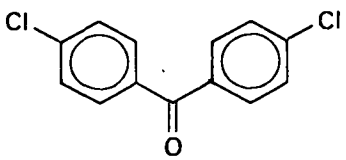
(18)

the two fluorine atoms. Although the molecule is disordered, the two different conformations revealed short bond lengths.

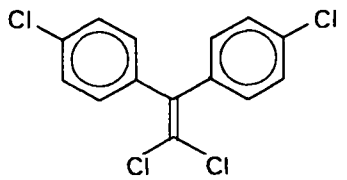
B. Aromatic Compounds

More than 400 observations for carbon–chlorine distances in aromatic compounds are available. The aromatic compounds may be divided into two main groups[39]: monochlorine-substituted aromatic compounds or polychlorine-substituted aromatic compounds in positions *meta* or *para* to each other, and a second group of aromatic compounds having chlorine atoms as substituents in positions *ortho* to each other. A histogram for the data observed in compounds of the first group is shown in Figure 6. The mean value of the C—Cl bond distance for 267 observations is 1.740(16) Å. The histogram shows fairly regular scattering of data.

The longest bond length observed[40] – one of 1.81(3) Å – seems to be an exceptional value due to isotropic refinement of the carbon atoms. A bond length of 1.792(5) Å was observed in 4,4′-dichlorobenzophenone[41] (**19**). However, shorter distances have been observed in similar compounds such as 2,2-bis(*p*-chlorophenyl)-1,1-dichloroethylene[42] (**20**) (1.753(8)–1.760(7) Å) (the vinylic C—Cl distances are shorter,



(19)



(20)

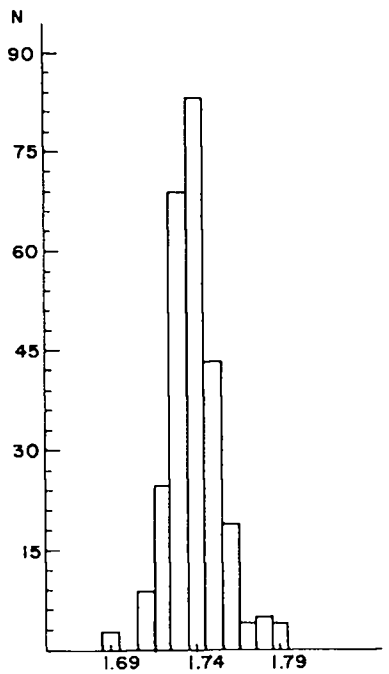
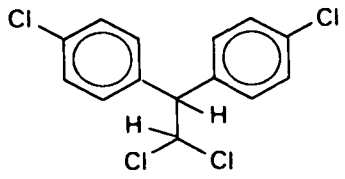
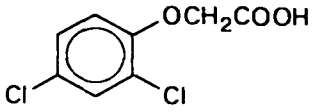


FIGURE 6. Histogram of C—Cl bond distances (Å) in aromatic compounds (excluding C—Cl bonds *ortho* to each other).



(21)

1.729–1.743(8) Å) and in 2,2-bis(*p*-chlorophenyl)-1,1-dichloroethane[42] (**21**) (1.727(11) and 1.737(12) Å) (the aliphatic C—Cl distances are longer, 1.790–1.791(11) Å). Some examples of aromatic compounds possessing chlorine atoms in *meta* positions which represent well refined structures are 2,4-dichlorophenoxyacetic acid[43] (**22**) (1.741(4) and 1.741(4) Å) and *N*-(2′,6′-dichlorobenzyl)-1-isoquinolone[44] (**23**) (1.738(3) and 1.742(3) Å). Introducing a third chlorine



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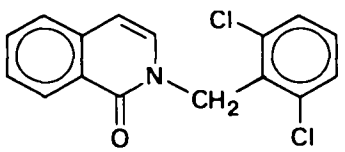
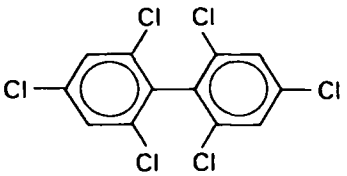


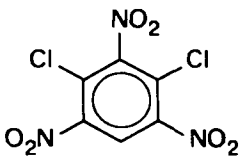
(23)

atom in a *meta* position reduces the C—Cl bond lengths, as in 2,2′,4,4′6,6′-hexachlorobiphenyl[45] (**24**) (1.720(7)–1.738(7) Å). However, there are not enough data to conclude that the shortening is due to the presence of a third chlorine atom in a *meta* position.



(24)

The shortest C—Cl bond, of 1.692(1) Å, was observed in 2,4-dichloro-1,3,5-trinitrobenzene (**25**)[46]. The shortening may be attributed to the strong electron-withdrawing properties of nitro groups in positions *ortho* (and *para*) to the carbon–chlorine bond.



(25)

A histogram for 206 observations of the second group of aromatic compounds possessing chlorine atoms in *ortho* positions is shown in Figure 7. The mean value for the C—Cl bond distance is 1.722(11) Å.

An excellent example which represents the whole range of experimental values is

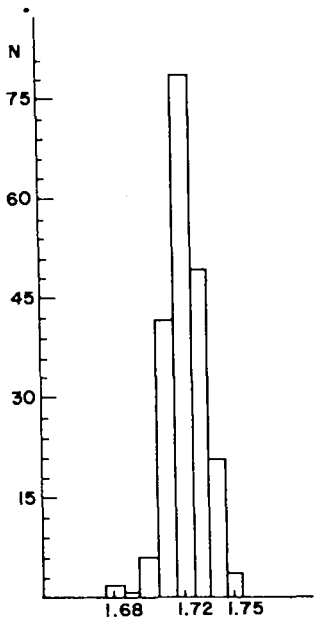
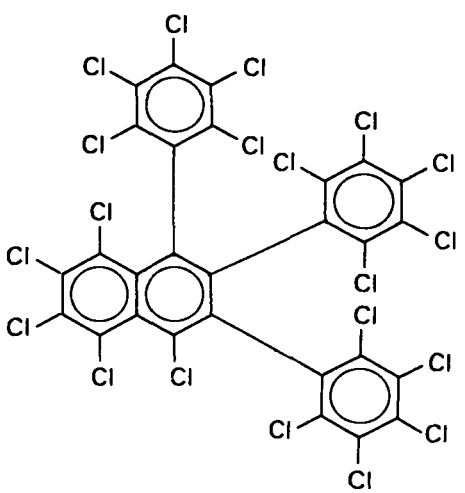


FIGURE 7. Histogram of C—Cl bond distances (Å) in aromatic compounds in which C—Cl bonds are in positions *ortho* to each other.

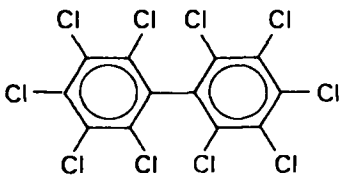


(26)

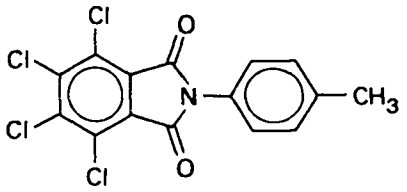
that of perchloro-1,2,3-triphenylnaphthalene[47] (**26**). There is one C—Cl bond (C(4)—Cl) that belongs to the former group of aromatic compounds and its bond length is the longest, having a value of 1.740(6) Å. The other distances observed in this overcrowded molecule range from 1.697(6) Å to 1.730(7) Å. In decachlorobiphenyl[48] (**27**) distances of 1.708(3)–1.728(3) Å were observed.

In *N*-*p*-tolyltetrachlorophthalimide (α-form)[49] (**28**) the chlorine atoms are involved in a strong intermolecular interaction with O atoms (Cl···O distance is 2.984 Å); however, the C—Cl bond distances are not affected (1.716(3)–1.724(3) Å).

The mean value for C—Cl bond length in perchlorinated aromatic compounds was



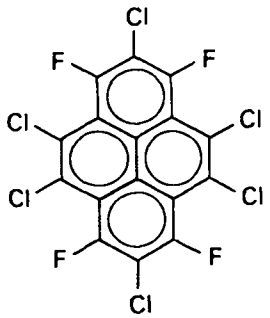
(27)



(28)

found to be 1.717 Å[11] (uncorrected) or 1.721 Å (with rough correction for thermal motion). This value is in a good agreement with the results presented here (1.722 Å).

The effect of a strong electronegative atom in an *ortho* position is well observed in 1,3,6,8-tetrafluoro-2,4,5,7,9,10-hexachloropyrene[50] (**29**). The C—Cl distances of those chlorine atoms in positions *ortho* to each other are 1.712(4) and 1.717(4) Å while that of a C—Cl bond *ortho* to two carbon–fluorine bonds is 1.704(4) Å.

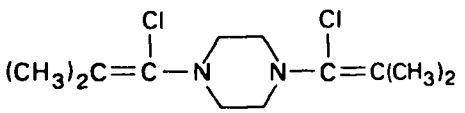


(29)

C. Olefinic Compounds

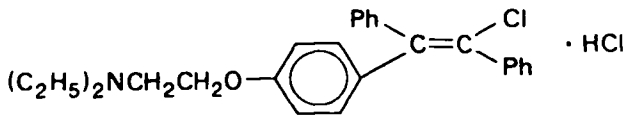
Olefinic C—Cl bonds average 1.712(21) Å and the histogram for 170 observations is shown in Figure 8.

The longest bond length, of 1.790(2) Å, was observed in *N,N'*-bis(1-chloro-2-methylpropenyl)piperazine[51] (**30**). Other distances longer than the mean value have



(30)

been observed in long-chain olefins such as (*E*)-1-[*p*-(diethylaminoethoxy)phenyl]-1,2-diphenyl-2-chloroethylene hydrochlororide[52] (form B) (**31**), where the value is 1.766(8) Å.



(31)

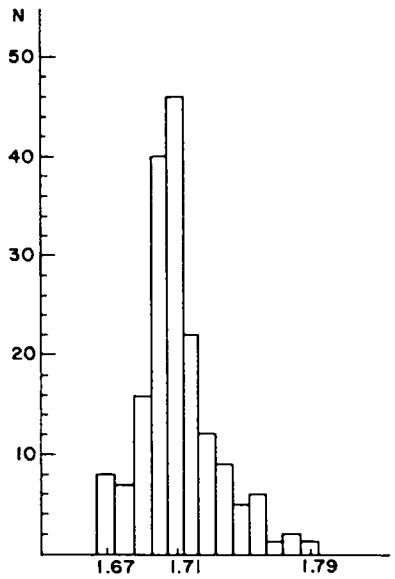
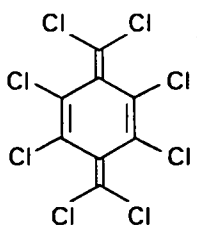
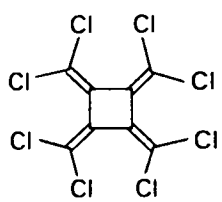


FIGURE 8. Histogram of C—Cl bond distances (Å) in olefinic compounds.

As already cited above, the bond distances tend to be shorter in polychlorinated compounds, and the shortest are in those compounds in which a second chlorine atom is bonded to the same carbon atom. In perchloro-*p*-xylylene[53] (**32**), the ethylenic chlorine–carbon bonds are 1.681(13)–1.720(8) Å long while the others are 1.706(10)–1.762(10) Å in length. In perchlorotetramethylenecyclobutane[54] (**33**) these distances range between 1.708(4) and 1.716(4) Å.



(**32**)



(**33**)

The shortest C—Cl bond lengths (1.672(3) and 1.674(3) Å) were observed in 4,4′-dichloro-3,3′-ethylenebis(sydnone)[55] (**34**). These short bonds are probably due to delocalization of the chlorine lone pair electrons on the positive nitrogen atom.

The quinones, which were previously considered as a subgroup of the aromatic compounds[7], should now be considered as a subgroup of the olefinic compounds. The mean value for C—Cl bond length from 56 observations, shown by a histogram in Figure 9, is 1.712(15) Å, which is identical to the mean value obtained for olefinic compounds. There is no clear evidence in favour of the explanation given[7], i.e. that the shortening compared to distances in aromatic compounds is due to a possible resonance with the chlorine atoms. For example, the crystal structure of tetrachloro-*p*-benzo-

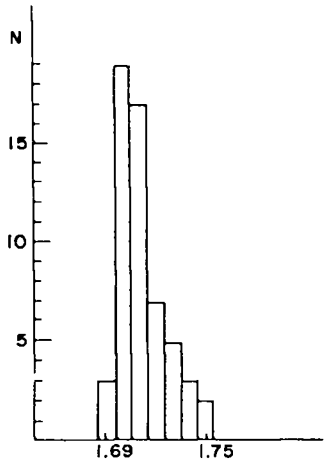
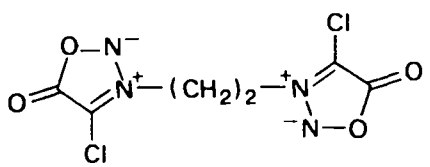
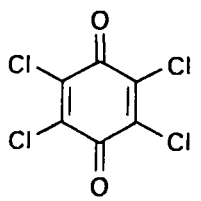


FIGURE 9. Histogram of C—Cl bond distances (Å) in quinone derivatives.



(34)



(35)

quinone[56] (**35**) at room temperature revealed distances of 1.738–1.747 Å while at low temperature[57] (110 K) the values are 1.700(1)–1.702(1) Å. The data obtained for the same compounds from various charge transfer complexes range from 1.689 to 1.718 Å. The similarity to olefinic compounds is clear as the distances between carbon atoms within the ring show the presence of distinct C=C double bonds and $C(sp^2)$—$C(sp^2)$ single bonds.

D. Acetylenic Compounds

The C—Cl bond distance in acetylenic compounds is 1.634(9) Å, as obtained from the crystal structure of chlorocyanoacetylene[58]. Calculations using microwave spectroscopic data[32] lead to a value of 1.637(2) Å. The C—Cl bond length in cyanogen chloride was calculated[32] to be 1.631(2) Å.

IV. CARBON–BROMINE BONDS

A. Saturated Compounds

The mean value for $C(sp^3)$—Br bond distances in aliphatic compounds is 1.959(35) Å. The large estimated standard deviation indicates a large scattering of observed data. The histogram for 180 observations is shown in Figure 10(a). The longest bond distances were observed in 17β-bromoacetoxy-3-methoxy-8α-methyl-1,3,5(10),6-oestratetraene[59] (2.08(2) Å). Other long C—Br distances were found in (−)-2,2′-bis(bromomethyl)-1,1′-binaphthyl[60] (**36**) (2.03(2) and 1.97(2) Å).

In aliphatic compounds where more than a single bromine is bonded to the same carbon atom, the bond length tends to be shorter. A histogram for 53 observations is

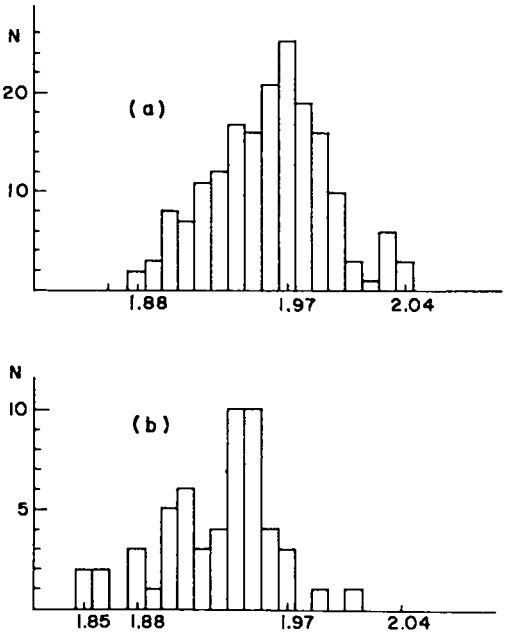
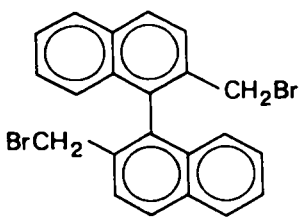
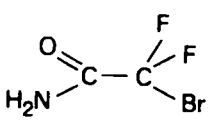


FIGURE 10. Histogram of C—Br bond distances (Å) in aliphatic compounds: (a) C atom is monosubstituted by Br atom; (b) C atom is polysubstituted by Br atoms.



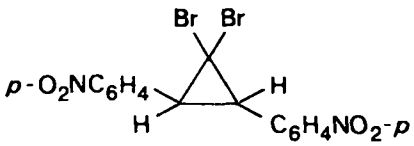
(36)

given in Figure 10(b). The mean value is 1.928(34) Å. Although the mean value of the distance in polybromo aliphatic compounds is smaller than in the simplest aliphatic ones, one should be aware of the fact that the mean value is based on a small number of observations which are widely scattered. As bromine is much less electronegative than F and Cl, other factors such as the size of the bromine atom should be considered. However, one should note the effect of other electronegative atoms such as fluorine. In bromodifluoroacetamide[61] (37) the C—Br bond length is 1.90(2) Å, which is significantly shorter than the mean value.

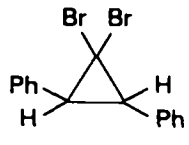


(37)

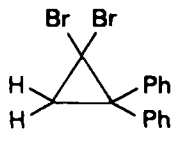
The same shortening was observed in cyclopropane derivatives, where the major effect on the bond length is a lowering of the hybridization state of the C atom from sp^3 by increasing the s-character. The values are 1.900(3) Å in 1,1-dibromo-*trans*-2,3-bis(*p*-nitrophenyl)cyclopropane[62] (**38**), 1.911(3) Å in 1,1-dibromo-*trans*-2,3-diphenylcyclopropane[62] (**39**) and 1.910(4) and 1.915(4) Å in 1,1-dibromo-2,2-diphenylcyclopropane[63] (**40**).



(38)



(39)



(40)

B. Aromatic Compounds

The vast amount of data available for aromatic compounds containing a bromine atom shows a regular histogram given in Figure 11. A previous mean value of 1.897(24) Å was obtained from 58 observations using a full normal probability plot[10]. The value obtained here using 337 observations is 1.899(24) Å, which is in excellent agreement with the previous one.

Some long distances were observed in jujubogenin *p*-bromobenzoate[64] (1.98(4) Å) and in 3β-*p*-bromobenzoyloxy-14α,15α-epoxy-5α-cholest-7-ene[65] (1.98(3) Å). However, in both structures the e.s.d.s are too large to give significance to the lengthening.

The shortest C—Br bond length (1.814 Å) was found in bis(*p*-bromo-α,α-dimethylbenzyl)diaziridinone[66] (**41**), but it is exceptional and unexplained.

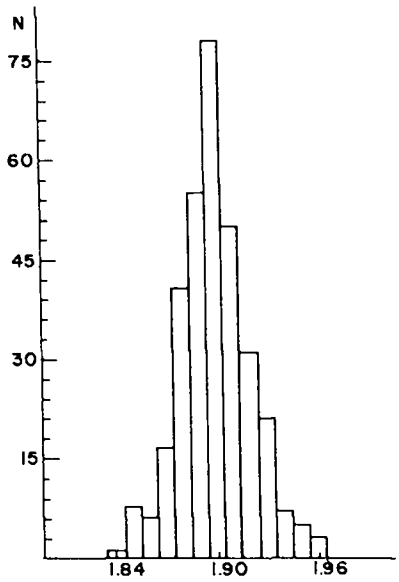
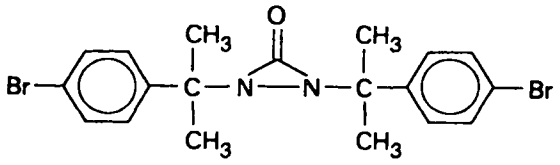
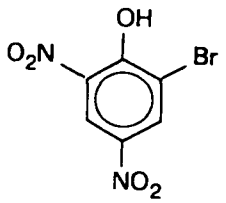


FIGURE 11. Histogram of C—Br bond distances (Å) in aromatic compounds.



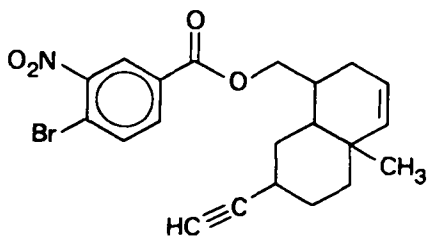
(41)

The effect of electron-withdrawing groups in positions *ortho* to the bromine atom is well illustrated in the following examples. In 2-bromo-4,6-dinitrophenol[67] (**42**), where

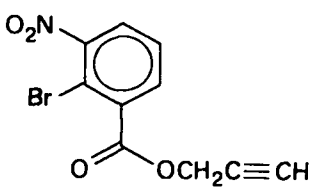


(42)

the nitro groups are in positions *meta* to the bromine atom, the C—Br bond length is 1.889(5) Å, but in chamaecynenol 4-bromo-3-nitrobenzoate[68] (**43**), where the nitro group is *ortho* to the bromine atom, this distance is shorter (1.87(1) Å). The same



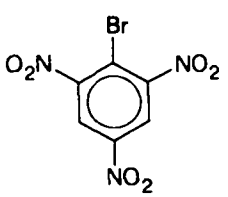
(43)



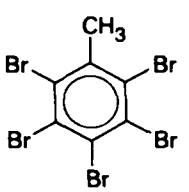
(44)

bond length (1.87(1) Å) was found in propargyl 2-bromo-3-nitrobenzoate[69] (**44**) and in picryl bromide (**45**) in its complex with fluoranthene (1.875(4) Å)[70].

Only a few examples of aromatic compounds with two, or more, bromine atoms in positions *ortho* to each other have been investigated, and in these compounds the C—Br bond distances tend to be shorter. In pentabromotoluene[71] (**46**) distances of 1.873(12), 1.866(10) and 1.857(10) Å were observed.



(45)



(46)

C. Olefinic Compounds

Figure 12 shows a histogram of 72 observations for C—Br bond lengths in olefinic compounds. The mean value is 1.888(27) Å.

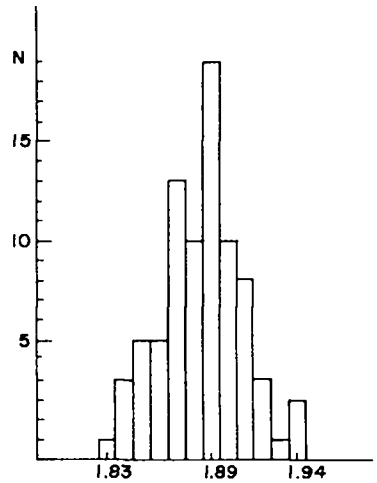
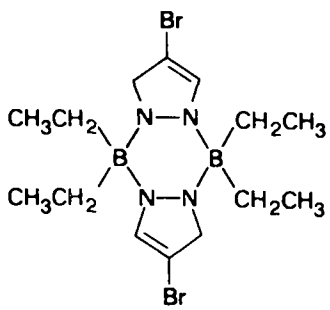


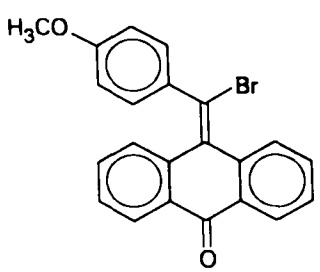
FIGURE 12. Histogram of C—Br bond distances (Å) in olefinic compounds.

The longest C—Br bond distance of 1.97(5) Å was found in 2,6-dibromo-4,4,8,8-tetraethylpyrazabole[72] **(47)**. However, the other C—Br distance observed in this compound is 1.92(6) Å, and the large standard deviation in the bond length suggests an insignificant lengthening.

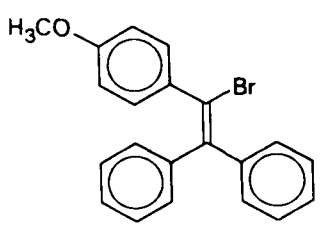


(47)

In compounds **48** and **49**, distances of 1.927(5) and 1.923(3) Å, respectively, have been observed[73]. These slightly longer bond lengths may be associated with non-



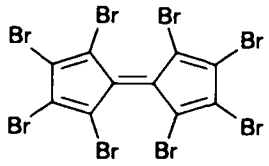
(48)



(49)

bonding interactions with the *ortho* hydrogen atoms of the aromatic ring on the neighbouring carbon.

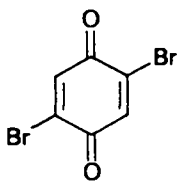
In tetrabromoethylene and in the molecular complex between pyrazine and tetrabromoethylene[74] the mean distance is 1.88 Å. These values are somewhat longer than those expected in polybromo olefinic compounds. In octabromopentafulvalene[75] (**50**)



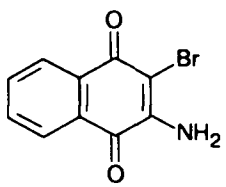
(**50**)

the C—Br bond distances are 1.839(9), 1.839(9), 1.853(9) and 1.856(8) Å, in agreement with expectation. It is also noted that the shorter distances are those which have two adjacent C—Br bonds and the longest are those having only a single adjacent C—Br bond.

The C—Br distances in quinones range from 1.87(3) Å in 2,5-dibromo-1,4-benzoquinone[76] (**51**) to 1.91 Å in 2-amino-3-bromo-1,4-naphthoquinone[77] (**52**).



(**51**)



(**52**)

D. Acetylenic Compounds

The C—Br distance in acetylenic compounds was found from the crystal structure of bromocyanoacetylene[58] to be 1.76(2) Å (1.77(2) Å when corrected for libration). Calculations[32,78] using microwave spectroscopic data revealed a value of 1.789(2) Å for C—Br in cyanogen bromide.

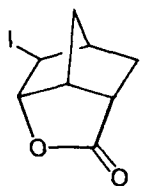
V. CARBON–IODINE BONDS

A. Saturated Compounds

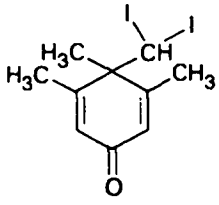
In saturated compounds C(sp^3)—I distances range from 2.057 to 2.288 Å. The large scattering of distances emerges mainly from experimental problems in X-ray studies when refining the positions of light atoms (C, N, O) in the presence of heavy atoms (I), which cause inaccuracies in the positions of the light atoms. Therefore small variations in bond lengths cannot be considered together with second-order effects such as electronegativity. The mean value of C—I bond lengths, obtained from 35 observations, is 2.155(50) Å.

The longest bond distance was observed in 5-*exo*-iodo-6-*endo*-norbornanol-2-*endo*-carboxylic acid lactone[79] (**53**). The two C—I distances in the two independent molecules are 2.28(8) and 2.20(2) Å (There are two molecules in the unit cell which are not related by symmetry elements.)

When more than a single iodine atom is bonded to the same carbon atom the distances do not change. In 4-diiodomethyl-3,4,5-trimethylcyclohexa-2,5-dienone[80]



(53)



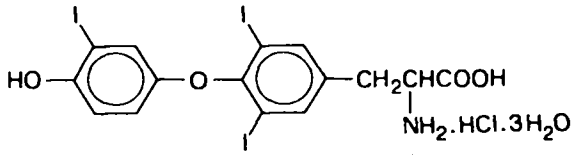
(54)

(54) those distances are 2.14(1) and 2.18(1) Å, similar to the mean value for the monosubstituted compounds (2.155 Å).

B. Aromatic Compounds

A histogram for 76 C—I bond lengths in aromatic compounds is shown in Figure 13. The mean value for C—I bond is 2.097(27) Å.

The longest bond length observed in this group of compounds is 2.17 Å, found in the structure of sodium antibiotic K-41 *p*-iodobenzoate monohydrate *n*-hexane solvate[81]. One bond distance of 2.15 Å was observed in 3,5,3'-tri-iodo-L-thyrosine hydrochloride trihydrate[82] (**55**), but the other distances are 2.11 and 2.06 Å. These results reflect the scattering of the C—I distances.



(55)

The only example of an aromatic compound containing iodine atoms *ortho* to each other is that of hexaiodobenzene[83]. The distances of 2.09(3), 2.09(3) and 2.10(4) Å are no shorter than those in aromatic compounds possessing no iodine in *ortho* positions. Consequently, there is no indication of an influence similar to that found in the other aromatic halogen compounds.

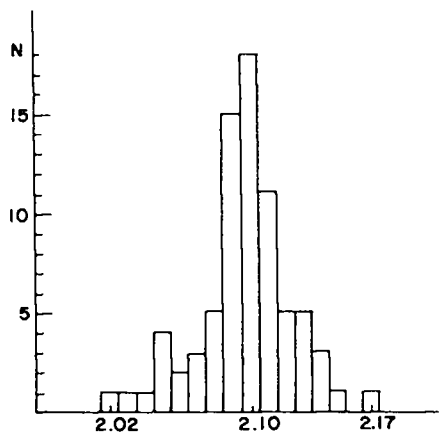
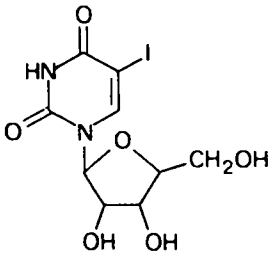


FIGURE 13. Histogram of C—I bond distances (Å) in aliphatic compounds.

C. Olefinic Compounds

C(sp^2)—I bond distances in olefinic compounds range from 2.02 Å, found in 5-iodouridine[84] (**56**), to 2.18(2) Å, found by neutron diffraction study of tetraiodoethylene[85]. The other values found in the latter compound are 2.07, 2.09 and 2.09 Å (mean value 2.114(16) Å).



(56)

The mean value of C(sp^2)—I bond length deduced from 14 observations is 2.097(47) Å.

In quinone derivatives the C—I bond distances observed range from 2.03(2) to 2.09(9) Å, found in 2-hydroxy-3-iodo-1,4-naphthoquinone[86], 3-iodo-1,4-naphthoquinone[87] and tetraiodo- *p*-benzoquinone[88].

D. Acetylenic Compounds

An early crystal structure study of iodocyanoacetylene[89] revealed a C(sp)—I bond length of 1.79 Å. In the molecular complex of diiodoacetylene with cyclohexane-1,4-dione[90] a longer distance of 1.98 Å was found, and in the 1,4-dithiane[91] complex even longer distances of 2.05 and 2.15 Å were observed. The longer distances could be a result of the strong interaction with the dithiane molecule. A crystal structure determination of diiodoacetylene[92] of lesser accuracy revealed C—I distances of 1.99 Å.

VI. CONCLUSION

There are some limitations as regards the data available.

Bond lengths calculated from microwave spectral data are limited to very simple molecules which cannot reflect the entire possible range of factors affecting variations in bond distances.

Most of the data have been obtained from crystal structures elucidated by X-ray diffraction methods. This is the most direct method for obtaining geometrical parameters for a given molecule, but some limitations affect the precision of that data. Refinement of crystal structures containing light atoms (C, N, O) in the presence of heavy atoms (Br, I) leads to less accurate positioning of the light atoms, resulting in less accurate geometrical parameters. Terminal groups often suffer from large vibrational motions resulting in artificial shortening of bond lengths.

By using large data sets one might overcome some difficulties in obtaining meaningful 'mean values' of structural parameters. However, this method is strongly dependent on the choice of classes or subgroups among the compounds under study.

The limits stated above enable one to account only for the grosser variations in bond length which are explicable in terms of hybridization changes on the carbon atom, and of the effect of electronegativity in cases where strong electronegative atoms or groups are bonded to the same carbon atom.

Another important and significant variation in bond length is shown by the shortening of the carbon–halogen bond in aromatic compounds possessing such bonds in positions *ortho* to each other[93]. This shortening can be due to a halogen···halogen interaction[94,95] or to an induction effect[96].

The detection of variations due to other minor effects, outlined in the introduction (Section I), is limited. Studies of these effects should be carried out by investigating a series of specific compounds and performing the crystal structure determination at the same experimental conditions (measurement at low temperature is preferred) by X-ray or neutron diffraction methods.

Table 1 summarizes the full range of carbon–halogen bond lengths according to the classification adopted in the previous sections.

VII. CARBON–PSEUDOHALOGEN BONDS

A. Introduction

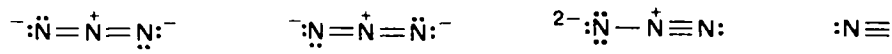
The group of organic radicals which have certain properties in common with the halogen atoms are sometimes called pseudohalides. The members of this group are azide (N_3), cyanide (CN), cyanate (OCN) and thiocyanate (SCN).

The pseudohalides resemble the halogens in having the ability to form either pseudohalide anions (X^-) or covalent pseudohalogens; they usually exert a negative inductive effect in the organic compounds which they form. However, the 'unsaturation' of the pseudohalides has no equivalent among the halogens.

The following sections will present the structural chemistry of the covalent pseudohalogens, namely the geometrical parameters of the carbon–pseudohalogen bond and those between atoms within the pseudohalogen group.

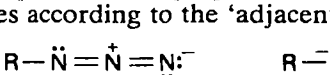
B. Carbon–Azide Bond

In the ionic crystal of NaN_3 and KN_3, the azide ion is linear and symmetrical. These observations led Pauling[1] to propose resonance among the four structures **57–60**. This proposal led to agreement between calculated and experimental N—N bond distances (1.15(2) Å) for the two nitrogen atom pairs.



(57) **(58)** **(59)** **(60)**

To account for the asymmetry in the bond lengths of the N—N bonds in covalent azides and for the angle between the azido group and the carbon atom, two canonical forms (**61**, **62**) were proposed[1]. This proposal followed the octet rule and ruled out other possible structures according to the 'adjacent charge rule'.



(61) **(62)**

Theoretical aspects and descriptions of the electronic structure of covalent azides have been reviewed[97].

Structural data for the carbon–azide bond, including interatomic distances and bond angles within the azide group, can be obtained from microwave spectroscopy and electron, neutron and X-ray diffraction. Most of the data available, especially for more complex compounds, were obtained from crystal structure elucidation by X-ray diffraction methods. Geometrical parameters are given in Table 2, using the notation shown in structure **63**.

TABLE 1. Summary of C—X bond distances, giving mean value (in ångstroms) and population e.s.d.s (in parentheses)

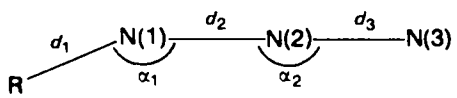
C—X bond	Aliphatic[a] compounds	No.[b]	Aliphatic compounds (polyhalogen substituents)	No.[b]	Olefinic compounds	No.[b]	Quinone (derivatives)	No.[b]	Aromatic[a] compounds	No.[b]	Aromatic compounds (halogens in *ortho* positions)	No.[b]	Acetylenic compounds
C—F	1.402(26)	41	1.347(17)[c]	101	1.348(10)	28	1.337(12)	7	1.359(12)	34	1.340(10)	85	1.279
C—Cl	1.788(26)	244	1.768(23)	234	1.712(21)	170	1.712(15)	56	1.740(16)	267	1.722(11)	206	1.634
C—Br	1.959(35)	180	1.928(34)	53	1.888(27)	72	1.882(30)	5	1.897(24)	58	1.870(12)	4	1.77
C—I	2.155(50)	35	2.136(51)	10	2.097(47)	14	2.065(25)	4	2.097(27)	76	2.095(06)	3	1.99

[a]Monohalogen–substituted or having polyhalogen substituents that are far away from one another.
[b]Number of observations used for establishing the average bond distance.
[c]The mean value for compounds where a C atom is bonded to two F atoms.

TABLE 2. Geometrical parameters of covalent azides[a]

Formula or compound	d_1, Å	d_2, Å	d_3, Å	α_1, deg	α_2, deg	Method	Ref.
CH_3N_3	1.468(5)	1.216(4)	1.130(5)	116.8(3)	180	E	98
CH_3N_3	1.46	1.24	1.13	117	180	M	99
$[C(N_3)_3]^+$	1.31(2)	1.41(2)	1.02(2)	107(1)	163(2)	X	100
	1.36(2)	1.36(2)	1.07(2)	108(2)	167(2)	X	100
	1.35(2)	1.40(2)	1.06(2)	108(1)	160(2)	X	100
64	1.62(8)	1.20(8)	1.08(8)	114(5)	176(5)	X	101
65	1.449(5)	1.245(5)	1.136(6)	113.3(4)	172.6(5)	X	102
65[c]	1.444(7)	1.212(9)	1.131(11)	115.5(5)	171.5(6)		103
	1.446(9)	1.210(12)	1.120(16)	112.8(6)	171.4(8)	X	103
66	1.50(1)	1.14(1)	1.19(2)	120.9(7)	174(1)	X	104
66[d]	1.53(2)	1.22(2)	1.15(2)	116(2)	169(2)	X	105
67	1.42(1)	1.24(1)	1.14(1)	114(1)	172(1)	X	106
	1.41(1)	1.28(1)	1.11(1)	112(1)	174(1)	X	106
68	1.42(2)	1.27(2)	1.13(2)	115(1)	173(1)	X	107
68[e]	1.46(2)	1.24(2)	1.12(2)	119(2)	168(2)	X	108
69	1.426(9)	1.248(9)	1.122(9)	116(1)	172(1)	X	109
70	1.444(6)	1.245(7)	1.115(7)	114.9(4)	174.2(5)	X	110
71	1.407(5)	1.244(5)	1.140(5)	114.2(3)	171.9(4)	X	111
72	1.408(7)	1.229(7)	1.116(7)	120.9(8)	168.0(8)	X	112

[a]Notation according to formula **63**.
[b]E ≡ gas phase electron diffraction; M ≡ microwave spectroscopy; X ≡ X-ray diffraction.
[c]β-isomer of **65**.
[d]Additional ethyl substituent on the five-membered ring adjacent to the methyl group.
[e]Three nitro groups in positions *meta* to each other.



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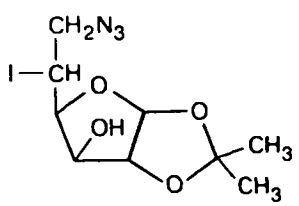

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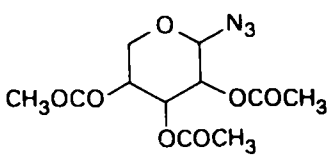

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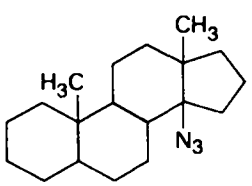

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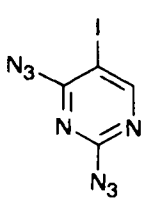

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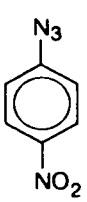

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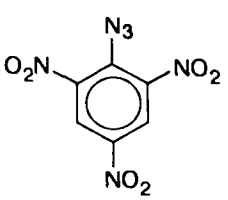

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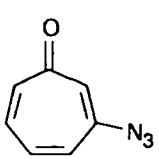

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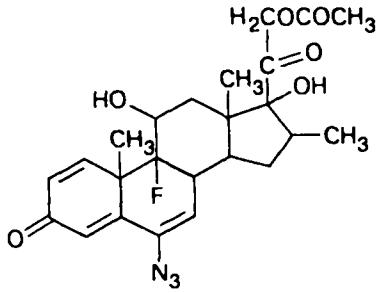

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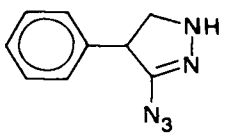

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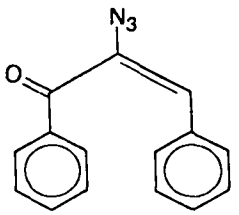
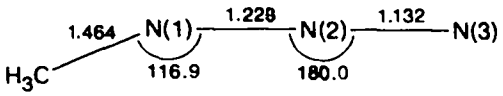


(72)

The small number of observations makes it difficult to detect and delineate the various factors which might affect variations in bond lengths and angles. In the first approximation the various compounds have been subdivided into different classes according to the state of hybridization of the carbon atom bonded to the azido group. The weighted mean values[8,9] for bond distances and unweighted mean values for bond angles are given below for methyl azide (**73**), for an azide group bonded to an sp^3 carbon (**74**) (excluding **69** due to large thermal motion), for an azide group bonded to an aromatic ring (**75**) and for an azide group bonded to an sp^2 carbon (**76**).



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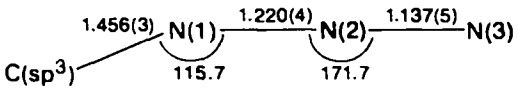

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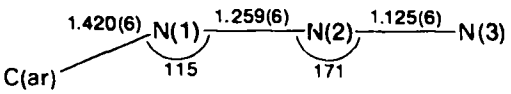

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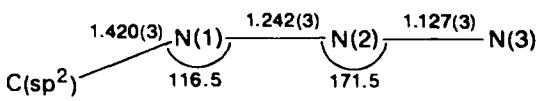
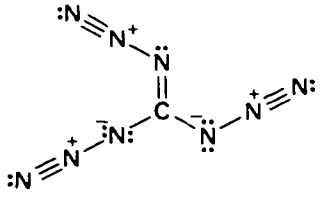


(76)

There is a good agreement between the bond lengths in methyl azide observed by electron diffraction in the gas phase, calculated values obtained from microwave spectroscopy and mean values obtained from crystal structure elucidation by X-ray diffraction methods of compounds where the azide group is bonded to an sp^3-hybridized carbon. The geometrical parameters in the other two groups (**75**, **76**) are very similar. The differences between bond distances in the azide groups among the various classes are explicable in terms of the two canonical forms **61** and **62**. In the compounds of azide bonded to $C(sp^3)$ the canonical form **61** is predominant, leading to an N(1)—N(2) bond distance of 1.22 Å and to a partial N(2)—N(3) triple bond (1.13 Å). In the other classes the canonical form **62** predominates, hence N(1)—N(2) bond distances are longer (1.259(6) and 1.242(3) Å) and N(2)—N(3) bond distances are shorter (1.125(6) and 1.127(3) Å).

A special feature of the covalent azide group was found in the $C(N_3)_3^+$ ion. The mean values of the geometrical parameters of the three azido groups in the $C(N_3)_3^+$ ion are $d_1 = 1.34(2)$, $d_2 = 1.39(2)$, $d_3 = 1.05(2)$ Å, $\alpha_1 = 108(1)°$, $\alpha_2 = 163(2)°$. These values suggest strongly that the main canonical form is **62**, as suggested by Pauling[1], who pointed out that the angle α_1 would be 108° in that canonical form. Three canonical forms of type **77** can be written. The contributions of these canonical forms are proved by the following facts: (a) the C—N bond distances are equal (1.31(2), 1.35(2) and 1.36(2) Å) and are in good agreement with the bond order of 1.33[113]; (b) the



(77)

N(1)—N(2) bond distances range between 1.36(2) and 1.41(2) Å and are slightly shorter than a single bond (1.44 Å), suggesting attractive forces resulting from different partial charges; (c) the N(2)—N(3) bond lengths range between 1.02(2) and 1.07(2) Å, values which are typical for a triple bond.

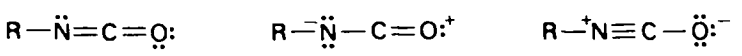
The bond angle at N(2) was expected to be 180° according to theoretical considerations[114]. However, in all covalent azide compounds it was found that the azide group is significantly non-linear. The deviation from linearity is *ca.* 17° in the $C(N_3)_3^+$ ion and *ca.* 9° in other compounds. It was also found that the carbon atom is always *trans* to the terminal N(3) atom. The reasons for these observations are not known and this problem remains open.

C. Carbon–Cyanate and Carbon–Thiocyanate Bonds

The cyanate (OCN), isocyanate (NCO), thiocyanate (SCN) and isothiocyanate (NCS) anions form a large group of inorganic pseudohalide compounds; some of them have been reviewed previously[115]. Most of the work which has dealt with the structural features of covalent isocyanates (RNCO) and isothiocyanates (RNCS) is theoretical and spectroscopic. There is not even a single crystal structure of a covalent isocyanate and only one crystal structure of covalent isothiocyanate has been reported.

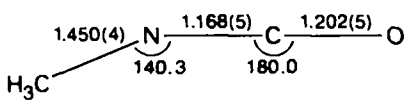
Theoretical and spectroscopic studies on covalent cyanates (ROCN) and covalent thiocyanates (RSCN) are rare. There is only a single report on the crystal structure of a covalent cyanate and five reports on covalent thiocyanates.

Pauling[1] proposed resonance between the three structures **78**, **79** and **80** for covalent isocyanate. In all the three possible structures, the isocyanate group is expected to be



(78) (79) (80)

linear. Geometrical parameters for CH_3NCO which were obtained by electron diffraction[95] are given in **81** and those obtained by microwave spectroscopy in **82**[116].



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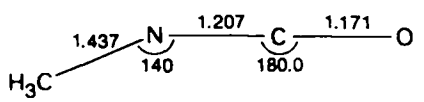
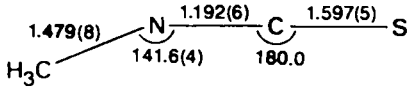


(82)

There is a contradiction between the values of the N=C and C=O bond distances obtained by the two methods. It was found that in the electron diffraction method the peaks in the radial distribution curve assigned to the N=C and C=O distances overlap, so that these distances are strongly correlated; it seems probable that the alternative – assignment with N—C (1.202(5) Å) and C—O (1.168(5) Å) – is more appropriate. With that assignment, the data obtained by microwave spectroscopy is in good agreement with that obtained by electron diffraction. These bond lengths

correspond to those expected for approximately equal contribution of structures **78–80**.

Pauling proposed very similar resonance structure for covalent isothiocyanates. Electron diffraction[98] and microwave spectroscopy[116] of CH_3NCS revealed the geometrical parameters which are given in **83** and **84**, respectively. Crystal structure of



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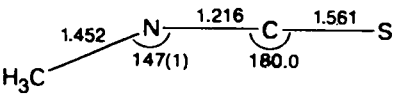
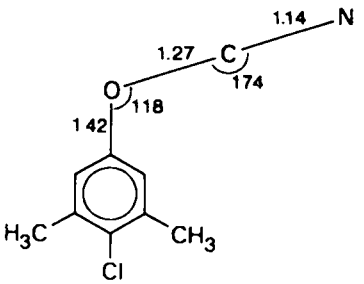


(84)

p-bromophenyl isothiocyanate[117] revealed the following bond lengths: H_3C—N 1.44 Å, N—C 1.21 Å, C—S 1.58 Å. The C—N—C bond angle was given as 159.1°. These values agree well with the assumption of almost equal contribution among three hybrid structures similar to those of the covalent isocyanate.

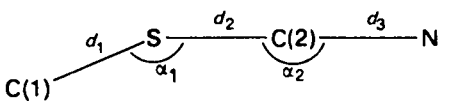
The only available data for a covalent cyanate (ROCN) is that obtained from the crystal structure of 4-chloro-3,5-dimethylphenylcyanate (**85**)[118]. The C—N bond



(85)

distance is a typical triple bond, while the C—O distance of 1.27 Å is found for double bonds in zwitterion forms. The bond distances and angles are not accurate enough for any prediction as regards the contribution of possible resonance structures.

Geometrical parameters in covalent thiocyanates obtained from crystal structures of covalent thiocyanate compounds are given in Table 3 by using the notation given in **86**.

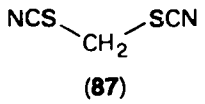


(86)

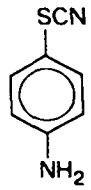
TABLE 3. Geometrical parameters of covalent thiocyanates

	d_1, Å[a]	d_2, Å[a]	d_3, Å[a]	α_1, deg[a]	α_2, deg[a]	Ref.
87	1.806(6)	1.677(9)	1.194(12)	98.2(4)	176.1(1)	119
88[b]	1.786(3)	1.698(3)	1.136(4)	99.9(5)	178.6(5)	120
89[b]	1.795(7)	1.717(7)	1.144(9)	99.0(8)	173.3(8)	121
90	1.80(1)	1.63(1)	1.18(2)	99.4(7)	172.5(13)	122
91	1.81(1)	1.60(1)	1.19(2)	97.9(6)	180(1)	123
	1.83(1)	1.67(1)	1.14(1)	99.3(6)	176(1)	

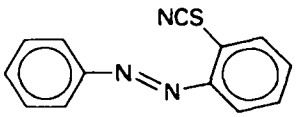
[a]Notation according to **86**.
[b]Standard deviations estimated from the Cambridge Data Base[12].



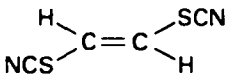
(87)



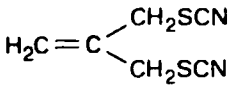
(88)



(89)

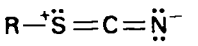


(90)

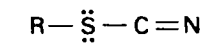


(91)

On the basis of microwave spectroscopic data the bond lengths and angles in CH_3SCN have been calculated[124]. The bond distances for C(1)—S (1.81 Å), S—C(2) (1.61 Å), C(2)—N (1.21 Å) and the C(1)—S—C(2) bond angle (142°) led Pauling[1] to propose a 70% contribution of structure **92** and 30% of structure **93**, but he pointed out that the bond angle seems to be too large. In a later publication[125] the possibility of an error in the interpretation of the microwave spectral data was suggested. New values have been calculated[126] which resulted in the correction of the bond angle to 99.6°. These new results agree well with the Pauling proposal, but suggest only 10% contribution of resonance structure **93**.



(92)



(93)

The geometrical parameters given in Table 3 do not show significant variations in the C(1)—S bond distances with the change in the state of hybridization of the carbon atom. These distances range between 1.806(6) Å, when the state of hybridization of the carbon atom is sp^3, and 1.80(1)–1.83(1) Å, when the state of hybridization is sp^2. There is no explanation for these facts and the question remains open.

The S—C(2) bond length varies from 1.60(1) to 1.717(7) Å and the C(2)—(N) bond length varies from 1.136(4) to 1.194(Å). These variations could be explained in terms of differences in the relative contributions of the two resonance structures.

The bond angle at the sulphur atom is fairly constant (mean value 99.0°). The basic assumption is that sulphur atom in a low oxidation state does not form hybrid orbitals but uses its p orbitals for σ bonds as in H_2S (92.1°), and the opening of that angle to 99.0° may be attributed to steric repulsion of the larger bonded atoms[1].

The thiocyanate group is significantly non-linear (172.5–180°). In this respect it has the same feature as the other pseudohalogens discussed above.

D. Conclusion

Calculations of structural parameters for pseudohalides from electron diffraction or microwave spectral data were based on the assumption that the group is linear. This assumption was introduced in order to simplify the structural analysis. Crystal structure elucidation by X-ray diffraction shows that these groups are significantly non-linear. The deviation from linearity has been ascribed to the influence of intermolecular forces. However, such an interpretation cannot hold when the number of examples in which the non-linearity is significant increases. It was shown, in more accurate calculations where the linearity assumption has been relaxed, in microwave

studies of ONCN[127], ClNCO[128] and ClN_3[129], that the fragment is bent. Unless more accurate calculations are conducted for the simple covalent pseudohalogens, we will have to rely on the structural data revealed by X-ray diffraction methods.

It is consistently found that the bond angle on a N atom bonded to the C atom is significantly smaller in covalent azide (<120°, see Table 2) than in covalent isocyanates (RNCO) (~140°, calculated) and in covalent isothiocyanates (RNCS). This has been rationalized[1,98,130] in terms of the contribution of resonance structure **80** in isocyanate, the azide analogue of which is less favourable because of excessive charge separation. In terms of this rationalization it is expected that the angle in isothiocyanates should be smaller than that in isocyanates, due to an even less favoured resonance structure because of the less electronegative sulphur atom. However, the angle was found to be greater (141.6° and 147° calculated[98,116] and 159.1° observed[117])!

Comparison of the bond distance between a pseudohalogen nitrogen atom and the carbon atom in the same state of hybridization shows that it is shorter in covalent isocyanates than in isothiocyanates or in azides. It seems that the number of observations is too small to deduce conclusions from this difference. More structural data should be obtained (mainly from X-ray and neutron diffraction methods) in order to make reliable generalizations and then to explain the variations in the structural parameters of the covalent pseudohalogens.

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CHAPTER **25**

Halonium ions

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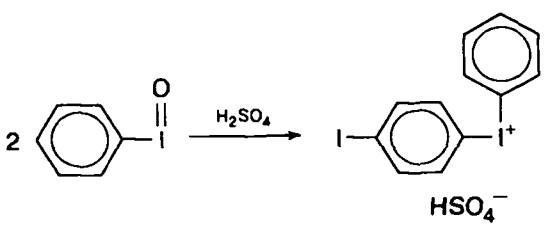
I. INTRODUCTION

In 1894, Hartmann and Meyer reported the generation of phenyl(*p*-iodophenyl) iodonium bisulphate (**1**) by the autocondensation of iodosobenzene in the presence of sulphuric acid, thus providing the first example of an organohalonium ion[1]. Since then, hundreds of diaryliodonium ions ($Ar—I^+—Ar'$) have been synthesized, these exhibiting considerable variations in substituent type, degree of sub-



(1)

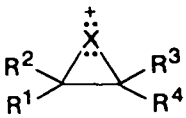
(**1**)

stitution and pattern of substitution in each aromatic ring, and existing in combination with such a diversity of anions that the number of known salts must be well over a thousand. They include acyclic and cyclic salts, heteroaromatic analogues and salts with more than one aryliodonio function per molecule.

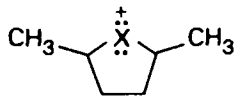
Most synthetic procedures for diaryliodonium salts involve the use of iodoxyarenes ($ArIO_2$) or members of the 'iodoso' family of compounds, i.e. the iodosoarenes (ArIO), (diacyloxyiodo)arenes ($ArI(OCOR)_2$), (dichloroiodo)arenes ($ArICl_2$) and related organoiodine(III) species. Since the corresponding hypervalent organochlorine and organobromine species are unknown (except for several unusual

examples), the diarylchloronium and diarylbromonium salts are relatively uncommon. Most of those which are known have been prepared by the decomposition of aryldiazonium salts in the presence of chloro- and bromoarenes, a synthetic procedure that is less versatile and less efficient than the approaches to diaryliodonium salts[2,3].

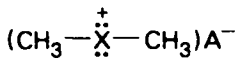
Cyclic dialkylhalonium ions (**2**) with the halogen atom incorporated into three-membered rings have been recognized as plausible intermediates in addition reactions of molecular halogens to alkenes and in various neighbouring group reactions since 1937[4-6]. Five-membered cyclic dialkylhalonium ions (**3**) were posited in 1963 as likely intermediates in reactions of various 5-halo-1-hexenes with trifluoroacetic acid, and their probable involvement in solvolysis reactions has also been recognized[7,8]. However, it was not until 1970 that the first report of the isolation of stable dialkyhalonium salts appeared. Dimethyliodonium, dimethylbromonium and dimethylchloronium fluoroantimonates (**4**) were prepared by the action of $CH_3F \rightarrow SbF_5$ on a slight excess of the corresponding halomethanes in liquid sulphur dioxide at $-40°C$. They were isolated as 'fluffy white crystalline' compounds and observed to be stable at room temperature in the absence of atmospheric moisture[9]. Since 1967[10], a variety of arylalkylhalonium ions and acyclic and cyclic dialkylhalonium ions have been prepared in non-nucleophilic solvents at low temperatures and observed by various spectroscopic techniques. Their chemistry has also been studied, but most have not been isolated from the reaction media utilized in their generation.



(**2**)



(**3**)



(**4**)

X	A^-
Cl	$Sb_2F_{11}^-$
Br	$Sb_2F_{11}^-$
I	SbF_6^-

Several reviews of the preparation and properties of halonium salts have appeared. The first of these is a monograph published by C. Willgerodt in 1914, entitled *Die organischen Verbindungen mit mehrwertigem Jod*, in which the synthesis and physical properties of diaryliodonium salts and vinylaryliodonium salts reported up to 1912 are thoroughly summarized[11]. In 1956, Beringer and Gindler published an extensive compendium of the physical properties of known polyvalent organoiodine compounds, including iodonium salts, with many valuable references to the original literature[12]. Other reviews of a more general nature include articles by Sandin (1943)[13] and Banks (1966)[14], both on polyvalent organoiodine compounds. In 1971, Peterson summarized the literature on the involvement of five-membered and larger cyclic halonium ions as reaction intermediates[8]. Finally, in 1975, Olah published a book entitled *Halonium Ions*, which focuses on the synthesis and chemistry of all classes of organohalonium ions[15].

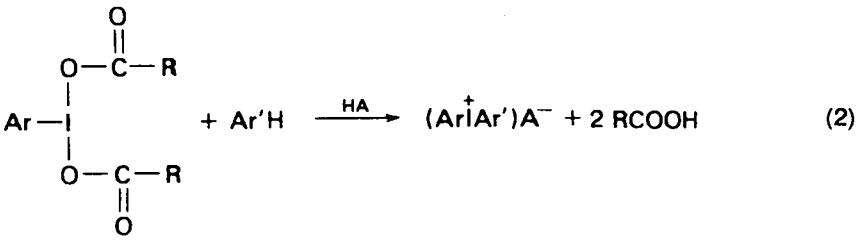
II. DIARYLIODONIUM SALTS

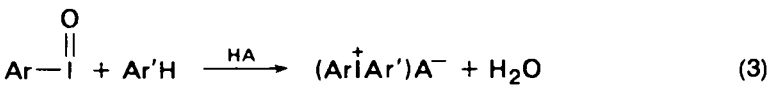
A. Synthesis

Diaryliodonium salts can be synthesized in a variety of ways. Several methods involve the use of a strong acid medium while one classic procedure employs a basic medium, and still other methods require neutral organic solvents. Some procedures are specific for symmetrical iodonium salts while others provide access to unsymmetrical analogues. Some approaches permit the regiospecific placement of substituents in both rings of diaryliodonium salts; others do not.

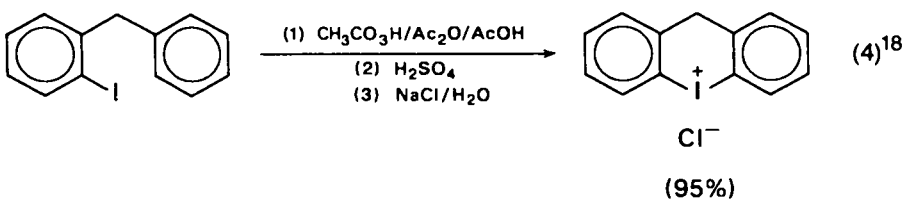
1. Iodosoarenes and (diacyloxyiodo)arenes with aromatic substrates

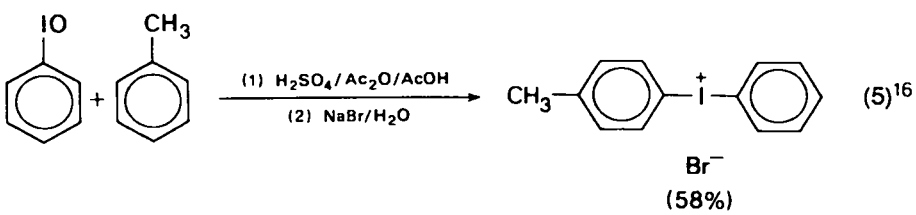
The condensation of either iodosoarenes or (diacyloxyiodo)arenes, especially the diacetoxy analogues, with aromatic substrates in the presence of strong acid is a particularly versatile approach to diaryliodonium salts and one that is commonly employed[16,17]. A typical reaction medium for such condensations consists of

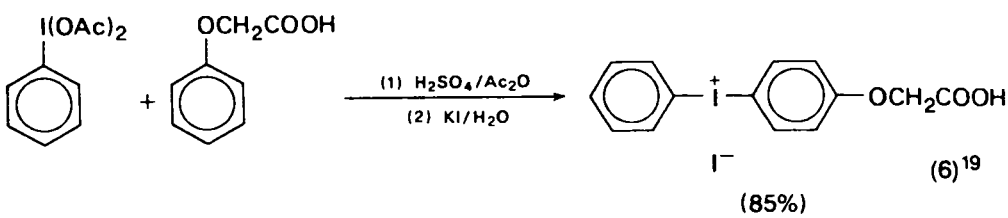


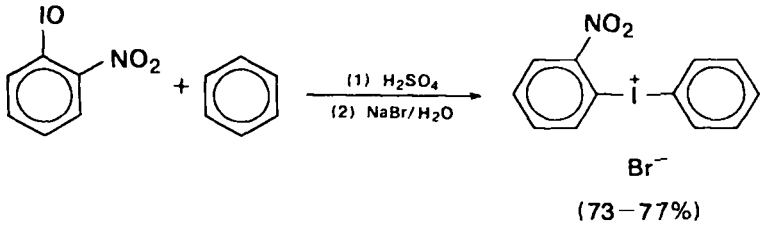


concentrated sulphuric acid in a mixture of acetic acid and acetic anhydride. However, sulphuric acid may sometimes be used by itself, and variations in both the solvent and acid catalyst are not unusual. Several reactions are shown in equations (4)–(10) to illustrate the basic methodology.

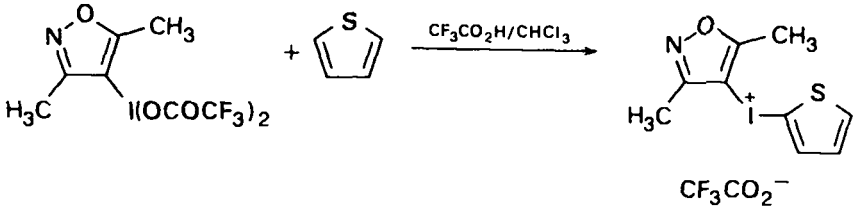




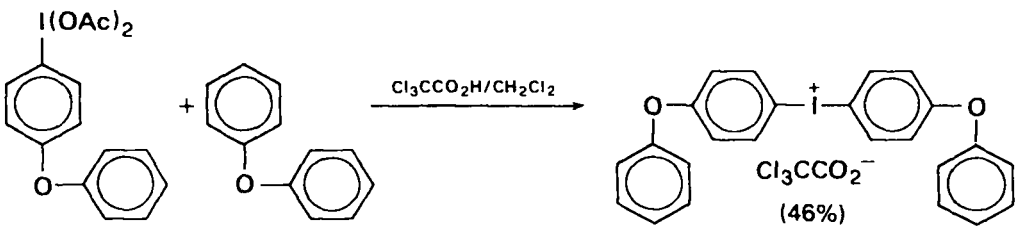




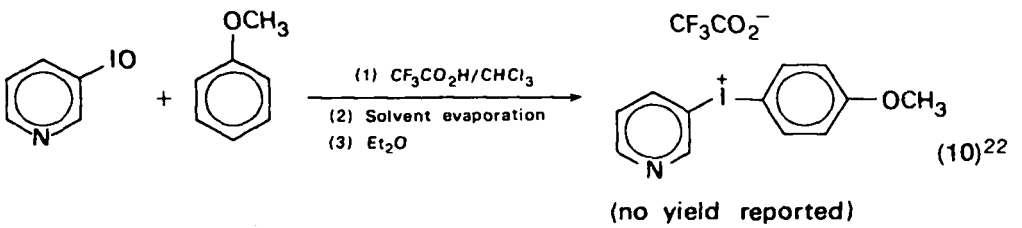
(7)[16]



(8)[20]



(9)[21]

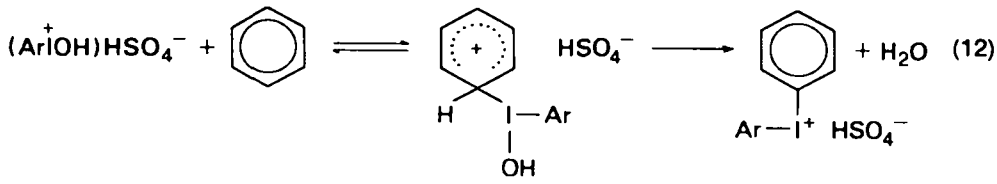


(10)[22]

One disadvantage of the use of iodosoarenes compared to (diacyloxyiodo)arenes is that the former may suffer reduction to the corresponding iodoarenes instead of coupling with the aromatic substrate. For example, attempted condensations of iodosobenzene with bromobenzene and naphthalene in $H_2SO_4/Ac_2O/AcOH$ gave iodobenzene and did not yield iodonium salts[16]. It has also been noted that iodosoarenes with electrophilic substitutents may be utilized effectively in sulphuric acid alone while those bearing nucleophilic substituents undergo more efficient condensations in $H_2SO_4/Ac_2O/AcOH$[17].

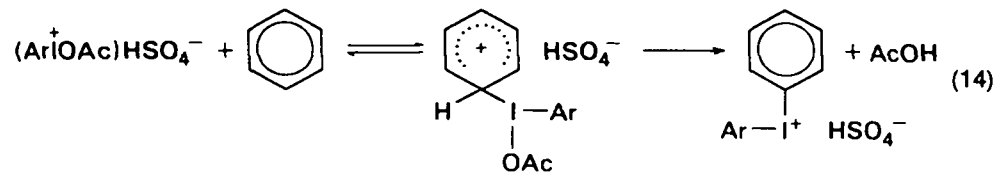
It seems likely that these reactions proceed by the initial formation of ion pair species such as $(ArI^+OH)HSO_4^-$ and $(ArI^+OAc)HSO_4^-$ followed by a typical electrophilic substitution process[17].

$$ArIO + H_2SO_4 \rightleftharpoons (\overset{+}{Ar}IOH)HSO_4^- \qquad (11)$$



(12)

(13)

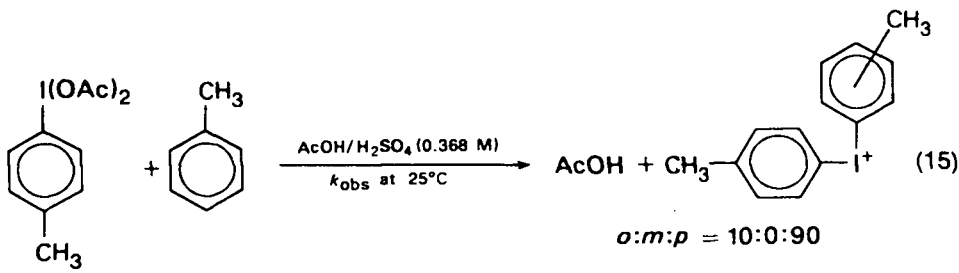


(14)

The iodine(III)–oxygen bonds in (diacetoxyiodo)benzene are hypercovalent, not ionic[23,24], and it is reasonable to assume that the less basic bisulphate ligand will at least be less tightly bound to the iodine centre than the acetate ligand it replaces. It also seems likely that the dipolar iodoso function of iodosoarenes (Ar—Ï=Ö: ↔ Ar—Ï—Ö:⁻) will undergo facile protonation at oxygen in the presence of strong acids.

Systematic mechanistic studies of these condensation reactions are surprisingly rare. However, several types of experimental evidence may be advanced which are consistent, at least, with the mechanisms delineated in equations (11)–(14).

Kinetic evidence. A detailed kinetic analysis of the condensation of *p*-(diacetoxyiodo)toluene with toluene in AcOH/H_2SO_4 (0.368 M) at 25°C under pseudo-first-order conditions has been reported[25].



(15)

The reaction is best described by the rate equation,

$$-d[ArI(OAc)_2]/dt = k[ArI(OAc)_2]\,[PhMe]\,[H_2SO_4]^{2.6}.$$

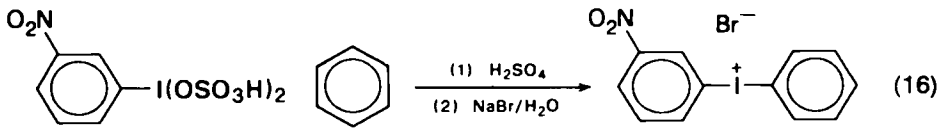
A plot of 3 + log k_{obs} versus (C_{BH^+}/C_B) for the indicator base 2-nitro-4-chloroaniline is linear, as are similar plots for the reactions of *m*-(diacetoxyiodo)chlorobenzene with toluene and (diacetoxyiodo)benzene, *p*-(diacetoxyiodo)toluene and *p*-(diacetoxyiodo)nitrobenzene with benzene, the lines of all five reactions being parallel and exhibiting a mean slope of 1.90 ± 0.04[25]. A plot of log(C_{BH^+}/C_B) versus [H_2SO_4] is likewise linear with a slope of 1.34. The product of those slopes is 2.54, in good agreement with the observed kinetic order (2.6) of sulphuric acid.

Two reaction mechanisms were considered, one involving (ArI^+HSO_4)HSO_4^- as the active electrophile and another positing the intermediacy of (ArI^+OAc)HSO_4^-. Since

the rate constants correlate well with a J_0-type acidity function, the latter alternative was favoured. The powerful catalytic effect of sulphuric acid, then, is to influence the concentration levels of $(ArI^+OAc)HSO_4^-$. It was noted that a 30-fold increase in $[H_2SO_4]$ corresponds to a 5000-fold increase in k_{obs}.

The coupling of various (diacetoxyiodo)arenes, $(AcO)_2I—C_6H_4—R$, (R = *p*-Me, *m*-Me, H, *p*-Cl, *m*-Cl, *p*-NO_2), with toluene in $HOAc/H_2SO_4$ (0.368 M) at 25°C does not provide a *linear* correlation between log k_{obs} and the appropriate substituent constants[25]. However, the rate constants do decrease as the electron-withdrawing power of the substituent increases (e.g. k_{obs} = 0.84 min^{-1} when R = *p*-Me, k_{obs} = 0.31 min^{-1} when R = *p*-NO_2). The effect of electron-withdrawing substituents is probably to decrease the basicity of the acetoxy ligands towards sulphuric acid, thus resulting in diminished concentration levels of $(ArI^+OAc)HSO_4^-$. These results are in qualitative accord with the previously mentioned observation that iodosoarenes bearing electron-withdrawing substituents are more effectively utilized in concentrated H_2SO_4 than in $H_2SO_4/Ac_2O/AcOH$.

Conclusions about the exact nature of the active electrophilic species must, however, be made cautiously. For example, bis(bisulphatoiodo)-*m*-nitrobenzene has actually been isolated and, when mixed with benzene in concentrated sulphuric acid, gives a 62% yield of phenyl(*m*-nitrophenyl)iodonium bromide (after anion metathesis)[16]. In this case, the most likely electrophilic intermediate is $(m\text{-}O_2NC_6H_4I^+OSO_3H)HSO_4^-$.



(16)

It is also difficult to pin-point the actual aryliodinating species in those reactions in which other solvents and acids are employed. For example, for the reaction shown in equation (9), is the reactive intermediate $(ArI^+OCOCH_3)Cl_3CCO_2^-$, or is it $(ArI^+OCOCCl_3)Cl_3CCO_2^-$?

Isomer distributions. If the condensations under consideration are indeed electrophilic aromatic substitution reactions, they should respond in a predictable way to the presence of electron-donating and electron-withdrawing substituents in the aromatic substrate. In one study, isomer distributions for the condensations of *p*-(diacetoxyiodo)toluene and *o*-(diacetoxyiodo)toluene with toluene in H_2SO_4/Ac_2O and for the condensations of *p*-(diacetoxyiodo)chlorobenzene and *o*-(diacetoxyiodo)chlorobenzene in $H_2SO_4/Ac_2O/AcOH$ with chlorobenzene were determined and are given in Table 1[26].

It can be seen from the data that the aryliodinating species generated from all four (diacetoxyiodo)arenes exhibit very high *ortho*:*para* selectivities (i.e. the lower limit for detection of the *meta* isomers was set at 0.2%). The results are fully consistent with the expectations of an electrophilic aromatic substitution mechanism involving a rather 'tame' electrophile (i.e. positional selectivity is generally inversely related to reactivity).

The electrophilic intermediate originating from *p*-(diacetoxyiodo)toluene and sulphuric acid in AcOH is also substrate selective and, under the same conditions, reacts with toluene about 230 times faster than it reacts with benzene[25].

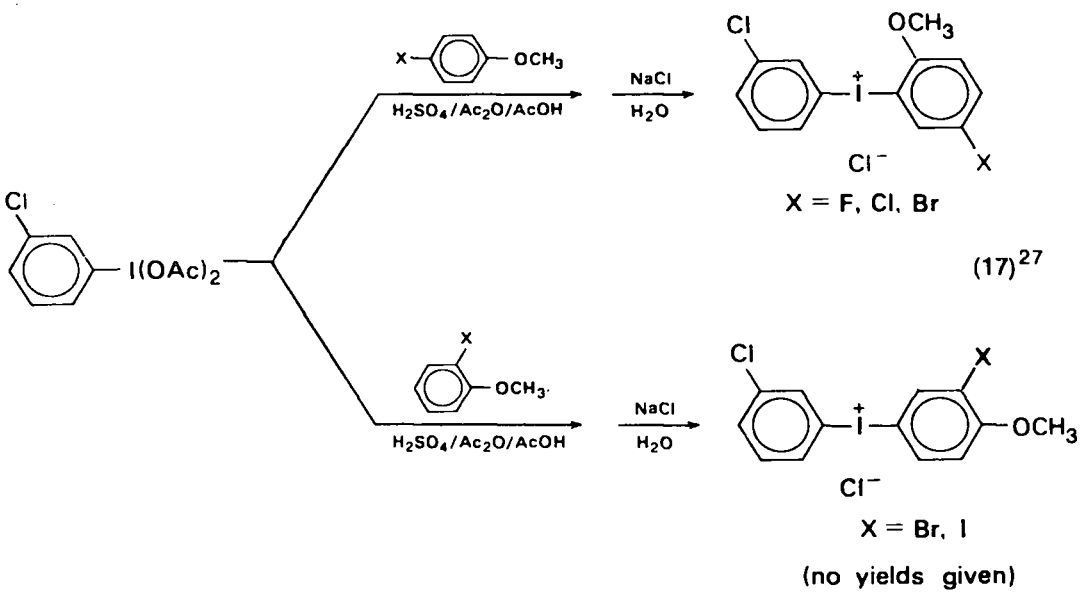
In most studies of iodonium salt formation, investigators have focused on the synthesis of a particular product rather than on the mechanistic nuances of how that product is formed and have not, therefore, concerned themselves with isomer distributions. However, of three possible isomers that might be formed in a given

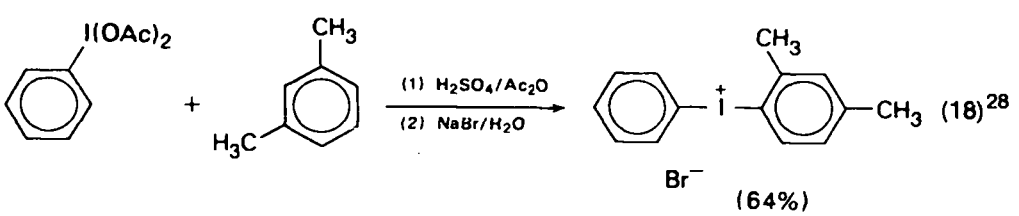
TABLE 1. Isomer distributions of diaryliodonium salts from the condensations of (diacetoxyiodo)arenes with toluene and chlorobenzene[26]

Reactant[c]	Substrate	Isomer distribution[a,b], %		
		Ortho	*Meta*	*Para*
p-$MeC_6H_4I(OAc)_2$	Toluene	10	0	90
o-$MeC_6H_4I(OAc)_2$	Toluene	10	0	90
p-$ClC_6H_4I(OAc)_2$	Chlorobenzene	3	0	97
o-$ClC_6H_4I(OAc)_2$	Chlorobenzene	22	0	78

[a]Relative yields.
[b]Refers to site of attack on PhMe and PhCl.
[c]Generated *in situ* followed by addition of aromatic substrate and sulphuric acid.

condensation reaction, only one is usually reported and is consistent with the mechanism that has been presented (e.g. refer to equations (4)–(10)). This appears to be true for disubstituted substrates as well (refer to the following examples).





Several other methods commonly employed in the synthesis of diaryliodonium salts are closely related to the acid-catalysed condensations of (diacyloxyiodo)arenes and iodosarenes with aromatic substrates.

2. *Iodyl sulphate with aromatic substrates*

When molecular iodine and an alkali metal iodate are stirred in concentrated sulphuric acid, a yellow solid suspension of iodyl sulphate results[16]. The addition of aromatic substrates to such mixtures eventuates in the formation of symmetrical diaryliodonium bisulphates[16,17,29–31]. This is a potent reaction medium and is particularly well suited for the preparation of iodonium salts bearing electron-withdrawing groups[17]. *Ortho*, *para*-directing substituents in the aromatic substrate afford

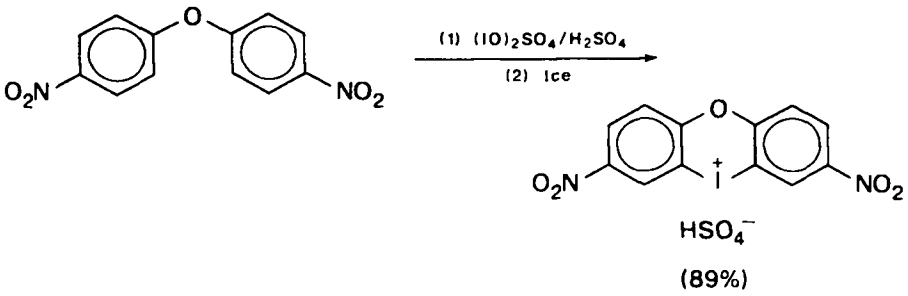
$$I_2 + KIO_3 \xrightarrow{H_2SO_4} (IO)_2SO_4 \qquad (19)$$

$$2\ ArH + (IO)_2SO_4 \xrightarrow{H_2SO_4} (Ar\overset{+}{I}Ar)\ HSO_4^- \qquad (20)$$

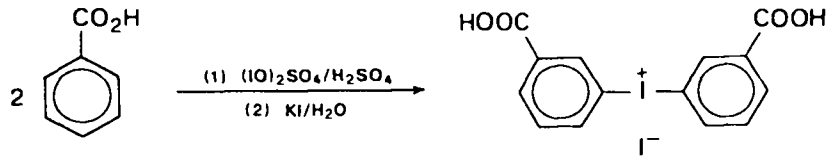
diaryliodonium salts with a 4,4′-disubstitution pattern while *meta*-directing substituents yield 3,3′-disubstituted salts. From a mechanistic standpoint, it seems likely that the iodyl cation first attacks an aromatic molecule to give an iodoso intermediate which then condenses with a second aromatic molecule in the manner already described[17].

$$ArH + {}^{+}\ddot{I}{=}O \rightleftharpoons Ar\ddot{I}{=}O + H^+ \rightleftharpoons Ar\overset{+}{\ddot{I}}OH \xrightarrow{ArH} Ar\overset{+}{I}Ar + H_2O \qquad (21)$$

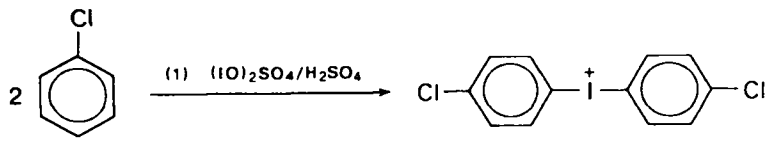
Several exemplative reactions are shown in equations (22)–(24). It is interesting to note that the reaction of iodyl sulphate with 4,4′-dimethyldiphenyl ether gave only 4% of the corresponding cyclic iodonium salt as opposed to an 89% yield of product when 4,4′-dinitrodiphenyl ether was the substrate.



(89%) (22)[32]



(53%) (23)[16]



HSO_4^-

(60%) (24)[17]

3. *Alkali metal iodates with aromatic substrates*

Admixture of an arene with sodium or potassium iodate in $H_2SO_4/Ac_2O/AcOH$ likewise affords *symmetrical* diaryliodonium salts[17]. This procedure is useful for the preparation of salts bearing electron-donating substituents. We are unaware of any

$$2\ ArI + KIO_3 \xrightarrow{H_2SO_4/Ac_2O/AcOH} (Ar\overset{+}{I}Ar)\,HSO_4^- + \langle O\rangle \qquad (25)$$

mechanistic studies of this condensation reaction, and, apparently, the fate of the indicated oxygen radical has not yet been ascertained. A plausible mechanism is one involving the *in situ* genesis of an iodoxyarene and its subsequent deoxidative coupling with a second molecule of the aromatic reactant. Precedent for such a process is provided by the known condensation of iodoxyarenes with arenes in the presence of sulphuric acid to give diaryliodonium salts.

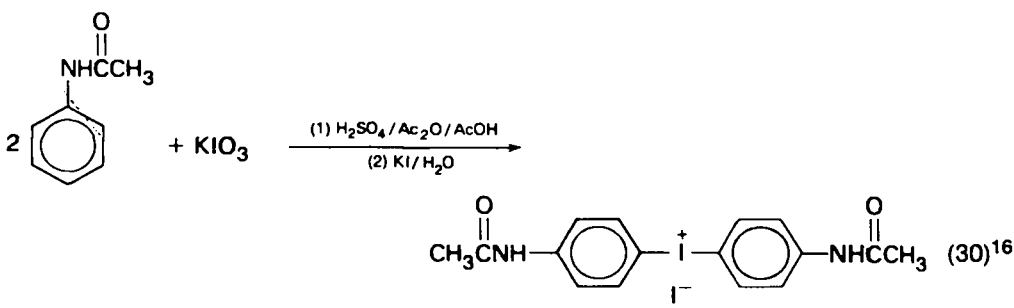
$$IO_3^- + H_2SO_4 \rightleftharpoons HOIO_2 + HSO_4^- \qquad (26)$$

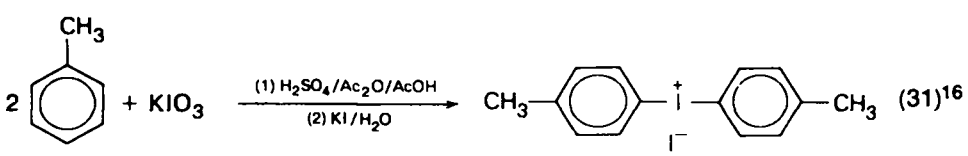
$$HOIO_2 + H_2SO_4 \rightleftharpoons H_2O + {}^+IO_2\ HSO_4^- \qquad (27)$$

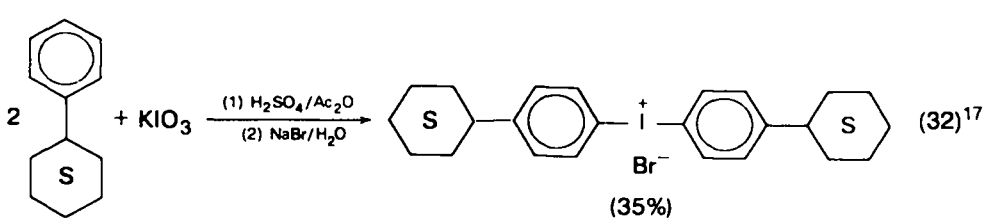
$$ArH + {}^+IO_2\ HSO_4^- \longrightarrow ArIO_2 + H_2SO_4 \qquad (28)$$

$$ArIO_2 + ArH \xrightarrow{H_2SO_4} (Ar\overset{+}{I}Ar)HSO_4^- + \langle O\rangle \qquad (29)$$

Equations (30)–(32) are examples of such reactions.

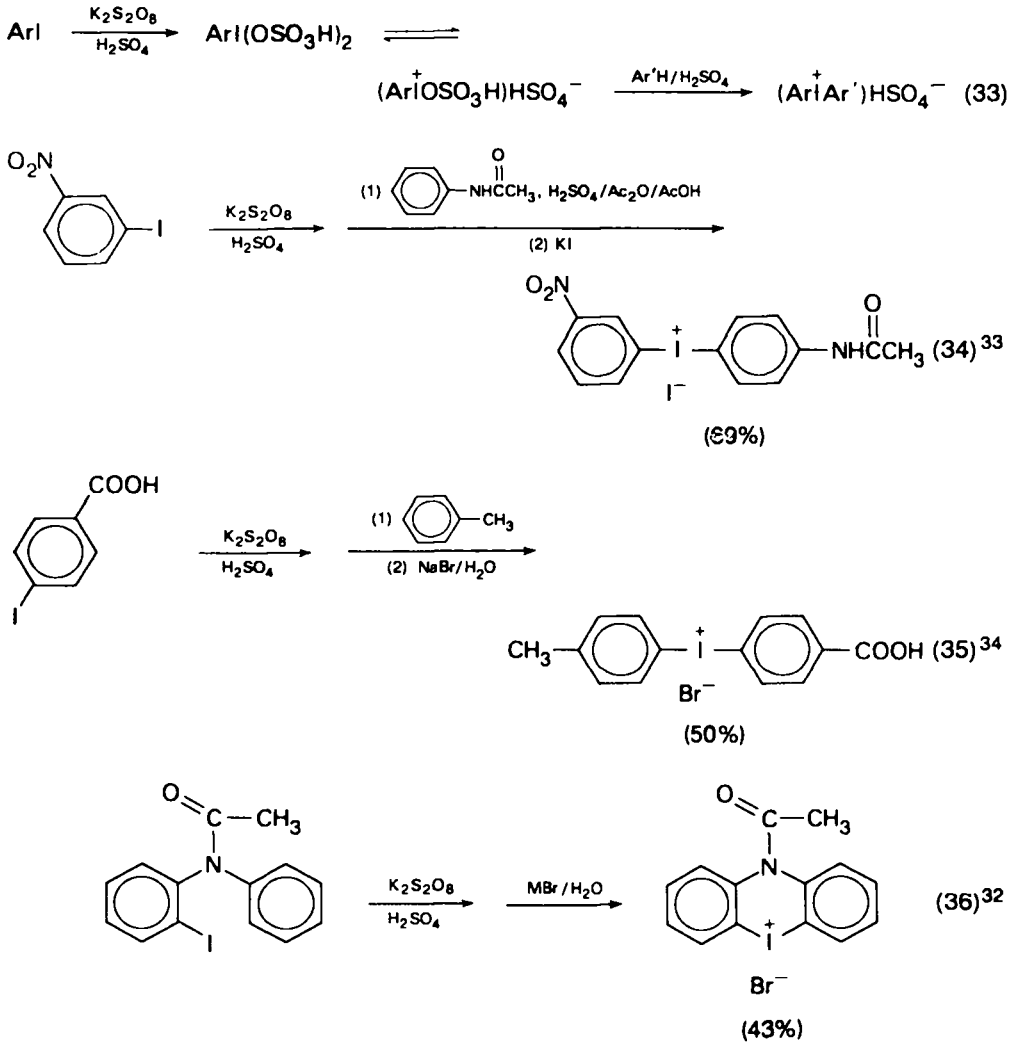






4. 'Iodoso' intermediates generated in situ *and their subsequent condensations with aromatic substrates*

Treatment of iodoarenes first with potassium persulphate and then with aromatic substrates in sulphuric acid affords diaryliodonium salts. This method, which involves the ***in situ*** formation of 'iodoso' intermediates (perhaps bis(bisulphatoiodo)arenes), is adaptable to the synthesis of symmetical and unsymmetrical diaryliodonium compounds[17]. Other oxidants (e.g. H_2O_2, BaO_2, CH_3CO_3H), in conjunction with appropriate solvent systems, may be employed instead of potassium persulphate. For examples, see in addition to equations (34)–(36) below, see also equation (4) and Table 1.



The preparative procedures considered thus far are sufficiently general to permit access to a large variety of diaryliodonium compounds. They do, however, suffer from two serious limitations. First, the incorporation of acid-sensitive functional groups and

acid-sensitive aromatic rings (e.g. the furyl nucleus) into the product structures is automatically precluded by the composition of the reaction medium. Secondly, the regiospecific placement of substituents in both aromatic rings is not possible due to the mechanistic features of the aryliodination process. For example, suppose that the 3,3′-dimethyldiphenyliodonium ion is targeted for synthesis. The acid-catalysed condensation of *m*-(diacetoxyiodo)toluene with toluene would yield, primarily, the 3,4′-isomer while the iodyl sulphate and iodate coupling methods would afford the 4,4′-isomer.

5. *Base-catalysed condensations of iodosoarenes with iodoxyarenes*

One classic approach to diaryliodonium salts, used extensively by early investigators, involves the condensation of an iodosoarene with an iodoxyarene in the presence of an appropriate base[11, 13, 14, 35]. This method takes time because the iodoso and iodoxy components must first be prepared[36,37], and it excludes the incorporation of base-sensitive functional groups. It does, however, permit regiocontrol over the placement of substituents in diaryliodonium salt structures.

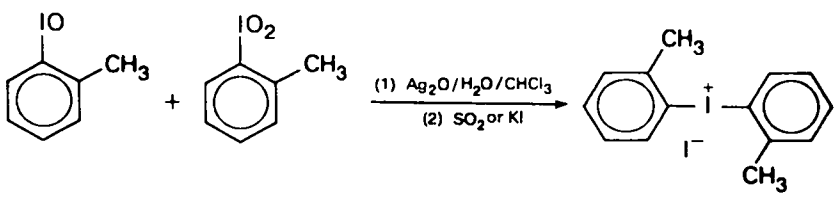
Such reactions are typically conducted in one of two ways: (1) a mixture of the iodoso- and iodoxyarenes in water is stirred with freshly prepared silver(I) oxide and (2) the iodoso- and iodoxyarenes are condensed in aqueous sodium hydroxide.

$$ArIO + ArIO_2 \xrightarrow{Ag_2O/H_2O} Ar-\overset{OH}{\underset{|}{I}}-Ar + IO_3^- \qquad (37)^{11}$$

$$ArIO + ArIO_2 \xrightarrow{NaOH/H_2O} (Ar-\overset{+}{I}-Ar)IO_3^- + OH^- \qquad (38)^{35}$$

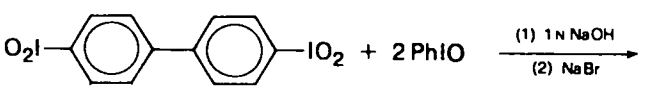
The resulting, largely *water-soluble*, products have been formulated alternatively as hydroxide and iodate salts. In any event, they are usually precipitated from solution as the less soluble halide (or other salts by the addition of $M^+ X^-$ (e.g. KI, NaBr) to the aqueous medium.

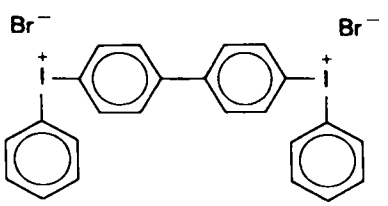
Examples are given in equations (39)–(41).



(39)[38]

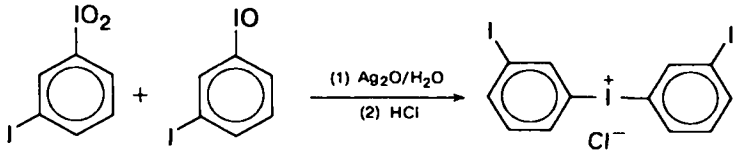
(43.5–73%)





(40)[39]

(36%)



(41)[40]

(no yield given)

6. *Aryllithium reagents with (dichloroiodo)arenes*

When (dichloroiodo)arenes are subjected to the action of aryllithium reagents in solvents such as ether or tetrahydrofuran (THF), diaryliodonium salts are obtained in moderate yields[41]. Based on limited evidence, the use of arylmagnesium halides

$$ArICl_2 + Ar'Li \xrightarrow{Et_2O/THF} (Ar\overset{+}{I}Ar')Cl^- \qquad (42)$$

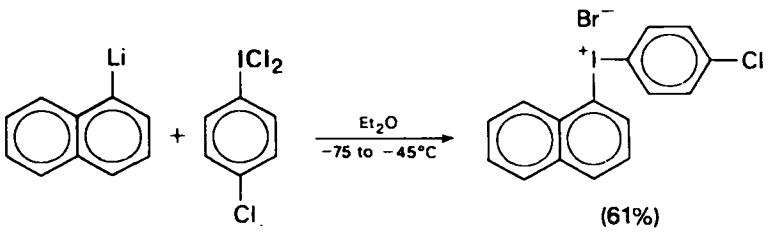
instead of the aryllithium component would appear to be disadvantageous. Thus, the treatment of (dichloroiodo)benzene with phenyllithium in THF in the presence of lithium bromide at −55 to −65°C has been reported to give diphenyliodonium bromide in 18% yield. With ether as the solvent, the iodonium bromide yields ranged from 19 to 35%[41]. When (dichloroiodo)benzene was allowed to react with phenylmagnesium bromide in THF at −72 to −60°C, diphenyliodonium bromide was obtained in 3% yield.

This method offers the advantage of a neutral reaction solvent and provides the flexibility for preparing unsymmetrical iodonium salts with regiocontrol over the placement of ring-bound substituents. It is, of course, limited to those substituents and ring systems which are insensitive to aryllithium reagents. Another potential limitation resides in the dissociative reaction of (dichloroiodo)arenes shown below[42]. The

$$ArICl_2 \underset{}{\overset{Solvent}{\rightleftharpoons}} ArI + Cl_2 \qquad (43)$$

equilibrium constants are not large in those reactions for which they have been measured, but molecular chlorine might offer significant kinetic competition for a given aryllithium species.

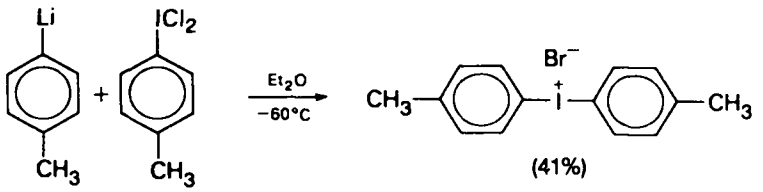
Examples are given in equations (44)–(46).



(44)[41]

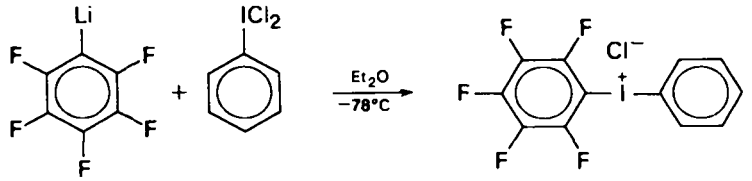
(61%)

(Br⁻ apparently originates from preparation of the lithium reagent from α-bromonaphthalene)



(45)[41]

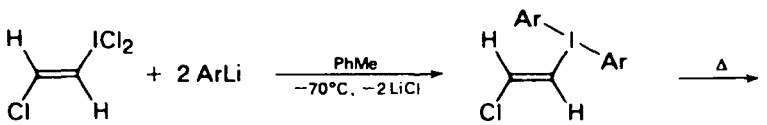
(41%)



(23%) (46)[43]

7. *Aryllithium reagents with* trans-*1-(dichloroiodo)-2-chloroethylene*

When iodine trichloride is dissolved in hydrochloric acid in ice–water and subjected to the action of acetylene, *trans*-1-(dichloroiodo)-2-chloroethylene (**5**) precipitates from the reaction mixture. It is unstable to decomposition at room temperature, but it can be stored at −20°C or below for at least 2 months. The addition of 2 equivalents of an aryllithium reagent to toluene solutions of this compound (1 equiv.) at low temperature and subsequent warming of the reaction mixture to 0°C or above results in the formation of symmetrical diaryliodonium salts[44,45]. This reaction proceeds via the initial formation of a tricovalent iodine(III) intermediate which subsequently decomposes to acetylene and an iodonium salt.



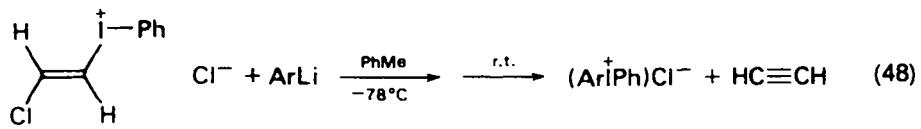
(**5**)

$(ArIAr)Cl^- + HC{\equiv}CH$ (47)

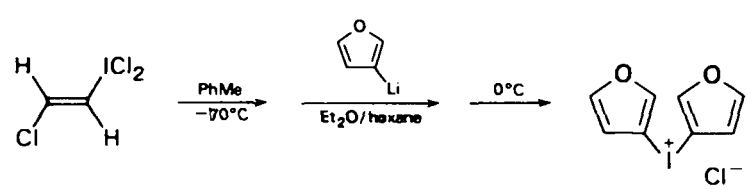
This method has proved particularly efficacious for the preparation of dithienyliodonium salts and difuryliodonium salts, the bis(furyl) analogues being especially novel since they cannot be prepared by the methods involving strong acids and since the iodoso- and iodoxyfurans are unknown[44,46,47].

Simple extension of this methodology to *trans*-chlorovinylphenyliodonium chloride as the starting reagent permits the synthesis of the unsymmetrical arylphenyliodonium salts, although this approach has thus far been little utilized.

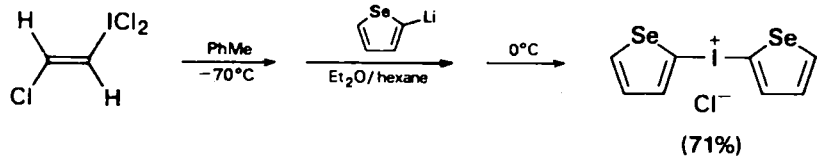
Examples are given in equations (49)–(53).



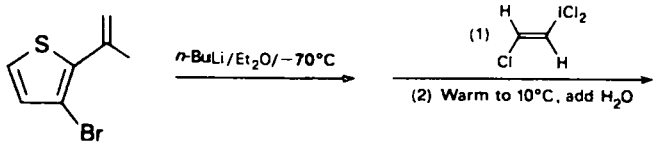
(48)

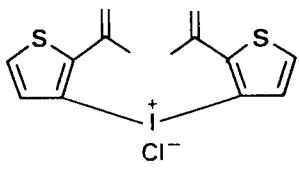


(54%) (49)[47]

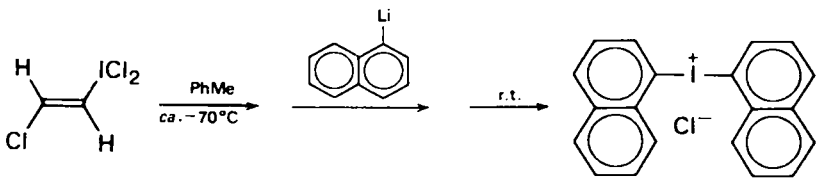


(50)[47]

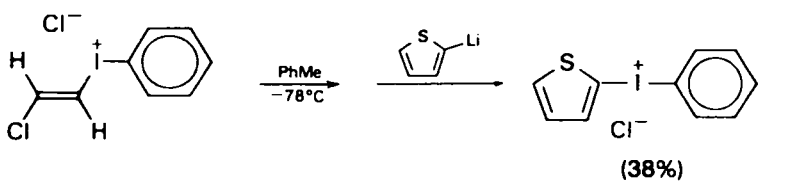




(51)[48]



(52)[45]

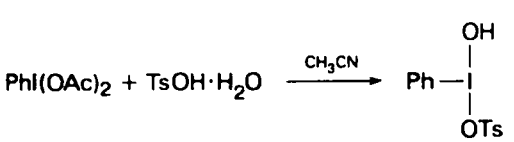


(53)[44]

Attempts to adapt this methodology to the preparation of pyridyliodonium salts and furylaryliodonium salts were unsuccessful.

8. [*Hydroxy(tosyloxy)iodo*]*arenes with (trimethylsilyl)arenes*

A recently reported approach to diaryliodonium salts is based on the use of [hydroxy(tosyloxy)iodo]arenes, relative newcomers to the 'iodoso' family of compounds. [Hydroxy(tosyloxy)iodo]benzene (**6**), first reported in 1970, can be prepared conveniently by the action of $TsOH{\cdot}H_2O$ on a suspension of (diacetoxyiodo)benzene in acetonitrile, and it can be recrystallized from the same solvent. It is a stable, white crystalline solid which can be stockpiled and stored[49,50].



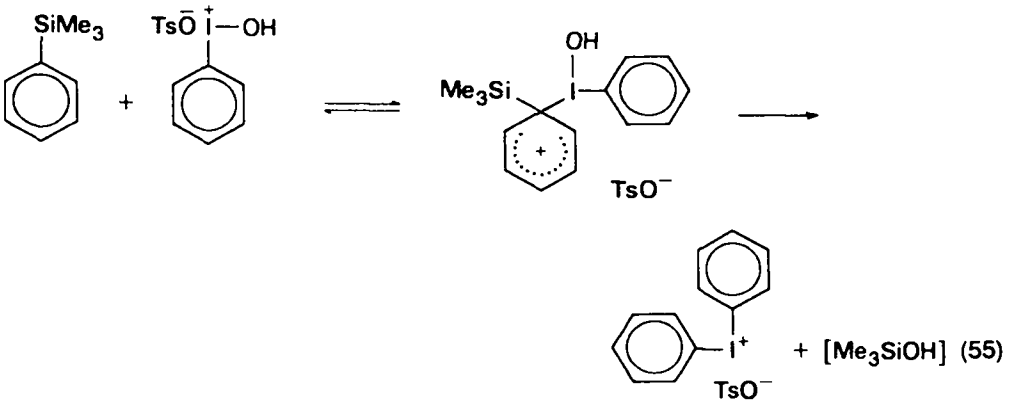
(54)

(6)

A single-crystal X-ray study of [hydroxy(tosyloxy)iodo]benzene has shown it to possess substantial ionic character in the solid state[51]. Thus, while the I—OH bond is a little shorter in length than the sum of the covalent radii of the oxygen and iodine atoms, the I——OTs bond is somewhat elongated. By application of Pauling's equation which relates bond order to bond length, a bond order of 0.16 is computed for the I——OTs bond[52].

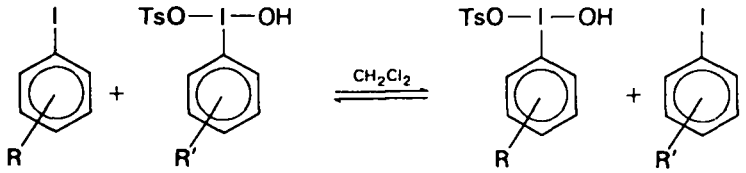
Reactions of **6** may be conducted in hot acetonitrile, a neutral non-hydroxylic solvent, and even though **6** is *nearly* insoluble in dichloromethane, reactions will also proceed in that solvent. In short, [hydroxy(tosyloxy)iodo]benzene may be viewed as a 'salt' and is a convenient shelf-source of PhI^+OH, the active electrophile postulated to exist in $PhIO/H_2SO_4$ and $(IO)_2SO_4/H_2SO_4$ condensations with arenes, and it can be utilized in mild organic solvents over a range of temperatures.

However, the electrophilicity of **6** is somewhat attenuated. Thus, while [hydroxy(tosyloxy)iodo]benzene reacts directly with anisole in acetonitrile to give phenyl(*p*-anisyl)iodonium tosylate[49,53,54] and with 2-iodothiophene in dichloromethane to give phenyl-2-(5-iodothienyl)iodonium tosylate[54,55], it does not so react with benzene, toluene or bromobenzene in acetonitrile[53]. That is, the electrophilic replacement of a ring-bound hydrogen atom does not typically occur. However, when [hydroxy(tosyloxy)iodo]benzene and (trimethylsilyl)benzene are heated in acetonitrile, diphenyliodonium tosylate is obtained in 46% yield after workup[53]. Thus, the trimethylsilyl group 'activates' the ring and directs the regiochemistry. A likely mechanism for this reaction involves electrophilic attack of the hydroxyphenyliodonium ion at the carbon bound to silicon (i.e. *ipso* phenyliodination) to give a sigma complex, the collapse of which is facilitated by the formation of a silicon–oxygen bond.



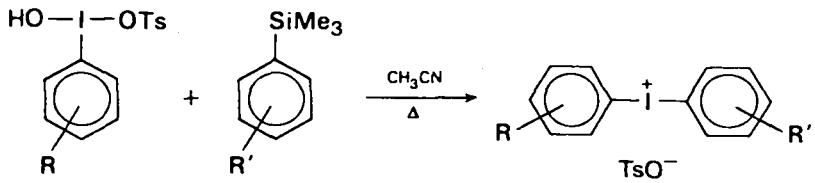
Although this method has not yet been extensively employed, it offers potential as a general, mild, regiospecific synthesis of diaryliodonium salts. A variety of (trimethylsilyl)arenes are known[56] and a number of [hydroxy(tosyloxy)iodo]arenes are accessible by the action of $TsOH{\cdot}H_2O$ on the corresponding (diacetoxyiodo)arenes[50,54]. The (diacetoxyiodo)arenes can be conveniently prepared by peracetic acid oxidations of the corresponding iodoarenes[57]. [Hydroxy(tosyloxy)iodo]arenes have also been prepared by the ligand transfer reactions shown below.

A nice demonstration of the utility of this method is provided by the regiospecific syntheses of all six ditolyliodonium tosylates from the reactions of isomeric [hydroxy(tosyloxy)iodo]toluenes with the isomeric (trimethylsilyl)toluenes. The results are summarized below[53,59].



(56)

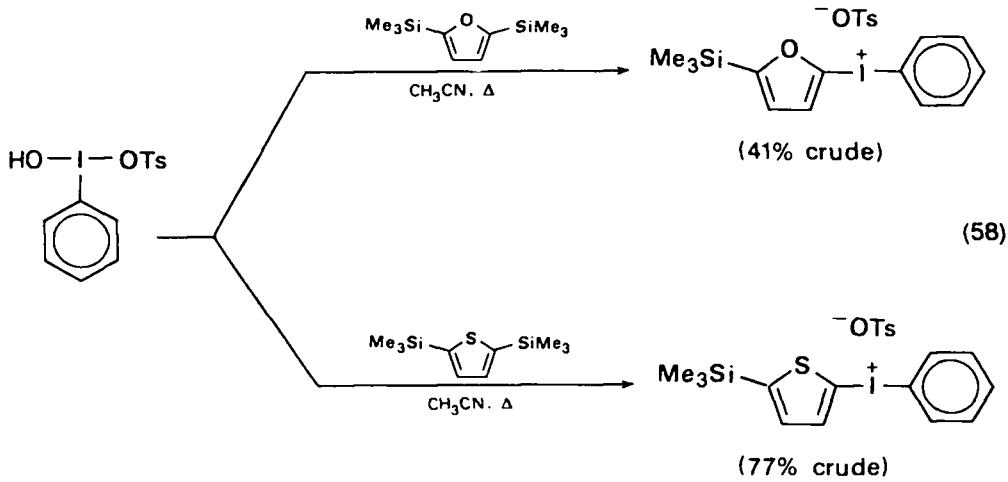
R′ = H; R = *p*-Cl, *p*-Br, *p*-I, *p*-CH_3, *p*-NO_2, *p*-Ph, 2,3-benzo[55]
R′ = *o*-CH_3; R = *p*-F, *m*-NO_2[58]



(57)

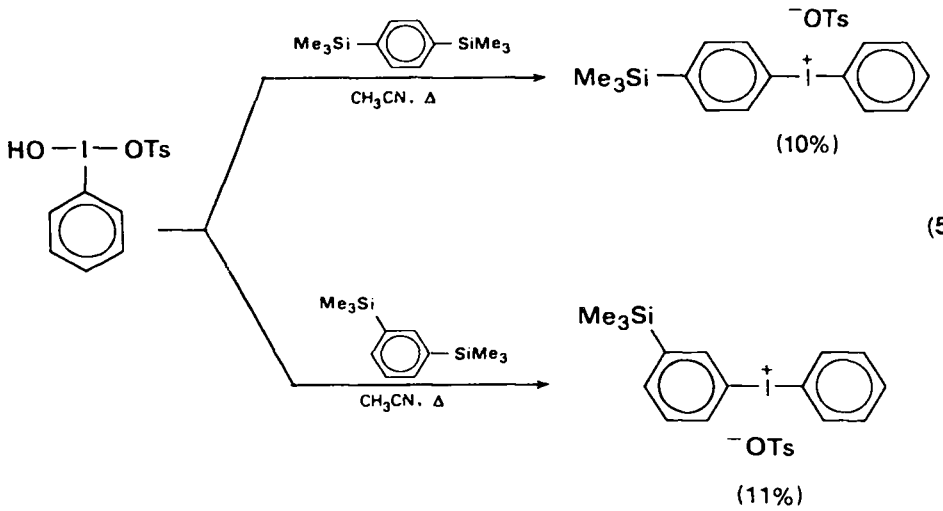
R	R′	Time	Product	Yield
o-Me	*o*-Me	4 h	2,2′	84% (crude), 64% (recrystallized)
m-Me	*m*-Me	5 h	3,3′	77% (crude), 42% (recrystallized)
p-Me	*p*-Me	4 h	4,4′	79% (crude)
o-Me	*m*-Me	9 h	2,3′	58% (recrystallized)
p-Me	*o*-Me	6 h	2,4′	59% (after crystallization of crude syrup)
m-Me	*p*-Me	3.75 h	3,4′	82% (crude), 59% (recrystallized)

Similar reactions of [hydroxy(tosyloxy)iodo]benzene with 2,5-bis(trimethylsilyl)-thiophene and 2,5-bis(trimethylsilyl)furan give corresponding monoidonium tosylates, the furyl analogue being the first example of an isolated arylfuryliodonium salt[60]. Bis(trimethylsilyl)arenes likewise react with [hydroxy(tosyloxy)iodo]benzene to give



(58)

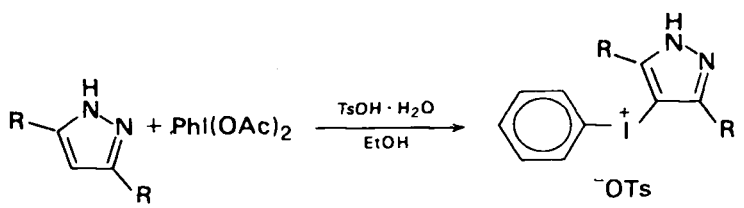
monoiodonium salts with one trimethylsilyl function intact[60]. It is not likely that a trimethylsilyl substituent could be introduced into a diaryliodonium salt nucleus by any of the methods that involve strong acid media since the silicon–carbon bonds



(59)

of arylsilanes are sensitive to electrophilic cleavage reactions, including that of protonolysis.

A reaction which may involve the intermediate formation of [hydroxy(tosyloxy)-iodo]benzene and its subsequent action as a phenyliodinating agent is the formation of arylpyrazolyliodonium salts from the corresponding pyrazoles and (diacetoxyiodo)-benzene in the presence of *p*-toluenesulphonic acid[61].

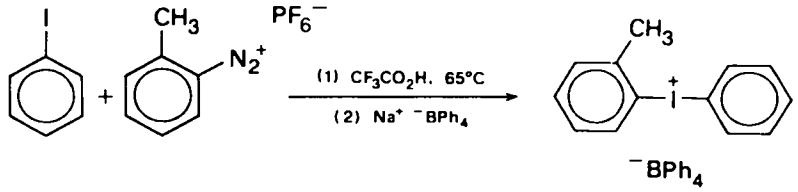


(60)

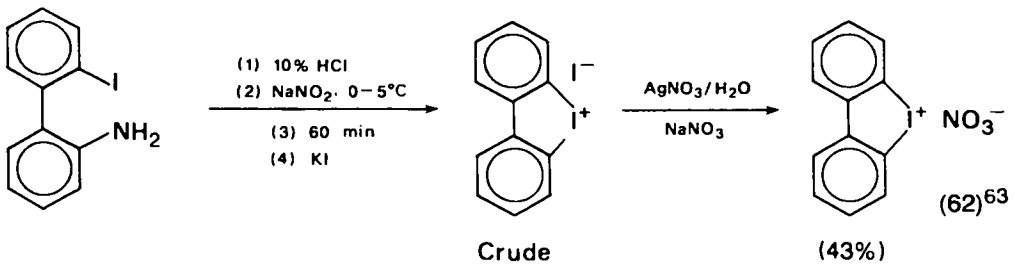
R	Yield, %
H	70
Me	94
Ph	75

9. *Other synthetic approaches to diaryliodonium salts*

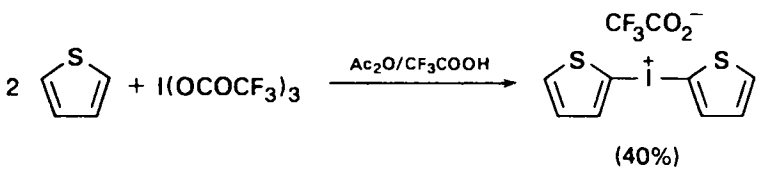
Other methods which have been utilized for the synthesis of diaryliodonium salts include (1) the thermal decomposition of aryldiazonium salts (i.e. those with relatively non-nucleophilic counterions) in the presence of iodoarenes, and (2) the coupling of two aromatic molecules in the presence of tris(trifluoroacetoxy)iodine (which can be prepared by an early procedure developed for the synthesis of other tris(organo-carboxy)iodine analogues[62]), an approach somewhat analogous to the iodyl sulphate coupling method, and (3) the reactions of diarylmercury compounds and (trichloro-stannyl)arenes with (dichloroiodo)arenes or with iodine trichloride. Examples are given in equations (61)–(67).



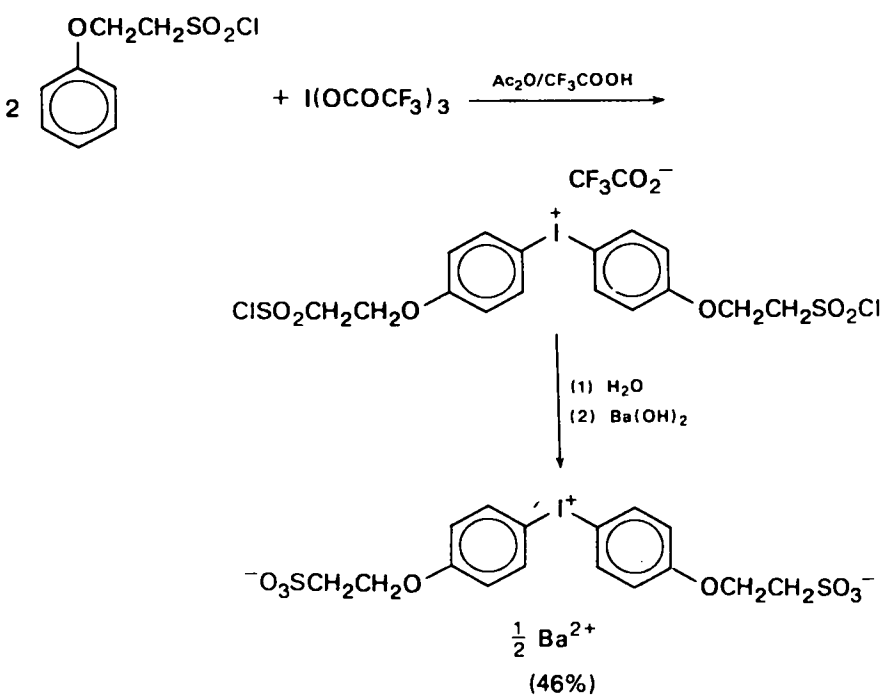
(61)[2]



(62)[63]



(63)[64]



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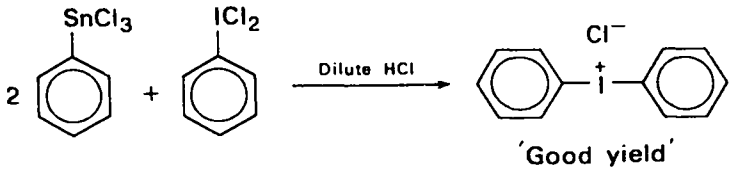
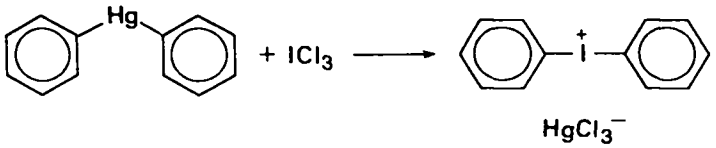
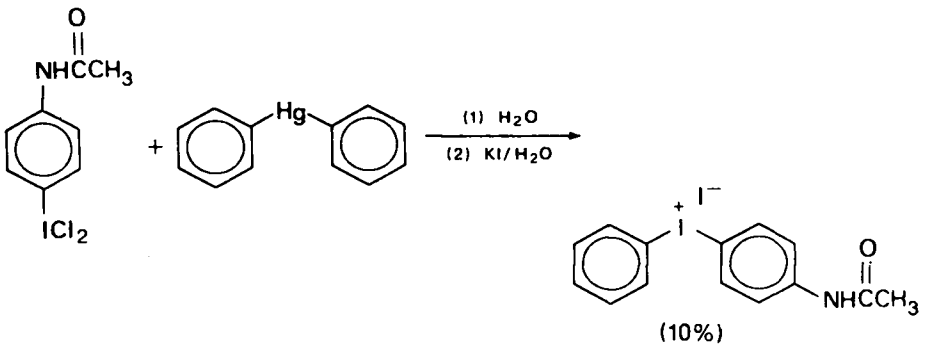


(65)[65]

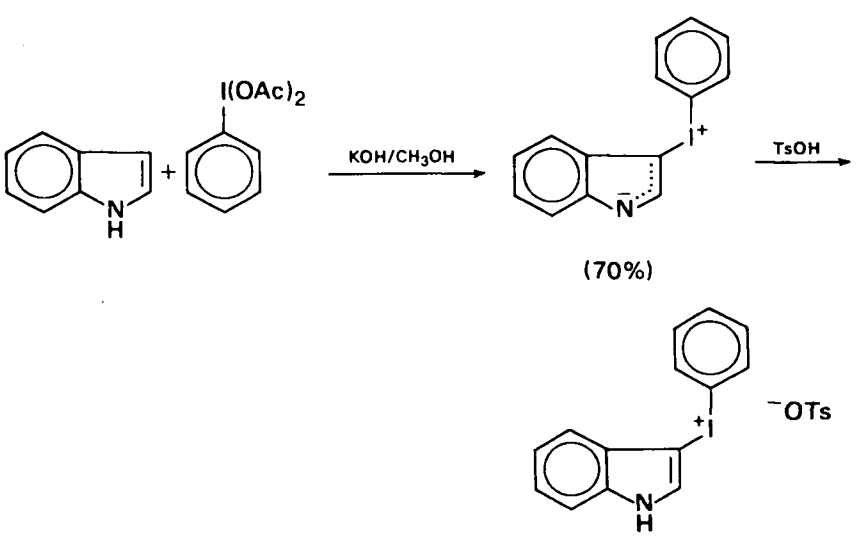


(66)[65]



(67)[33]

Another interesting approach to iodonium salts involves the protonation of the corresponding iodonium ylides with Brønsted acids. For example, the condensation of indole with (diacetoxyiodo)benzene in methanolic potassium hydroxide gives an iodonium ylide which, upon treatment with *p*-toluenesulphonic acid, affords phenyl(β-indolyl)iodonium tosylate[66].



(68)

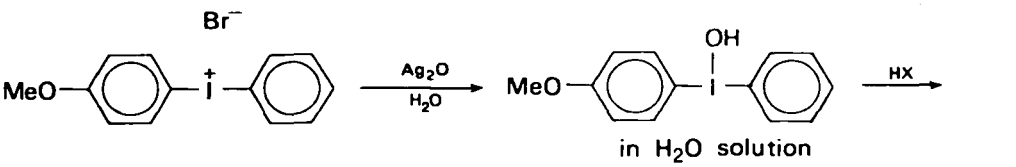
10. Anion metathesis

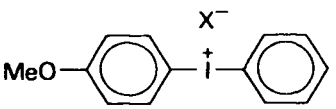
Diaryliodonium ions can be coupled with a diversity of counterions in diaryliodonium salts. Such anions may include F^-, Cl^-, Br^-, I^-, HSO_4^-, SO_4^{2-}, RCO_2^-, $CF_3CO_2^-$, picrate, IO_3^-, ClO_4^-, BF_4^-, Ph_4B^-, $ArSO_3^-$, PF_6^-, SbF_6^-, AsF_6^-, HO^-, $HgCl_3^-$ and NO_3^-, and this list is by no means complete.

The conversion of one diaryliodonium salt into another one via anion exchange (i.e. metathesis) is a common practice. However, the procedural details for accomplishing this are sufficiently varied that it is difficult to write a general prescription. One standard approach is to dissolve a given iodonium salt in some solvent (e.g. H_2O, 90% HCOOH, alcohol) and to then precipitate a less soluble anionic analogue from solution by the addition of an appropriate inorganic salt. For example, diaryliodonium halides can be precipitated from solutions of the corresponding bisulphate salts with added sodium and potassium halides, a procedure which may or may not involve the initial isolation of the bisulphate. Among the diaryliodonium halides, the typical solu-

$$(ArI^+Ar)HSO_4^- + M^+X^- \xrightarrow{H_2O} (ArI^+Ar)X^- + M^+HSO_4^- \qquad (69)$$

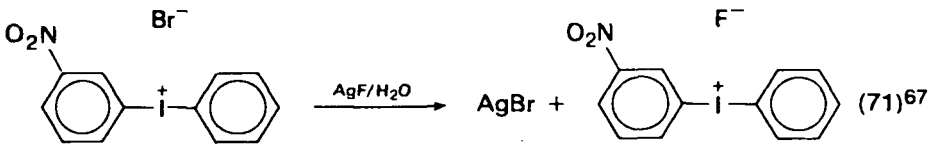
bility trend is $I^- < Br^- < Cl^-$ [16,17]. Diaryliodonium nitrates and fluoroborates can be prepared by the action of silver nitrate or silver tetrafluoroborate on suspensions or solutions of diaryliodonium halides in appropriate solvents. Solutions of diaryliodonium hydroxides can be treated with various acids, HA, to give salts of general structure $Ar_2I^+A^-$ which may precipitate from solution or may require solvent evaporation prior to their isolation. Some examples of metathesis procedures are given in equations (70)–(76).



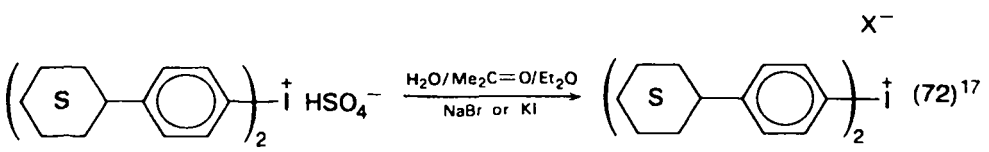


(70)[67]

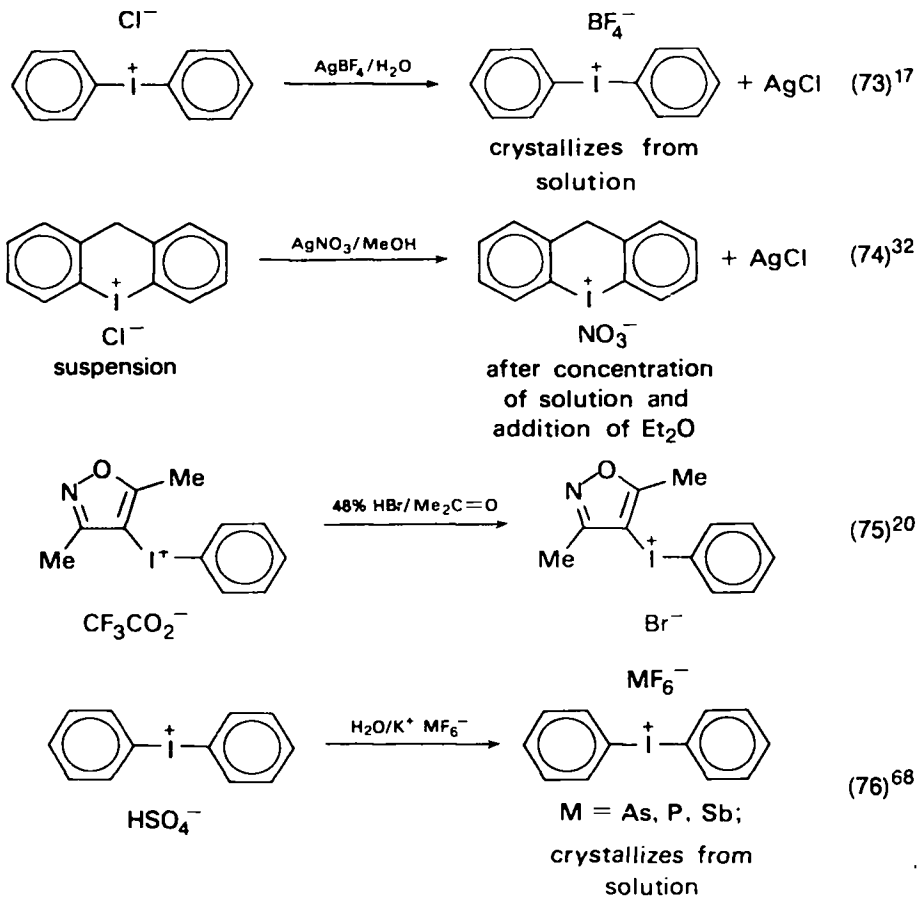
$X^- = {}^-OTs, CF_3CO_2^-, F^-, BF_4^-$



(71)[67]

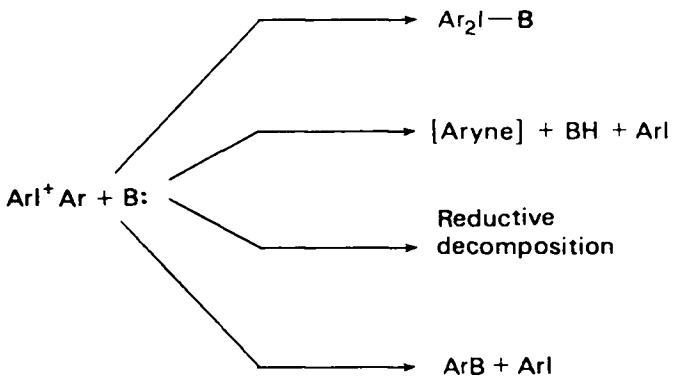


(72)[17]



B. Reactions with Nucleophiles

Diaryliodonium salts react with a broad spectrum of nucleophilic species. Some nucleophiles afford tricovalent iodine(III) adducts, others initiate a process of reductive decomposition, and, in rare instances, intermediate arynes are generated.



Most typically, however, the *formal* transfer of an aryl 'cation' from the iodonium centre to a lone pair of the nucleophile occurs. Indeed, the diaryliodonium salts, especially those with non-nucleophilic anions, appear to be emerging as reagents of choice for arylation reactions.

1. Arylation reactions

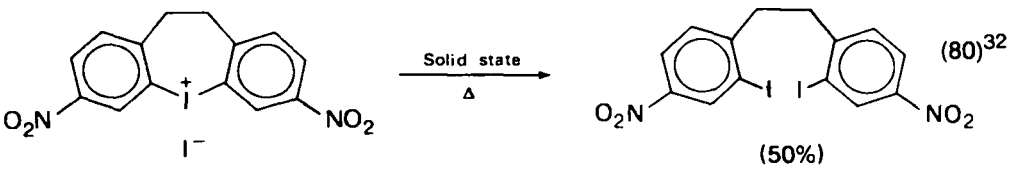
The ability of diaryliodonium ions to arylate nucleophiles has long been recognized as a convenient tool for ascertaining iodonium ion structures. A typical approach would be to first isolate an 'unknown' diaryliodonium ion as one of its halide salts and to then heat it in the solid state to its decomposition point. From an identification of the haloarenes thus formed, the structure of the original cation would follow. Such analyses can be simplified by selecting X^- to be the iodide ion, thereby limiting the

$$(Ar—I^+—Ar')X^- \xrightarrow{\Delta} ArI + Ar'X + Ar'I + ArX \qquad (78)$$

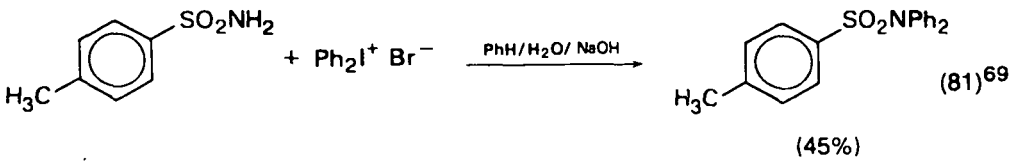
decomposition mixture to two products, these being formed in a 1:1 mole ratio. The thermolysis of symmetrical acyclic diaryliodonium iodides and all cyclic diaryliodonium iodides would, of course, eventuate in only one nucleophilic decomposition product. High boiling solvents (e.g. DMF) may also be employed to mediate such fragmentation reactions.

$$(Ar—I^+—Ar')I^- \xrightarrow{\Delta} ArI + Ar'I \qquad (79)$$

In addition to the halides, examples of nucleophiles which have been arylated by iodonium ions include various inorganic anions (e.g. HO^-, H^-, NO_2^-, CN^-, N_3^-, SCN^-, SO_3^{2-}), alkoxides, aryloxides, carboxylates, thiolates, amines, sulphides, selenides, phosphines, pyridine *N*-oxides, and carbanions. This is not to imply that all of these classes of nucleophiles have been investigated to the same extent nor does this list identify all nucleophiles studied thus far. Some specific examples of arylation reactions, taken from the literature, are given in equations (80)–(93) in order to illustrate the synthetic utility of diaryliodonium salts.



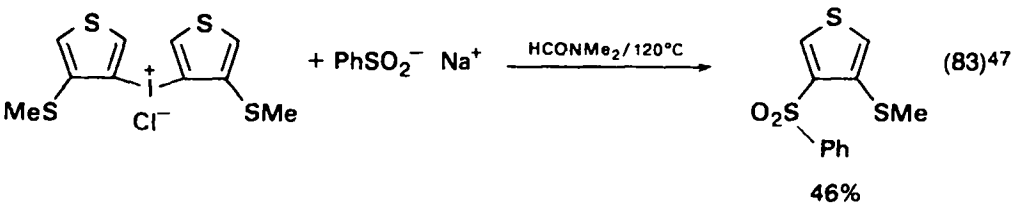
(80)[32]

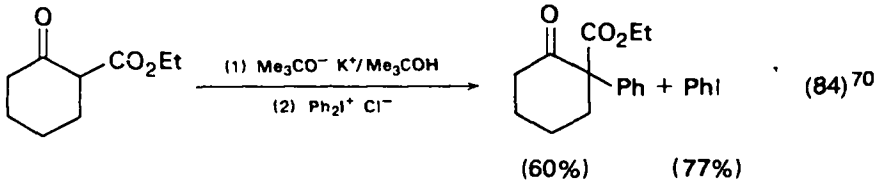


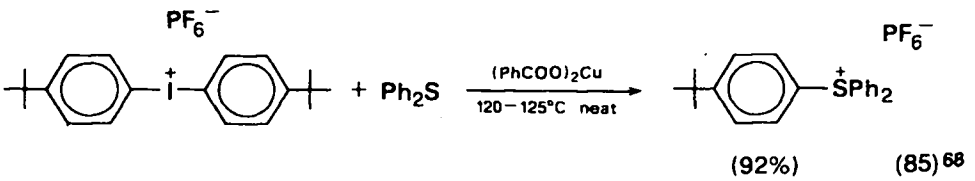
(81)[69]

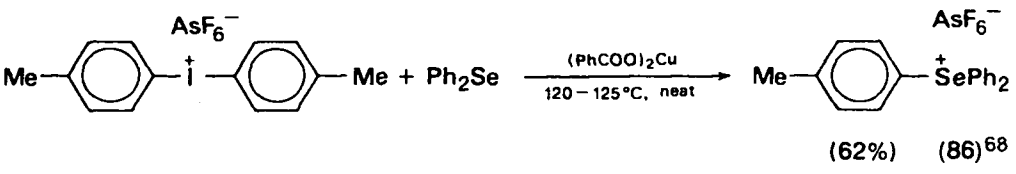
$$Ph_2I^+ Br^- + LiAlH_4 \xrightarrow{Et_2O} PhH + PhI + PhBr \qquad (82)^{69}$$

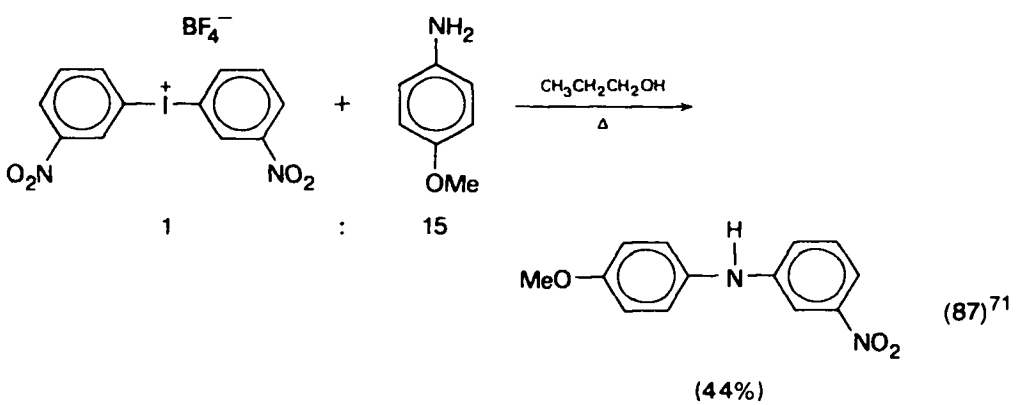
(41%) (81%) (2.6%)

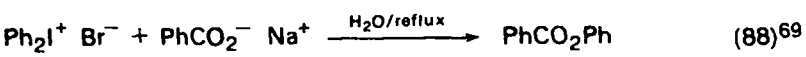

S
S
MeS
I
Cl⁻
SMe
+ PhSO2⁻ Na⁺
HCONMe2/120°C
S
O2S
SMe
Ph
46%
(83)47

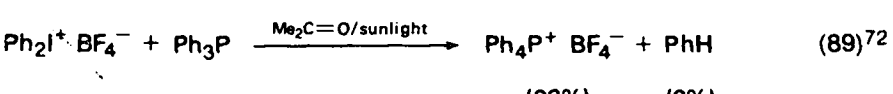

O
CO2Et
(1) Me3CO⁻ K⁺/Me3COH
(2) Ph2I⁺ Cl⁻
O
CO2Et
Ph + PhI
(60%)
(77%)
(84)70

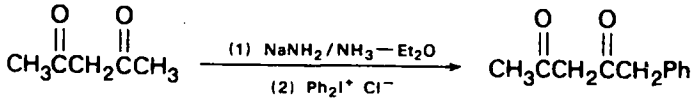

PF6⁻
I
+ Ph2S
(PhCOO)2Cu
120–125°C neat
PF6⁻
SPh2
(92%)
(85)68


AsF6⁻
Me
I
Me + Ph2Se
(PhCOO)2Cu
120–125°C, neat
AsF6⁻
Me
SePh2
(62%)
(86)68

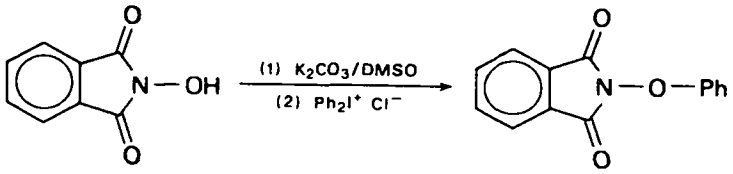

BF4⁻
I
O2N
NO2
+
NH2
OMe
CH3CH2CH2OH
Δ
1 : 15
H
N
MeO
NO2
(44%)
(87)71


Ph2I⁺ Br⁻ + PhCO2⁻ Na⁺
H2O/reflux
PhCO2Ph
(40%)
(88)69

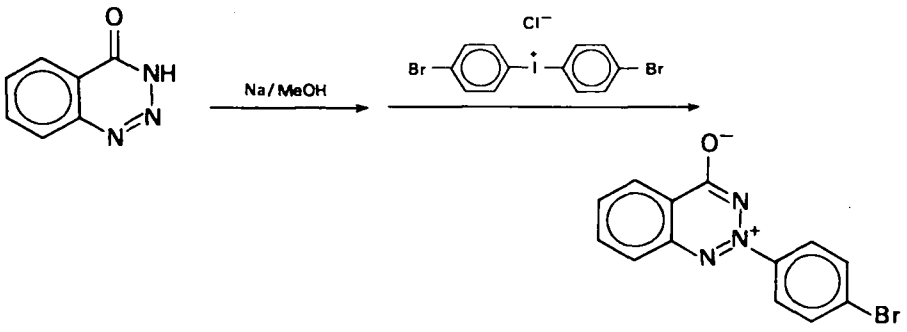

Ph2I⁺ BF4⁻ + Ph3P
Me2C=O/sunlight
Ph4P⁺ BF4⁻ + PhH
(82%)
(9%)
(89)72



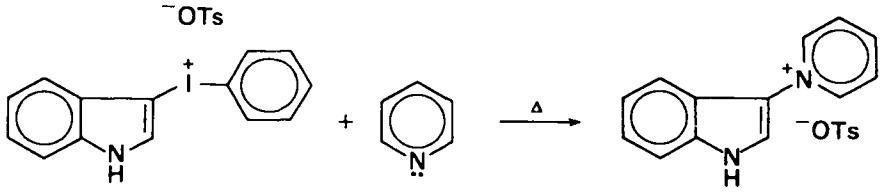
(92%) (90)[73]



(90%) (91)[74]

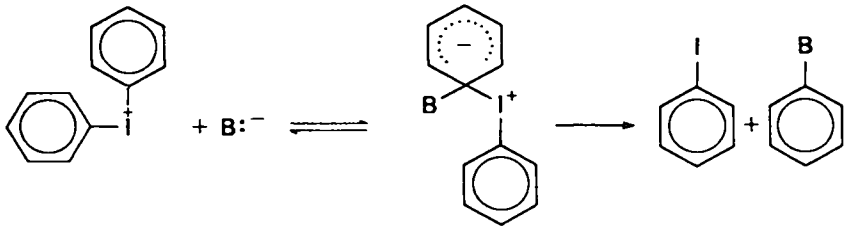


(53%) (92)[75]



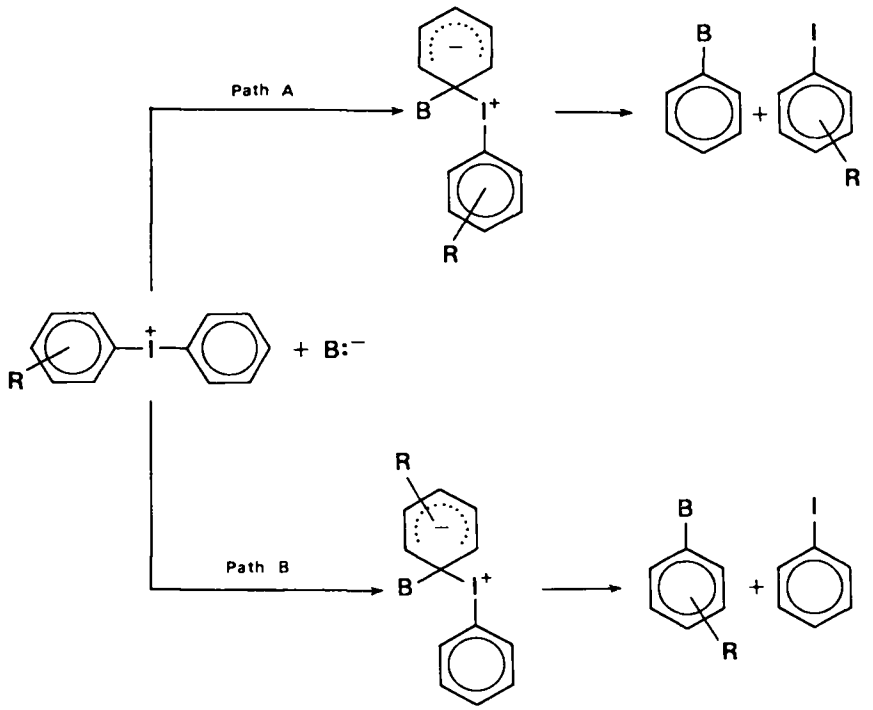
(98%) (93)[66]

Most arylation reactions of the type under consideration appear to proceed by one or the other of two mechanisms. For those nucleophiles which are not easily oxidized, a polar process resembling the classic S_NAr mechanism for nucleophilic aromatic substitution is indicated by the experimental evidence and is illustrated below for the reaction of the general nucleophile, $B:^-$, with the diphenyliodonium ion. On the other hand, those nucleophiles having relatively low oxidation potentials appear to react by a mechanism involving the intermediate formation and decomposition of diaryliodinanyl radicals, $Ar_2I^{\bullet}$.



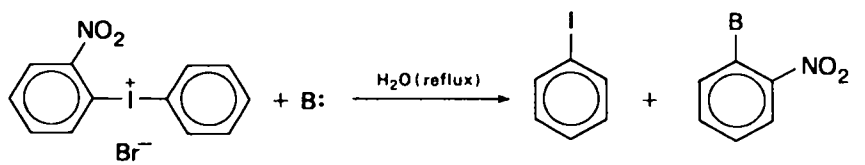
(94)

a. The S_NAr *mechanism.* One type of evidence pointing to the S_NAr mechanism for reactions of certain nucleophiles with diaryliodonium salts is the regioselective nature of the cleavage process with unsymmetrical substrates. For arylphenyliodonium ions, it is expedient to define two reaction pathways, one characterized by nucleophilic attack on the unsubstituted ring (path A) and another characterized by nucleophilic attack on the substituted ring (path B). If the S_NAr mechanism is indeed operative, A:B ratios significantly greater than 1.0 would be anticipated when R is electron donating while A:B ratios significantly less than 1.0 would be expected when R is electron with-



drawing. On the other hand, for those reactions proceeding via the intermediate formation and homolytic decomposition of arylphenyliodinanyl radicals, ArI·Ph, A:B ratios of about 1.0 should be observed regardless of the electronic nature of the substituent.

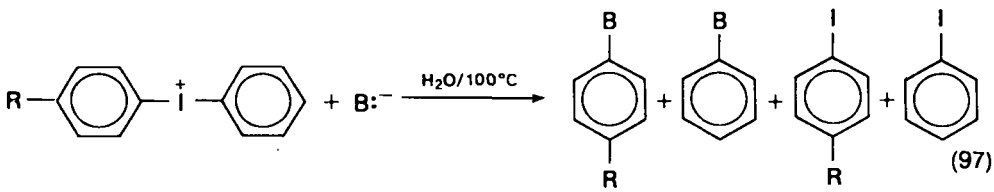
Early studies of this type, if not quantitative , are at least indicative. For example, the treatment of phenyl(*o*-nitrophenyl)iodonium bromide with sodium nitrite in water at reflux has been reported to afford *o*-dinitrobenzene in 84% yield (based on *isolation*)[69]. Thus, the *o*-nitrophenyl ring is *at least* 5.2 times as reactive as the phenyl nucleus toward nucleophilic attack by nitrite ion under those conditions (i.e. A:B $\leqslant$ 0.19). Similar results were obtained with other nucleophilic species, and they are summarized below[69].



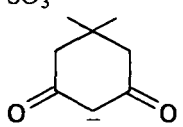
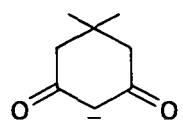
B:	Isolated product	Yield, %	Maximum A:B ratio
NO_2^-	o-$O_2NC_6H_4NO_2$	84	0.19
$PhCO_2^-$	o-$O_2NC_6H_4OOCPh$	85	0.18
Me_2NH	o-$O_2NC_6H_4NMe_2$	83	0.20
SO_3^{2-}	o-$O_2NC_6H_4SO_3^-$	79	0.27
MeO^-	o-$O_2NC_6H_4OMe$	71*	0.41
HO^-	o-$O_2NC_6H_4OH$	76	0.32
$EtO_2CCH_2CO_2^-$	o-$O_2NC_6H_4OOCCH_2CO_2Et$	68	0.47

*Reaction conducted in MeOH.

In another more quantitative study, phenyl(*p*-nitrophenyl)iodonium tosylate and phenyl(*p*-anisyl)iodonium trifluoroacetate were each subjected to the action of several different nucleophiles in water at 100°C[76]. The iodoarenes thus formed were isolated by steam distillation, and the RC_6H_4I/C_6H_5I compositions were determined by infrared analysis, these, of course, being directly related to A:B competition ratios. For the *p*-nitroiodonium ion, the A:B ratio was determined to be *less* than 0.1 with sulphite ion as the nucleophile (i.e. no *p*-nitroiodobenzene was detected) while the A:B ratio for the reaction of the same nucleophile with the *p*-methoxyiodonium ion was determined to be *greater* than 10 (i.e. no iodobenzene was detected). The more oxidizable dimedonate ion exhibited no regiopreference at all with either iodonium substrate, consistent with a change in reaction mechanism.



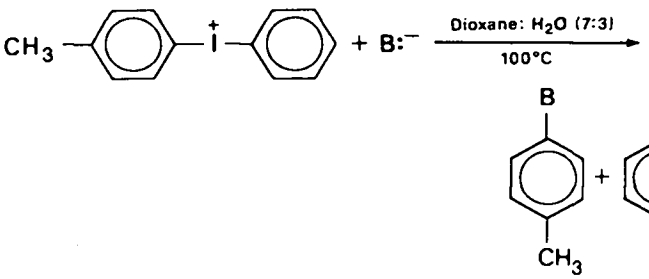
(97)

R	B:⁻	A:B
NO_2	SO_3^{2-}	<0.1
		1.0
OMe	SO_3^{2-}	>10
		1.0

Solid/molten state decompositions of phenyl(*p*-tolyl)iodonium chloride, bromide and iodide (radioactive) at 235 ± 3°C have been conducted and product mixtures determined by gas–liquid chromatographic analysis[28]. The A:B ratios are 1.7, 1.9 and 1.6 respectively. Larger values might be expected for the corresponding phenyl(*p*-anisyl)iodonium salts, and such is the case for the iodide salt (A:B = 4.3). However,

for the bromide salt, the A:B ratio was determined, from an average of 12 decomposition runs, to be 1.3[28].

The nucleophilic cleavage of the phenyl(*p*-tolyl)iodonium ion appears to be a bit more regioselective in the solution phase. Thus, in dioxane/H_2O, the A:B ratios for the reactions of phenyl(*p*-tolyl)iodonium tetrafluoroborate with nitrite, azide, thiocyanate and cyanide ions range from 2.3 to 5.0[77]. It is noteworthy that the *absolute* yields of nucleophilic cleavage products are much lower with cyanide ion than with other nucleophiles due to a *competing* radical chain decomposition reaction. It has been observed that these regioselectivities are typical of phenyl versus *p*-tolyl selectivities in other S_NAr reactions[77].

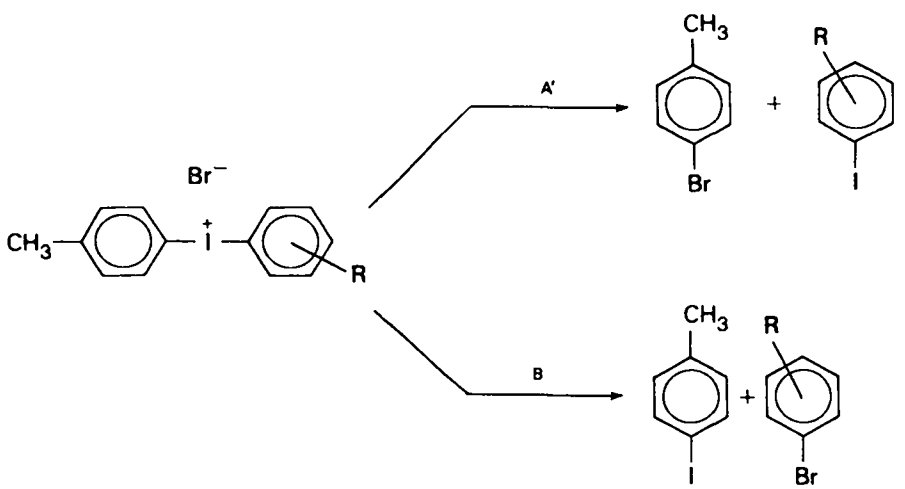


(98)

B:⁻	A:B
NO_2^-	2.4
N_3^-	2.5*
SCN^-	2.3
CN^-	5.1

*80°C.

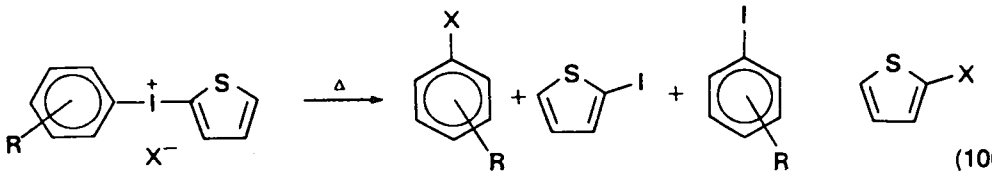
Cleavage ratios for a series of aryl(*p*-tolyl)iodonium bromides both in the molten state at 235°C and in dimethylformamide (DMF) solution at 100°C have also been measured[34]. When the competing aryl nucleus is either phenyl or *p*-anisyl, the molten decomposition is more regioselective. However, when the aryl nucleus bears electron-withdrawing substituents, the solution phase decomposition is more regioselective. In all cases, though, the regiochemistry is consistent with that expected for the S_NAr mechanism (equation 99).



(99)

R	A':B	
	Molten phase	DMF solution
p-MeO	4.24	2.69
H	0.62	0.37
p-Cl	0.67	0.45
m-Cl	0.53	0.24
p-COOH	0.15	0.08
p-NO_2	0.04	—

The thermal decompositions of various aryl(2-thienyl)iodonium chlorides and bromides at 235°C are characterized by a preference for nucleophilic attack at the aryl nucleus[78] (equation 100). Indeed, for those chloride salts with R = H, *m*-Me, *m*-Cl and *p*-Cl, the decompositions are regiospecific. Regiospecific attack at the aryl nucleus likewise occurs with certain bromide salts (R = H, *m*-Cl and *m*-Me), but with others (R = *p*-Cl, *p*-Me and *p*-MeO) nucleophilic attack of bromide ion at the thienyl nucleus is a competitive process.



(100)

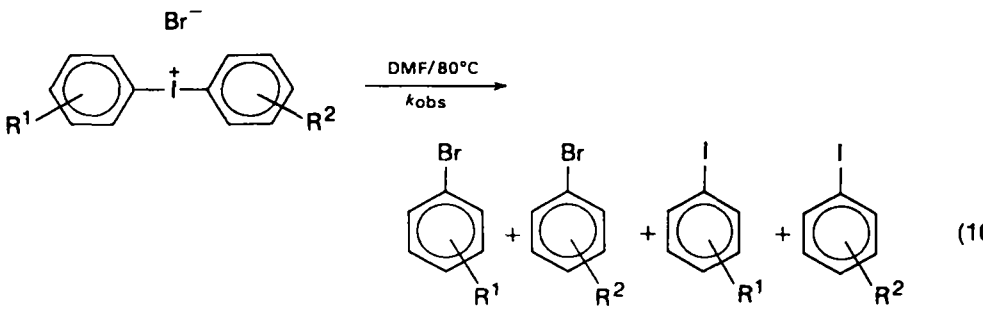
An alternative mechanism for the nucleophilic cleavage of diaryliodonium salts and one which has been considered from time to time is an S_N1 process involving the initial formation of aryl cations. Such a mechanism is, however, clearly inconsistent with the aforementioned regioselectivities and would demand A:B and A':B ratios in the opposite direction.

$$ArI^+ Ar \longrightarrow Ar^+ + ArI \quad (101)$$

$$Ar^+ + B: \longrightarrow ArB \quad (102)$$

A second type of evidence for the S_NAr mechanism in reactions of nucleophiles with diaryliodonium ions is provided by data on gross iodonium salt reactivities.

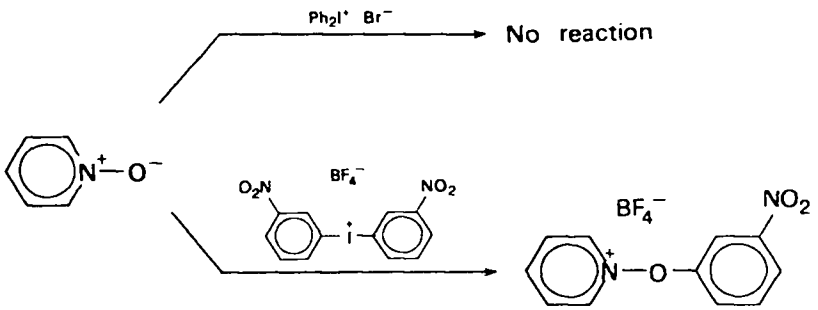
Substituent effects on the first-order decompositions of various diaryliodonium halides in dimethylformamide conform to expectations[79]; that is, those iodonium ions bearing electron-withdrawing groups decompose more rapidly than those with electron-donating groups. For example, bis(*m*-nitrophenyl)iodonium bromide collapses 51.6 times more rapidly than bis(*p*-anisyl)iodonium bromide does in DMF solution at 80°C. The log k_{obs} values are not, however, related in a linear way to the Hammet substituent constants (see equation 103).



(103)

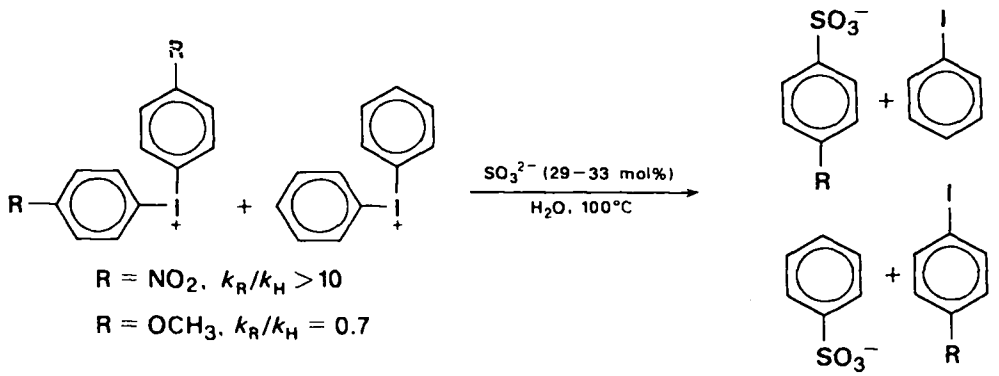
R^1	R^2	k_{obs}, h^{-1}
m-NO_2	*m*-NO_2	19.6
H	H	10.0
p-Cl	*p*-Cl	7.7
p-Me_3C	*p*-Me_3C	4.23
p-Me	*p*-Me	3.82
p-F	*p*-F	17.3
p-OMe	*p*-OMe	0.38
m-NO_2	H	18.9
p-OMe	H	5.1

Such reactivity patterns may manifest themselves in the synthetic arena. For example, pyridine *N*-oxide has been reported to undergo a 'high yield' arylation reaction with di(*m*-nitrophenyl)iodonium tetrafluoroborate, but, with diphenyliodonium bromide, no arylation occurs[80].



(104)

These results are corroborated by data on intermolecular competition reactions. In one experiment, a 1:1 mole mixture of diphenyliodonium nitrate and 4,4′-dinitrodiphenyliodonium tosylate was allowed to react with a limited quantity (29–33 mol%) of sulphite ion in water at 100°C[76]. Infrared analysis of the steam-volatile iodoarenes thus produced revealed only *p*-nitroiodobenzene. Thus, the 4,4′-dinitroiodonium ion is at least 10 times more reactive than the unsubstituted one under these conditions. In a similar experiment, the di(*p*-anisyl)iodonium ion was determined to be 0.7 times as reactive as the diphenyliodonium ion toward sulphite ion[76].



R = NO_2, $k_R/k_H > 10$

R = OCH_3, $k_R/k_H = 0.7$

(105)

For reactions of diaryliodonium ions with nucleophiles other than those introduced as counterions, second-order kinetics might reasonably be anticipated for an S_NAr process. Unfortunately, kinetic studies of uncatalysed reactions of this type are uncommon. The reaction of the diphenyliodonium ion (i.e. Cl^-, NO_3^- salts) with phenoxide ion in 1:1 dioxane:H_2O to give diphenyl ether has been studied and exhibits second-order kinetics over temperatures ranging from 45 to 70°C (E_a = 25.9 kcal mol^{-1})[81]. In 5:1 dioxane:H_2O the kinetic order for the same reaction is 1.5, a result which manifests the increasing importance of ion pair formation in solvents of low polarity.

$$Ph_2I^+ + PhO^- \xrightarrow{\text{Dioxane : } H_2O} PhI + Ph_2O \qquad (106)$$

A kinetic analysis of the reaction between the diphenyliodonium ion and hydroxide ion in water was complicated by the operation of consecutive reactions, and the overall reaction order was not established definitively[82].

$$Ph_2I^+ + OH^- \xrightarrow{H_2O} PhI + PhOH \qquad (107)$$

$$PhOH + OH^- \rightleftharpoons PhO^- + H_2O \qquad (108)$$

$$Ph_2I^+ + PhO^- \longrightarrow PhI + Ph_2O \qquad (109)$$

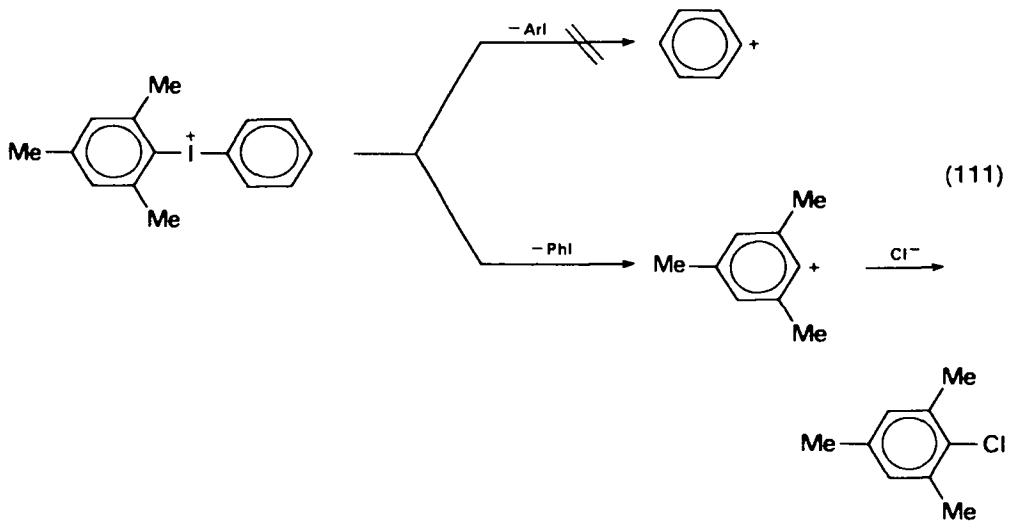
The polar reactions of diaryliodonium salts with nucleophiles are not without their mechanistic idiosyncrasies. One particularly interesting phenomenon relates to the regioselectivity of nucleophilic attack on unsymmetrical iodonium ions and has been dubbed the '*ortho* effect'. The general expectation that the more electron-deficient ring will be preferentially attacked by nucleophilic species is contradicted when alkyl groups occupy *ortho* positions in one of the arene rings. For example, although the A:B cleavage ratio for the pyrolysis of phenyl(*p*-tolyl)iodonium chloride at 235°C is 1.70, a similar pyrolysis of phenyl(*o*-tolyl)iodonium chloride affords an A:B ratio of 0.19. That is, *o*-tolyl nucleus is attacked by chloride ion about 5.25 times more efficiently than the phenyl nucleus is. For phenyl(mesityl)iodonium chloride, the A:B ratio is 0.053. Thus, despite the presence of three electron-donating alkyl substituents, the mesityl ring is 19 times more reactive than the phenyl ring toward chloride ion at 235°C. Similar observations have been recorded for various bromide and iodide salts[28,83].

$$(Ar—I^+—Ph)Cl^- \xrightarrow{235°C} ArCl + PhI + ArI + PhCl \qquad (110)[28]$$

Ar	A:B ratio
p-Tolyl	1.7
o-Tolyl	0.19
Mesityl	0.05

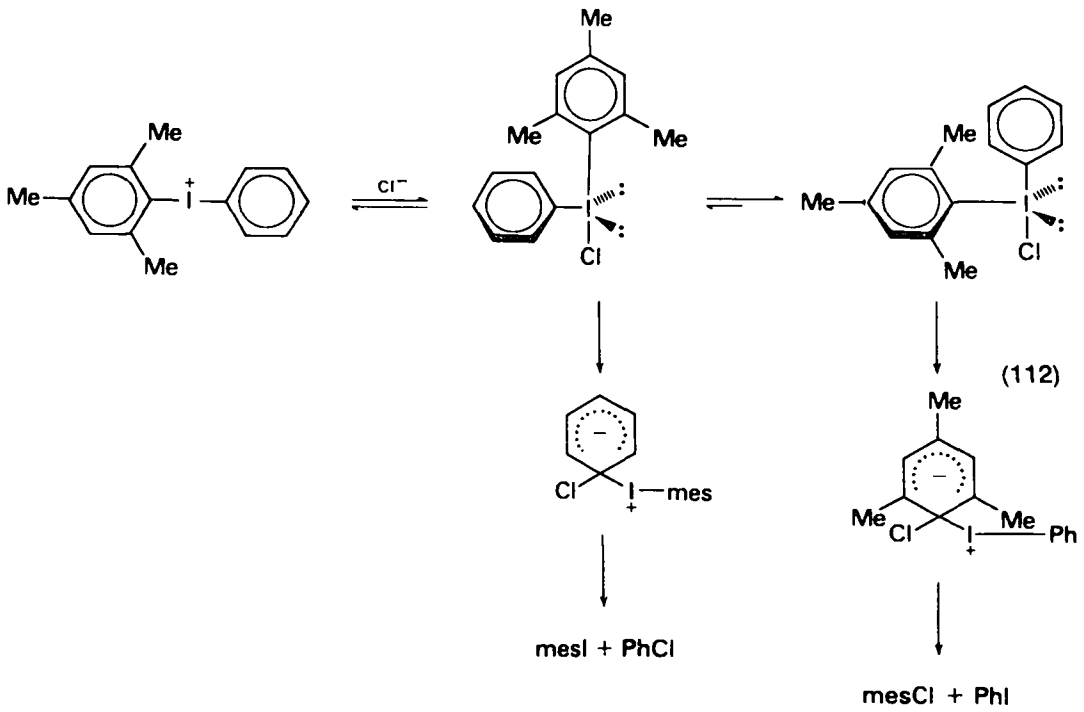
One explanation which has been advanced for the '*ortho* effect' is based on the assumption of a change in mechanism for nucleophilic cleavage from the S_NAr mode to the S_N1 mode[83]. The *o*-tolyl and mesityl cations, being more stable than the phenyl cation, would experience preferential S_N1 ionization and, therefore, preferential conversion into the corresponding chloroarenes (equation 111).

Another explanation, and one preferred by this author, posits the existence of tricovalent iodine(III) intermediates prior to S_NAr collapse[28]. Hypercovalent



(111)

iodine(III) compounds are T-shaped (as are diaryliodonium salts in the solid state)[84], and it has been suggested that the bulkier of the two arene rings in iodonium salts will prefer the equatorial bonding site over the more restricted axial sites when the halide ion becomes covalently bound to the iodine centre. Since the equatorial ring is in closer proximity to the 'nucleophile' in such covalent species than the axial ring is, it will be more favourably disposed for S_NAr collapse.



(112)

b. The radical mechanism for arylation. A variety of α-carbonyl anions undergo moderately efficient arylation reactions with diphenyliodonium salts (refer to the examples given in Table 2). Such carbanions have relatively low oxidation potentials (compared to $PhCO_2^-$, R_2S, RO^-, X^-, etc.), and these arylation reactions are thought, in some cases, to proceed by a radical mechanism involving three essential steps: (1) one-electron transfer (ET) from the nucleophile to the iodonium centre to give the caged radical pair $\overline{Ar_2I^{\bullet}B^{\bullet}}$; (2) loss of iodoarene from the diaryliodinanyl radical to give the new caged radical pair $\overline{A^{\bullet}B^{\bullet}}$; and (3) radical coupling within the cage to give the arylated nucleophile[76,86]. The nature and timing of the electron-transfer process is unclear. It might occur concomitantly with ionic collisions or it might be preceded by the formation of tight ion pairs and/or tricovalent iodine(III) intermediates. Indeed, tricovalent iodine(III) compounds are known to undergo homolytic decomposition reactions, and ion pair intermediates have been implicated in reactions of certain nucleophiles with diaryliodonium salts[81].

$$Ar_2I^+ + B:^- \xrightarrow{ET} \overline{Ar_2I^{\bullet}B^{\bullet}} \quad (113)$$

$$Ar_2I^+ + B:^- \rightleftharpoons Ar_2I^+B:^- \xrightarrow{ET} \overline{Ar_2I^{\bullet}B^{\bullet}} \quad (114)$$

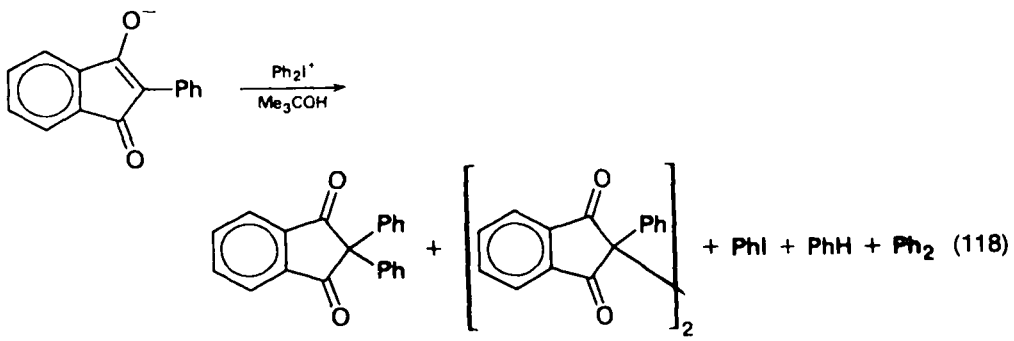
$$(Ar_2I^+ + B:^- \rightleftharpoons Ar_2I^+B:^-) \longrightarrow Ar_2I{-}B \xrightarrow{Homolysis} \overline{Ar_2I^{\bullet}B^{\bullet}} \quad (115)$$

$$\overline{Ar_2I^{\bullet}B^{\bullet}} \longrightarrow ArI + \overline{Ar^{\bullet}B^{\bullet}} \quad (116)$$

$$\overline{Ar^{\bullet}B^{\bullet}} \longrightarrow ArB \quad (117)$$

The evidence for such a mechanism is largely circumstantial and based primarily on the observation of by-products such as ArH, Ar_2 and B_2 which often accompany carbanion arylations. These can be conveniently explained if it is assumed that the diffusion of $Ar^{\bullet}$ and $B^{\bullet}$ radicals from the solvent cage into the bulk medium is competitive with geminate combination.

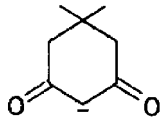
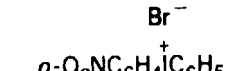
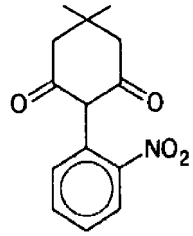
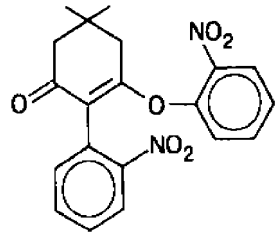
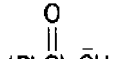
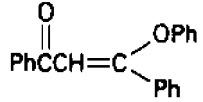
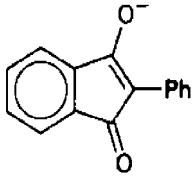
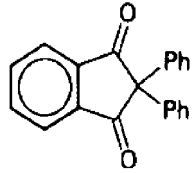
For example, the reaction of sodium 2-phenyl-1-,3-indanedionate with diphenyliodonium chloride in *t*-butyl alcohol affords benzene (20%) and detectable quantities of biphenyl and a dehydro dimer of 2-phenyl-1,3-indanedione in addition to 2,2-diphenyl-1,3-indanedione (86%) and iodobenzene (28%)[86].

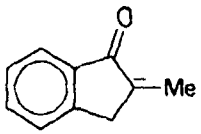
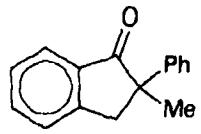
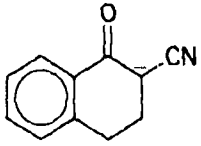
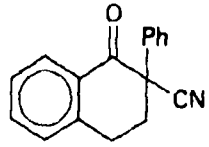
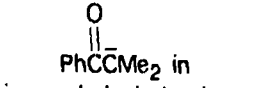
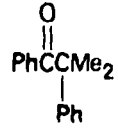
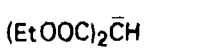
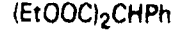


(118)

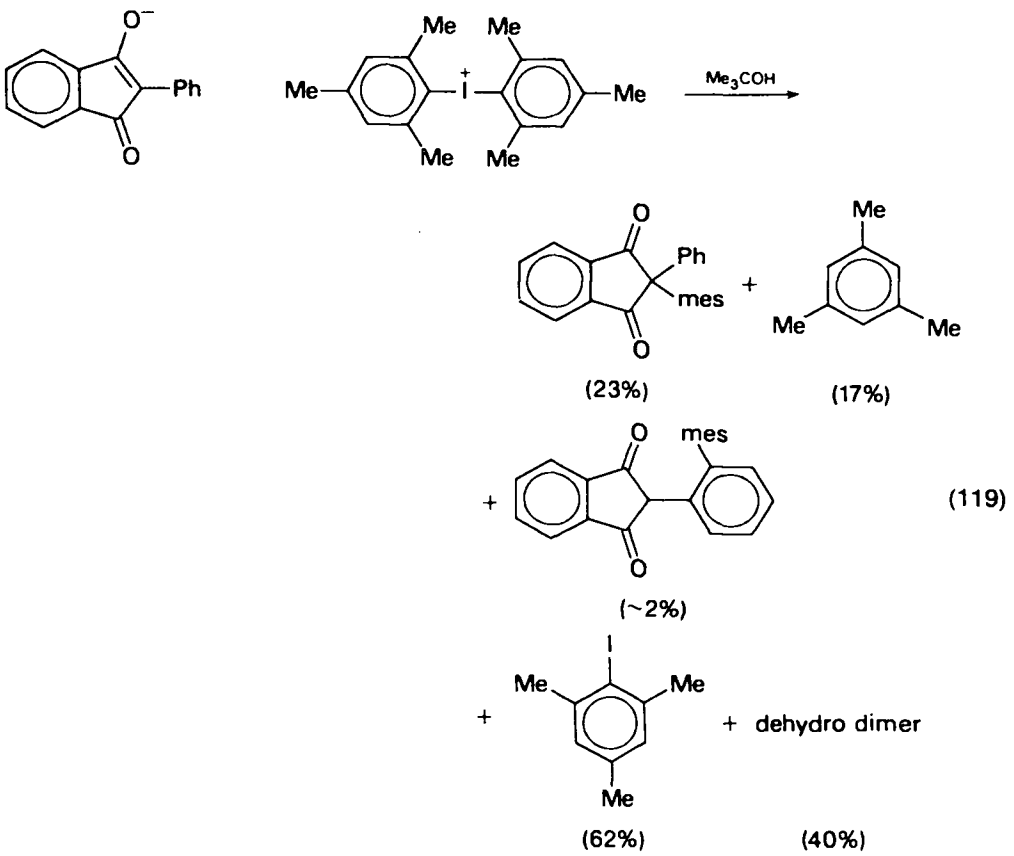
It is important to note, when interpreting many of these carbanion arylation studies, that the reported yields are based on isolation techniques and not on gas chromatography analyses of crude product mixtures. Thus, the yield of iodobenzene given above represents its isolation by fractional distillation and may be lower than the actual yield.

TABLE 2. Selected arylation reactions of α-carbonyl carbanions in *t*-butyl alcohol

Carbanion	$Ar_2I^+X^-$	Products (% yield)	Reference
		 (29%)  (8%)	85
		 (31%)  (9%)	85
		 (86%)	86

	$Ph_2I^+ Cl^-$	 (68%)	87
	$Ph_2I^+ Cl^-$	 (50%)	87
 in isoamyl alcohol solvent	$Ph_2I^+ Cl^-$	 (81%)	87
	$Ph_2I^+ Cl^-$	 (67%)	70

The replacement of the diphenyliodonium ion with its bulkier dimesityl analogue as the arylation reagent results in a lower yield (23%) of the arylation product and a higher yield of the dehydro dimer[88]. This is consistent with the proposed mechanism since an increase in steric bulk of the arylating species should permit the diffusion manifold to compete more effectively with the coupling of caged radicals.



The formation of diaryliodinanyl radicals by electron-transfer from oxidizable nucleophiles to diaryliodonium ions finds precedent in several electrochemical studies. Polarographic reductions of diaryliodonium ions at a dropping mercury electrode are attended by at least three waves, these originating from one-electron, two-electron and four-electron processes[89-92].

$$Ar-\overset{+}{I}-Ar + e^- \longrightarrow Ar-\dot{I}-Ar \quad (120)$$

$$Ar-\overset{+}{I}-Ar + H^+ + 2e^- \longrightarrow ArH + ArI \quad (121)$$

$$Ar-\overset{+}{I}-Ar + 2H^+ + 4e^- \longrightarrow 2\,ArH + I^- \quad (122)$$

The half-wave potentials for the reduction of the diphenyliodonium ion in 1:1 ethanol–H_2O at an apparent pH of 8.6 and with tetraethylammonium phosphate as the supporting electrolyte have been reported to be −0.193, −1.142 and −1.645 V respectively[91]. The half-wave potentials for the formation of diaryliodinanyl radicals

(equation 120) are relatively insensitive to the electronic nature of ring-bound substituents[91].

Under different conditions (i.e. related to the maximum suppressors employed), two polarographic waves for the one-electron reduction of diphenyliodonium ion are observed, one wave corresponding to the production of $Ph_2I^{\bullet}$ radicals adsorbed on the surface of the mercury (at −0.13 V) and another corresponding to the production of $Ph_2I^{\bullet}$ in solution (at −0.53 V)[92]. The adsorbed radicals eventuate in diphenylmercury and iodobenzene while those in 'solution' decompose to iodobenzene and phenyl radicals[92,93].

2. *Reductive decomposition reactions*

The formation of products such as ArH, Ar_2 and B_2 in conjunction with ArB in reactions of nucleophiles with diaryliodonium salts does not constitute unequivocal evidence for an arylation mechanism involving the cage combination of radical pairs. The reaction of sodium isopropoxide with diphenyliodonium tetrafluoroborate to give phenyl isopropyl ether, iodobenzene, benzene, biphenyl and acetone is an interesting case in point[94]. When this reaction is conducted in the presence of 1,1-diphenylethylene, a radical scavenger, the product composition is altered rather

$$Ph_2I^+ + Me_2CHO^- \xrightarrow[71°C]{\text{argon, } Me_2CHOH} PhOCHMe_2 + PhI + PhH + Ph_2 + Me_2C{=}O \quad (123)$$

No additive	51%	72%	73%	0.2%	68%
$Ph_2C{=}CH_2$ added	69%	100%	32%	0.0%	33%

drastically. For example, the yield of the arylation product increases from 51% to 69%, while the yields of benzene and acetone decrease from 73% to 32% and from 68% to 33% respectively.

These results have been interpreted in terms of two *competing* mechanisms, the phenyl isopropyl ether arising via the S_NAr manifold and benzene, biphenyl and acetone by the radical chain decomposition pathway shown in equations (124)–(129)[94]. The effect of 1,1-diphenylethylene is to suppress the radical process, thereby permitting the S_NAr trajectory to compete more effectively. With methoxide ion in methanol, the S_NAr process is dominant, even in the absence of 1,1-diphenylethylene, the yields of anisole and benzene being 79% and 7% respectively. This is not surprising in view of the fact that $Ph_2I{-}OCHMe_2$ should be a much more efficient chain-carrying species than $Ph_2I{-}OMe$[94].

Initiation

$$Ph_2I^+ + Me_2CHO^- \rightleftharpoons Ph_2I{-}OCHMe_2 \rightleftharpoons \overline{Ph_2I^{\bullet}\ {}^{\bullet}O{-}CHMe_2}$$

$$PhI + Ph^{\bullet} + Me_2CHO^{\bullet} \longleftarrow Ph_2I^{\bullet} + Me_2CHO^{\bullet} \quad (124)$$

Propagation

$$Ph_2I{-}OCHMe_2 + Ph^{\bullet} \longrightarrow PhH + Ph_2I{-}O\dot{C}Me_2 \quad (125)$$

$$Ph_2I{-}O\dot{C}Me_2 \longrightarrow Ph_2I^{\bullet} + Me_2C{=}O \quad (126)$$

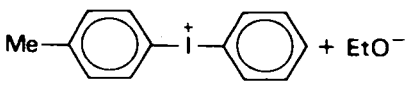
$$Ph_2I^{\bullet} \longrightarrow Ph^{\bullet} + PhI \quad (127)$$

Termination

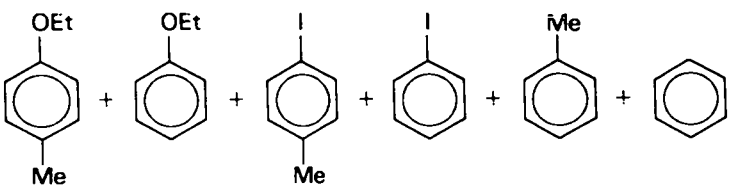
$$2\,Ph^{\bullet} \longrightarrow Ph_2 \quad (128)$$

$$Ph^{\bullet} + Me_2CHO^{\bullet} \longrightarrow PhOCHMe_2 \quad (129)$$

Supporting evidence for the concept of competing S_NAr and radical decomposition manifolds is provided by the reaction of ethoxide ion with the phenyl(*p*-tolyl)iodonium ion in ethanol[94]. The radical process is dominant in the absence of added 1,1-diphenylethylene, but the ratio of phenetole to *p*-methylphenetole is 4.2:1, consistent with previously observed S_NAr regioselectivities. Furthermore, the ratio of toluene to benzene is approximately 1:1, as would be expected for the homolytic decomposition of phenyl(*p*-tolyl)iodinanyl radicals. With added 1,1-diphenylethylene, the S_NAr process is, by far, the dominant mode of reaction.



(130)



No additive	1.7%	7.2%	45%	55%	37%	33%
$Ph_2C{=}CH_2$ added	25%	51%	60%	31%	4.3%	4.8%

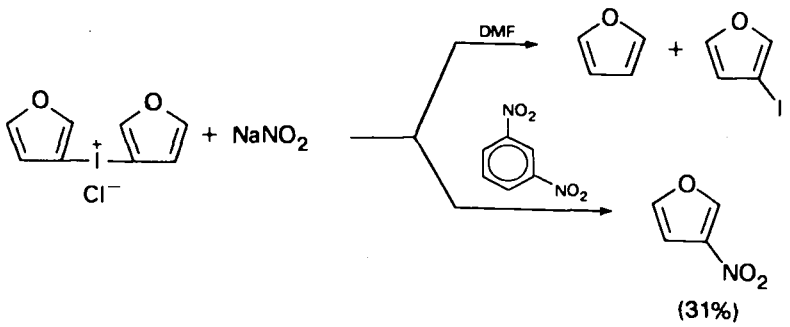
In a dioxane:water medium, the reactions of nitrite, azide and thiocyanate ions with diphenyliodonium tetrafluoroborate proceed primarily along the S_NAr pathway and are little affected by the presence of 1,1-diphenylethylene[77]. With cyanide ion, however, the major process is that of reductive cleavage, and a radical chain decomposition mechanism involving an initial electron transfer from the cyanide ion to the diphenyliodonium ion has been proposed[77]. Once again, added 1,1-diphenylethylene favours the competing S_NAr process. A similar reaction of cyanide ion with phenyl(*p*-

$$Ph_2I^+ + CN^- \xrightarrow[\text{Argon}]{\text{Dioxane: } H_2O} PhCN + PhI + PhH + PhOH + Ph_2 \quad (131)$$

No additive	8.8%	98%	76%	0.4%	6%
(5 equiv) $Ph_2C{=}CH_2$ added	42%	97%	5%	0.9%	26%

tolyl)iodonium ion eventuates in $C_6H_5CN/p\text{-}MeC_6H_4CN$ and C_6H_6/MeC_6H_5 ratios consistent with the model of two competing reaction mechanisms[77]. The tendency of cyanide ion, compared with the nitrite, azide and thiocyanate ions, to initiate radical decomposition has been related to the nucleophile constants, E_N, first proposed by Edwards[77,95].

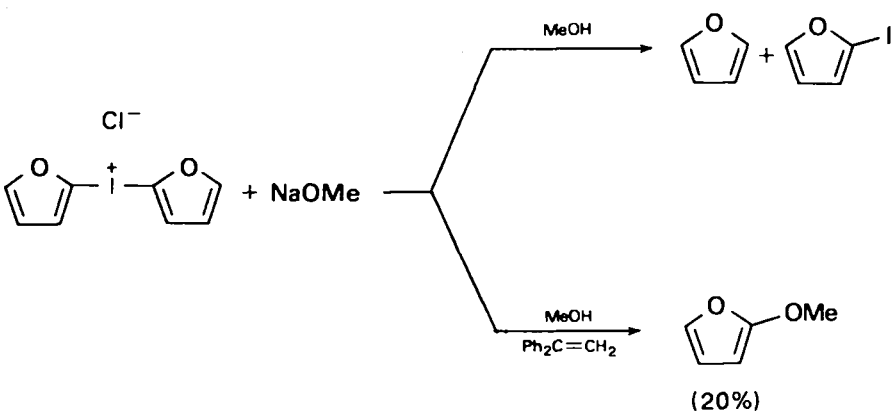
The involvement of competing polar arylation and radical chain decomposition pathways appears to play a role in the reactions of difuryliodonium salts with nucleophiles. While the reaction of di(3-furyl)iodonium chloride with sodium nitrite in dimethylformamide yields furan and 3-iodofuran but no 3-nitrofuran, the latter com-



(132)

pound is obtained in 31% when *m*-dinitrobenzene is the solvent[46]. It seems likely that *m*-dinitrobenzene functions analogously to 1,1-diphenylethylene in suppressing the chain decomposition manifold, thereby permitting the polar arylation process to emerge.

The reaction of di(2-furyl)iodonium chloride with sodium methoxide in methanol has been reported to give 'only furan and 2-iodofuran'. However, with added 1,1-diphenylethylene, 2-methoxyfuran is obtained in 20% yield[47].



(133)

Radical decompositions of diaryliodonium salts initiated by nucleophiles do not always proceed by a chain mechanism. An interesting example of an alternative process is provided by the reactions of several aliphatic amines with diaryliodonium salts in hydroxylic solvents (or acetone)[96-99]. These reactions typically afford poor yields of arylated amines and good yields of the corresponding alkylammonium salts in addition to by-products characteristic of the reductive homolysis of diaryliodonium ions. For example, diphenyliodonium tetrafluoroborate reacts with a 15 M excess of diethylamine in methanol to give diethylammonium tetrafluoroborate, iodobenzene, a very low yield of *N,N*-diethylaniline and detectable amounts of benzene and biphenyl[96]. Other examples are given in Table 3. These reactions are thought to involve the initial

$$Ph_2I^+\ BF_4^- + Et_2NH \xrightarrow[65°C,\ 6h]{MeOH} (Et_2\overset{+}{N}H_2)BF_4^- + PhNEt_2 + PhI + PhH + PhPh$$

(77.5%) (1%) (40%) (detected) (134)

formation and subsequent homolytic decomposition of iodonium ion–amine complexes (the authors did not use the term 'covalent adducts') according to the

TABLE 3. Selected reactions of aliphatic amines with diaryliodonium salts in hydroxylic solvents

Reactants	Molar ratio	Solvent and conditions	Products	Yield, %	Ref.
$(C_6H_5)_2I^+ BF_4^-$	1	MeOH,	$C_6H_5NEt_2$	1	96
Et_2NH	15	65°C, 6 h	$(Et_2N^+H_2)BF_4^-$	77.5	
			C_6H_5I	40	
			C_6H_6, $(C_6H_5)_2$	Detected	
$(C_6H_5)_2I^+ BF_4^-$	1	H_2O,	$C_6H_5NMe_2$	20	96
Me_2NH	5	100°C, 6 h	$(Me_2N^+H_2)BF_4^-$	99	
			C_6H_5I	43	
$(m\text{-}O_2NC_6H_4)_2I^+ BF_4^-$	1	MeOH,	$m\text{-}O_2NC_6H_4NHC_6H_{13}$	2	97
$n\text{-}C_6H_{13}NH_2$	5	Reflux, 5 h	$(C_6H_{13}N^+H_3)BF_4^-$	42.6	
			$m\text{-}O_2NC_6H_4I$	47	
			$C_6H_5NO_2$	Detected	
$(o\text{-}O_2NC_6H_4I^+C_6H_5)Br^-$	1	H_2O,	$o\text{-}O_2NC_6H_4NMe_2$	18	99
Me_2NH	5	100°C, 3 h	$C_6H_5NMe_2$	Trace	
			$(Me_2N^+H_2)Br^-$	100	
			C_6H_5I, $C_6H_5NO_2$	Detected	
$(p\text{-}MeOC_6H_4I^+C_6H_4NO_2\text{-}m)BF_4^-$	1	MeOH,	$m\text{-}O_2NC_6H_4NMe_2$	5	99
Me_2NH	9	Reflux, 4.5 h	$p\text{-}MeOC_6H_4NMe_2$	Trace	
			$(Me_2N^+H_2)BF_4^-$	100	
			$p\text{-}MeOC_6H_4I$	66	
			C_6H_5OMe, $m\text{-}O_2NC_6H_4OMe$ $C_6H_5NO_2$, $m\text{-}O_2NC_6H_4I$	Detected	

$$Ar_2I^+ X^- + \ddot{N}R^1R^2R^3 \rightleftharpoons (Ar_2I{:}NR^1R^2R^3)^+ X^- \quad (135)$$

$$(Ar_2I{:}NR^1R^2R^3)^+X^- \longrightarrow Ar_2I^{\cdot} + (^+\dot{N}R^1R^2R^3) \quad (136)$$

$$Ar_2I^{\cdot} \longrightarrow ArI + (Ar^{\cdot}) \longrightarrow Ar_2 + ArH \quad (137)$$

$$(R^1R^2R^3\dot{N}^+)X^- \xrightarrow{\text{Solvent}} (R^1R^2R^3N^+H)X^- \quad (138)$$

mechanism in equations (135)–(138). It has been suggested that the arylation products might arise by a direct reaction between the amines and the intermediate diaryliodinanyl radicals.

$$Ar_2I^{\cdot} + R^1R^2NH \longrightarrow ArI + ArNR^1R^2 + <H^{\cdot}> \quad (139)$$

Another possibility, of course, is that these reactions proceed via caged radical pairs (i.e. $[Ar_2\dot{I}\ddot{N}R^1R^2R^3]$ and $[Ar\ddot{N}R^1R^2R^3]$) and that the arylation of amines is a cage combination process. If this is the case, radical diffusion into the bulk medium would appear to be much more efficient than it is in those reactions involving the arylation of carbanions. However, the regioselectivities observed with unsymmetrical substrates (see, for example, Table 3) are not inconsistent with amine arylations via the S_NAr manifold.

It is also to be noted that in an earlier investigation of the reactions of dimethylamine with phenyl(*o*-nitrophenyl)iodonium bromide and phenyl(*m*-nitrophenyl)iodonium bromide under similar conditions, much higher yields of arylation products were reported (see equation 98 and reference 69).

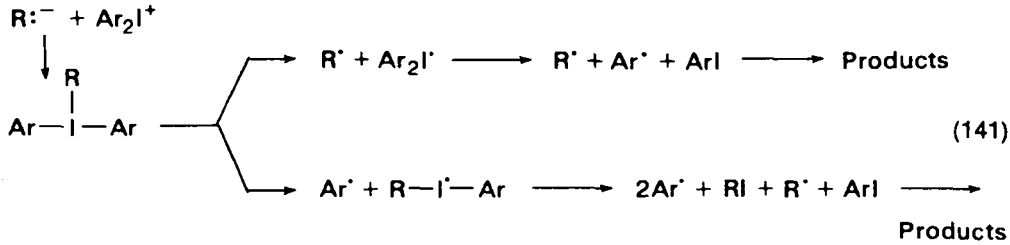
Kinetic studies of the reactions of ethanolamine with diphenyliodonium chloride in dimethylsulphoxide and of dibutylamine with diphenyliodonium chloride in dimethylsulphoxide/ethanol to give mainly benzene and iodobenzene have been reported[100,101]. In each case, a radical *chain* decomposition mechanism is thought to obtain, the *initiation* stage involving the events shown in equations (135) and (136).

The reactions of alkyl Grignard reagents with diaryliodonium salts likewise lead to an array of products best understood in terms of a free radical mechanism, but not one involving a radical chain sequence. For example, the reaction of ethylmagnesium bromide with diphenyliodonium chloride in ether at −40°C affords iodobenzene, benzene, biphenyl, ethylbenzene and iodoethane[41].

$$\underset{200\ \text{mmol}}{Ph_2I^+\ Cl^-} + \underset{200\ \text{mmol}}{EtMgBr} \xrightarrow[-40°C]{Et_2O} PhI + PhH + Ph_2 + \underset{20\ \text{mmol}}{PhEt} + \underset{25\ \text{mmol}}{EtI} \quad (140)$$

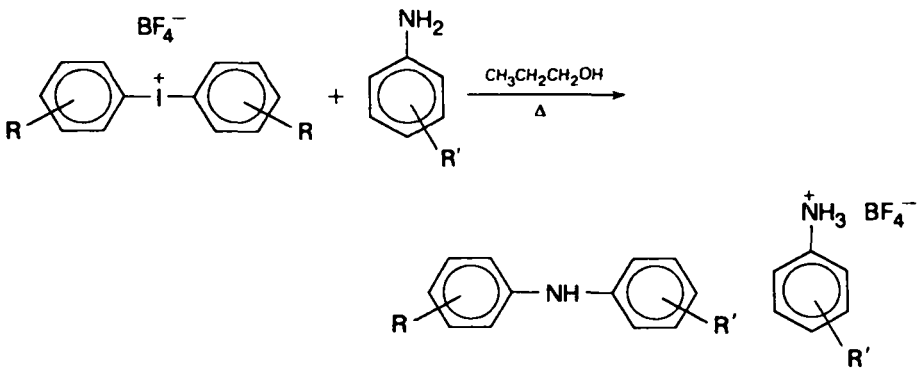
It has been proposed that these reactions involve the initial formation and subsequent homolytic decomposition of tricovalent iodine(III) intermediates (equation 141). Once again, the yield of arylated nucleophile (i.e. ArR) should depend on combination versus diffusion from caged radical pairs such as $\overbrace{Ar^{\cdot}\ R^{\cdot}}$.

Whereas aliphatic amines react with diaryliodonium salts primarily by a reductive decomposition pathway, and arylation is a relatively unimportant process, arylation is a significant process when aniline derivatives are employed as reactants[71,102,103]. For example, when diphenyliodonium tetrafluoroborate is treated in boiling propanol, with a 2:1 molar excess of aniline, diphenylamine and anilinium tetrafluoroborate are obtained in 38% and 44% yields respectively[71]. The yield of diphenylamine, based on



(141)

unrecovered iodonium salt, is 76%. Under similar conditions, *p*-methoxyaniline gives a 49% yield of phenyl(*p*-anisyl)amine and a 100% yield of *p*-methoxyanilinium tetrafluoroborate. On the other hand, *p*-nitroaniline affords significantly lower yields of both types of products. The effects of *p*-methoxy and *m*-nitro substituents in the iodonium nucleus on the product yields have also been determined. Some of these results are summarized in equation (142)[71].



(142)

R	R′	Yield diarylamine*, %	Yield anilinium salt, %
H	H	76	44
H	4-MeO	49	62
H	4-NO_2	17	6
4-MeO	H	30	14
3-NO_2	H	40	94

*Based on unrecovered $Ar_2I^+ BF_4^-$.

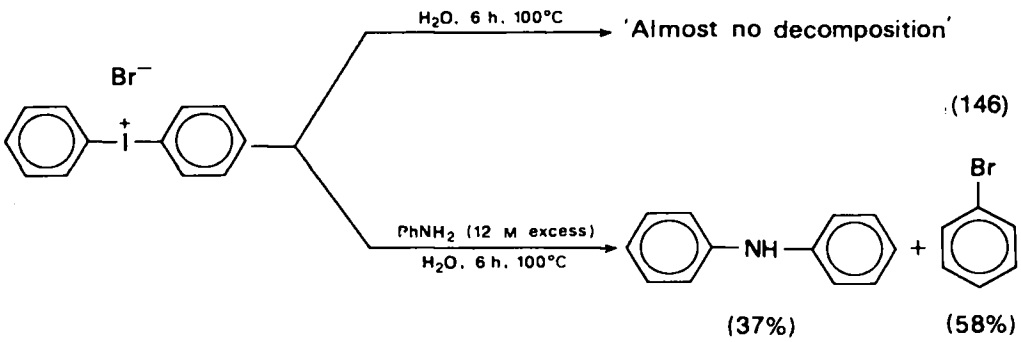
The reactions have been interpreted in terms of an intermediate 'molecular complex' between the starting amine and the iodonium ion[71]. The nature of the iodine–nitrogen bond in such complexes was not discussed, and the term 'covalent' was not employed. Homolytic decomposition of the intermediate, in an analogous way to that proposed for aliphatic amines, would account for the production of anilinium salts and free radical by-products. A novel arylation mechanism has been proposed involving nucleophilic attack of an aniline molecule on the *molecular complex* rather than on the free diaryliodonium ion. Such a process would also afford anilinium salts.

$$Ar_2I^+ BF_4^- + Ar'NH_2 \rightleftharpoons (Ar_2I{:}\overset{H}{\underset{H}{N}}Ar')^+ BF_4^- \qquad (143)$$

$$(Ar_2I{:}\overset{H}{\underset{H}{N}}Ar')^+ BF_4^- + Ar'NH_2 \longrightarrow Ar{-}\overset{Ar'}{\underset{H}{\overset{|}{\overset{+}{N}}}}{-}H\ BF_4^- + Ar'NH_2 + ArI \quad (144)$$

$$(Ar\overset{+}{N}H_2Ar')BF_4^- + Ar'NH_2 \longrightarrow ArNHAr' + (Ar'NH_3)^+ BF_4^- \quad (145)$$

A striking demonstration of the viability of this mechanism for arylation is provided by the thermal decomposition of 0.3 M diphenyliodonium bromide in water in the presence of a 12 M excess of aniline[103]. After 6 h at 100°C, all of the original iodonium salt is consumed. However, in addition to diphenylamine (37% yield), bromobenzene is formed in 58% yield. In the absence of aniline, the iodonium salt undergoes 'practically no decomposition' under the same conditions. This and similar experiments point clearly to the intimate involvement of aniline in the arylation of bromide ion and that, whatever the exact nature of the intermediate 'complex', the arene rings of the iodonium ion experience enhanced electrophilic reactivity.



3. *Copper catalysis*

The presence of Cu(I) and Cu(II) salts has been shown, in some instances, to exert a catalytic influence on reactions of diaryliodonium ions with nucleophiles. One reaction that has been studied in particular detail is the thermal collapse of diphenyliodonium chloride to chlorobenzene and iodobenzene in the solvents dimethylformamide, diethylene glycol and water[104]. In the former two solvents, the decomposition reaction

$$Ph_2I^+ Cl^- \xrightarrow[CuCl\ or\ CuCl_2]{Solvent} PhCl + PhI \quad (147)$$

exhibits first-order kinetics and is accelerated when either cuprous or cupric chlorides are added to the reaction medium. When water is the solvent, second-order kinetics obtain, and the reaction is catalysed with added cupric chloride (cuprous chloride was not studied). In the diethylene glycol system, the effect of added cuprous chloride is rather profound, as manifested in a lowering of the activation energy, E_a, from 31 kcal mol^{-1} for the uncatalysed reaction to 19 kcal mol^{-1} for the catalysed process. The mechanism of action of cuprous chloride was originally suggested to involve the initial genesis of the dichlorocuprate ion and a subsequent electron-transfer process within a diaryliodonium dichlorocuprate ion pair[76,90,104].

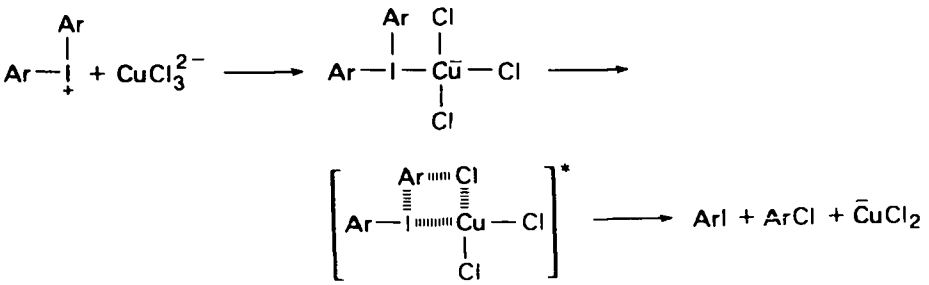
$$CuCl + Cl^- \longrightarrow \bar{C}uCl_2 \quad (148)$$

$$Ph_2I^+ + \bar{C}uCl_2 \rightleftharpoons Ph_2I^+\bar{C}uCl_2 \quad (149)$$

$$Ph_2I^+\ \bar{C}uCl_2 \xrightarrow{ET} \overline{Ph_2I^{\cdot}\ CuCl_2} \tag{150}$$

$$\overline{Ph_2I^{\cdot}\ CuCl_2} \longrightarrow PhCl + PhI + CuCl \tag{151}$$

Since the collapse of $\overline{Ph_2I^{\cdot}\ CuCl_2}$ (equation 151) might be expected to proceed in stepwise fashion via the intermediate formation of $\overline{Ph^{\cdot}\ CuCl_2}$ and PhI, it should be attended by small amounts of benzene and biphenyl. However, in a later investigation of the cuprous chloride-catalysed decomposition of diphenyliodonium chloride in each of the solvents water, acetone and methanol, such by-products were not detected by gas chromatographic analysis[105]. An alternative mechanism was formulated involving the concerted collapse of a diphenyliodonium dichlorocuprate or trichlorocuprate 'complex'.



(152)

The hydrolysis of diphenyliodonium benzenesulphonate, $Ph_2I^+PhSO_3^-$, in water has been shown to be catalysed by the addition of cupric sulphate[106]. Three possible mechanisms for the action of Cu(II) were considered, one of which posits the initial formation of a Cu(I) species. It was concluded, however, that while Cu(I) is probably the more active catalyst, the experimental data are consistent with catalysis by both Cu(I) and Cu(II) species[106].

In a related but independent study of the hydrolysis of phenyl(*p*-anisyl)iodonium salts, $(p\text{-}MeOC_6H_4IC_6H_5)^+\ X^-$, in water and in mixed aqueous solvents, slightly different conclusions were drawn[67]. It was suggested that hydrolysis occurs subsequent to the reduction of Cu(II) to Cu(I), and that Cu(I) is the effective catalytic agent (the reducing agent was not identified). This model was supported by an experiment in

$$Cu(II) \xrightarrow{e^-} Cu(I) \tag{153}$$

$$ArI^+Ar + Cu(I) \longrightarrow \overline{Ar_2I^{\cdot}\ Cu(II)} \tag{154}$$

$$\overline{Ar_2I^{\cdot}\ Cu(II)} + 2\ H_2O \longrightarrow ArI + ArOH + Cu(I) + H_3O^+ \tag{155}$$

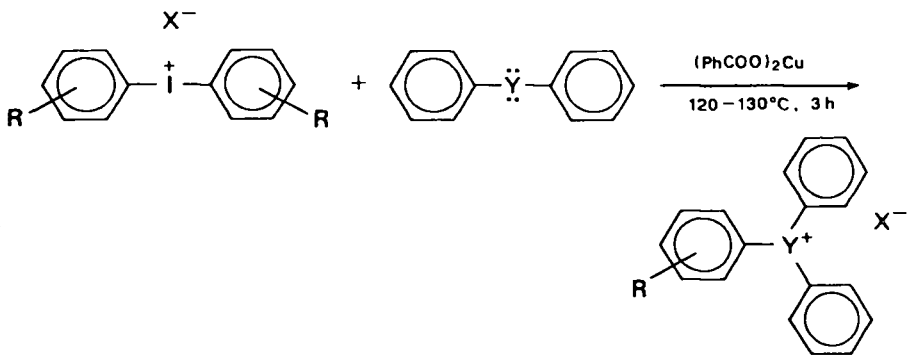
which phenyl(*p*-anisyl)iodonium tosylate was solvolysed in 50% ethanol in the presence of added *cupric* chloride and cuprion, a chelating agent specific for Cu(I)[67]. Compared to a control reaction in which cupric chloride was added and cuprion was omitted and which underwent smooth first-order solvolysis, the solvolysis in the presence of cuprion was almost completely inhibited.

That copper species may indeed promote the reduction of diaryliodonium ions to diaryliodinanyl radicals is indicated in a study of the regioselectivity of ring cleavage in the reaction of sulphite ion with unsymmetrical substrates[76]. It has already been noted than when sulphite ion reacts with the phenyl(*p*-nitrophenyl)iodonium ion in water at 100°C, there is a greater than 10-fold preference for nucleophilic attack at the *p*-nitrophenyl nucleus (i.e. A:B < 0.1). However, in the presence of 10 mol% $CuSO_4$,

that preference is reduced to 1.9 (A:B = 0.52), consistent with the competitive formation and homolytic decomposition of phenyl(*p*-nitrophenyl)iodinanyl radicals. With the phenyl(*p*-anisyl)iodonium ion, the preference for sulphite attack at the phenyl nucleus changes from >10 in the absence of $CuSO_4$ to about 1.1 in the presence of 10 mol% $CuSO_4$.

It has recently been observed that catalytic amounts of a Cu(II) compound reduce the solid state decomposition temperatures of diaryliodonium tetrafluoroborates, hexafluoroarsenates and hexafluorophosphates from 220–250°C to as low as 120–130°C[68]. This phenomenon has been exploited in the synthesis of a variety of triarylsulphonium salts and several triarylselenonium salts[68]. The synthesis of triphenylsulphonium tetrafluoroborate from diphenyliodonium tetrafluoroborate and diphenylsulphide, in the absence of a catalyst, requires rather severe reaction conditions (i.e. 220–230°C; 185°C, 35 h) to give yields of 60–64%[3,68,107,108]. Attempts to extend this reaction to the preparation of other triarylsulphonium salts eventuated in low yields of the target compounds[68].

However, when diaryliodonium hexafluoroarsenates and hexafluorophosphates (0.025 mol) are mixed *neat* with diaryl sulphides (0.025 mol) or diaryl selenides in the presence of cupric benzoate (0.0006 mol) and heated for 3 h at 120–130°C, excellent yields of the corresponding sulphonium and selenonium salts are obtained (examples are shown in equation 156[68]).



(156)

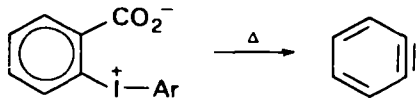
R	X^-	Y	Yield, %
H	AsF_6^-	S	97
4-Bu^t	PF_6^-	S	92
4-Pr^i	AsF_6^-	S	88
4-Et	AsF_6^-	S	100
4-Cl	AsF_6^-	S	94
4-Me	PF_6^-	S	87
3,4-Me_2	AsF_6^-	S	89
H	AsF_6^-	Se	90
4-Bu^t	AsF_6^-	Se	87
4-Me	AsF_6^-	Se	62
3,4-Me_2	AsF_6^-	Se	49

This method has also been utilized in the preparation of cyclic sulphonium salts[68].

The use of iodonium salts with non-nucleophilic anions is vital to the success of this methodology. Thus, when di(*p*-tolyl)iodonium chloride and diphenyl sulphide are heated in the presence of copper benzoate, only 4-chlorotoluene and 4-iodobenzene are obtained[68].

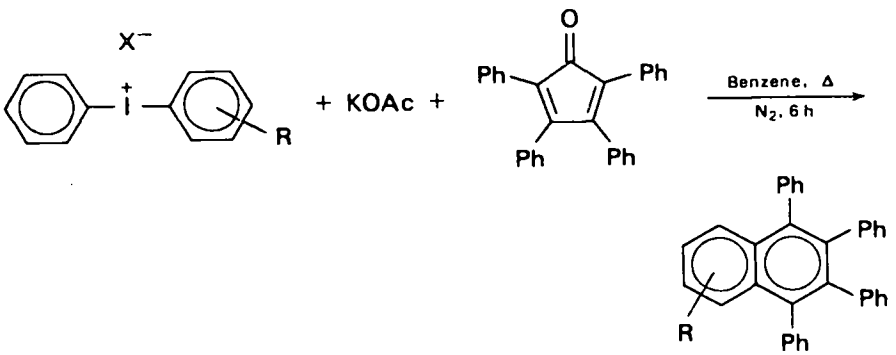
4. Benzynes from diaryliodonium salts and nucleophiles

The formation of benzyne intermediates by the thermal decomposition of *o*-aryliodoniobenzoates is now an established synthetic method[109–111].



(157)

In one fairly recent study, it has been shown that arynes can be generated in low yields by treatment of diaryliodonium halides with potassium acetate in hot benzene[112]. The evidence for this is based on trapping experiments with tetraphenylcyclopentadienone and the isolation of tetraphenylnaphthalenes. For example, treatment of diphenyliodonium bromide (1 mmol) with potassium acetate (1.2 mmol) in the presence of 1 mmol of the dienone in boiling benzene gives a 3% yield of 1,2,3,4-tetraphenylnaphthalene. With phenyl(*m*-nitrophenyl)iodonium chloride as the substrate, the product is primarily 5-nitro-1,2,3,4-tetraphenylnaphthalene, obtained in 12% yield and containing a trace amount of 1,2,3,4-tetraphenylnaphthalene. Similar results were observed with several other iodonium salts.

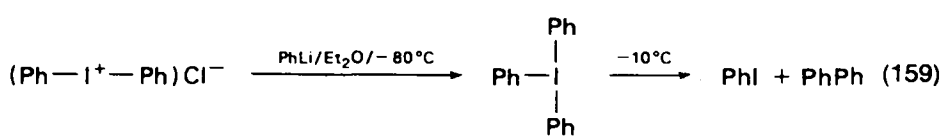


(158)

X	R	Yield, %
Br^-	H	3
Cl^-	*m*-NO_2	12

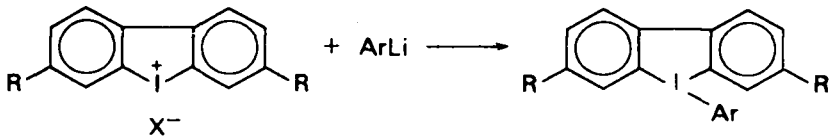
5. Tricovalent adducts from diaryliodonium salts and nucleophiles

The suggestion that tricovalent iodine(III) intermediates might be involved in reductive decomposition reactions of diaryliodonium ions with nucleophilic species finds corroboration in the fact that a few such adducts have been isolated (i.e. many tricovalent iodine(III) compounds are known, but they do not originate from iodonium salts). For example, diphenyliodonium chloride, when treated with phenyllithium at −80°C, affords triphenyliodine, an unstable yellow solid which undergoes homolytic decomposition at −10°C to iodobenzene and biphenyl[113,114]. Similar



(159)

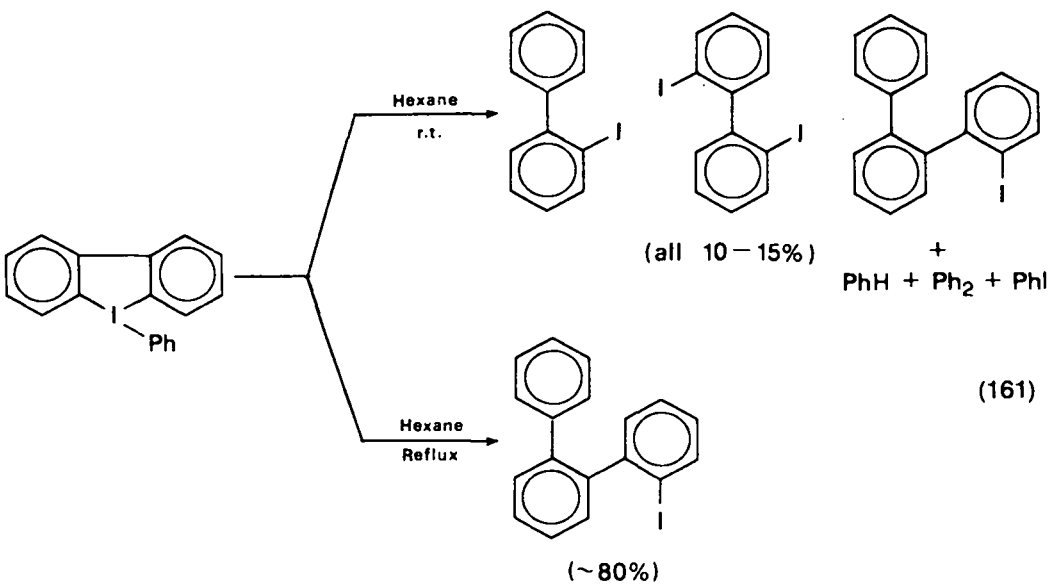
reactions of various aryllithium compounds with dibenziodolium salts yield the corresponding 5-aryl-5*H*-dibenziodoles as yellow solids, stable for several hours to several days at room temperature when maintained under an inert atmosphere[115–117].



(160)

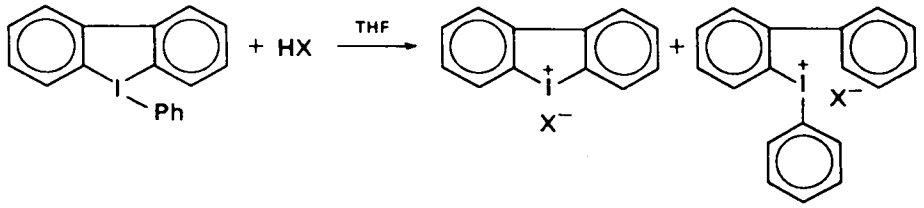
R	Ar
H	C_6H_5
H	*p*-MeC_6H_4
H	*p*-ClC_6H_4
H	α-Naphthyl
Me	C_6H_5
Me	*p*-$CF_3C_6H_4$

A suspension of 5-phenyl-5*H*-dibenziodole in hexane, when held at room temperature, undergoes random homolytic decomposition into benzene, biphenyl, iodobenzene, 2-iodobiphenyl, 2,2′-diiodobiphenyl and 2-iodo-*o*-terphenyl all in yields of 10–15%[117]. At reflux, the decomposition is more selective, the major product being 2-iodo-*o*-terphenyl (~80% yield).



(161)

The carbon–iodine bonds of 5-aryl-5*H*-dibenziodoles are also susceptible to heterolytic cleavage by electrophilic reagents, the products of such reactions being cyclic and acyclic diaryliodonium salts[117]. For example, the reaction of 5-phenyl-5*H*-dibenziodole with benzoic acid in tetrahydrofuran eventuates in a 98% yield of iodonium benzoates, the cyclic salt predominating over the acyclic one by a factor of *ca.* 4:1. With hydrogen chloride in THF, the cyclic:acyclic iodonium chloride ratio is 1:1 while nitric acid in THF affords a cyclic:acyclic iodonium nitrate ratio of



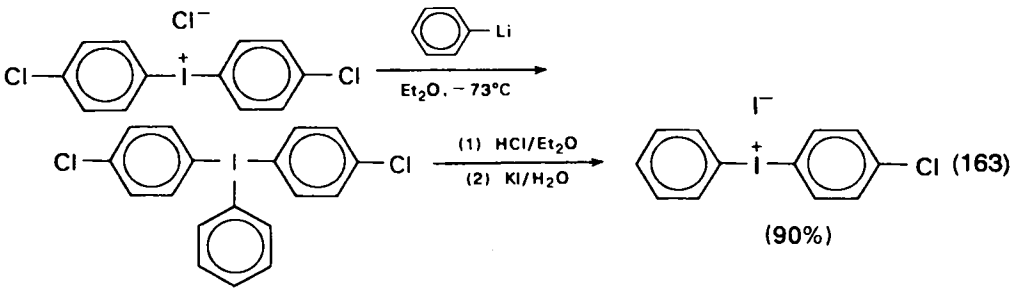
(162)

HX	Overall yield, %	Ratio cyclic salt:acyclic salt
PhCOOH	98	78.5:21.5
HCl	96	50:50
HNO_3	101	37:63

1:1.7. Other electrophilic reagents which have been studied include $MeCO_2H$, HF, $MeSO_3H$, HBF_4, I_2, Ph_3B and $AlCl_3$[117].

When *p*-chlorophenyl-5*H*-dibenziodole is the substrate, the electrophilic cleavage reaction induced by hydrogen chloride in tetrahydrofuran is *regiospecific* in favour of cyclic iodonium salt formation.

This phenomenon has been utilized in the synthesis of one iodonium salt from another one by a process involving aryl ligand exchange[118]. For example, when a suspension of 4,4′-dichlorodiphenyliodonium chloride in ether is treated with phenyllithium at −73°C and the resulting yellow mixture is treated with ethereal hydrogen chloride, phenyl(*p*-chlorophenyl)iodonium iodide is obtained in 90% yield (after anion metathesis). Evidence has been presented that such exchange reactions may proceed through an intermediate tetraaryliodate species formed by nucleophilic



(163)

attack of the aryllithium compound at the iodine atom of the first formed tricovalent adduct[118]. For example, when reaction mixtures containing 4,4′-dichlorodiphenyl-

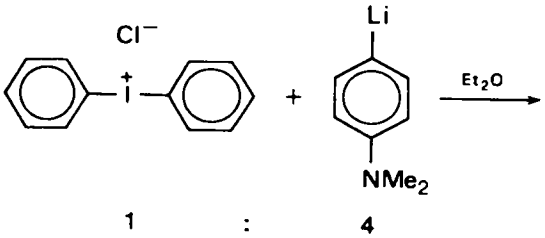
$$Ar_2I^+ X^- + 2\ Ar'Li \longrightarrow Ar_2IAr' + Ar'Li + LiX \quad (164)$$

$$Ar_2IAr' + Ar'Li \rightleftharpoons (Ar_2I^- Ar_2')Li^+ \quad (165)$$

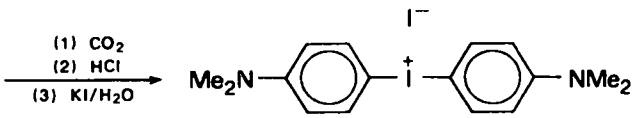
$$(Ar_2I^- Ar_2')Li^+ \rightleftharpoons ArIAr_2' + A_2' + ArLi \quad (166)$$

iodonium chloride and excess phenyllithium are quenched after 30 min with CO_2 followed by HCl, *p*-chlorobenzoic acid is obtained in addition to benzoic acid.

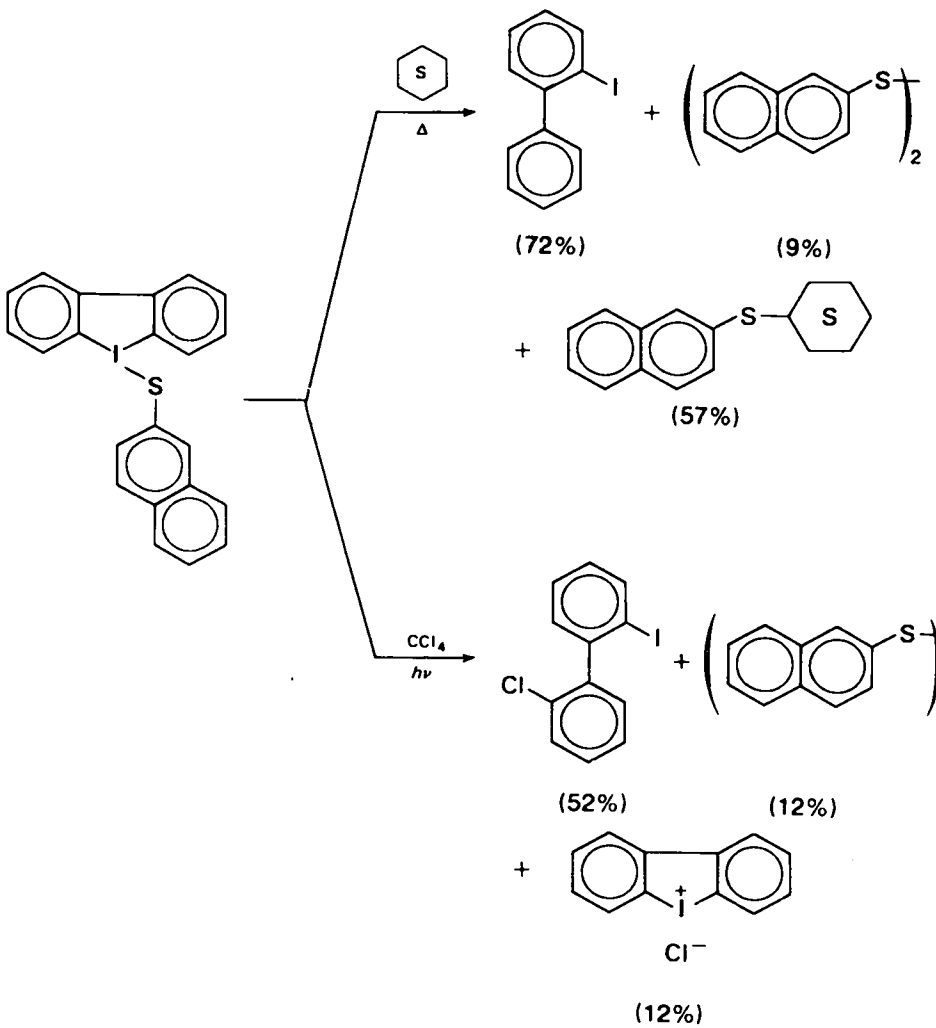
A useful synthetic application of this reaction is the synthesis in 73% yield of 4,4′-bis(dimethylamino)diphenyliodonium iodide from diphenyliodonium chloride[118] (equation 167). The reactions of dibenziodolium chloride and diphenyliodonium chloride with sodium β-naphthalenethiolate likewise afford stable, yellow covalent adducts, both of which undergo homolytic decomposition reactions (equation 168).


Cl⁻
Li
Et₂O
NMe₂

1 : 4


(1) CO₂
(2) HCl
(3) KI/H₂O
I⁻
Me₂N
NMe₂

(73%) (167)


S
Δ
I
S
(72%)
(9%)
S
S
(57%)
CCl₄
hν
Cl
I
S
(52%)
(12%)
Cl⁻
(12%)

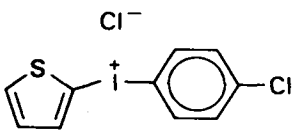
(168)

C. Practical Applications of Diaryliodonium Salts

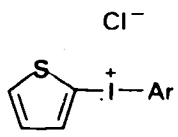
Considerable interest has been focused on practical applications of diaryliodonium salts and their heteroaromatic analogues, centred primarily about their antimicrobial and photochemical properties.

The strong microbicidal activity of several classes of such salts has been the subject of various patented claims relating to their toxicity towards bacterial organisms (i.e. both Gram negative and Gram positive types), fungi, yeasts, moulds, mildews and slimes and to their use against microorganisms responsible for rot and decay and against those that attack seeds, roots and above-ground portions of terrestrial plants. Such patents proceed, of course, from the general to the specific and contain tabulations of microorganisms subject to control by the particular iodonium compounds under consideration. For example, in US Patent 3,734,928, the 4,4-bis(aryliodonium) salts of diphenyl ether, $(ArI^+C_6H_4OC_6H_4I^+Ar)2A^-$, are reported to be 'highly toxic' to *Staphylococcus aureus*, *Salmonella typhosa*, *Bacillus subtilis*, *Escherichia coli*, *Pseudomonas aeruginosa*, *Mycobacterium phlei*, *Candida pelliculosa*, *Candida albicans*, *Aspergillus terreus*, *Aerobacter aerogenes*, *Trichophyton mentagrophytes*, *Bremia lactucae*, *Cephaloascus fragans*, *Ceratocystis ips*, *Trichoderm* sp. Madison P-24 and *Pullularia pullulans* and to small RNA viruses as well[120].

US Patent 3,944,498, covering the microbicidal action of aryl(2-thienyl)iodonium salts, gives a tabulation of minimum 'kill' levels of *p*-chlorophenyl(2-thienyl)iodonium chloride (**7**), dubbed 'Tiodonium Chloride', for 23 bacterial organisms and eight fungi and yeasts[121]. The structure of the iodonium salt is intimately related to its antimicrobial activity. In one experiment, a culture medium of *Salmonella typhosa* was subjected to the action of several arylthienyl- and diaryliodonium salts (**7**, **8a–8d** and **9a–9e**). Whereas the thienyl salts caused 100% kills of *S. typhosa* at minimum concen-



(7)



(8a) Ar = 2-thienyl

(8b) Ar = C_6H_5

(8c) Ar = 4-BrC_6H_4

(8d) Ar = 3,4-$Cl_2C_6H_3$

$(Ar^1—\overset{+}{I}—Ar^2)X^-$

(9a) $Ar^1 = C_6H_5$, $Ar^2 = C_6H_5$, X = Cl

(9b) $Ar^1 = C_6H_5$, Ar^2 = 4-ClC_6H_4, X = Cl

(9c) Ar^1 = 4-BrC_6H_4, Ar^2 = 4-BrC_6H_4, X = Cl

(9d) Ar^1 = 4-BrC_6H_4, Ar^2 = 4-BrC_6H_4, X = Br

(9e) Ar^1 = 2,4-$Cl_2C_6H_3$, Ar^2 = 2,4-$Cl_2C_6H_3$, X = Cl

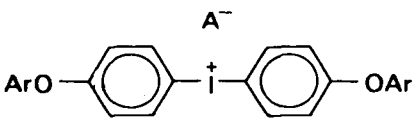
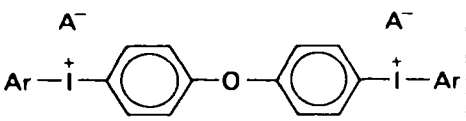
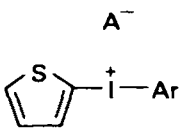
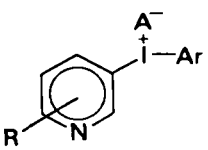
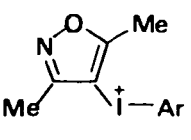
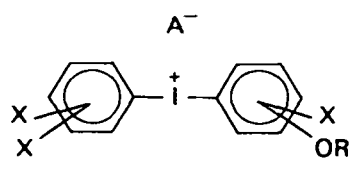
tration levels ranging from 1 to 5 p.p.m., the diaryliodonium salts were completely inactivate (i.e. 0% kill) at 10 p.p.m. (500 p.p.m. for diphenyliodonium chloride)[121].

It is important, of course, for an effective microbicide to be non-toxic towards mammals. One measure of such toxicity is provided by the LD_{50} parameter, the concentration level of the substance being tested which is required to kill 50% of the test animals employed after oral administration of the drug. The LD_{50} levels on mice for diphenyliodonium chloride and Tiodonium Chloride are 56.2 mg and >4000 mg respectively per kilogram body weight.

Table 4 lists various structural classes of iodonium salts and general claims relating to their microbicidal activity. Details can be found in the appropriate patents.

Because of their antimicrobial properties, iodonium salts find application as preservatives for various materials, some of these, included in patent claims, being textiles, latex paints, paper, inks, adhesives, greases, soaps, etc.

TABLE 4. Some general iodonium salt structures and associated claims set forth in the patent literature

Structure	Literature claims
	Control against bacteria, fungi, organisms that attack seeds, roots and above-ground portions of terrestrial plants, organisms responsible for mould, mildew, rot and decay[21]
	Control against bacteria, fungi, organisms that attack seeds, roots and above-ground portions of terrestrial plants, organisms responsible for mould mildew, rot and decay, small RNA viruses[120]
	Control against bacteria, fungi, slimes, moulds, organisms that attack seeds, roots and above-ground portions of terrestrial plants, organisms responsible for mould, mildew, rot and decay[121]
	Control against bacteria, fungi, organisms that attack seeds, roots and above-ground portions of terrestrial plants, organisms responsible for mould, mildew, rot and decay[22]
	Control against bacteria, fungi, yeasts, organisms that attack seeds, roots and above-ground portions of terrestrial plants, organisms responsible for mould, mildew, rot and decay[20]
 X = halogen	Control against bacteria; anthelmintic agents[27]

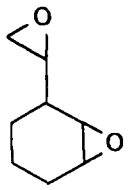
In one experiment, wooden panels were covered with a latex paint, with and without added Tiodonium Chloride, and exposed for 2 months to a tropical chamber (i.e. 95% humidity, 82°F = 28°C). After this time, those panels painted with unmodified latex experienced a 75% surface coverage of mould and mildew, while those painted with the modified latex were competely free of the same[121].

Tiodonium Chloride (**7**) is also effective against *Streptococcus mutans*, a microorganism responsible for tooth plaque[122], and formulations for a germicidal detergent and shampoo with added Tiodonium Chloride have been described[121]. The trifluoroacetate analogue has proven to be an active plant-stunting agent for corn and wheat[123].

Various microbes which reside in the rumen (i.e. the first stomach) of ruminant (i.e. cud-chewing) animals promote the deamination of amino acids and proteins, thereby preventing maximum protein utilization by such animals as food passes into the lower gut. Diaryliodonium salts, especially the di(*p*-tolyl)iodonium analogues, are active against such microbes and inhibit rumen microbial deamination. In one experiment, detailed in US Patent 3,862,333, thirty-two Hereford steers, paired according to body weight, were given a non-additive feed ration for 2 weeks. One animal of each pair was then switched to additive feed (i.e. containing 50 p.p.m. of di(*p*-tolyl)iodonium chloride). Those animals maintained on the non-additive ration subsequently gained 13% *less* weight while requiring 11% *more* feed[124].

Various diaryliodonium salts have been shown to exhibit carcinolytic activity against tumour cells in a KB (human nasopharyngeal carcinoma) tissue culture system, but none of the compounds tested showed selective antitumour activity against whole animal tumours[39].

Some diaryliodonium salts are photoactive and are useful initiators for cationic[125] and free radical polymerizations. They have, therefore, been employed as components in ultraviolet-curable formulations. The activity of a particular iodonium ion may depend on the associated counterion. In one experiment (described in US Patent 4,136,102), 3 mil films of 3-vinylcyclohexene dioxide (**10**), containing 3% by weight of



(10)

diphenyliodonium salts, were applied to glass slides and subsequently exposed to ultraviolet light (i.e. a GE H377 lamp at a distance of 6 in = 15 cm)[126]. The minimum times required for the production of tack-free films were 30 s, 20 s and 3–5 s respectively, for added $Ph_2I^+ BF_4^-$, $Ph_2I^+ PF_6^-$ and $Ph_2I^+ SbF_6^-$. Cure times for various di(*p*-tolyl)iodonium salts added as photoinitiators show a similar activity versus counterion trend: $SbF_6^- > AsF_6^- > PF_6^- > BF_4^-$.

Other patents describe the use of diaryliodonium salts as initiators for free radical polymerizations and the application of such reactions in the production of photographic images of various types[127,128]. Diphenyliodonium salts (BF_4^-, PF_6^-, AsF_6^-, $SbCl_6^-$, SbF_6^-, $(CF_3SO_2)_2CH^-$) are also useful as photocatalysts for the hydrolysis of silanes[129].

III. VINYLIODONIUM SALTS

Vinyliodonium salts are uncommon, and most which are known are of the vinylaryl structural type. In contrast to the systematic methodology available for the

preparation of diaryliodonium salts, synthetic procedures for vinyliodonium salts are limited and often inefficient. This is not surprising since members of the iodosoalkene family of compounds are rare, and, apparently, the iodosoarenes and (diacetoxyiodo)arenes do not condense with alkenes as they do with aromatic substrates.

Beringer and Gindler[12] tabulate two divinyliodonium ions and 33 arylvinyliodonium ions, all of which contain one or two chlorine atoms in the vinyl ligands. Taken together with the various counterions, the number of vinyliodonium salts listed in their compendium is 126[12]. Examples are given below.

$(R^1R^2C{=}CR^3I^+Ar)A^-$

R^1	R^2	R^3	Ar
Cl	H	H	C_6H_5
Cl	H	Cl	*o*-MeC_6H_4
Cl	Me	Cl	C_6H_5
Cl	H	Cl	*p*-$Me_3CC_6H_4$
Cl	Me	Cl	β-Naphthyl
Cl	H	H	2,5-$Br_2C_6H_3$

A. Synthesis

1. *Alkynylsilver complexes with (dichloroiodo)arenes*

The earliest reported preparative method for vinyliodonium salts entails the treatment of an alkynylsilver–silver chloride complex with an appropriate (dichloroiodo)arene (or with 1-(dichloroido)-2-chloroethylene). A general experimental procedure is given by Willgerodt[11] (see p. 237 therein). After the alkynylsilver complex is prepared, it is mixed with a (dichloroiodo)arene and subjected to a grinding operation in the presence of water. Willgerodt also provides relevant references to the early literature[11]. Examples taken from Willgerodt are as follows:

$$HC{\equiv}C{-}Ag\cdot AgCl + PhICl_2 \xrightarrow{H_2O} (Ph{-}\overset{+}{I}{-}\overset{Cl}{\underset{|}{C}}{=}\overset{Cl}{\underset{|}{C}}{-}H)Cl^- \qquad (169)$$

$$MeC{\equiv}C{-}Ag\cdot AgCl + o\text{-}MeC_6H_4ICl_2 \xrightarrow{H_2O} (o\text{-}MeC_6H_4{-}\overset{+}{I}{-}\overset{Cl}{\underset{|}{C}}{=}\overset{Cl}{\underset{|}{C}}{-}Me)Cl^- \qquad (170)$$

$$HC{\equiv}C{-}Ag\cdot AgCl + ClCH{=}CHICl_2 \xrightarrow{H_2O} ClCH{=}CH{-}\overset{+}{I}{-}\overset{Cl}{\underset{|}{C}}{=}\overset{Cl}{\underset{|}{C}}{-}H)Cl^- \qquad (171)$$

2. *Vinylmercury compounds with (dichloroiodo)arenes*

This method has been limited primarily to the treatment of *trans*-chlorovinylmercuric chloride with various (dichloroiodo)arenes in dilute hydrochloric acid and typically results in low to moderate yields of vinylaryliodonium trichloromercurates[130–132]. These can be converted to the corresponding chloride salts by the action of hydrogen sulphide. The replacement of the (dichloroiodo)arene with

iodine trichloride eventuates in the isolation of bis(β-chlorovinyl)iodonium $^-Cl{\cdot}2HgCl_2$ in 6% yield[130]. [130].

$$ClCH{=}CHHgCl + ArICl_2 \xrightarrow{3\%\ HCl} (ClCH{=}CH{-}I^+{-}Ar)X^- \quad (172)$$

$X^- = {}^-Cl{\cdot}HgCl_2$ or $^-Cl{\cdot}2HgCl_2$

Ar	Yield, %	Reference
C_6H_5	31	131
o-MeC_6H_4	40, 31	131, 132
m-MeC_6H_4	45	132
p-MeC_6H_4	43	132
o-ClC_6H_4	8, 10	132
m-ClC_6H_4	20	132
p-ClC_6H_4	18, 6	132, 131
o-$MeOC_6H_4$	43, 50	132
p-$MeOC_6H_4$	53	132
m-$NO_2C_6H_4$	5	131

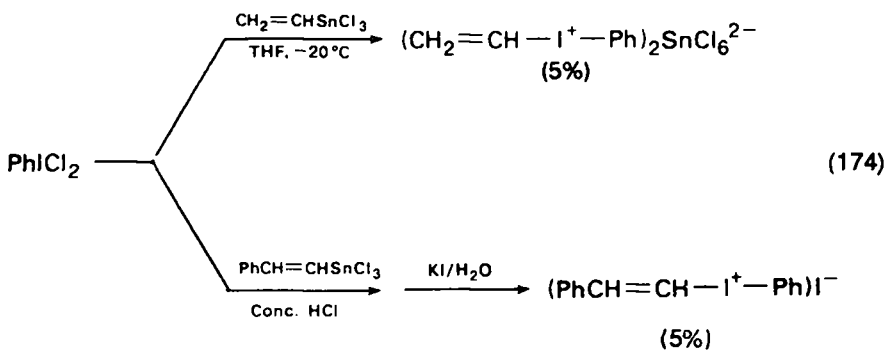
A vinylaryliodonium compound without chlorine substituents in the vinyl moiety is obtained from β-phenylethenylmercuric bromide and (dichloroiodo)benzene under similar reaction conditions[133].

$$PhCH{=}CHHgBr + PhICl_2 \xrightarrow[(2)\ NaI/Me_2C{=}O]{(1)\ 3\%\ HCl} (PhCH{=}CH{-}I^+{-}Ph)I^- \quad (173)$$

(4%)

3. *Organostannanes with (dichloroiodo)arenes and (dichloroiodo)alkenes*

This method has thus far seen only limited application, but vinylaryliodonium salts have been approached from two directions, one involving the reaction of (dichloroiodo)benzene with a vinyl(trichloro)stannane and the other involving the action of 1-(dichloroiodo)-2-chloroethylene on (trichlorostannyl)benzene[133,134].



(174)

$$PhSnCl_3 + \begin{matrix} H & & ICl_2 \\ & \diagdown\!\!=\!\!\diagup & \\ Cl & & H \end{matrix} \longrightarrow (ClCH{=}CH{-}I^+{-}Ph)Cl^- \quad (175)^{130}$$

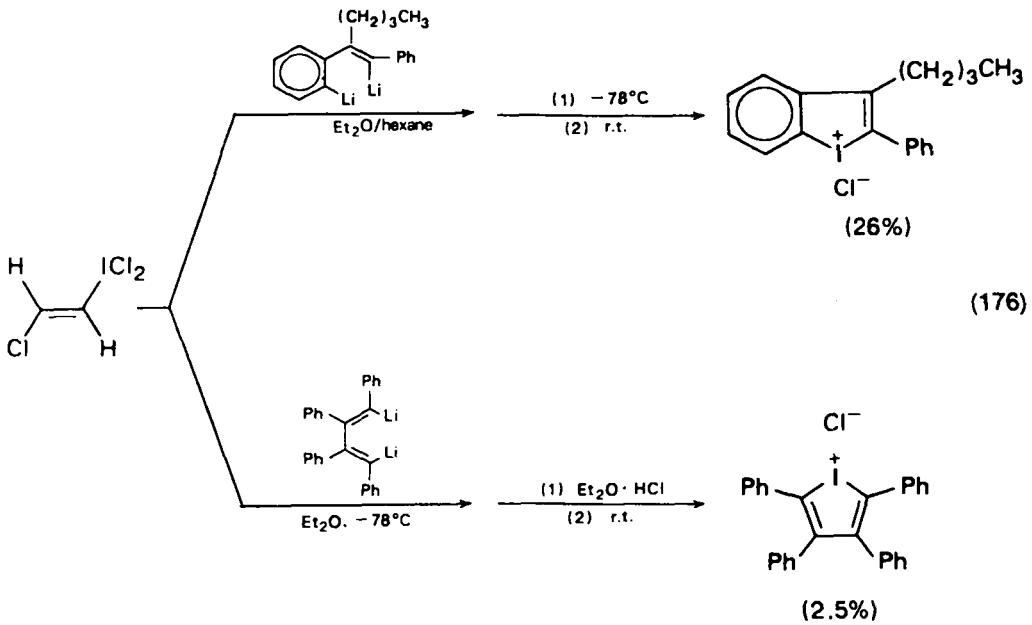
(31%)

It is noteworthy that the condensation of (trichlorostannyl)benzene with 1-(dichloroiodo)-2-iodoethylene (instead of the 2-chloro analogue) in 15% HCl does *not* yield a vinyliodonium salt but *does* afford a 50% yield of diphenyliodonium chloride[131].

4. *Organolithium compounds with* trans-*1-(dichloroiodo)-2-chloroethylene*

Two cyclic vinyliodonium species, the 3-butyl-2-phenylbenziodolium ion and the tetraphenyliodolium ion, have been isolated as their chloride salts from reactions of *trans*-1-(dichloroiodo)-2-chloroethylene with the appropriate dilithium reagents[135]. These reactions, analogous to those discussed in Section II.A.7 for the preparation of diaryliodonium salts, probably proceed by the elimination of acetylene from tricovalent iodine(III) intermediates.

The reaction of equivalent amounts of vinyllithium and (dichloroiodo)benzene in tetrahydrofuran at −70°C affords diphenyliodonium chloride (5%) but does not yield a vinyliodonium salt[135].

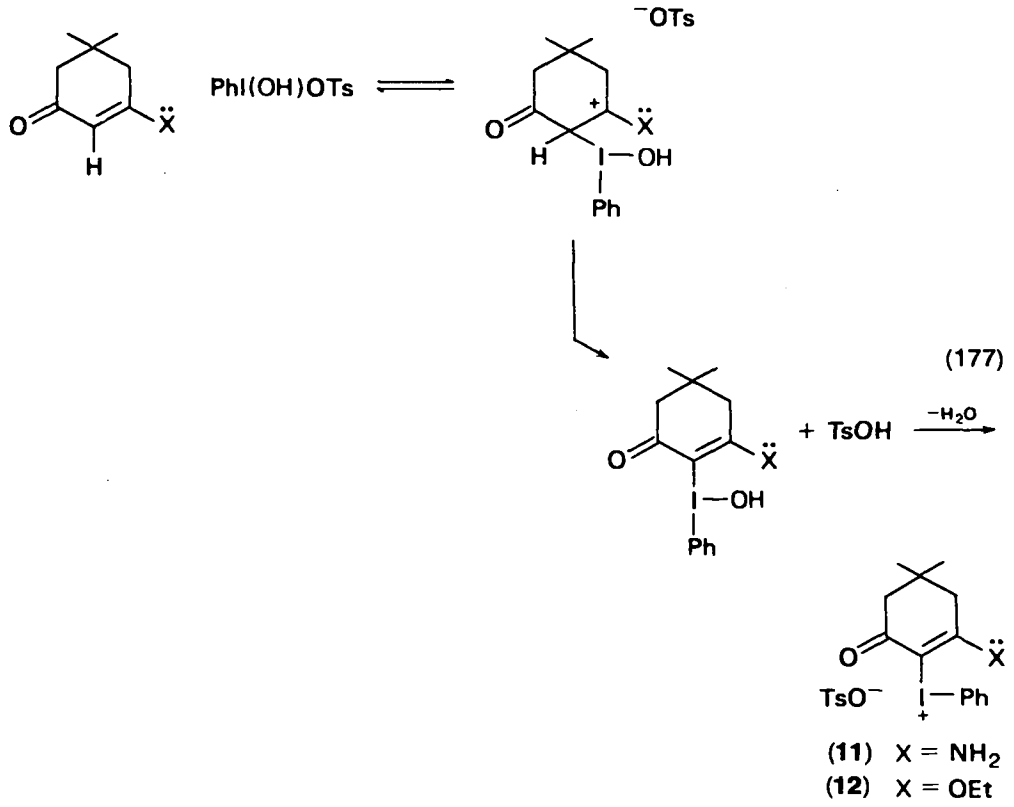


(176)

5. [*Hydroxy(tosyloxy)iodo*]*benzene with alkenes and alkynes*

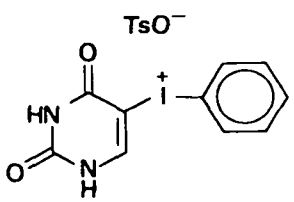
[Hydroxy(tosyloxy)iodo]benzene (**6**) has been reported to react with 3-amino- and 3-ethoxy-5,5-dimethylcyclohexenones in chloroform to give the vinyliodonium salts **11** and **12** in 87% and 40% yields respectively[49]. A likely mechanism for these reactions is one involving (1) initial electrophilic attack of the hydroxy(phenyl)iodonium ion at vinyl carbon, (2) deprotonation of the carbonium ion thus produced and (3) 'metathesis' of the resulting vinylaryliodonium hydroxide with toluenesulphonic acid generated in the second step (equation 177).

The condensation of uracil with (diacetoxyiodo)benzene in dimethylformamide in the presence of $TsOH \cdot H_2O$ affords the uracil derivative. **13** in 78% yield, which may be properly regarded as a vinylaryliodonium salt[136]. It seems plausible that



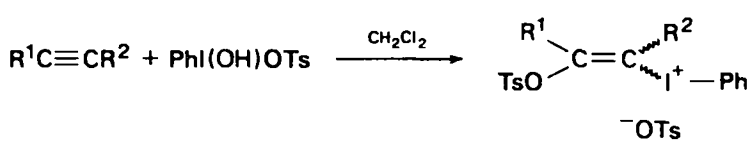
(177)

[hydroxy(tosyloxy)iodo]benzene is the active phenyliodinating species in this reaction since it is synthesized from (diacetoxyiodo)benzene and *p*-toluenesulphonic acid[49].



(13)

[Hydroxy(tosyloxy)iodo]benzene has recently been observed to condense with alkynes in dichloromethane to give moderate yields of β-tosyloxyvinyl-(phenyl)iodonium tosylates[137]. These reactions appear to offer potential for a general synthesis of vinylarliodonium salts if a method for the selective reductive cleavage of the β-tosyloxy function can be found.



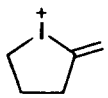
(178)

R^1	R^2	Time	Temperature	Yield, %
Me	Me	19 days	Room*	62
n-C_5H_{11}	H	26 h	Reflux	57 (crude)
n-C_4H_9	Me	2 days	Reflux	42 (crude), 32 (recrystallized)
Ph	Me	2 days	Reflux	56.5 (crude)

*Neat mixture.

6. *Dihalopropenes with antimony pentafluoride*

Although the methods which have been developed for the preparation of dialkyl- and arylalkylhalonium ions do not appear to be generally applicable to the synthesis of vinyliodonium salts, some success has been realized. Several 2,3-dihalopropenes, when treated with antimony pentafluoride in liquid sulphur dioxide at −78°C, afford the cyclic three-membered halonium ions **14**, **15** and **16**, each of which bears an exocyclic double bond[138]. Although these species have not been



(14) X = Cl

(15) X = Br

(16) X = I

(17)

isolated as stable salts, they have been characterized by proton magnetic resonance (PMR) analysis[138]. For example, the chloronium ion **14** exhibits a 2H singlet at δ4.72 and two 1 H singlets at 7.07 and 9.58 (SbF_5–SO_2, −80°C, external tetramethylsilane (TMS)).

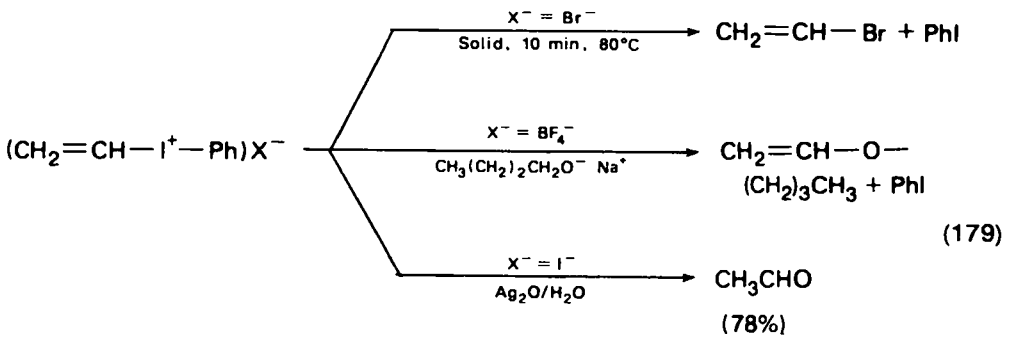
In $FSO_3H/SbF_5/SO_2$ at −60°C, 5-iodopentyne is converted to the five-membered analogue **17**, which has likewise been observed by PMR spectroscopy[138].

B. Reactions

The reactivity of vinyliodonium salts toward bases and nucleophiles has not yet received systematic study. A sufficient number of observations has been made, however, to indicate the regioselective preference of nucleophiles for the vinyl ligand in vinylaryliodonium ions. For example, the thermal decomposition of vinyl(phenyl)-iodonium bromide in the solid state has been reported to give iodobenzene and vinyl bromide in a 1:1 ratio[134]. Absolute yields were not determined, but no other products were found by gas chromatographic analysis. The tetrafluoroborate analogue reacts similarly with sodium n-butoxide in 1-butanol, giving iodobenzene and vinyl n-butyl ether in a 1:1.1 ratio[134]. The corresponding iodide salt, with water and silver oxide, affords a 78% yield of acetaldehyde[134] (equation 179).

The reaction of phenyl(β-phenylethenyl)iodonium tetrafluoroborate with aqueous sodium nitrite is a bit more difficult to interpret[133]. Thin layer chromatographic analysis of the product mixture revealed 1-nitro-2-phenylethylene, 1-iodo-2-phenyl-ethylene and iodobenzene, but no nitrobenzene. The origin of the iodobenzene has not been discussed, but, since nitrobenzene is apparently not formed, iodobenzene may arise via a competing reductive decomposition manifold (equation 180).

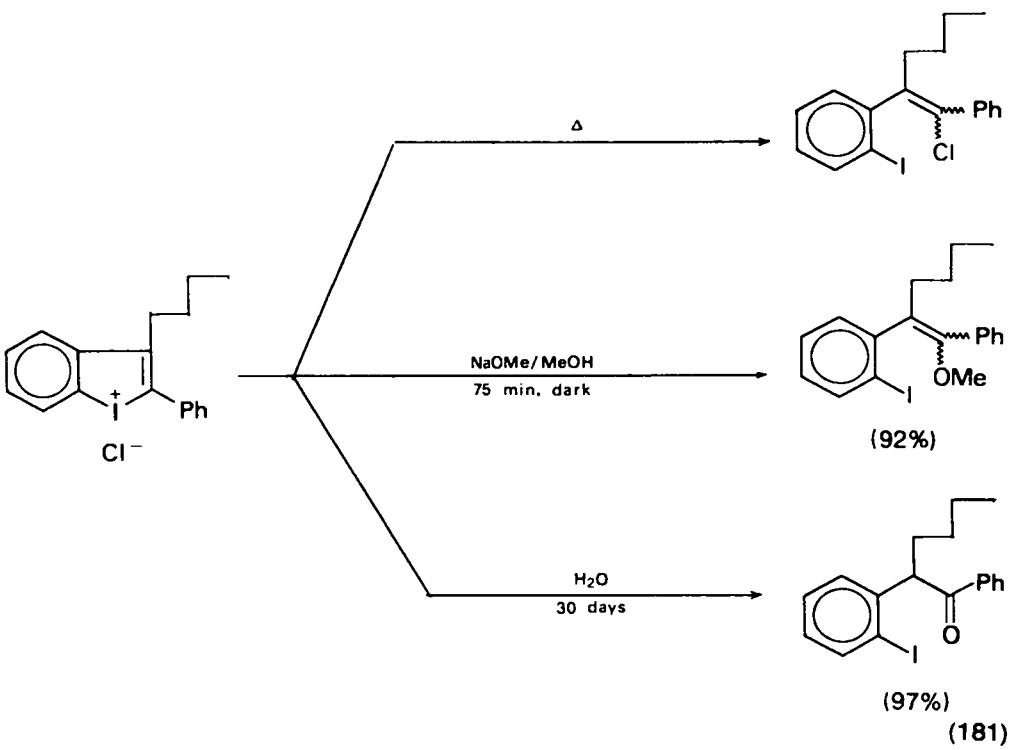
The thermal decomposition of 3-phenyl-2-butylbenziodolium chloride at its melting point has been reported to give a mixture of the corresponding *cis*- and *trans*-stilbene



(179)

$$(PhCH{=}CH{-}I^{+}{-}Ph)BF_4^- \xrightarrow[H_2O]{NaNO_2} PhI + PhCH{=}CHI + PhCH{=}CHNO_2 \quad (180)$$

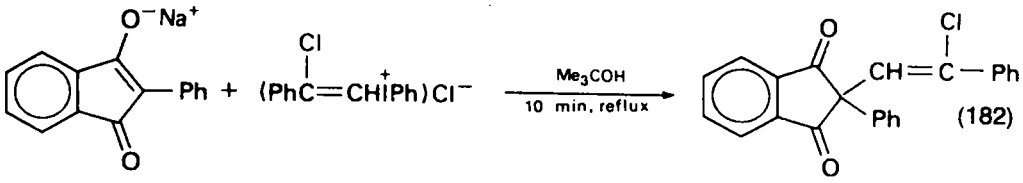
derivatives formed by attachment of chloride ion to vinyl carbon (absolute yields not reported)[135]. With methoxide ion in methanol, a 92% yield of *cis*:trans-2-*o*-iodophenyl-1-methoxy-1-phenyl-1-hexene is obtained[135]. When mixed neat with water in the absence of oxygen, 3-phenyl-2-butylbenziodolium chloride is converted mostly into 2-iodophenyl-1-phenyl-1-hexanone, the yield being 97% after a 30 day reaction period[135].



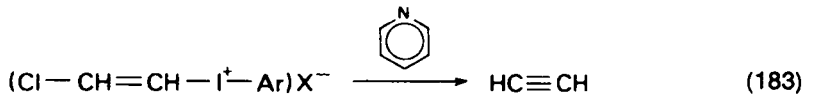
(181)

In another study, sodium 2-phenyl-1,3-indanedionate was treated with phenyl(β-chloro-β-phenylethenyl)iodonium chloride in *t*-butyl alcohol, the result being vinylation of the anion at C-2[139].

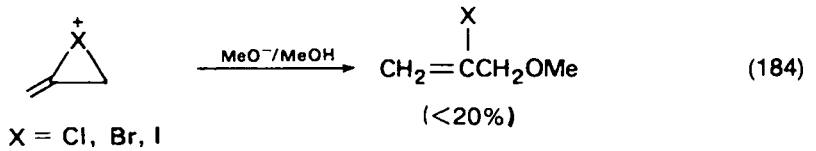
Aryl(β-chlorovinyl)iodonium salts exhibit a different reactivity pattern with the



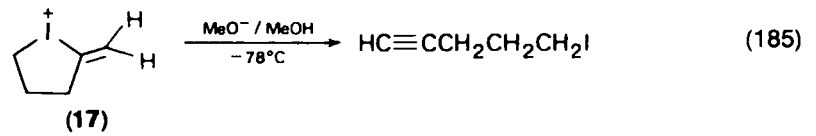
bases pyridine and sodium hydroxide, typically liberating acetylene in low to moderate yields[130,131]. The formation of acetylene may also accompany thermal decomposition reactions.



When solutions of the halonium ions **14**, **15** and **16** in liquid sulphur dioxide are quenched with methoxide ion in methanol, the nucleophile appears to prefer an alkyl to a vinyl carbon, the products being 3-methoxy-2-halopropenes[138]. However, the



identical products would be expected from a reaction sequence involving Michael attack of methoxide ion at the exocyclic vinyl carbon atom[138]. Similar quenching of **17** eventuates in 5-iodo-1-pentyne, a process requiring deprotonation of the exocyclic vinyl carbon atom[138].

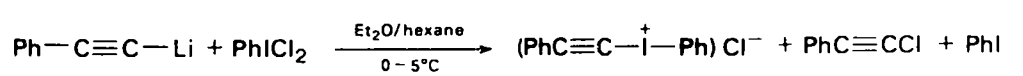


(17)

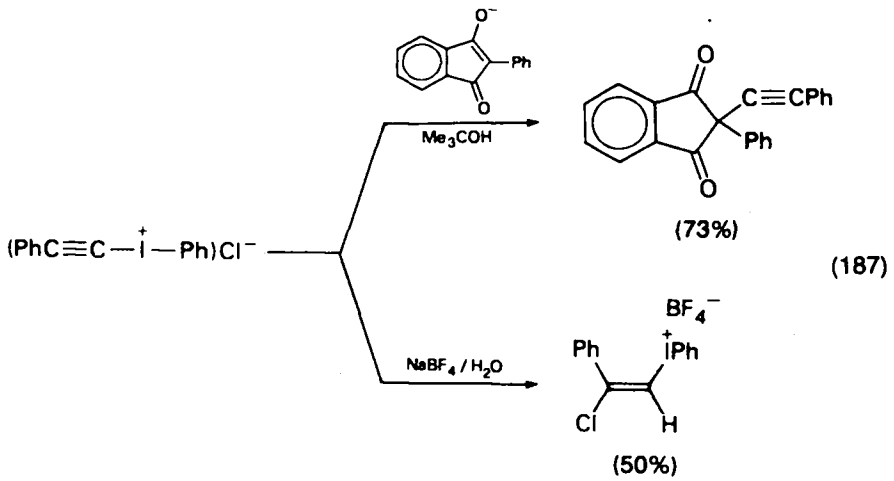
IV. ALKYNYLIODONIUM SALTS

Iodonium salts with alkynyl ligands bound to the iodine atom are extremely rare. We are aware of no reported examples of bis(alkynyl)iodonium salts, vinyl(alkynyl)iodonium salts, alkyl(alkynyl)iodonium salts or any examples of chloronium and bromonium salts bearing an alkynyl ligand.

The condensation of lithium phenylacetylide with (dichloroiodo)benzene in ether/hexane at 0–5%C has been found to yield phenyl(β-phenylethynyl)iodonium chloride in yields ranging from 12–20% in addition to iodobenzene, phenylacetylene and chlorophenylacetylene[139]. The iodonium salt is unstable and, upon standing at room temperature, decomposes into a 1:1 mixture of chloroacetylene and iodobenzene[139]. The potential of phenyl(β-phenylethynyl)iodonium chloride as an

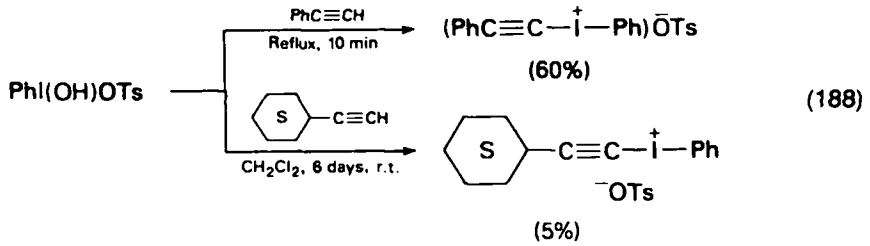


alkynylating agent has been demonstrated by its reaction with 2-phenyl-1,3-indanedionate ion in *t*-butyl alcohol which eventuates in a 73% yield of 2-phenyl-2-phenylethynyl-1,3-indanedione[139]. An attempt to metathesize the alkynyliodonium chloride to the corresponding tetrafluoroborate salt with sodium tetrafluoroborate in water led instead to 2-phenyl-2-chloroethenyl(phenyl)iodonium tetrafluoroborate, presumably via Michael addition of chloride ion to the carbon–carbon triple bond[139].



(187)

The reaction of [hydroxy(tosyloxy)iodo]benzene with phenylacetylene at *reflux* likewise affords the phenyl(*β*-phenylethynyl)iodonium ion as its tosylate salt in 60% yield[137]. Unlike the chloride, the tosylate is stable at room temperature. With cyclohexylacetylene in dichloromethane, [hydroxy(tosyloxy)iodo]benzene gives phenyl(*β*-cyclohexylethynyl)iodonium tosylate in 5% yield, a surprisingly stable compound[137]. A sample which exhibited a melting point of 125–127.5°C gave a melting point of 126–128°C after 7 months storage under ambient conditions.



(188)

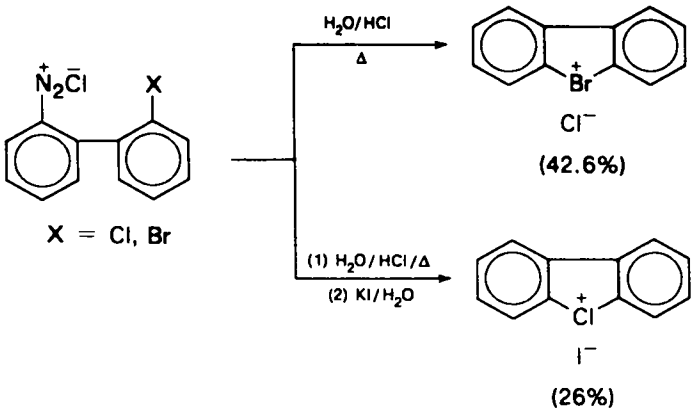
V. DIARYLBROMONIUM AND DIARYLCHLORONIUM SALTS

Compared to their iodonium analogues, diarylchloronium and diarylbromonium ions are uncommon. They are also relatively unstable toward nucleophilic cleavage reactions and are, therefore, usually prepared in conjunction with anions of low nucleophilicity (e.g. BF_4^-, PF_6^-).

A. Synthesis

The arylchloroso and arylbromoso families of compounds (i.e. Ar—X=O, Ar—X$(OOCCH_3)_2$, Ar—XCl_2, where X = Cl, Br) are unknown. Therefore, the

familiar synthetic procedures for diaryliodonium compounds cannot be applied to the preparation of chloronium and bromonium analogues. Most diarylchloronium and diarylbromonium salts have been synthesized by the thermal decomposition of aryldiazonium ions, coupled with non-nucleophilic counterions, in the presence of appropriate chloro- and bromoarenes. This method was first applied by Sandin and Hay in their syntheses of dibenzchlorolium iodide and dibenzbromolium chloride[63].



(189)

In two respects, this reaction is decidely atypical. First, the anion carried along in the cyclization process (i.e. chloride ion) is relatively nucleophilic. This is usually not good because the anion can compete with the halo substituent for the intermediate aryl cation generated upon nitrogen loss from the diazonium compound and because the chloronium and bromonium ions, once formed, can undergo S_NAr cleavage. Secondly, the observed yields are significantly higher than those of reactions eventuating in acyclic diarylhalonium compounds. The success here must reflect the favourable entropic factors associated with intramolecular versus intermolecular capture of the intermediate aryl cation and the higher stability of cyclic halonium ions compared with acyclic ones.

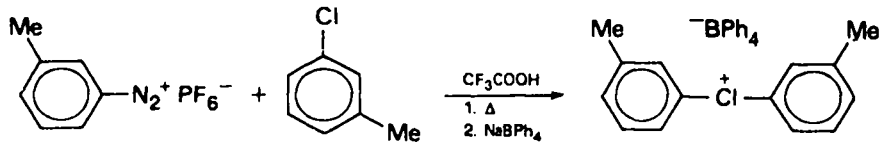
The first application of this method to the preparation of acyclic diarylchloronium and diarylbromonium ions involved the use of the tetrafluoroborate salts of aryldiazonium ions and provided the desired products in yields ranging from about 0.5% to 7%[3,140,141]. Acetone is a convenient mediating solvent for such decomposition

$$ArN_2^+\ BF_4^- + Ar'X \xrightarrow{\Delta} (ArX^+Ar')BF_4^- + N_2\ (g) \qquad (190)$$

X = Cl, Br

reactions. Of course, the tetrafluoroborate salts can be converted by metathesis to salts containing other counterions (e.g. Br^-, I^-, $^-BPh_4$, HgI_3^-, $PtCl_6^{2-}$). In most early work, the parent benzenediazonium ion was employed, and a variety of *unsymmetrical* salts was prepared, the substituent being introduced via the haloarene (with one exception)[3].

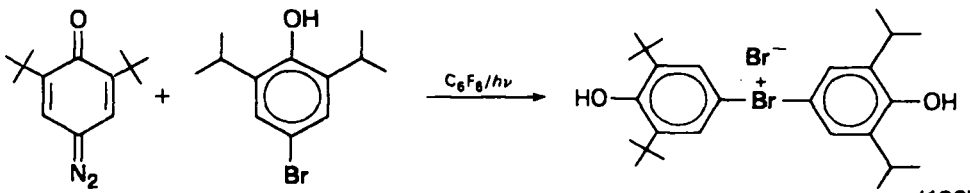
Improved yields, ranging from 5.7 to 14%, of symmetrical and unsymmetrical diarylchloronium and diarylbromonium salts have recently been realized by conducting the reactions of aryldiazonium hexafluorophosphates with haloarenes in the presence of trifluoroacetic acid or 2,2,2-trifluoroethanol[2]. Substituents in the halonium nucleus can be introduced via either aromatic component. For example, the decomposition of *m*-tolyldiazonium hexafluorophosphate with *m*-chlorotoluene in the presence of trifluoroacetic acid gives an 8.9% yield of 3,3′-ditolylchloronium tetraphenylborate (after anion metathesis)[3]. The major by-products of these reactions are aryl fluorides, which presumably arise from the Schieman reaction.



(191)

(8.9%)

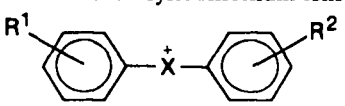
Other approaches to diarylbromonium salts, which have seen limited application, include the action of bromine trifluoride on arenes at low temperature[142], and the photochemical decomposition of 3,5-di-*t*-butylbenzene-1,4-diazooxide in the presence of 2,6-diisopropyl-4-bromophenol (see equation 192)[143].

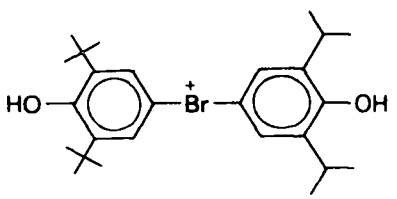
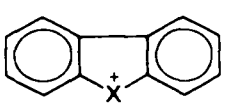


(192)

(15%)

TABLE 5. Known diarylchloronium and diarylbromonium ions



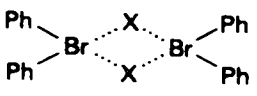
X = Cl			X = Br		
R^1	R^2	Reference	R^1	R^2	Reference
H	H	3, 2	H	H	3, 2
H	2-Me	3, 2	H	2-Me	3, 2
H	3-Me	2	H	4-Me	3, 2
H	4-Me	3, 2	H	$2,4\text{-Me}_2$	3
2-Me	2-Me	2	H	4-Cl	3
3-Me	3-Me	2	H	*p*-COOEt	3
4-Me	4-Me	2	H	3,4-Benzo	3
2-Me	3-Me	2	4-F	4-F	142
3-Me	4-Me	2	4-Me	4-Me	142
2-Me	4-Me	2			
H	$2,4\text{-Me}_2$	3, 2	*Others*		Reference
H	$2,3\text{-Me}_2$	2			143
2-Me	$2,4\text{-Me}_2$	2			
4-Me	$2,4\text{-Me}_2$	2			
2-Me	$2,3\text{-Me}_2$	2			
H	4-COOEt	3			
H	2-Cl	2			
H	4-Cl	3, 2			63
H	3-F	2			
H	4-F	2			

X = Cl, Br

A summary of reported diarylchloronium and diarylbromonium ion structures is given in Table 5.

B. Structure

A single-crystal X-ray study of diphenylbromonium bromide and iodide has shown that these molecules crystallize as centrosymmetric dimers (see structure **18**) in analogous fashion to diphenyliodonium salts[84,144]. The aromatic rings are tilted out of the indicated plane, and the C—BR—C angles are bent: 97.3° (Br^- salt), 98.0° (I^- salt). The carbon–bromine(III) bond distances in these salts are 1.90–1.91 Å and equal, therefore, to the sum of the covalent radii (i.e. 1.91 Å) of the carbon and bromine atoms.



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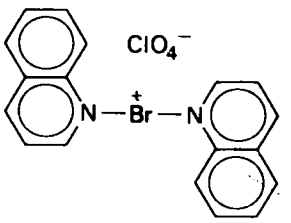


(19)

It is interesting to compare this structure with that of bis(*N*,*N*-quinolinyl)-bromonium perchlorate (**19**) which, in the solid state, exhibits a nearly linear N—Br—N angle (176.6°) and bromine–nitrogen bond lengths of 2.100 and 2.185 Å, significantly longer than the sum of the nitrogen and bromine covalent radii (1.84 Å)[145].

C. Reactions

The polarographic reductions of diphenylchloronium, bromonium and iodonium tetrafluoroborates to the corresponding diarylhalo radicals (wave I) in water/lithium perchlorate have been studied and afford half-wave potentials of −0.36 V, −0.26 V and −0.16 V respectively[146]. Since the tendency for one-electron reduction increases with increasing size of the halogen atom, it might be expected that diarylchloronium and diarylbromonium ions will permit cleaner arylations than diaryliodonium ions of those nucleophiles which initiate a competing reductive decomposition process. That this is indeed the case is beautifully demonstrated by the reaction of diphenyl-bromonium tetrafluoroborate with sodium ethoxide in ethanol which produces phenetole in 98 ± 2% yield and benzene in 2.6% yield[147]. This result stands in contrast to the analogous reaction of diphenyliodonium tetrafluoroborate which gives mostly benzene and little phenetole[94].

$$(Ph-\overset{+}{X}-Ph)BF_4^- + EtO^- \xrightarrow[71°C]{EtOH} PhX + PhOEt + PhH \qquad (193)$$

X = Br	100%	98%	2.6%
X = I	92%	14%	68%

Even with isopropoxide ion in isopropyl alcohol, the diphenylbromonium salt affords phenyl isopropyl ether in 83% yield, that yield being increased to 92% in the presence of added 1,1-diphenylethylene[147]. When phenyl(*p*-tolyl)bromonium ion is the substrate, the reaction with ethoxide ion produces phenetole and *p*-methylphenetole in a 3:1 ratio consistent with their formation via the S_NAr manifold[147].

Arylations of nitrite ion, azide ion, cyanide ion, diethylamine and pyridine with the diphenylbromonium ion have been reported[3,148], as has the phenylation of triphenylphosphine with the diarylchloronium and bromonium ions under photochemical conditions[72].

Nitroarene ratios for the reactions of 13 unsymmetrical diarylchloronium tetraphenylborates and two unsymmetrical diarylbromonium tetraphenylborates with sodium nitrite in an acetone/water medium have been measured[2]. The regioselectivities are consistent with expectations for the S_NAr mechanism when alkyl

$$(Ar-\overset{+}{X}-Ar')BPh_4^- + NaNO_2 \xrightarrow[2\text{ h, reflux}]{Me_2CO/H_2O\ (5:1)} ArNO_2 + Ar'NO_2 + ArX + Ar'X \quad (194)$$

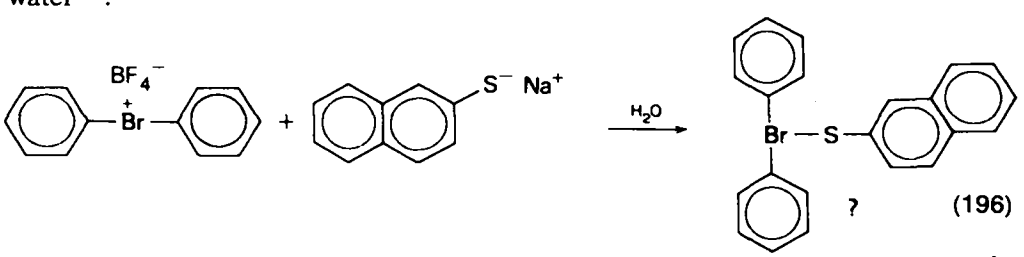
substituents do not occupy *ortho* positions in the aromatic rings. However, as observed with diaryliodonium salts, there is a pronounced '*ortho* effect' when *o*-alkyl substituents are present. For example, with the phenyl(*p*-tolyl)chloronium ion the ratio of nitrobenzene to *p*-nitrotoluene is 3:1, but when the phenyl(*o*-tolyl)chloronium ion is the substrate, the ratio of nitrobenzene to *o*-nitrotoluene is 1:4.7[2].

The reaction of diphenylhalonium ions with sodium thiophenolate in alcohol provides an excellent illustration of the competitive nature of the S_NAr and reductive decomposition manifolds[149]. As expected, the yield of benzene increases and the yield

$$Ph_2X^+\ BF_4^- + PhS^-\ Na^+ \xrightarrow{\text{Alcohol}} PhX + Ph_2S + PhH \quad (195)$$

X = Cl;	83%	3%
X = Br;	48%	43%
X = I;	30%	51%

of diphenyl sulphide decreases as the reduction potential of the diarylhalonium ion becomes more positive[149]. That these reactions may proceed via tricovalent halogen(III) intermediates is indicated by the isolation of an adduct from the reaction of diphenylbromonium tetrafluoroborate and sodium 2-thionaphtholate in water[149].



(196)

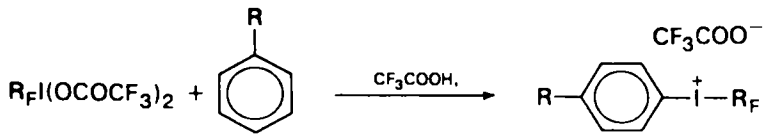
Diphenylchloronium and diphenylbromonium hexafluorophosphates have also been employed as initiators for cationic polymerization reactions[150].

VI. ALKYLHALONIUM IONS

A. Classical Approaches

The preparation of dialkyl- and arylalkylhalonium ions, for the most part, requires an entirely different methodology to that developed for their diaryl counterparts. Relatively few members of the iodosoalkane family of compounds are known, these being restricted to several fluoroalkyliodoso analogues and a few unstable (dichloroiodo)alkanes. We are unaware of any examples of *isolated* iodosoalkanes,

$R_HI{=}O$, (diacyloxyiodo)alkanes, $R_HI(OCOR')_2$, or iodoxyalkanes, R_HIO_2, wherein R_H is a saturated hydrocarbon radical. A rare example of the successful application of classical methodology to the preparation of alkylaryliodonium salts is provided by the reported condensations of two (ditrifluoroacetoxyiodo)perfluoroalkanes with toluene or benzene in trifluoroacetic acid to give perfluoroalkyl(aryl)-iodonium trifluoroacetates[151]. The perfluoropropyl(phenyl)- and perfluorohexyl(*p*-



(197)

R_F	R	Yield, %
$CF_3CF_2CF_2$	Me	42
$CF_3CF_2CF_2$	H	12 (Cl^-)
$CF_3(CF_2)_4CF_2$	Me	35 (Cl^-)

tolyl)iodonium ions were more conveniently isolated as their chloride salts after metathesis of the crude trifluoroacetates with sodium chloride in acetone/water. Although these iodonium salts can be isolated, their prolonged storage requires low temperatures and the absence of moisture.

In another study, attempts to synthesize 1-apocamphyl(phenyl)- and cyclopropyl(phenyl)iodonium salts by the reactions of phenyllithium with (dichloroiodo)cyclopropane and 1-(dichloroiodo)apocamphane respectively were unsuccessful[152].

The complementary approach of condensing iodosoarenes and (diacetoxyiodo)-arenes with alkanes will work only for those alkanes whose carbon–hydrogen bonds are 'activated' by electron-withdrawing substituents. For example, the condensation of (diacetoxyiodo)benzene with dinitromethane in ether affords phenyliodoniumdinitromethylide which, upon treatment with acids, affords phenyl(dinitromethyl(iodonium salts[153,154].

$$PhI(OAc)_2 + CH_2(NO_2)_2 \xrightarrow{Et_2O} Ph\overset{+}{I}-\overset{-}{C}(NO_2)_2 \xrightarrow{HX} Ph\overset{+}{I}CH(NO_2)_2X^- \quad (198)$$

Since aliphatic and aromatic compounds of the types ArXO, RXO, $ArX(OOCR)_2$, $RX(OOCR)_2$, $ArXCl_2$ and $RXCl_2$, where X = Br, Cl, have yet to be isolated, even the limited success of classical methodology in the preparation of alkylaryliodonium salts cannot be expected at this time for the chloronium and bromonium analogues.

B. Historical Perspective

The year 1967 witnessed a major breakthrough in the preparative methodology for organohalonium ions bearing saturated aliphatic ligands. In that year, the first direct observation of such species in the solution phase was reported. When various 2,3-dihalo-2,3-dimethylbutanes were treated in liquid sulphur dioxide at −60°C with antimony pentafluoride, the tetramethylethylenehalonium ions **20a–c** (i.e. tetramethylhaliranium ions) were generated and characterized *under those conditions* by PMR spectroscopy[10]. The structures assigned to **20a–c** were corroborated by the slow addition of their SO_2 solutions at −78°C to a suspension of potassium carbonate in methanol, this resulting in the production of the corresponding 2-halo-3-methoxy-2,3-dimethylbutanes (equation 199)[10].

$$(CH_3)_2C(X)-C(X')(CH_3)_2 \xrightarrow[-60°C]{SbF_5/SO_2(l)} (CH_3)_2C(X)-C^{+}(CH_3)_2\ SbF_5X'^{-} \xrightarrow[-78°C]{K_2CO_3/MeOH} (CH_3)_2C(X)-C(OMe)(CH_3)_2 \quad (199)$$

(**20a**) X = Cl
(**20b**) X = Br
(**20c**) X = I

X	X′	Initial product	δ, p.p.m.*	Δδ, p.p.m.
Cl	F, Cl	**20a**	2.72, s	0.95
Br	F, Br	**20b**	2.86, s	0.86
I	F	**20c**	3.05, s	0.75

*Relative to external TMS.

It is important, when assessing the relative abilities of charged chlorine, bromine and iodine atoms in organohalonium ions to deshield protons, to compare measured chemical shifts against those of appropriate covalent models. Proton shifts of **20a–c** in SbF_5/SO_2 relative to those of 2,3-dichloro-, 2,3-dibromo- and 2,3-diiodo-2,3-dimethyl butanes in CCl_4 (internal TMS) are given under equation (199) as the Δδ parameter. Thus, even though the singlet for the iodonium ion **20c** is at lower field than that of the chloronium analogue **20a**, the chloronium function actually causes more proton deshielding than the iodonium function does on a relative basis.

One difficult problem in this area is that of discernment between halonium ion structures and rapidly equilibrating acyclic carbenium ions. The Δδ parameter is useful

$$(CH_3)_2C(X)-C^{+}(CH_3)_2 \overset{Rapid}{\rightleftharpoons} (CH_3)_2C^{+}-C(X)(CH_3)_2 \quad (200)$$

in this regard since it is reasonable to anticipate larger Δδ values for carbenium ions with positive charge highly localized on carbon than for halonium ions with positive charge highly localized on the halogen centre. Indeed, when 2,3-difluoro-2,3-dimethylbutane is subjected to SbF_5/SO_2 at −90°C, rapidly equilibrating carbenium ions are observed, the PMR spectrum featuring a doublet at δ3.10 (J_{HF} = 11 Hz) and a Δδ value of 1.76, approximately twice those observed for the halonium analogues[10]. It is noteworthy that while ions **20a–c** in SbF_5/SO_2 at −78°C show no decomposition after several weeks, the β-fluorocarbenium ion is completely decomposed after 1 week under the same conditions.

The 1967 paper also describes the generation of **20a–c** from 2-halo-3-methoxy- and 2-halo-3-acetoxy-2,3-dimethylbutanes either in the SbF_5/SO_2 system or in an $SbF_5/FSO_3H/SO_2$ system. However, the reactions are not so clean as those originating from 2,3-dihalo precursors.

The first direct observation of tetramethylenehalonium ions (i.e. halolanium ions) in the solution phase was reported shortly thereafter (1968), the parent ions **21a–c** being generated by the action of antimony pentafluoride on appropriate 1,4-dihalobutanes in liquid sulphur dioxide at −78°C[155]. Variations in the synthetic methodology were also described. Thus, the 2-methylchlorolanium ion (**22**) was prepared from either

$$X(CH_2)_4X \xrightarrow{SbF_5/SO_2/-78°C} \overset{+}{X} \quad (201)$$

X = Cl, Br, I

(21a) X = Cl
(21b) X = Br
(21c) X = I

$$\begin{matrix} & OOCCF_3 & \\ & | & \\ ClCH_2CH_2CH_2CHCH_3 & & \end{matrix}$$

or

$$ClCH_2CH_2CH_2CH{=}CH_2$$

$$\xrightarrow[-78°C \text{ or } -60°C]{FSO_3H/SbF_5/SO_2} \overset{+}{Cl}\!-\!CH_3 \quad (202)$$

(22)

1-chloro-4-trifluoroacetoxypentane or 5-chloro-1-pentene by their treatment with fluorosulphonic acid–antimony pentafluoride in liquid sulphur dioxide. The 'π-route' to organohalonium ions was also applied in the preparation of 2,4-dimethylhalolanium ions **23a–c** from the corresponding 5-halo-1-hexenes[155].

$$\begin{matrix} & X & \\ & | & \\ CH_2{=}CH(CH_2)_2CHCH_3 & & \end{matrix} \xrightarrow[-60°C]{FSO_3H/SbF_5/SO_2} CH_3\!-\!\overset{+}{X}\!-\!CH_3 \quad (203)$$

X = Cl, Br, I

(23a) X = Cl
(23b) X = Br
(23c) X = I

These publications were followed in 1969[156] by the first reported observation of acyclic dialkylhalonium ions and in 1970[9] by the first reported isolations of the same. In the initial work, dialkylhalonium ions were generated either by treatment of excess haloalkane with anitmony pentafluoride in liquid sulphur dioxide or by treatment of excess haloalkane with methyl hexafluoroantimonate[157] in liquid sulphur dioxide[156]. The former procedure is limited to the preparation of symmetrical halonium ions while

$$2\ RX + SbF_5{-}SO_2 \xrightarrow[\text{Low temperature}]{SO_2(l)} (\overset{+}{R}X R)\bar{S}bF_5X \quad (204)$$

$$RX + CH_3F{-}SbF_5 \xrightarrow[\text{Low temperature}]{SO_2\ (l)} (\overset{+}{R}XCH_3)\bar{S}bF_5X \quad (205)$$

the latter permits the production of symmetrical and unsymmetrical analogues. In the 1969 paper, PMR data (SO_2, $-60°C$, external TMS) are tabulated for Me_2X^+, Et_2X^+, $Pr^i_2X^+$, MeX^+Et (X = Cl, Br, I), $Pr^n_2X^+$ (X = Br, I) and Pr^iCl^+Me, other species later being added to this list[156,158].

The reactions of methyl hexafluoroantimonate with excess chloro- and bromoethanes, in each case, afford mixtures of diethyl- and methylethylhalonium ions, but when iodomethane is the substrate only the methylethyliodonium ion is generated[156]. With the *n*-propyl halides as reactants, the tendency for the production of isopropylmethylhalonium ions conforms to the trend: Cl > Br >I. Both of these results are consistent with the superior ability of iodine to accommodate localized positive charge.

TABLE 6. NMR spectra of dimethylhalonium ions

Structure	$\delta^{13}C$, p.p.m.[a]	$\Delta\delta^{13}C$, p.p.m.[b]	$\delta^{1}H$, p.p.m.[c]
$CH_3—Cl^+—CH_3$	144.9	29.0	4.20, s
$CH_3—Br^+—CH_3$	156.2	25.8	4.13, s
$CH_3—I^+—CH_3$	184.3	23.5	3.60, s

[a] $SO_2(l)$, relative to $^{13}CS_2$.
[b] Measured against CH_3X (X = Cl, Br, I) in $SO_2(l)$. $(CH_3)_2\overset{+}{X}$ resonances at lower field.
[c] $SO_2(l)$, relative to external TMS.

The successful isolation of dimethylchloronium, dimethylbromonium and dimethyliodonium fluoroantimonate salts, **4a–c** (see Section I) was achieved by treatment of a *slight* excess of the corresponding halomethanes with methyl hexafluoroantimonate in liquid sulphur dioxide at −78°C under a nitrogen atmosphere[9,158]. The resulting solu-

$$MeX + MeF—SbF_5 \xrightarrow{SO_2(l)} (Me\overset{+}{X}Me)A^- \qquad (206)$$

(4a) X = Cl, $A = Sb_2F_{11}$
(4b) X = Br, $A = Sb_2F_{11}$
(4c) X = I, $A = SbF_6$

tions were stirred for about 5 min at −40°C, and the solvent was subsequently evaporated, leaving **4a–c** as 'fluffy, white crystalline' materials, stable at room temperature under nitrogen but extremely reactive to atmospheric moisture. The PMR and carbon magnetic resonance (CMR) chemical shifts for the dimethylhalonium ions are summarized in Table 6[9,158]. In so far as ^{13}C chemical shifts manifest the degree of positive charge character at carbon, it can be seen from the $\Delta\delta^{13}C$ values that positive charge 'leakage' from the halonium centre to carbon apparently increases in the order I < Br < Cl, albeit not to any great extent.

These researches established the fundamental technology for the preparation of cyclic and acyclic alkylhalonium ions. Closely related *general* methods involve the treatment of haloalkanes with fluoroantimonic acid or with silver hexafluoroantimonate in liquid sulphur dioxide[158].

$$2\ RX + HF—SbF_5 \longrightarrow (R\overset{+}{X}R)SbF_5X^- \qquad (207)$$

$$2\ RX + \overset{+}{Ag}SbF_5^- \xrightarrow{SO_2(l)} (R\overset{+}{X}R)SbF_6^- \qquad (208)$$

C. Some General Observations on Preparative Methodology

1. *The hyperelectrophilic carbon component*

Since the general approach to alkylhalonium ions involves alkylation of the weakly nucleophilic halogen atoms of haloalkanes and haloarenes, presumably via s_N reaction manifolds, it is necessary to provide a complementary reactant (or reaction site in intramolecular cycloalkylations) possessing a hyperelectrophilic carbon atom. This is typically achieved by the selection of compounds with functional groups which can be converted into excellent S_N leaving groups by their complexation with appropriate Lewis acids. The functional group of choice is usually carbon-bound halogen, but others may be employed. The 'π-route' to alkylhalonium ions, of course, does not require a leaving group.

2. The solvent

Alkylhalonium ions are extremely reactive to a broad spectrum of nucleophiles, even very weak ones. It is, therefore, essential that the reaction solvent utilized in their preparation be one of minimum nucleophilicity. One could not hope, for example, to generate persistent alkylhalonium ions in solvents such as acetone or ether. Sulphur dioxide and sulphuryl chloride fluoride have proven to be useful solvents for alkyl halonium ions, the latter solvent offering the advantage of being a liquid over a broader temperature range: SO_2 (m.p. −72.7°C, b.p. −10°C); SO_2ClF [m.p. −124.7°C, b.p. 7.1°C][159] (the physical properties of the pure solvents will, of course, suffer modification with additives such as SbF_5). Sulphuryl chloride fluoride is also more 'weakly nucleophilic' than sulphur dioxide. For example, the bis(chloromethyl)-chloronium ion (**24**) can be prepared by the action of antimony pentafluoride on dichloromethane in sulphuryl chloride fluoride at −130°C[160]. When, however, a solution of **24** is treated with sulphur dioxide, chloromethylation of the sulphur dioxide occurs.

$$CH_2Cl_2 \xrightarrow[-130°C]{SbF_5/SO_2ClF} (ClCH_2-\overset{+}{Cl}-CH_2Cl) \xrightarrow{SO_2} ClCH_2-\overset{+}{O}=S=O \qquad (209)$$

(24)

3. The counterion

The counterions of alkylhalonium ions must, like the reaction solvent, be of very low nucleophilicity. In those cases where the leaving group (or some modification thereof) of the hyperelectrophilic carbon component in the S_N alkylation of haloalkanes and haloarenes eventuates as the counterion (see, for example, equations 204 and 205), the nature of Lewis acid employed as the complexing agent is critical. One might expect, for example, to enjoy greater success in generating persistent alkylhalonium ions from haloalkanes and SbF_5 where the counterion would be SbF_5X^- or $Sb_2F_{10}X^-$ than from haloalkanes and $AlCl_3$ where the counterion would be $AlCl_3X^-$.

When silver salts are employed to generate the hyperelectrophilic carbon component, the counterion of Ag^+ becomes the counterion of the alkylhalonium ion. Obviously, the use of such salts as silver nitrate would preclude the generation of persistent alkylhalonium ions. The same logic applies to Brønsted acids when, for example, the hyperelectrophilic carbon species is produced by the protonation of an alcohol function or a carbon–carbon double bond, i.e. FSO_3H will work, but HCl would cause the ultimate destruction of the halonium ion.

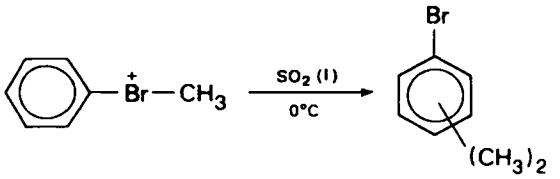
4. Temperature

Low temperatures, typically in the range −60°C to −80°C but sometimes lower, are generally employed for the generation of persistent alkylhalonium ions. At higher temperatures, secondary reactions such as disproportionation, autocondensation and fluorination may become significant.

For example, the bis(chloromethyl)chloronium ion is stable up to −85°C in SbF_5/SO_2ClF, but above that temperature it is converted into difluoromethane[160].

$$(ClCH_2-\overset{+}{Cl}-CH_2Cl)Sb_2F_{10}Cl^- \xrightarrow[T > -85°C]{SbF_5/SO_2ClF} CH_2F_2 \qquad (210)$$

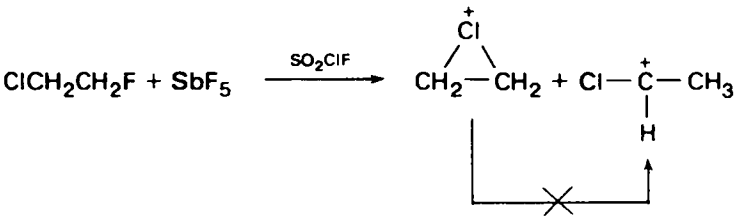
The methyl(phenyl)bromonium ion remains intact in liquid sulphur dioxide at temperatures up to −20°C. However, when it is warmed in a sealed tube, to 0°C, a mixture of bromoxylenes is obtained[161]. The ethyl(phenyl)bromonium ion undergoes a similar transformation at −70°C.



(211)

Unsymmetrical dialkylhalonium ions are subject to disproportionation and autocondensation reactions at −30°C[158] and, in some cases, the transformations of alkylhalonium ions that occur at higher temperatures have simply been described as decomposition reactions.

The effect of temperature on halonium ion synthesis may manifest itself in competing reactions instead of consecutive ones, a case in point being the reaction of 1-fluoro-2-chloroethane with antimony pentafluoride in sulphuryl chloride fluoride. Both the chloriranium and methyl(chloro)carbenium ions are produced in a ratio that depends on the reaction temperature[162]. When the reagents are mixed carefully at −80°C, the chloriranium ion predominates. However, it has been demonstrated that the chlorocarbenium ion does not originate from the halonium ion[162].

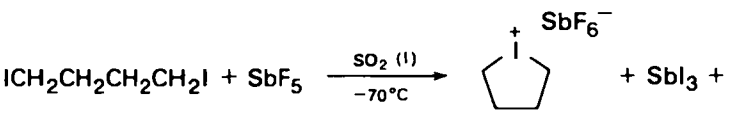


(212)

D. Isolation

Numerous alkylhalonium ions have been observed under stable ion conditions, but few have been isolated from the medium in which they were prepared. In addition to the dimethylhalonium fluoroantimonates **4a–c**, the isolation of tetramethyleneiodonium and pentamethyleneiodonium hexafluoroantimonates has been achieved.

The iodolanium salt (i.e. a five-membered ring) was generated in liquid sulphur dioxide at −70°C by reaction of 1,4-diiodobutane with antimony pentafluoride[163]. The by-products of the reaction (i.e. SbI_3, I_2) were then removed by filtration, and the

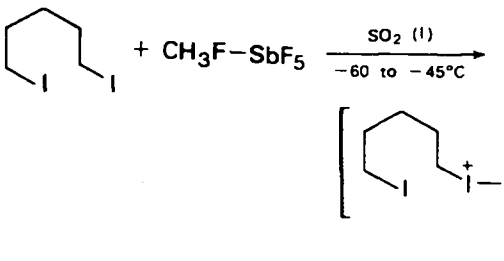


(213)

solvent was evaporated *in vacuo* at −70°C. The crude salt so obtained was washed with dichloromethane and recrystallized from SO_2/CH_2Cl_2 at −70°C as colourless needles having an elemental composition (C, H, I, Sb, F) in complete accord with the assigned structure[163]. The cyclic salt is less stable than its dimethyliodonium analogue, and decomposes in the solid state within 20–25 min at 25°C. The isolation of analogous bromonium and chloronium salts by the same procedure has been mentioned, but no further details were given[163].

The iodanium salt (i.e. a six-membered ring) was prepared by the action of methyl hexafluoroantimonate on 1,5-diiodopentane in liquid sulphur dioxide and pre-

ciptitated from solution by the addition of dichloromethane[164]. It is stable indefinitely at −65°C. This reaction probably proceeds by the intermediate formation and nucleophilic collapse of the methyl(5-iodopentyl)iodonium ion.



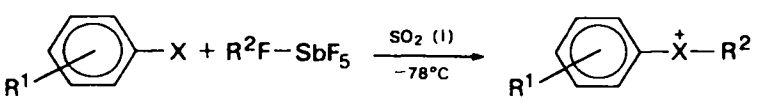
(214)

E. The Alkyl Fluoride–Antimony Pentafluoride–Sulphur Dioxide System

The 'alkyl hexafluoroantimonates' in $SO_2(l)$ or $SO_2ClF(l)$ are clearly the reagents of choice for the preparation of unsymmetrical alkylhalonium ions. In addition to the unsymmetrical dialkylhalonium ions of general structure $(R^1—X^+—R^2)A^-$ already discussed, alkyl hexafluoroantimonates have been utilized in the generation of alkyl(haloalkyl)halonium ions[160,165], alkyl(aryl)halonium ions[161,165], di- and trihalonium ions[165] and alkyl(cyclopropyl)halonium ions[166]. Selected examples of each of these reactions are given in equations (215)–(220).

$$ClCH_2X + CH_3F—SbF_5 \xrightarrow[-130°C]{SO_2ClF} ClCH_2\overset{+}{X}CH_3 \quad (215)$$

X = Cl, Br, I



(216)

R^1	X	R^2
H	I, Br	Me, Et
p-F	I, Br	Me, Et
p-Me	I, Br	Me
o-Br	Br	Me

$$XCH_2CH_2X + RF—SbF_5 \xrightarrow[-78°C]{SO_2(l)} R—\overset{+}{X}CH_2CH_2\overset{+}{X}—R \quad (217)$$

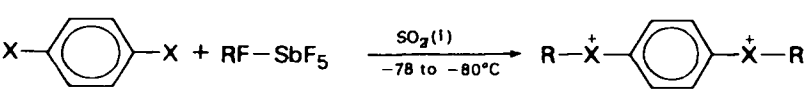
(excess)

X = I; R = Me, Et

$$XCH_2CH_2CH_2X + RF—SbF_5 \xrightarrow[-78°C]{SO_2(l)} R—\overset{+}{X}CH_2CH_2CH_2\overset{+}{X}—R \quad (218)$$

(excess)

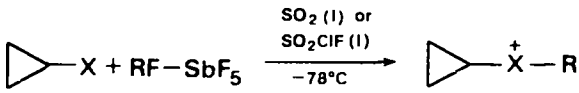
X = Br, I; R = Me, Et



(219)

X = I; R = Me, Et

X = Br; R = Me



(220)

X	R
I	Me, Et, Pr^i
Br	Me, Et, Pr^i
Cl	Me, Pr^i

It has been suggested that 'methyl hexafluoroantimonate' actually exists primarily as $(CH_3{-}O^+{=}S{=}O)SbF_6^-$ (or $Sb_2F_{11}^-$) when it is present in liquid sulphur dioxide[167]. Indeed, when sulphur dioxide is added to a solution of methyl hexafluoroantimonate in sulphuryl chloride fluoride at −78°C, a white solid is obtained which reacts with methyl alcohol to give dimethyl sulphite. The methylating capacity of $CH_3F{-}SbF_5$ is

$$CH_3F{-}SbF_5 + SO_2 \xrightarrow[-78°C]{SO_2ClF} \text{White ppt} \xrightarrow[-65°C]{CH_3OH} CH_3O\overset{\overset{O}{\|}}{S}OCH_3 \quad (221)$$

rather remarkable. Thus, even though sulphuryl chloride fluoride is not alkylated by secondary and tertiary carbocations, evidence has been presented for the methylation of this solvent with $CH_3F{-}SbF_5$ at 0°C[168].

F. Other Preparative Methods

Certain alkylhalonium ions are accessible by methods other than those already considered. These procedures are, however, limited in scope and complicated by competing reactions.

1. *Chlorinolysis of alkanes*

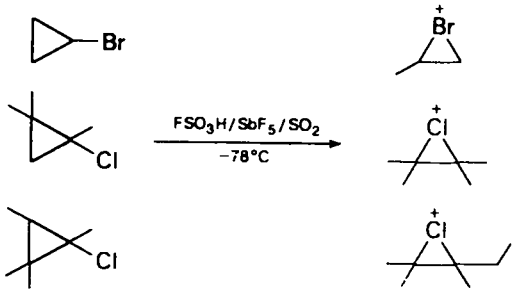
The condensation of molecular chlorine into an SbF_5/SO_2ClF solution at −78°C affords a reagent sufficiently potent to effect the electrophilic chlorinolysis of sigma bonds[169]. Thus, methane is converted cleanly, by this system, into the dimethylchloronium ion[169]. When ethane is the substrate, the dimethyl- and diethylchloronium ions are generated in a 7:3 ratio in addition to the methyl(ethyl)chloronium ion. Propane is converted primarily into the bis(isopropyl)chloronium ion, but a mixture of the *t*-butyl, *t*-amyl and *t*-hexyl cations also results. Mixtures of chloronium

$$CH_3{-}CH_3 + Cl{-}\overset{+}{Cl}{-}{}^-SbF_5 \xrightarrow[-78°C]{SO_2ClF} (CH_3)_2\overset{+}{Cl} + (CH_3CH_2)_2\overset{+}{Cl} + CH_3CH_2\overset{+}{Cl}CH_3 \quad (222)$$

ions and tertiary carbocations are likewise generated when the high alkanes (i.e. butanes, pentanes, hexanes, heptanes and octanes) are subjected to the action of this reagent[169].

2. *Protonolysis of halocyclopropanes*

The treatment of cyclopropyl bromide, 1,2,2-trimethylcyclopropyl chloride and 1,2,2,3-tetramethylcyclopropyl chloride with FSO_3H/SbF_5 in $SO_2(l)$ eventuates in haliranium ions, presumably via protonolysis of the carbon–carbon bonds of the cyclopropane nucleus[170]. Similar treatment of 2,2,3,3-tetramethylcyclopropyl



(223)

bromide, however leads to equilibrating β-bromocarbenium ions while pentamethylcyclopropyl chloride collapses to the pentamethylallyl cation[170].

It is finally to be noted that alkylhalonium ions have been generated by the action of alkyl hexafluoroantimonates on either alkali metal halides or *t*-alkyl halides in $SO_2(l)$[158].

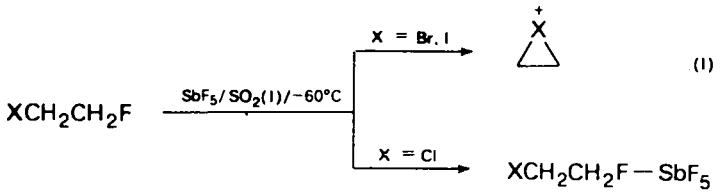
For detailed tabulations of structures and spectral properties of those alkylhalonium ions prepared prior to 1975, the reader is directed to an earlier review[15].

G. Cyclic Analogues; Observations on Stability and Electronic Structure

1. *Haliranium ions*

The preparation of ethylenehalonium ions[162,171], methylethylenehalonium ions[171], 1,2-dimethylethylenehalonium ions[171], 1,1-dimethylethylenehalonium ions[172], 1,1,2-trimethylethylenehalonium ions[172] and tetramethylethylenehalonium ions[10] by the direct ionization of dihaloalkanes with antimony pentafluoride in liquid sulphur dioxide has been achieved.

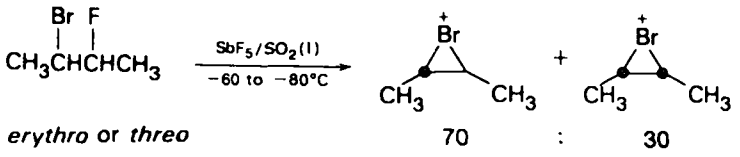
One of the more striking facts that emerges from such studies is the relative difficulty of generating chloronium analogues, consistent with the observation that, among organohalonium ions of all sorts, the general stability trend seems to iodonium > bromonium > chloronium. For example, while the ionizations of 2-iodo- and 2-bromo-1-fluoroethanes with SbF_5 in SO_2 at −60°C eventuate in the iodiranium and bromiranium ions, similar treatment of 1-fluoro-2-chloroethane affords only an acid–base complex[171]. *Erythro*-D,L- and *threo*-D,L-2-fluoro-3-bromobutanes, under the



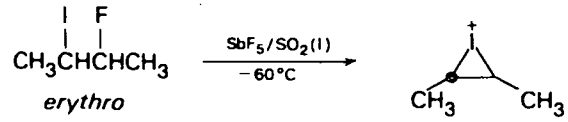
(224)

same ionization conditions, each lead to a 30:70 mixture of *cis*- and *trans*-1,2-dimethylbromiranium ions. The ionizations of the corresponding iodo substrates are at least 95% stereospecific, the *erythro* diastereomer giving *trans*-1,2-dimethyliodiranium ion and the *threo* diastereomer affording the *cis* isomer. The ionization of 2-fluoro-3-chlorobutane, on the other hand, takes a markedly different course and results in the production of a mixture of carbenium ions (equations 225–228).

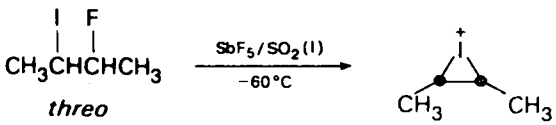
Similar ionizations of 1,2-dichloropropane[171] and 1-chloro-2-fluoro-2-methylpropane[172] likewise fail to yield the 1-methyl- and 1,1-dimethylchloriranium ions. However, with the preparation of trimethyl- and tetramethylhaliranium



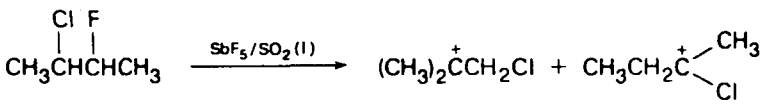
erythro or *threo* 70 : 30 (225)



erythro (226)



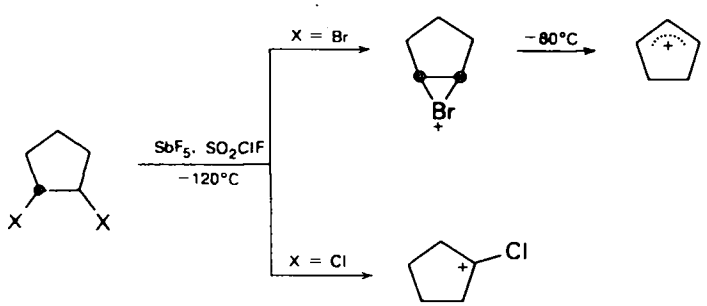
threo (227)



40 : 60 (228)

ions, chloroalkanes conform to the same reactivity pattern as the bromo- and iodoalkanes do[10,172].

In another study, a bicyclic bromiranium ion was prepared by the reaction of *trans*-1,2-dibromocyclopentane with SbF_5 in SO_2ClF at $-120°C$[173]. Similar treatment of trans-1,2-dichlorocyclopentane, however, gives a chlorocarbenium ion instead of a bicyclic chloriranium ion.

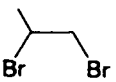
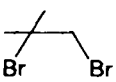
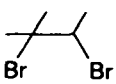
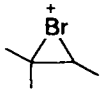
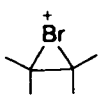


(229)

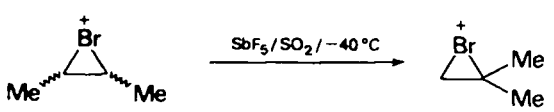
The ability of alkyl substituents to stabilize the haliranium nucleus has been placed on a quantitative basis for the bromonium family of compounds[174]. Relative heats of formation for several bromiranium ions from appropriate dibromoalkanes in 11.5 mol% SbF_5/FSO_3H at $-60°C$ are presented in Table 7, the standard state of the precursors taken to be their carbon tetrachloride solutions at 25°C[174]. It can be seen that the placement of each methyl substituent in the bromiranium nucleus is attended by a stabilization factor of about 5 kcal mol^{-1}, and, when three methyl groups are present, the bromonium ion is comparable in stability to the *t*-butyl cation.

Although the heats of formation of the 1,2-dimethyl analogues were not determined, the clean isomerization of a mixture of *cis*- and *trans*-1,2-dimethylbromiranium ions to the 1,1-dimethylbromiranium ion in SbF_5/SO_2 at $-40°C$ has been observed, thus establishing the greater thermodynamic stability of the latter

TABLE 7. Heats of formation of alkylbromiranium ions from dibromoalkanes in 11.5 mol% SbF_5/FSO_3H at $-60°C$[174]

Bromoalkane	Product ion	ΔH (kcal mol^{-1})
		−3.29 ± 0.51
		−8.39 ± 0.87
		−13.4 ± 0.90
		−22.9 ± 4.00
$Me_3C—Br$	Me_3C^+	−14.5 ± 2.0

species[171]. The analogous isomerization of the 1,2-dimethyliodiranium ion does *not* occur, however, even after 10 min at $-15°C$[171].



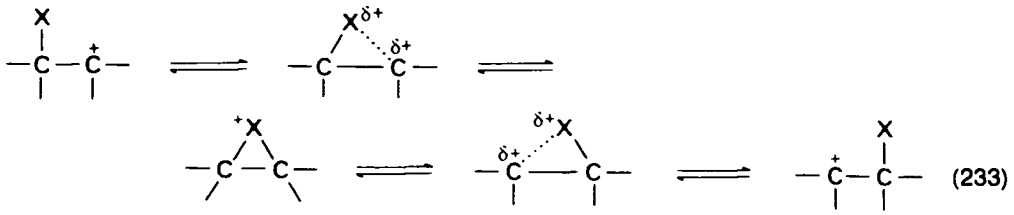
(230)

The ionizations of precursors that should give rise to symmetrical haliranium ions do indeed eventuate in cationic species whose PMR and ^{13}CMR spectra reveal proton and carbon equivalences consistent with static bridged structures. For example, the CMR spectrum of the ethylenebromonium ion (SO_2, $-40°C$, internal $^{13}CS_2$) exhibits only a singlet at +120.8 p.p.m.[175,176]. The PMR spectrum (SbF_5/SO_2, $-60°C$, external TMS) likewise features a broad singlet at 5.53 p.p.m.[171]. Similarly, the tetramethylethylenebromonium ion reveals carbon resonances at +54.1 p.p.m. (ring carbons) and +167.1 p.p.m. (methyl carbons)[175] and a proton singlet at $\delta 2.72$[10].

However, such spectral features do not provide unequivocal evidence for static, symmetrically bridged bromonium ions. The *gross* spectral characteristics are also consistent with rapidly equilibrating β-bromocarbenium ions or rapidly equilibrating unsymmetrically bridged ions or, for that matter, a system containing various combinations of such species in a state of rapid dynamic interconversion. Static unsymmetrical structures can, however, be ruled out[175].

(231)

(232)

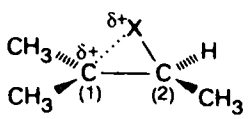


(233)

One useful probe for distinguishing among these possibilities rests on comparisons of ^{13}C chemical shifts and ^{13}CH coupling constants of 'haliranium ions' with those of classical carbenium ions taken as models. On the basis of such comparisons, it has been argued that the parent bromiranium ion possesses a symmetrically bridged structure[176]. If, for example, the bromiranium ion in $SO_2(l)$ is actually a pair of β-bromoethyl cations in a state of rapid degenerate interconversion, the observed ^{13}C chemical shift should be an average of those of the carbocation and sp^3 carbon centres. Estimates of these shifts based on model compounds, are −115 and 156 p.p.m. respectively, the average of which is drastically different from the observed value of 120.8 p.p.m.; equilibrating carbenium ions, therefore, seem an unlikely structural alternative[176].

The very fact that *cis* and *trans* modifications of the 1,2-dimethylbromiranium ion can be observed is thought to be compelling evidence for their existence as symmetrically bridged species[175]. Open ion structures would be expected to promote rapid *cis* ⇌ *trans* interconversion on the NMR time scale and, therefore, mask the distinction between them. The exact structure of the tetramethyl analogue as it exists in solution is, however, still an open question[175].

With unsymmetrically substituted alkylhaliranium ions, unsymmetrical bridging is indicated by spectral evidence. The PMR spectra of the trimethylhaliranium ions **25a–c** exhibit two intriguing features[172]. First, the geminal methyl substituents in all three ions are more highly deshielded than the remaining methyl group, a phenomenon consistent with more carbenium ion character at the tertiary carbon atom than at the secondary carbon atom and, therefore, unsymmetrical bridging. Second, when X = I, the *gem*-methyl groups are magnetically non-equivalent, as



(25a) X = Cl

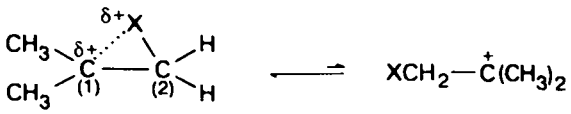
(25b) X = Br

(25c) X = I

expected for a static bridged species, but, when X = Br, or Cl, the *gem*-methyl groups in each case are equivalent, possibly indicative of C_1—C_2 bond rotation via an open ion intermediate. However, with classical cations, such as the *t*-amyl cation, CH_3—CH_2—$C^+(CH_3)_2$, long range H···H coupling through the carbenium centre is observed. The absence of such coupling in the 1,1,2-trimethylchloriranium and -bromiranium ions would seem to indicate that, if an open species such as $CH_3CH(X)$—$C^+(CH_3)_2$ does exist in solution, its concentration must be very low. It has been suggested that the *gem*-methyl equivalence in these two ions is fortuitous[172].

The ^{13}C chemical shifts of the ring carbons of the 1,1-dimethylbromiranium and -iodiranium ions are more consistent with unsymmetrically bridged structures than with open carbenium ion structures[175]. For the former species the $C_{(1)}$ and $C_{(2)}$ shifts

(SO_2, $-40°C$, $^{13}CS_2$) are -17.6 and 133.3 p.p.m. respectively, and for the latter ion they are 7.8 and 141.0 p.p.m. The carbon shifts for the 1,1-dimethylbromiranium ion are also relatively temperature independent between -20 and $-80°C$. Thus, if the bridged ion is in equilibrium with an open ion in solution, the concentration of the open species must be very low[175].

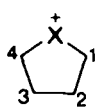


(234)

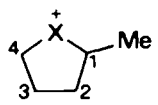
2. *Halolanium ions*

The generation of a variety of tetramethylenehalonium ions (i.e. halolanium ions) in liquid sulphur dioxide has been accomplished, usually via the ionization of halo precursors, but, for some ions, other approaches have also beem employed. A listing of reported structures is given in Table 8 along with appropriate literature references.

Several studies have focused on the ^{13}C NMR spectra of halolanium ions[180–182]. Chemical shifts at $C_{(1)}$ and $C_{(4)}$ (SO_2(1), $-65°C$, $^{13}CS_2$) for the parent species and their 1-methyl analogues are given below[182].



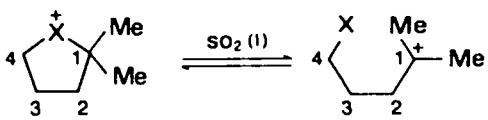
X	$\delta^{13}C$ (p.p.m.)
Cl	+115.3
Br	+122.5
I	+144.3



	$\delta^{13}C$ (p.p.m.)	
X	$C_{(1)}$	$C_{(4)}$
Cl	+80.0	+118.3
Br	+87.1	+124.1
I	+110.2	+144.1

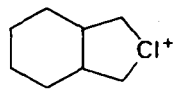
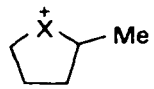
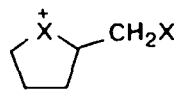
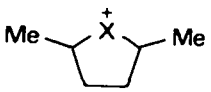
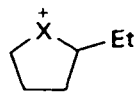
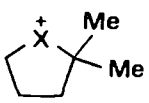
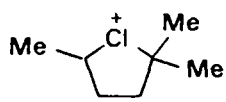
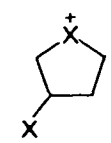
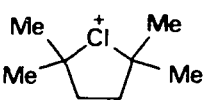
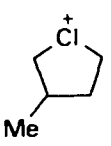
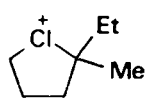
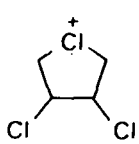
The placement of a methyl group at $C_{(1)}$ of the halolanium nucleus is attended by a downfield shift of about 35 p.p.m. in all three cases. This has been compared to a downfield shift of 290 p.p.m. characteristic of the conversion of a hydrocarbon to a carbenium ion[182]. Thus, the methyl group appears to increase the cationic character of α-carbon in halolanium ions by a factor of 12%[182]. With the 1,1-dimethylhalolanium ions, the ^{13}C shift differential between $C_{(1)}$ and $C_{(4)}$ is more drastic, but it is not the same for all halogen atoms. At $-56°C$ in SO_2(l), the ^{13}C chemical shifts for the 1,1-dimethylchlorolanium ion are $C_{(1)}$ (-4.6 p.p.m.) and $C_{(4)}$ (128.3 p.p.m.), while those of the bromolanium analogue are $C_{(1)}$ (48.1 p.p.m.) and $C_{(4)}$ (127.8 p.p.m.)[180].

The NMR spectra recorded for halolanium ions are not always those of pure, static, cyclic species but may, in some cases, be the composite spectra of halolanium ions in *rapid* equilibrium with open carbocations, especially when $C_{(1)}$ is tertiary and $C_{(4)}$ is primary. Such equilibrium processes can be effectively probed by ^{13}C NMR spectroscopy. When such equilibria pertain, the $C_{(1)}$ chemical shifts should exhibit a marked dependence on temperature whereas the $C_{(2)}$, $C_{(3)}$ and $C_{(4)}$ chemical shifts



(235)

TABLE 8. Various halolanium ion structures reported in the chemical literature

Structure	Reference	Structure	Reference
 X = Cl, Br, I	155		178
 X = Cl, Br, I	155	 X = Cl, Br	179
 X = Cl, Br, I	155	 X = Cl, Br, I	180
 X = Cl, Br, I	177		180
 X = Cl, Br	178		180
	178		181
	178		

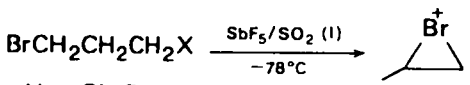
should be relatively insensitive to the same. For, the 1,1-dimethylchlorolanium ion, this is indeed observed[180]. As the temperature is raised from −69.3 to −56.1 to −41.3°C, the gross appearance of the CMR spectrum remains the same, but the $C_{(1)}$ resonance moves downfield (i.e. from 1.4 to −4.6 to −11.0 p.p.m.). The chemical shift of $C_{(1)}$ in the 1,1-dimethylbromolanium ion exhibits a similar dependence on temperature, but the effect is not nearly so pronounced, this being indicative of a much lower equilibrium concentration of the isomeric carbenium ion[180]. At −69.3°C in

$SO_2(l)$, the equilibrium constants for the 1,1-dimethylchlorolanium and -bromolanium ion isomerizations are 0.31 and 0.049 respectively[180].

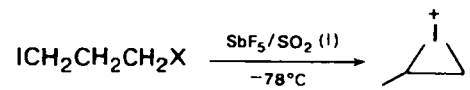
Sulphuryl chloride fluoride appears to be somewhat better than sulphur dioxide at stabilizing halolanium ions. In one study, the equilibrium constants for the conversion of the 1,1-dimethylchlorolanium ion to the open tertiary carbocation were determined and are 0.31 in $SO_2(l)$ and 0.21 in $SO_2ClF(l)$ at $-60°C$[183]. This result probably reflects the greater nucleophilicity of sulphur dioxide and, therefore, its greater ability to solvate carbenium ions.

3. *Haletanium and halanium ions*

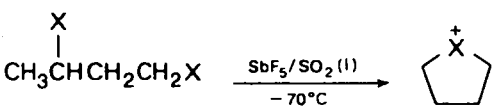
Although a number of haliranium and halolanium ions have been observed under stable ion conditions, the four-membered and six-membered analogues are rare. Attempts to prepare such ions by direct ionization procedures usually eventuate in three- and five-membered cyclic halonium ions. Examples of such reactions are given in equations (236)–(240).



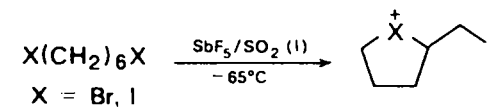
(236)[184]



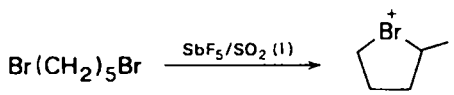
(237)[184]



(238)[184]

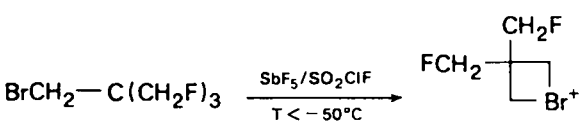


(239)[180]



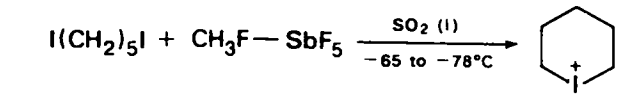
(240)[163]

A rare example of a trimethylenehalonium ion (i.e. haletanium ion) is provided by the generation of the 3,3′-bis(fluoromethyl)brometanium ion by the action of antimony pentafluoride on 1-bromo-3-fluoro-2,2-bis(fluoromethyl)propane in sulphuryl chloride fluoride[185]. The structure of this brometanium ion was established by PMR analysis and by its solvolysis in K_2CO_3/MeOH at $-78°C$[185].

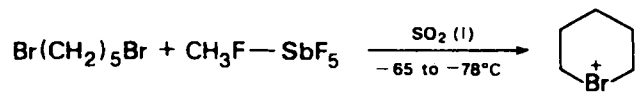


(241)

The best approach to pentamethylenehalonium ions (i.e. halanium ions) seems to be the treatment of 1,5-dihalopentanes with alkylating reagents such as CH_3F:SbF_5 or $(CH_3)_2X^+$ [163]. Some indication of the greater stability of five-membered halonium ions compared to their six-membered analogues is provided by the observation of the



95 : 5 (242)



(55−72%) (45−28%) (243)

(73%) (27%) (244)

isomerization of the bromanium ion to the 2-methylbromolanium ion at −20°C (50% in 20 min, presumably in SO_2(l))[163]. The equilibrium constant for the isomerization of the 2,2-dimethylchloranium ion to the corresponding open tertiary carbenium ion in liquid sulphur dioxide at −59.7°C has also been determined and is 6.8 ± 2.0[181].

(245)

The greater apparent stability of cyclic halonium ions with an odd number of ring atoms compared with those containing an even number of ring atoms has been rationalized in terms of a bonding model relating the symmetries of Walsh type molecular orbitals in the ring to the symmetries of d-orbitals on the heteroatom[186].

H. Reactions with Nucleophiles

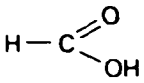
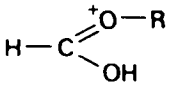
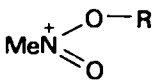
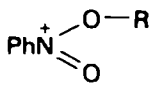
Alkylhalonium ions are potent alkylating agents for a broad spectrum of weakly nucleophilic species. Some example reactions of dimethyl- and diethylchloronium and -bromonium ions with various N-donor nucleophiles are given under equation (246). The methodology employed in this particular study was to (1) add aliquots of the dialkylhalonium ion in SO_2(l) at *c.* −60°C to the nucleophile at −78°C, (2) warm the reaction mixtures to −15°C and, after 5 min, recool them to −60°C, and (3) identify the products by NMR analysis[158,187]. It is noteworthy that the corresponding iodonium ions failed to alkylate the indicated nucleophiles either in SO_2(l) or SO_2FCl(l) at temperatures ranging from −78 to 0°C[158].

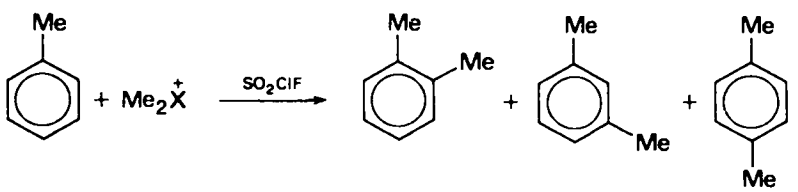
The dialkylhalonium ions also react with arenes in typical Friedel–Crafts fashion[158]. For example, the dimethylchloronium and -bromonium ions react readily with toluene in SO_2ClF at −50°C to give a mixture of xylenes, and, the dimethyliodonium ion reacts similarly but requires temperatures of 0°C or above (equation 247).

In another study, the chlorolanium ion was generated in SO_2(l) by the treatment of 1,4-dichlorobutane with two equivalents of antimony pentafluoride. Various nucleophiles were then added at −60°C, and the initial alkylation products were ascertained by NMR analysis[179]. In preparative runs, reaction mixtures were subjected to a water workup, and the yields of the resulting products were determined by gas chromatographic methods[179]. The results are summarized in equation (248).

$$R-\overset{+}{X}-R + B: \xrightarrow{SO_2(l)} R-\overset{+}{B} + RX \qquad (246)$$

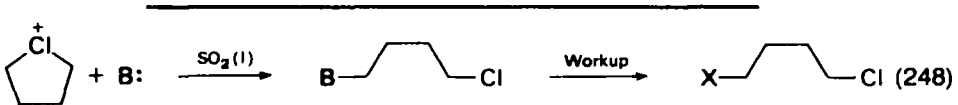
X = Cl, Br; R = Me, Et

B:	RB^+
Me_2O	Me_2O^+R
MeOH	$MeO^+(H)R$
$Me_2C{=}O$	$Me_2C{=}O^+{-}R$
$MeCH{=}O$	$MeCH{=}O^+{-}R$
	
$MeNO_2$	
$PhNO_2$	
Et_2S	Et_2S^+R
$Bu^t{-}SH$	$Bu^t{-}S^+(H)R$
Et_3N	Et_3N^+R



(247)

X	Time, min	Temperature, °C	*o*:*m*:*p* ratio
Cl	5	−50	52.3:15.7:32.0
Br	5	−50	57.8:9.5:32.7
I	10	0	53.9:11.8:34.3



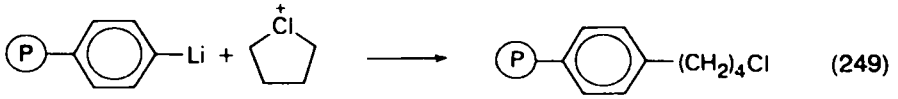
(248)

Initial product

B:	B	X (yield)
CH_3OH		$CH_3O{-}$ (70–80%)
CH_3CN	$CH_3C{\equiv}N^+{-}$	$CH_3CONH{-}$ (86%)
CH_3OCH_3	$(CH_3)_2O^+{-}$	$CH_3O{-}$ (91%)
$CH_3CH_2CH_2OCH_3$	$CH_3CH_2CH_2O^+CH_3$	$CH_3O{-}$ (28%); $CH_3CH_2CH_2O{-}$ (63%)
$(CH_3)_2C{=}O$	$(CH_3)_2C{=}O^+{-}$	HO− (50%)
CH_3COOH		$CH_3COO{-}$ (62%)

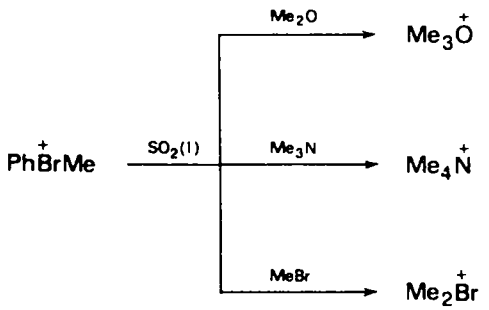
*Worked up with CH_3OH/Na_2CO_3.

More recently, the chlorolanium ion has been utilized to functionalize polystyrene via polystyryllithium[188]. The iodolanium and 2,2-dimethylbromolanium ions are, however, inferior in this regard.



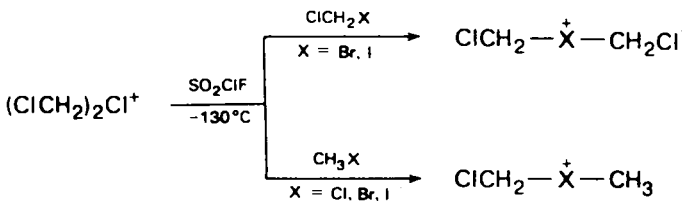
(249)

As one might expect, the methyl(phenyl)bromonium ion is an alkylating reagent and not an arylating reagent, as evidenced by its reactions with dimethyl ether, trimethylamine and bromomethane in $SO_2(l)$[161]. It is interesting that the reaction with bromomethane is irreversible, thus pointing to the greater thermodynamic stability of the dimethylbromonium ion. The bis(chloromethyl)chloronium ion has proven to be a



(250)

particularly useful reagent in reactions with halomethanes as nucleophiles, the result being chloromethylation of a lone pair on halogen[160].

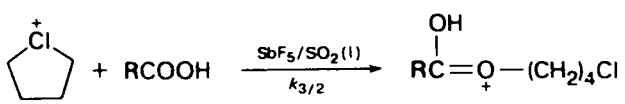


(251)

The kinetics of the reactions of various aliphatic carboxylic acids with the chlorolanium ion in $SbF_5/SO_2(l)$ have been investigated[189]. With acetic acid as the nucleophile, the rate law was determined to be

$$-d[CH_3COOH]/dt = k_{3/2}[\text{halonium ion}][CH_3COOH]^{1/2}.$$

The fractional order in acetic acid may manifest a prior equilibrium between the monomeric acid and its dimer, if the equilibrium constant for the dissociation of the dimeric species is $\leq 10^{-4}$ and if the monomeric species is alkylated exclusively[189]. At $-65.6°C$, the relative rates for the carboxylic acids studied are HCOOH (1.37),



(252)

CH_3COOH (1.00), $ClCH_2COOH$ (0.102), $Cl_2CHCOOH$ (0.0056) and CF_3COOH (0.000 21). A plot of log $k_{3/2}$ versus pK_a is linear, although the point for formic acid is somewhat deviant, and a better correlation results if the rate constant for that acid is

divided by a factor of two. A plot of $\log(k_X/k_H)$ versus $\Sigma\sigma_1$ for the acetic acid family of compounds likewise generates a straight line with $\rho_I = -2.39$[189].

In other studies, the use of the chlorolanium ion[190] and the iodanium ion[164] as substrates for the construction of nucleophilicity scales has been described.

I. Occurrence in the Gas Phase

Although the focus of this chapter has been on the solution phase chemistry of organohalonium ions, the past 8 years have witnessed an increasing interest in the stability and chemical transformations of such species in the gas phase.

Such studies include the recognition of chlorolanium and bromolanium ions as abundant fragments in the mass spectra of *n*-alkyl chlorides and bromides comprised of six to 18 carbon atoms[191,192], the measurement of equilibrium constants for ion-molecule reactions of the type $R^+ + CH_3Cl \rightleftharpoons (RClCH_3)^+$, where $R^+ = CH_3\overset{+}{C}H_2$ or $(CH_3)_2\overset{+}{C}H$[193], the determination, by ion cyclotron resonance, of bromide ion affinities for various bromiranium and bromolanium ions[194], a comparison of the stabilities of chloriranium and bromiranium ions with isomeric carbenium ions of the type $CH_3\overset{+}{C}HX$[195], and an assessment of the stereochemistry of acid-induced nucleophilic displacement reactions of 2,3-dihalobutanes involving haliranium ion intermediates[196].

Finally, several molecular orbital studies of organohalonium ions have been published[197–200].

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CHAPTER **26**

Carbon–carbon bond formation involving organic halides and transition metal compounds

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I. INTRODUCTION

The formation of C—C bonds is the abecedarian reaction of organic synthesis. A host of methods is available to carry out such a fundamental process, but this review will focus on the use of organometallic reagents. Several excellent books on this topic have been published in the last few years[1-9].

Among the various types of substrates which can be reacted with organometallics, organic halides are very familiar. Indeed, these compounds undergo an extensive series of reactions. Often, however, the organic chemist cannot fully appreciate their importance. This is mainly due to the fact that traditionally the behaviour of organic halides is 'diluted' in discussions dealing with specific reagents and a variety of substrate types. In this review we will concentrate on the halides in an attempt to cover the most significant of their reactions with organometallics leading to C—C bond formation. However, in order to restrict the topics to be considered to within reasonable limits, we have selected only those processes which involve the use of transition metal derivatives either as reagents or as catalysts. In fact, simple non-transition metal organoderivatives are much less versatile in the formation of the C—C bonds with halides due to competing reactions such as metal–halogen exchange, elimination and homocoupling.

A large proportion of this chapter (Sections II and III) will be devoted to the cross-coupling reactions between organometallics and halides because we agree with Negishi's, view[1] that 'if one could achieve any type of cross-coupling at will, most of the problems of organic skeletal construction would be solved'. The coupling between

two identical halide molecules will be discussed in Section IV. We shall also see (Section V) that, in the presence of transition metal complexes, organic halides can undergo a variety of C—C bond formations with alkenes or alkynes. In Section VI attention will be focused on the special role of π-allylnickel complexes. Section VII will be devoted mainly to a series of cyclocoupling reactions involving α,α'-dihaloketones. Discussions of carbonylation and cyanation reactions (Sections VIII and IX) will conclude the chapter.

II. REACTIONS OF ORGANOCOPPER(I) REAGENTS

A. Introduction

The title reagents are enjoying deserved popularity and providing broadly applicable procedures for the formation of carbon–carbon σ bonds[10–14]. Although these reagents have been known for a long time, recent years have witnessed their increasing use. Indeed, phenylcopper was prepared by Reich[15] in 1923 but copper acetylides, which can be considered the oldest members of the family, were known more than a century ago[16]. Cuprates were introduced forty-five years ago by Gilman and Straley[17]. However, the synthetic potential of these reagents was uncovered by Corey and Posner[18] in 1967 and fully developed in subsequent years.

Oganocopper(I) reagents can be divided into two main classes: (i) mono-organic reagents and (ii) cuprates. The reagents of the first type are usually prepared according to the following equation:

$$RM + CuX \longrightarrow RCu + MX \quad (1)$$

R = alkyl, aryl, vinyl, etc.; M = Li, MgX; X = I, Br, Cl

The isolation and characterization of some of the above organocopper compounds are mainly due to the efforts of Costa, Camus and their coworkers[19]. Fundamental work on the same subject has been also carried out by Noltes, van Koten and their coworkers[20].

Several types of cuprate can be prepared and used profitably: i.e. symmetric homocuprates (equations 2 and 3), unsymmetric homocuprates (equation 4) and heterocuprates (equation 5).

$$RCu + RM \longrightarrow R_2CuM \quad (2)$$

$$2\,RM + CuX \longrightarrow R_2CuM + MX \quad (3)$$

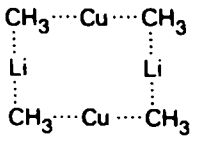
$$RCu + R^1M \longrightarrow RR^1CuM \quad (4)$$

$$YCu + RM \longrightarrow RYCuM \quad (5)$$

Y = PhS, PhO, *t*-BuO, CN; M = Li, MgX

Throughout this review we shall deal in most cases with cuprates and notations will be used similar to those presented in equations (2)–(5). However, it is worth noting that the actual structures of these reagents are not well known[21–23]. The structure **1** has been suggested for lithium dimethylcuprate in ether solution[21] and similar conclusions have been reached in the case of the 4-tolyl derivatives[22].

Ligands (such as dimethyl sulphide or phosphines) are used to dissolve the copper(I) halide necessary for the formation of cuprates according to equation (3). Also, stabilization of the species formed is increased due to the intervention of these ligands. Such a stabilization is particularly necessary in the case of tertiary dialkylcuprates[24].



(1)

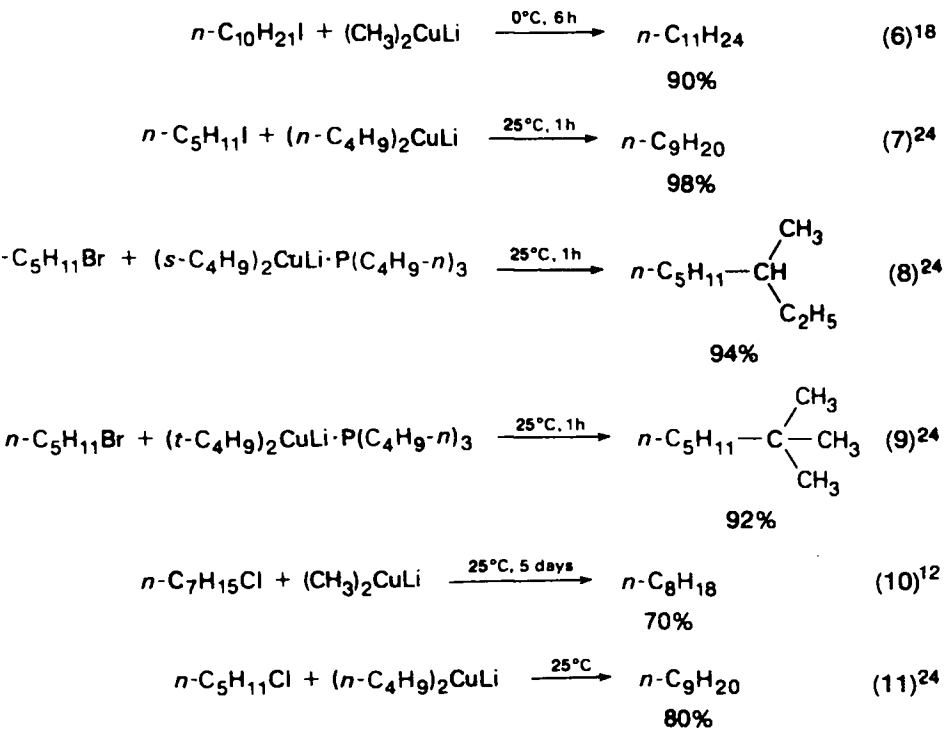
Furthermore, reagents obtained by mixing 2 equivalents of alkyllithium with 1 equivalent of polymer-bound iodo(triarylphosphine)copper(I) have been found to give results which in some cases are superior to those obtained with homogeneous reagents[25].

Cuprates react rather easily, usually in ether or tetrahydrofuran (THF), and in the temperature range −78 to 25 °C, with almost any kind of halide, giving cross-coupling products. We shall devote this section to these reactions using a classification based upon the nature of the substrate.

B. Cross-coupling Reactions with Alkyl Halides

The success of cross-coupling between cuprates and alkyl halides depends on the nature of the reagent and on that of the substrate.

Primary halides react with a variety of cuprates in good yields and no particular problem is faced. From the representative cases reported below it appears that iodides (equations 6 and 7), bromides (equations 8 and 9), or chlorides (equations 10 and 11) can be used, the last-mentioned type of halide being the least reactive. As shown by equations (12)–(14), the procedure tolerates a variety of functional groups (e.g. olefin, carboxy, amide, ester).



$$n\text{-}C_{10}H_{21}I + (CH_3)_2CuLi \xrightarrow{0°C,\ 6\,h} n\text{-}C_{11}H_{24} \quad (6)^{18}$$

90%

$$n\text{-}C_5H_{11}I + (n\text{-}C_4H_9)_2CuLi \xrightarrow{25°C,\ 1\,h} n\text{-}C_9H_{20} \quad (7)^{24}$$

98%

$$n\text{-}C_5H_{11}Br + (s\text{-}C_4H_9)_2CuLi\cdot P(C_4H_9\text{-}n)_3 \xrightarrow{25°C,\ 1\,h} n\text{-}C_5H_{11}\text{—}CH(CH_3)(C_2H_5) \quad (8)^{24}$$

94%

$$n\text{-}C_5H_{11}Br + (t\text{-}C_4H_9)_2CuLi\cdot P(C_4H_9\text{-}n)_3 \xrightarrow{25°C,\ 1\,h} n\text{-}C_5H_{11}\text{—}C(CH_3)_2(CH_3) \quad (9)^{24}$$

92%

$$n\text{-}C_7H_{15}Cl + (CH_3)_2CuLi \xrightarrow{25°C,\ 5\ days} n\text{-}C_8H_{18} \quad (10)^{12}$$

70%

$$n\text{-}C_5H_{11}Cl + (n\text{-}C_4H_9)_2CuLi \xrightarrow{25°C} n\text{-}C_9H_{20} \quad (11)^{24}$$

80%

$$CH_2{=}CHCH_2OCH_2CH_2CD_2I + (CH_3)_2CuLi \xrightarrow{0°C,\ 12\,h} CH_2{=}CHCH_2OCH_2CH_2CD_2CH_3 \quad (12)^{26}$$

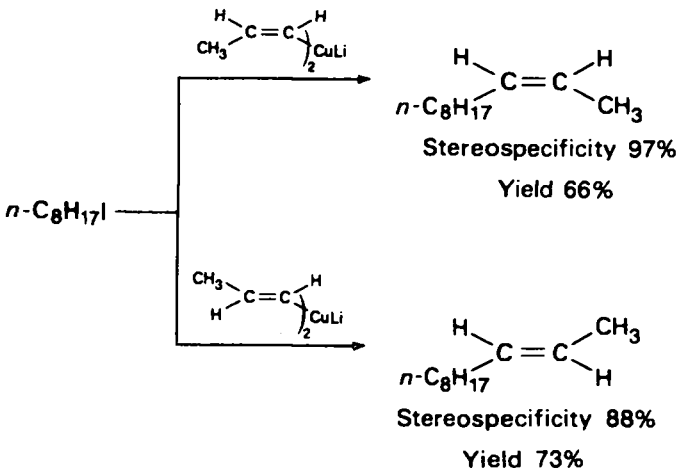
$$RCO(CH_2)_{10}I + (n\text{-}C_4H_9)_2CuLi \longrightarrow RCO(CH_2)_{13}CH_3 \quad (13)^{27}$$

R = OH, $Ph(CH_3)N$ 60–80%

$$C_2H_5O_2C(CH_2)_{10}I + CH_2{=}CH(CH_2)_8\overset{CH_3}{\overset{|}{C}}H_2CuMgCl \longrightarrow CH_2{=}CH(CH_2)_{19}CO_2C_2H_5 \quad (14)^{28}$$

79%

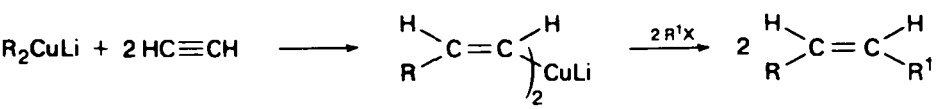
The reaction of primary halides with alkenyl cuprates occurs with retention of the configuration of the double bond present in the reagent, thus permitting a stereospecific entry into olefins:



(15)[29]

In the reaction of equation (15) a $(CH_3O)_3P$ complexed cuprate was used. In the case of the *E*-isomer a higher degree of stereospecificity (96%) can be reached by carrying out the reaction in the presence of HMPT[30].

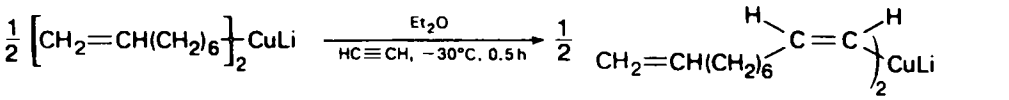
As far as the synthesis of *Z*-olefins is concerned, much progress has been made by the group of J. F. Normant with the use of the *Z*-dialkenylcuprates generated by the *syn* addition of dialkylcuprates to acetylene[31]. The overall process occurs according to the following equation:



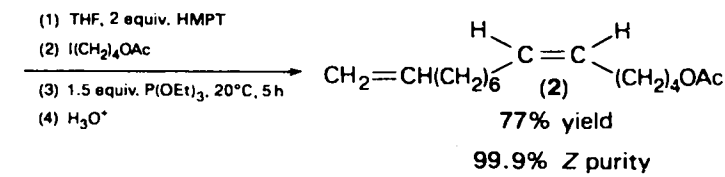
(16)

A variety of cases have been reported[32]. The products are usually obtained in good yields (70–95%). However, the impressive result is the very high isomeric purity of the products (>99.95%). For instance, in the case of *Z*-2-decene only 0.03% of the *E*-isomer was detected. Therefore, the method appears very well suited for the synthesis of some insect sex pheromones where the presence of even 1–2% of *E*-isomer often has an inhibiting effect on the biological activity of the *Z* counterpart[33].

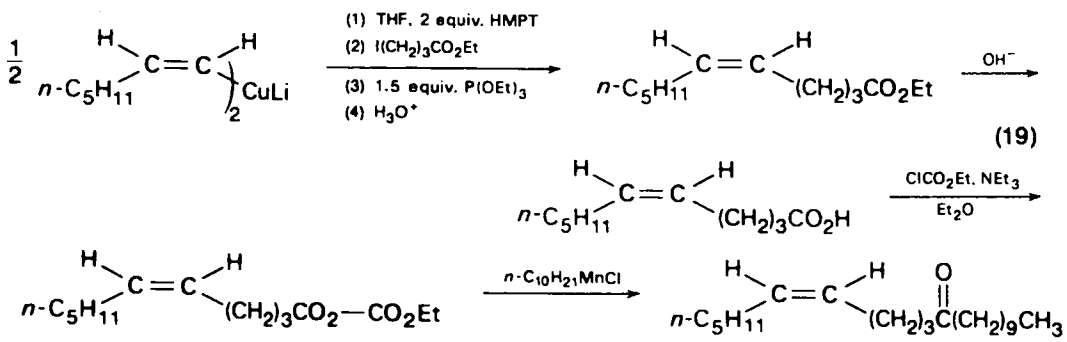
The syntheses of the sex pheromones of *Cossus cossus* (**2**), *Eupoecilia (Clysia) ambiguella* Hb (**3**) and *Orgyia pseudotsugata* (**4**), are reported below:



(17)

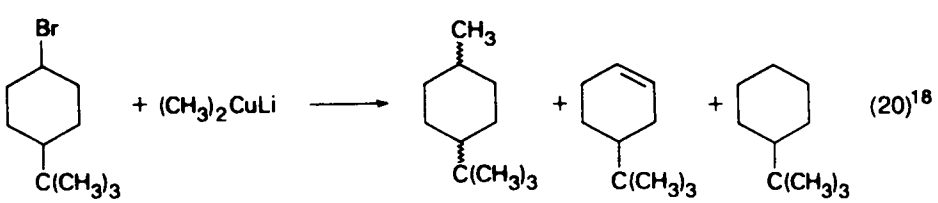


(18)

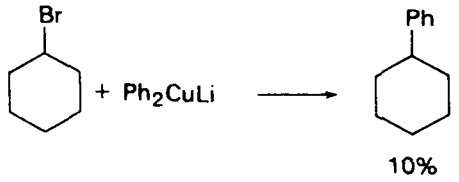


(19)

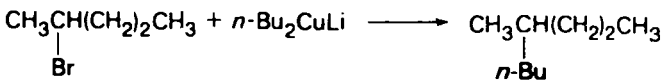
The success of a cross-coupling reaction involving a secondary halide appears to depend on the nature of the organocopper reagent and that of the substrates. Reductive dehalogenation and elimination appear as competitive reactions (equations 20, 24, 25) and yields of cross-coupling products may range from very poor (equations 21 and 22) to good (equation 23).



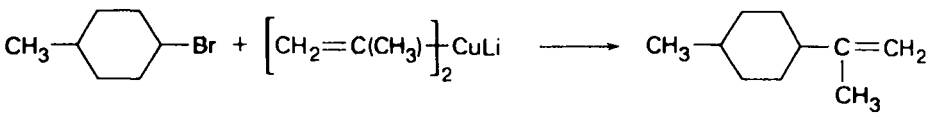
(20)[18]



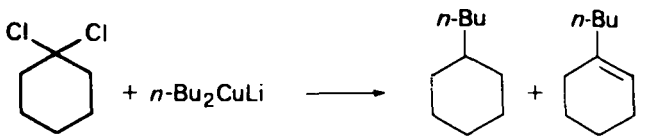
(21)[24]



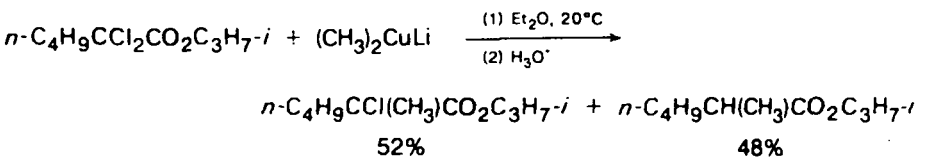
(22)[24]



(23)[34]



(24)[12]



(25)[35]

The monoalkylation observed in the case of the geminal dihalocompounds (equations 24 and 25) could be due to the neutralization of a monoalkylated organometallic species[35]. In the case of geminal dihalocyclopropanes such a species has been intercepted using an organic halide as the electrophile[36–39]. It has been suggested that intervention of a copper carbenoid (**5**) occurs in the first step (equation 26)[36]. The consecutive alkyl migration and X^- elimination produce the copper derivatives (**6**), which can undergo the cross-coupling with added organic halide.

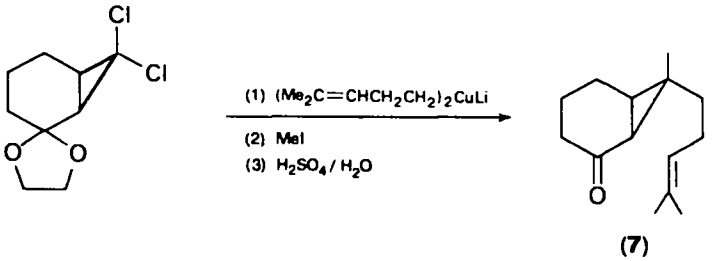
The procedure has been applied to the preparation of the key intermediate (**7**) of the D,L-sesquicarene and D,L-sirenin synthesis (equation 27)[36,37].

(26)

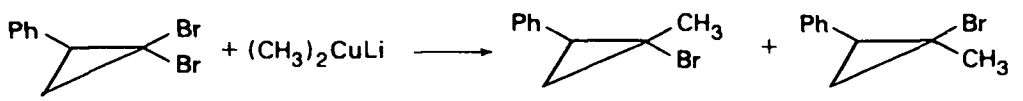
(**5**) (**6**)

X = halogen

However, for some cuprates it is also possible to obtain monoalkylated halogen compounds. For instance, lithium dimethylcuprate converts 1,1-dibromo-2-phenylcyclopropane into 1-bromo-1-methyl-2-phenylcyclopropane (equation 28)[37].



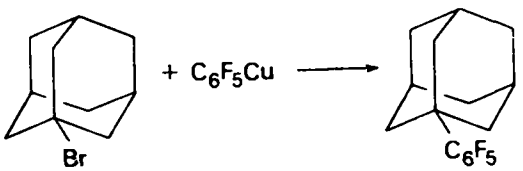
(7) (27)



57% 43% (28)

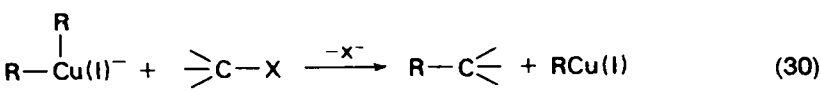
49% overall yield

As suggested by a few cases investigated[12,24], tertiary halides do not appear to react with organocopper(I) reagents. However, an exception is represented by the cross-coupling between pentafluorophenylcopper and 1-bromoadamantane[40] (equation 29).

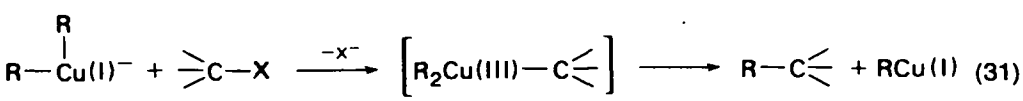


93% (29)

From the examples reported so far the synthetic potential of the cross-coupling between alkyl halides and copper(I) reagents appears quite clear. However, in spite of the well recognized usefulness of the methodology, very few mechanistic studies have been performed. These suggest that two types of mechanism are the most likely candidates for the reactions between alkyl halides and cuprates[12,21,24,41] (equations 30 and 31):



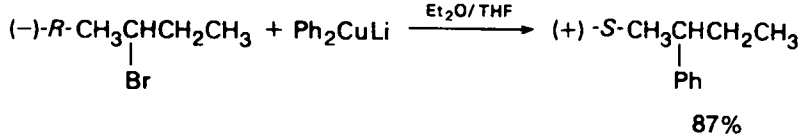
(30)



(31)

The mechanism reported in equation (30) involves the direct attack of the carbon atom of the reagent on the carbon bearing the leaving group in a S_N2 process. The alternative mechanism of equation (31) represents an oxidative addition–reductive elimination pathway. The leaving group effect[41] (OTs > Br ≈ I > Cl) and the stereochemical course of the reaction between lithium diphenylcuprate and

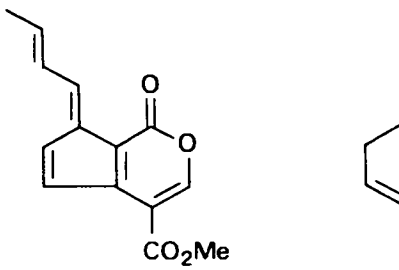
2-bromobutane[24] (where inversion is observed; see equation 32) are in agreement with both mechanistic possibilities:



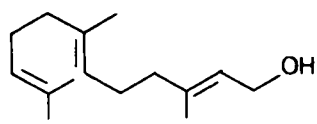
(32)

C. Cross-coupling Reactions with Alkenyl Halides

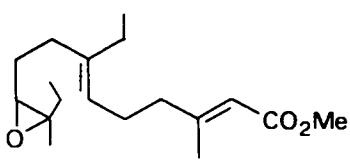
Alkenyl halides react with organocopper(I) reagents giving cross-coupling products. The reaction has served as a useful tool in the synthesis of a variety of natural compounds such as fulvoplumierin[42] (**8**), *trans,trans*-farnesol[43] (**9**), insect juvenile hormone[44](**10**) and the enantiomers of seudenol[45], the pheromone of Douglas fir beetle (**11**).



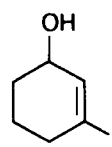
(**8**)



(**9**)



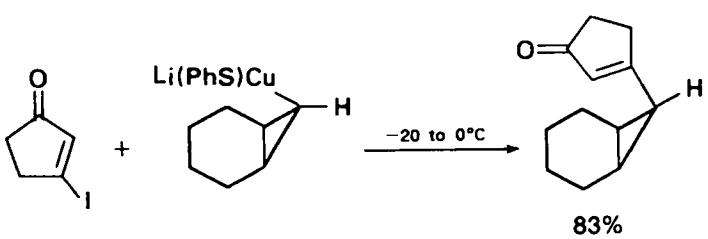
(**10**)



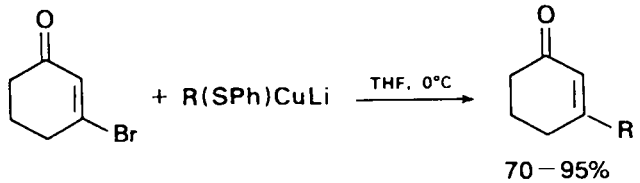
(**11**)

Iodides, chlorides or bromides can be used and, provided that a suitable activating group is present at the double bond, fluoride ion can also be displaced[46,47].

A type of substrate frequently used is represented by halogenocyclopentenones and halogenocyclohexenones. A few illustrative cases are reported below (equations 33–36). In the final example (equation 36) the use of a biscuprate permits the combination of substitution and addition processes to yield a spirocompound.



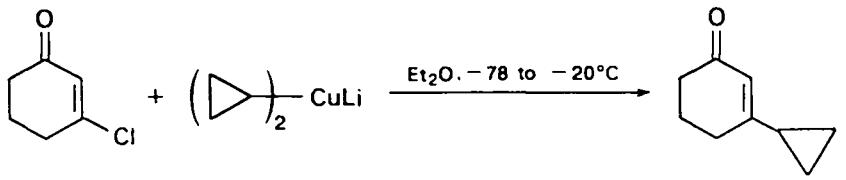
(33)[48]



70–95%

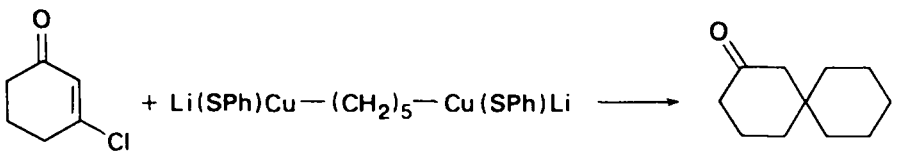
R = CH_3, *n*-Bu, *s*-Bu, *t*-Bu

(34)[49]



80%

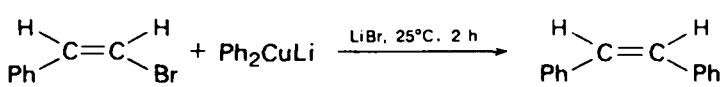
(35)[50]



40%

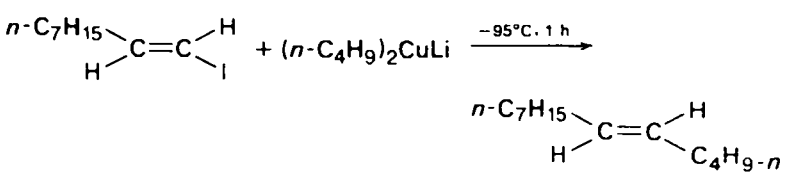
(36)[51]

An important feature of the process is that in several systems retention of configuration is observed[18,24,27,42,43,52–55]. A few examples are reported below:



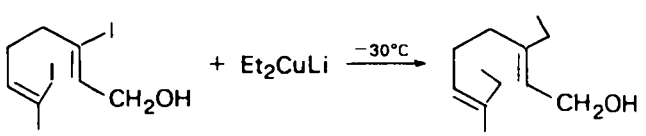
73%

(37)[24]



71%

(38)[27]

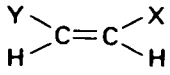


60%

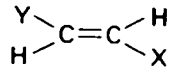
(39)[44]

However, an extension of this stereochemical result to all systems is not correct. Indeed, work performed in these laboratories[46,47] suggests a more complex pattern. It appears that the components of an isomeric pair might react with retention or inversion depending upon several factors, among which the nature of the substrate appears as the most important.

A mechanistic analysis has been performed using two types of systems: *Z* and *E*-1-halogeno-2-phenylethylenes (**12–15**) and *Z*- and *E*-1-halogeno-2-phenylsulphonylethylenes (**16–21**):



(**12**) Y = Ph, X = Br
(**13**) Y = Ph, X = Cl
(**14**) Y = Ph, X = F
(**16**) Y = $PhSO_2$, X = Br
(**17**) Y = $PhSO_2$, X = Cl
(**18**) Y = $PhSO_2$, X = F



(**15**) Y = Ph, X = Br
(**19**) Y = $PhSO_2$, X = Br
(**20**) Y = $PhSO_2$, X = Cl
(**21**) Y = $PhSO_2$, X = F

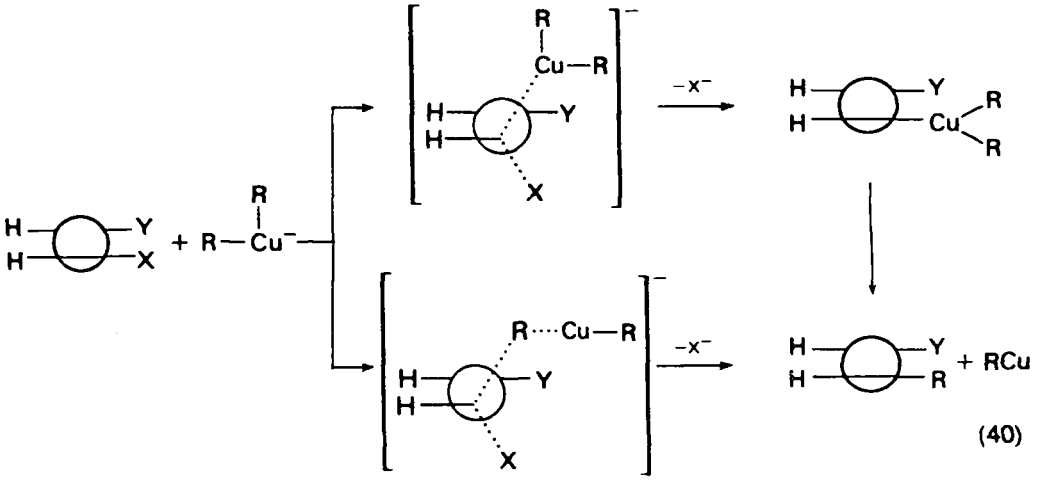
The styrene system reacts with lithium dimethylcuprate following a stereochemical course of retention. Furthermore, the reactivity order upon changing the halogen is Br > Cl and the *β*-fluorostyrene is completely unreactive under comparable conditions. Retention of configuration is still observed in the case of the *E*-sulphonyl compounds **19–21**. However, at variance with the styrene system, in the *Z* isomers the stereochemical course of the substitution is influenced by the leaving group and the nature of the cuprate. From the representative data reported in Table 1 it appears that lithium dimethylcuprate gives a high degree of retention if the bromo compound is used, whereas when the fluoride ion is the leaving group a 35% inversion is observed. Complete inversion is observed with lithium di-*t*-butylcuprate independent of the

TABLE 1. Reactions between 1-benzenesulphonyl-2-halogenoethylenes and cuprates (R_2CuLi) at −30 °C in Et_2O

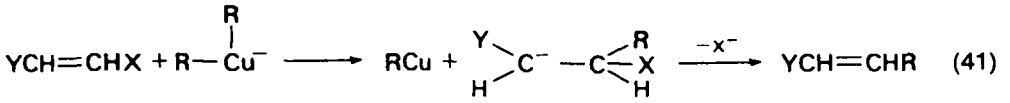
		Products		
Substrate	R	*Z*-$PhSO_2CH{=}CHR$	*E*-$PhSO_2CH{=}CHR$	Overall yield, %
16	Me	90	10	
16	*n*-Bu	90	10	70
16	*s*-Bu	76	24	75
16	*t*-Bu		100	70
16	Ph	45	55	82
19	Me		100	
19	*n*-Bu		100	70
19	*s*-Bu		100	75
19	*t*-Bu		100	78
19	Ph		100	73
18	Me	65	35	
18	*n*-Bu	22	78	73
18	*s*-Bu	5	95	85
18	*t*-Bu		100	73
18	Ph	5	95	95
21	Me		100	
21	*n*-Bu		100	73
21	*s*-Bu		100	85
21	*t*-Bu		100	78
21	Ph		100	83

nature of the leaving group. With lithium diphenylcuprate the degree of inversion is comparable with that of retention when the bromine is the leaving group, but moving to the fluoride **18**, inversion becomes again largely preferred. Furthermore, the order of reactivity found in the case of the sulphonyl systems is Br ~ Cl ~ F, in marked contrast to the results obtained with the halogenostyrenes.

Two main mechanistic pathways with blurred boundaries were suggested[46] to explain the results obtained: concerted substitution of the halogen (equation 40) and addition–elimination (equation 41).



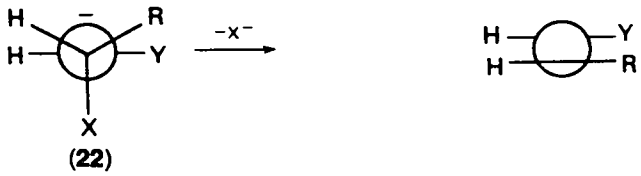
(40)



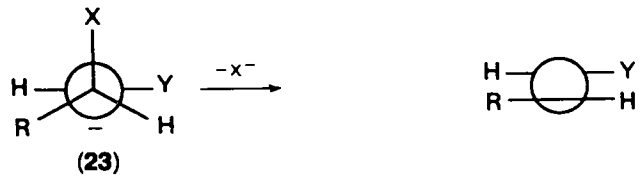
(41)

Both routes would involve attack at the same vinyl carbon atom as a slow step. As shown for the concerted substitution, the attacking centre of the reagent could be either the carbon atom of the reagent or the copper atom. In the latter case the concerted substitution of the halogen would lead to an intermediate copper(III) species, as already seen for the similar oxidative addition–reductive elimination discussed in the case of the substitution at an aliphatic centre. The concerted mechanism in the reaction of cuprates with vinyl halides has also been advocated for other systems[53,56].

The mechanism of equation (41) involves the intermediacy of a carbanion and the situation becomes rather similar to that met in the case of the substitution with more common nucleophiles[57]. The retention of configuration as well as the marked leaving group effect observed in the case of β-halogenostyrenes would easily be accommodated within the framework of the concerted substitution. On the other hand, the lack of significant leaving group effect and the variable stereochemical course observed for the sulphonyl compounds are best explained in terms of the carbanionic mechanism. In fact, it is known that, when this mechanism is followed, the stereochemical course will depend upon the lifetime of the intermediate. This should be longer when the fluoride ion is the leaving group, due to the greater strength of the C—F bond[58–60]. The inversion observed when the *Z* olefin reacts with large cuprates (i.e. di-*t*-butylcuprates) should derive from a preference for transition state **22** with respect to **23** during the product-determining step, as shown in equations (42) and (43), where an sp^2 hybridization is assumed for the carbanion[47].



(22) (42)



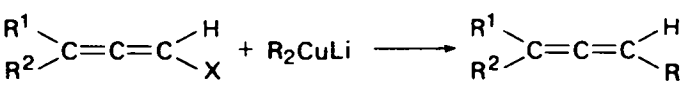
(23) (43)

Independently from the validity of the rationale presented above, it is clear that caution has to be used in regarding the reaction of cuprates with vinylic halides as stereospecific, at least when activated systems are used.

Lastly, it is worth noting that the reductive dehalogenation, which is a competitor in the case of the substitution at an aliphatic centre, often plays a role also when alkenyl halides are used. The product of reduction should derive from various possible alkenyl–metal species which could be formed in the reaction mixture and should also be responsible for the diene-forming dimerization. Stereochemical aspects of these processes, as well as their competition with the cross-coupling, have been investigated in the halogenostyrene and halogenophenylsulphonylethylene systems[46].

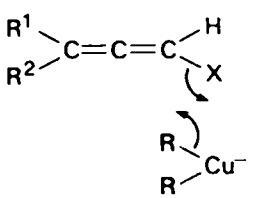
D. Cross-coupling Reactions with Allenyl Halides

Cross-coupling between lithium dialkylcuprates and 1-iodo- or 1-bromoallenes occurs smoothly in ether according to the following equation[61]:



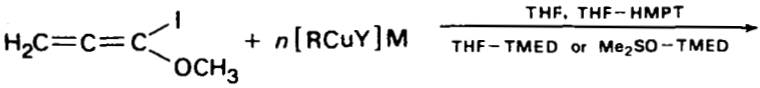
(44)

A concerted mechanism has been proposed[61] which involves a four-centre transition state (**24**).



(**24**)

The situation should then be similar to that discussed for the substitution at the vinylic centre. However, it appears that a completely different pathway is also available to the allenic halide. In fact, it has been found that under suitable conditions the reactions between various cuprates and 1-iodo-1-methoxypropadiene lead to 1-alkynyl ethers (**25**) in 65–85% yield (equation 45)[62]. The number of factors controlling the regioselectivity of the attack of the organometallic reagent deserves further attention.



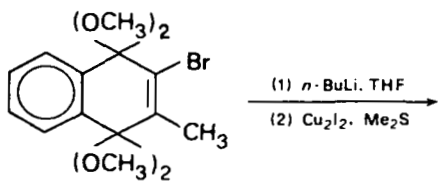
$$RCH_2C{\equiv}COCH_3 \quad (45)$$
(25)

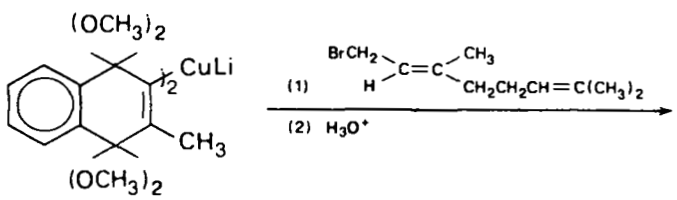
R = alkyl, vinyl, Ph or $C{\equiv}CR^1$; Y = Br ($n = 1.0$) or R($n = 0.5$); M = Li or MgX·LiBr

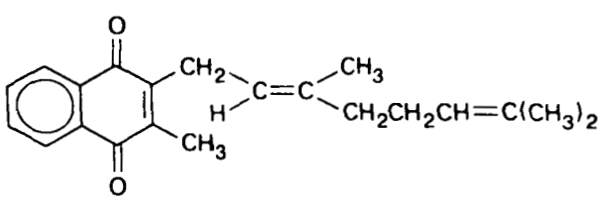
E. Cross-coupling Reactions with Allyl Halides

The coupling reaction between allyl halides (or related substrates) and a variety of organometallic reagents has been employed by a large number of workers for synthetic purposes[63]. With this kind of substrate a problem arises due the possibility of attack at the α or γ position with respect to the leaving group.

Frequently, copper(I) reagents have been used and many attempts have been made to control the regioselectivity. As far as the halides are concerned, an α-attack is most frequently met (equations 46–51), but hindered substrates appear to prefer a γ-attack (equation 52). However, this conclusion does not have general validity. Indeed, cases with prevailing γ-attack are known even for primary halides (equations 53–55). The examples reported below, which include the synthesis of menaquinone-2 (**26**), *Z*- and *E*-α-bisabolenes (**27** and **28**) and triene trityl ether (**29**) (a precursor of *Cecopria* juvenile hormone), clearly point to a rather complex pattern.

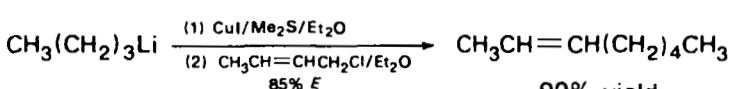






(46)[64]

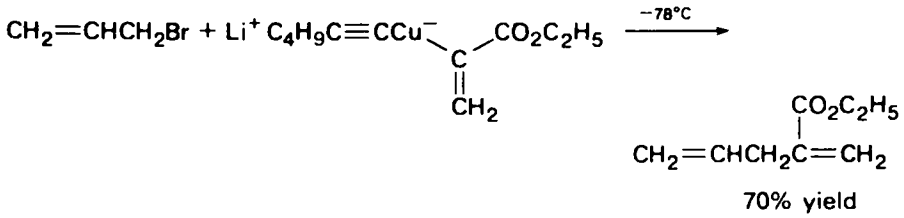
(26) 96% yield



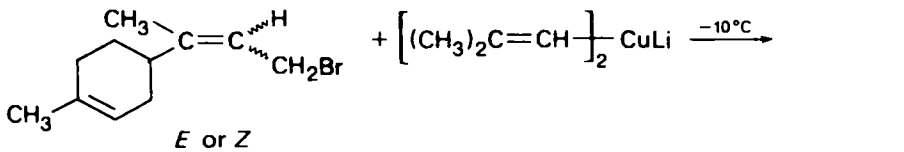
(47)[65]

90% yield

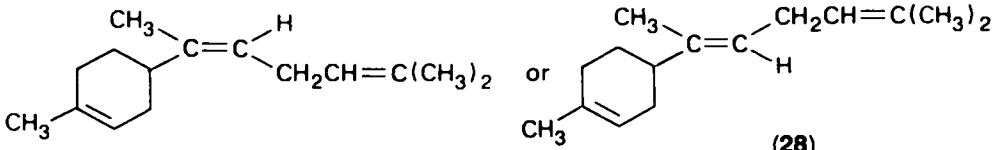
85% *E*



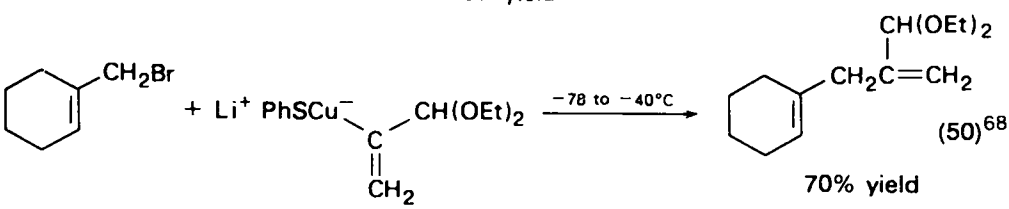
(48)[66]



(49)[67]

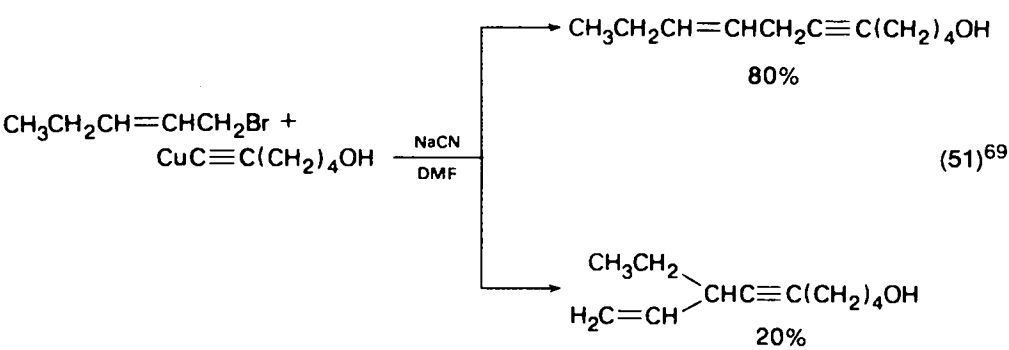


(27) 70% yield (28)

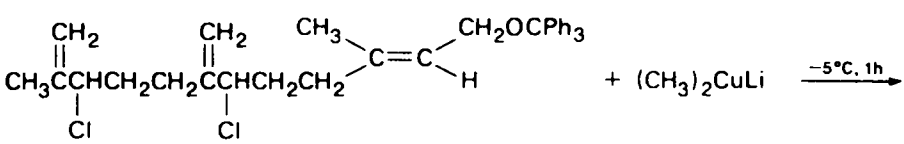


(50)[68]

70% yield



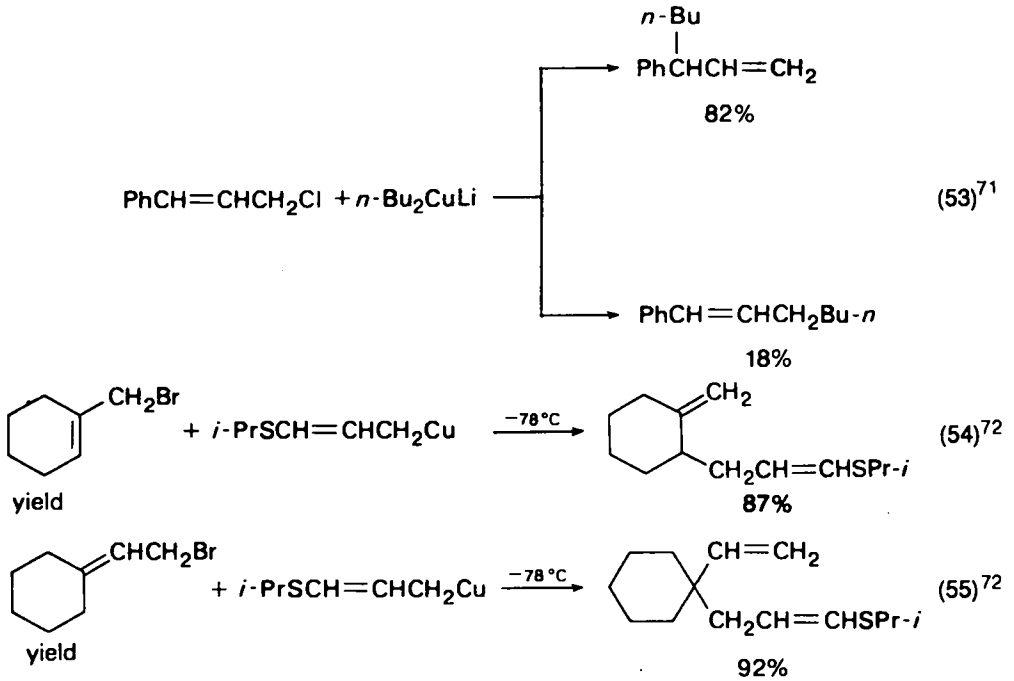
(51)[69]



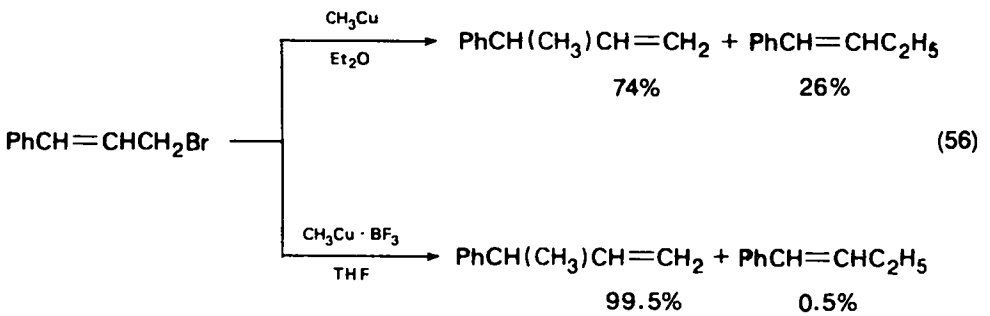
(52)[70]

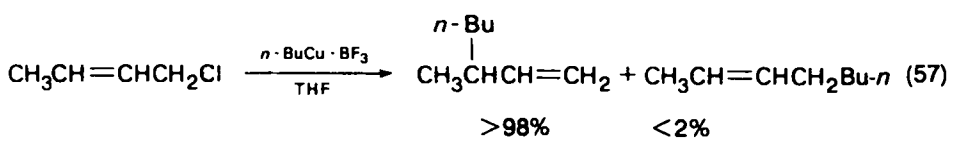
(29)

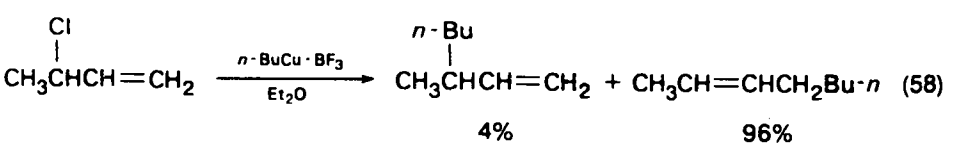
50% yield



A successful effort to control the regiochemistry has been performed by Maruyama and Yamamoto[71,73], who found that the γ-attack could reach regioselectivity values in the range 90–99% by using $RCu{\cdot}BF_3$ as alkylating reagent (equations 56–58). The high regioselectivity was not lost even when γ,γ-disubstituted allyl halides were used as substrates (equation 59).



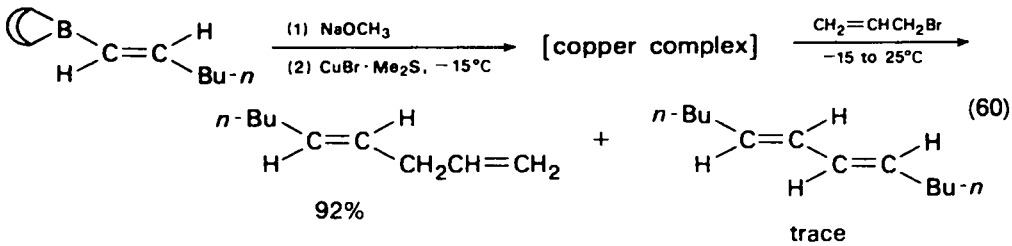




$$(CH_3)_2C{=}CHCH_2Br \xrightarrow[Et_2O]{RCu\cdot BF_3} CH_3\overset{\displaystyle CH_3}{\underset{\displaystyle R}{C}}CH{=}CH_2 + (CH_3)_2C{=}CHCH_2R \qquad (59)$$

$R = CH_3$	94%	6%
$R = n\text{-Bu}$	90%	10%

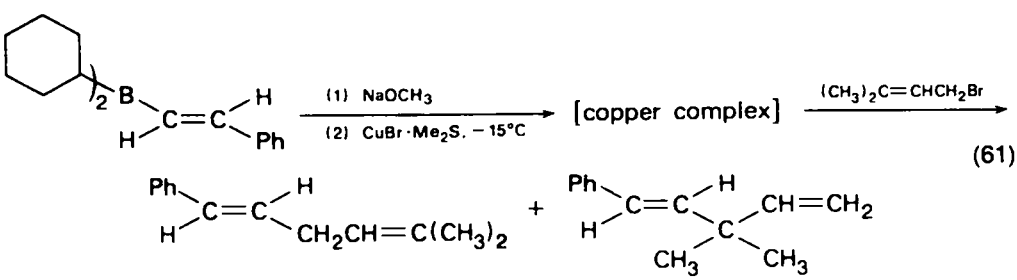
The combination of copper(I) and boron chemistry has proved very useful in other cross-coupling reactions[74]. Brown and Campbell have treated sterically defined alkenylboranes with sodium methoxide and $CuBr\cdot Me_2S$ to obtain 1,3-dienes with defined stereochemistry[75]. An alkenyl copper species was considered as a possible intermediate in the process. In order to intercept such a species an allyl halide was added and a 1,4-diene was formed[76]. In the example reported below it can be seen that this procedure permits the cross-coupling of an alkenylborane with an allyl halide in high yield (equation 60). Furthermore, the intermediate copper complex from



(60)

B = 9-borabicyclo [3.3.1] nonane (9-BBN)

(*E*)-β-styryldicyclohexylborane was treated with prenyl bromide with the purpose of getting information on the role of the allylic transposition. The predominant product was found to be the one derived from the α-attack (equation 61).



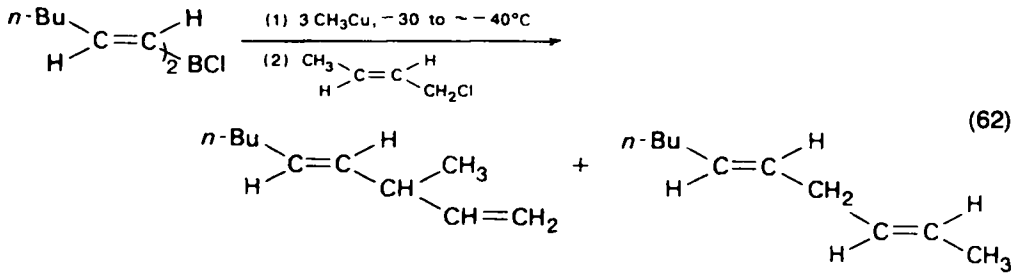
(61)

Regioselectivity α:γ = 75:25

90% overall yield

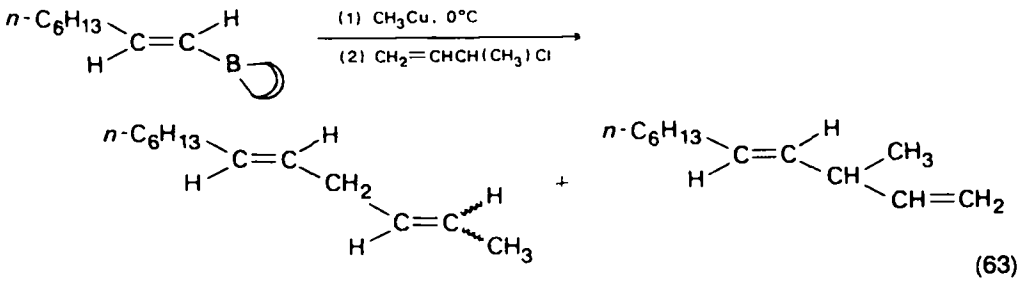
Similar cross-coupling, but with an opposite regioselectivity (predominant γ-attack) can be carried out successfully by treating dialkenylchloroborane–methylcopper or alkenyl-9-BBN–methylcopper with allyl halides[77,78] (equations 62 and 63).

The regioselectivity of the dialkenylchloroborane–methylcopper system (equation 62) is similar to that observed in the case of the corresponding free alkenylcopper. This result may also support the intermediacy of an alkenylcopper species in the reaction of the above system. On the other hand, the higher regioselectivity observed



(62)

Regioselectivity $\gamma : \alpha = 73 : 27$
50% overall yield

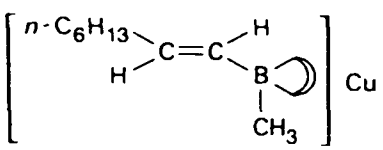


(63)

$2E,5E : 2Z,5E = 83 : 17$

Regioselectivity $\gamma : \alpha = 87.5 : 12.5$
60% overall yield

in the case of the alkenyl-9-BBN–methylcopper system (equation 63), together with other differences concerning its behaviour, suggests the intermediacy of an 'ate' complex such as **30**[78].

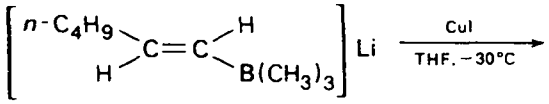


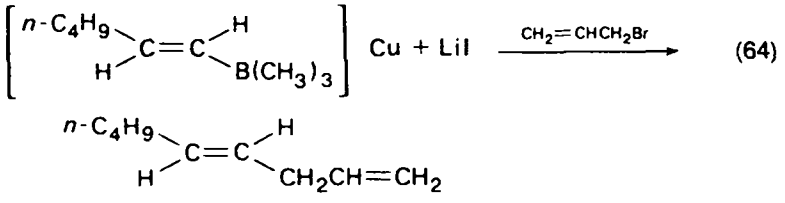
(30)

In a related work[79] similar 'ate' complexes, obtained from lithium alkenyltrimethylborate and copper iodide, were reacted with allyl bromides to give 1,4-alkadienes (equation 64).

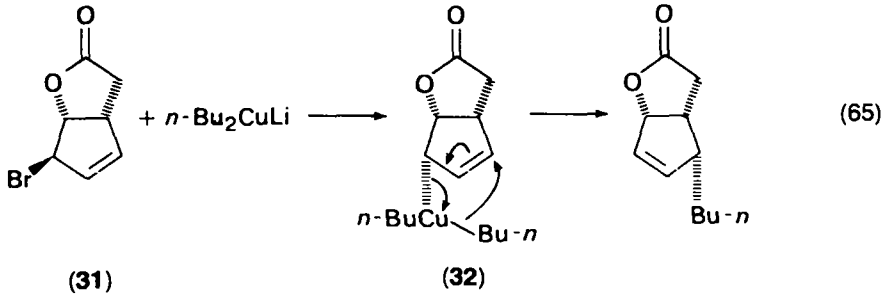
With cyclic allyl halides an interesting stereochemical problem arises. Indeed, a *syn* or an *anti* course can be followed in the reactions of the copper reagents with suitable derivatives. In some cyclopentenyl systems the predominant stereochemical mode appears to depend upon the nature of the substrate[80,81]. For the process involving the lactone **31** (equation 65) the preferential γ-attack follows an *anti* mode.

A copper(III) species (**32**) can be suggested as the intermediate responsible for an intramolecular alkylation. On the other hand, a *syn* attack is observed in the case of the dihalogeno ester (**33**). This was explained by assuming that the intermediacy of the copper(III) species is prohibited by steric crowding due to the acetate group and the





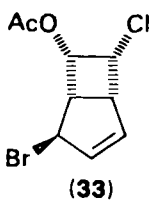
(64)



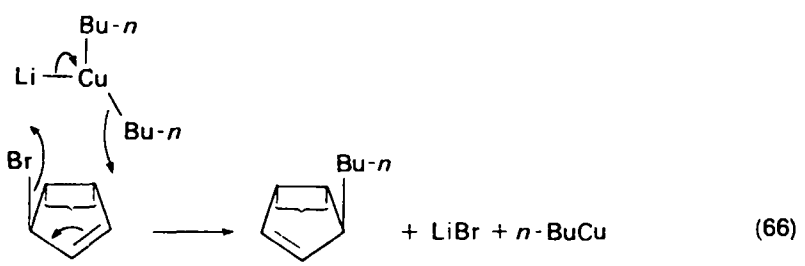
(65)

(31) (32)

chlorine atom. Thus an S_N2' process can take place, circumventing the cycloalkenyl copper(III) intermediate and a *syn* stereochemical course can be followed (equation 66).



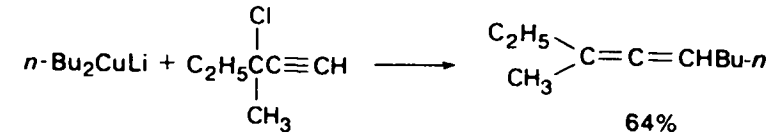
(33)



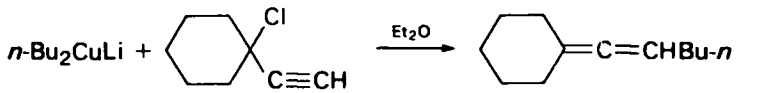
(66)

F. Cross-coupling Reactions with Propargyl Halides

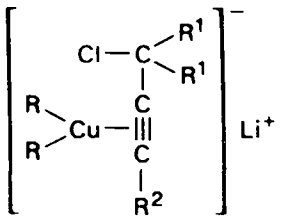
Dialkylcuprates react with propargyl chlorides to form allenes in good yields (equations 67 and 68). The π-type complex **34** has been suggested[82] as responsible for the attack leading to the allenic compound.



64% (67)[61]

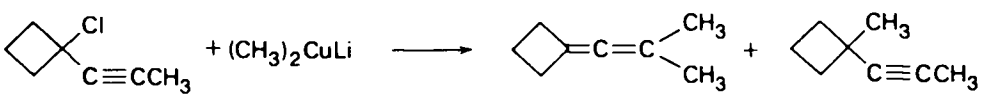


90% (68)[82]



(34)

In principle, as in the case of the allylic substrates, the possibility of the α-attack exists. Indeed, this type of attack shows up in the case of the reaction of 1-(1-propynyl)cyclobutyl chloride with lithium dimethylcuprate (equation 69), where the steric strain present in the allenic product is sufficiently high to permit the intervention of the cross-coupling leading to the acetylenic product. However, in this reaction the alkyne and the allene are both produced in low yields.

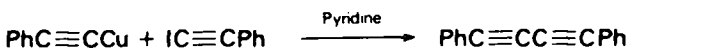


12% 8% (69)

The complex series of factors which influence the distribution of these products has been carefully studied for propargylic substrates having leaving groups different from halide ions (e.g. OAc, OTs or OCO_2CH_3)[83].

G. Cross-coupling Reactions with Alkynyl Halides

Copper acetylides have been suggested as intermediates in the Cadiot–Chodkiewicz coupling, which involves the reaction of a terminal alkyne with a 1-halogeno-1-alkyne in the presence of copper salts[84]. Thus, the reaction of copper acetylide with such a halide can be considered an extension of this process and, actually, it has been performed successfully (equation 70).



96% (70)[85]

Similar results have been obtained by using perfluorophenyl-[86], perfluoroalkyl-[87] and phenyl copper[88,89] compounds (equations 71–74). Due to the possibility of removing the protective group by treatment with alkali, the reaction with halogenoethynyl(trialkyl)silane (equations 71 and 72) represents a route to

arylacetylenes. This type of process is complementary to the Stephens–Castro coupling between an aryl iodide and a cuprous alkynylide[90].

$$C_6F_5Cu + BrC{\equiv}CSiEt_3 \xrightarrow{THF} C_6F_5C{\equiv}CSiEt_3 \quad (71)^{86}$$
85%

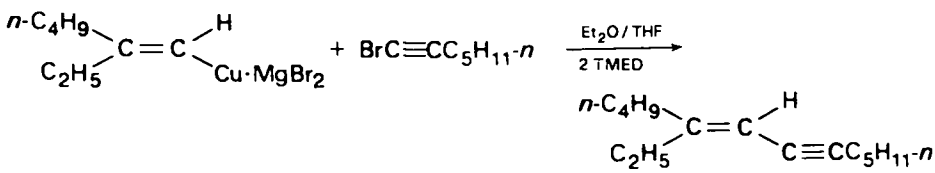
$$PhCu + IC{\equiv}CSiMe_3 \xrightarrow{THF} PhC{\equiv}CSiMe_3 \quad (72)^{88}$$
64%

$$CF_3(CF_2)_4Cu + IC{\equiv}CPh \xrightarrow{DMSO} CF_3(CF_2)_4C{\equiv}CPh \quad (73)^{87}$$
23%

$$PhCu{\cdot}MgBr_2 + IC{\equiv}COEt \xrightarrow{THF/DMF} PhC{\equiv}COEt \quad (74)^{89}$$
60%

In more recent studies alkyl- and alkenylcopper(I) compounds have been reported to couple with alkynyl halides[91] (equations 75 and 76).

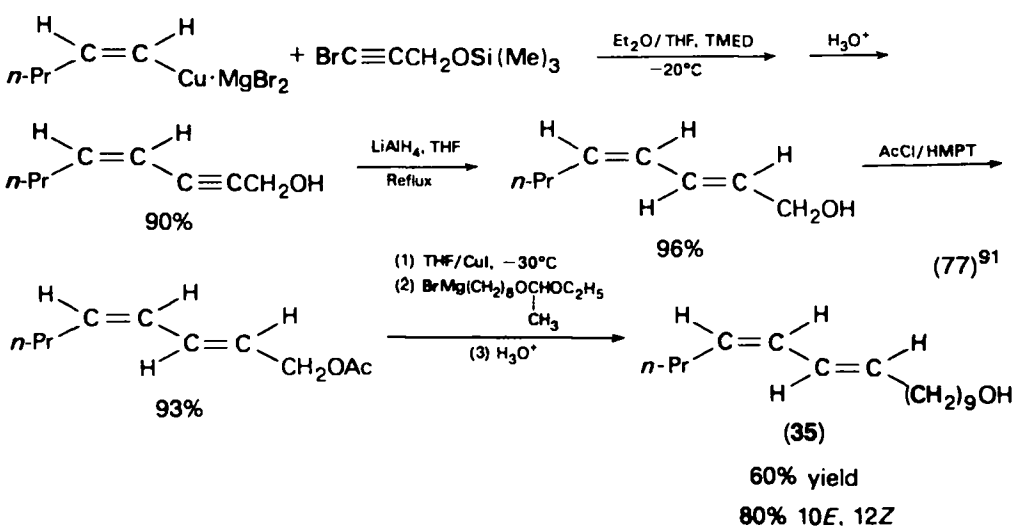
$$n\text{-}BuCu{\cdot}MgX_2 + IC{\equiv}CBu\text{-}n \xrightarrow{THF} n\text{-}BuC{\equiv}CBu\text{-}n \quad (75)$$
72%



(76)

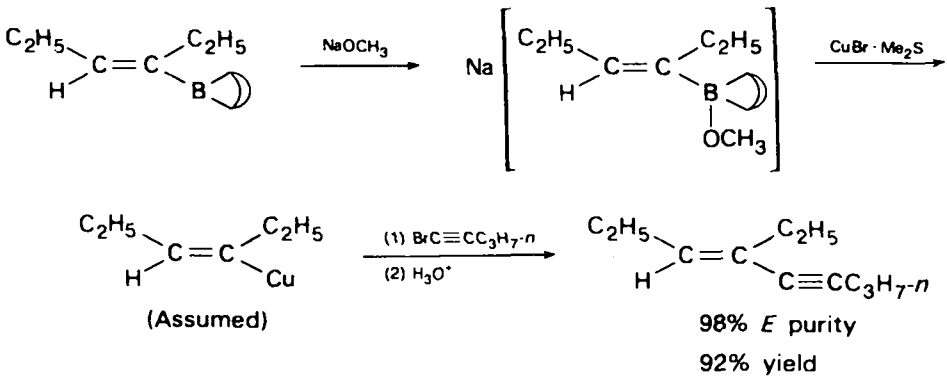
78%

The reaction of the vinyl copper(I) reagent (equation 76) appears of special interest from a synthetic point of view. Indeed, the coupling occurs with retention of configuration and the use of suitable substrates leads to conjugated and functional enynes from which conjugated dienes can be obtained. The synthesis of the *E*–*Z* diene fragment of the bombykol **35** has been achieved using this approach:



(77)[91]

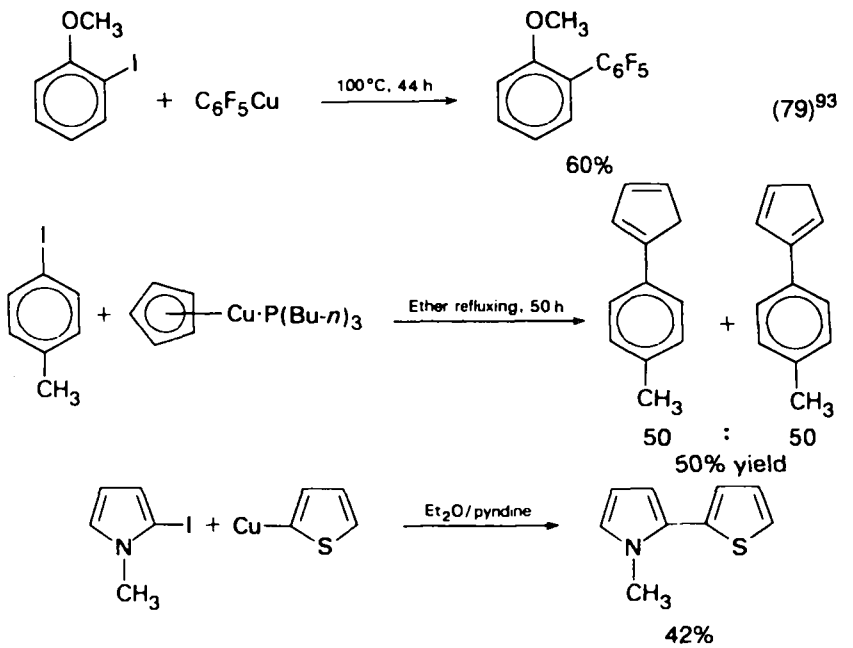
Similar cross-coupling can also be carried out successfully by using alkenyl copper intermediates generated from alkenylboron derivatives of 9-borabicyclo[3.3.1]-nonane[92]. As seen in the case of the allylic substrates, the cross-coupling with 1-halogeno-1-alkynes provides stereo-defined conjugated enynes of high isomeric purity and in excellent yields (equation 78). The differences in the stereochemistry and the substitution patterns between the alkenylcopper generated by carbometallation[91] and those prepared from organoboranes via hydroboration render the two procedures complementary.

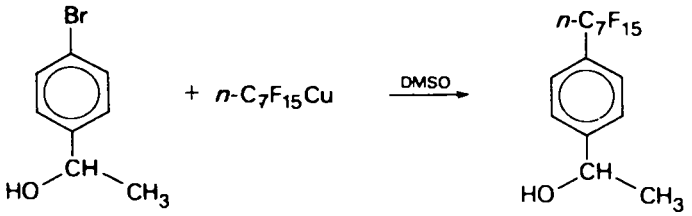


(78)

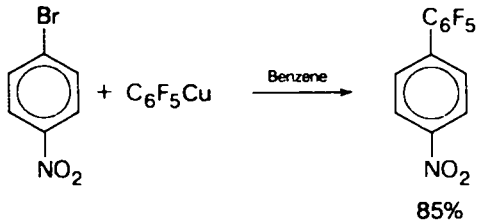
H. Cross-coupling Reactions with Aryl and Heteroaryl Halides

Organocopper reagents of the RCu type (including many perfluoroalkyl- and perfluoroarylcopper species) have been reported to react with aryl and heteroaryl iodides or bromides[93–97] (equations 79–83). Substitution of a chlorine atom can be obtained in activated systems[98] (equation 84).

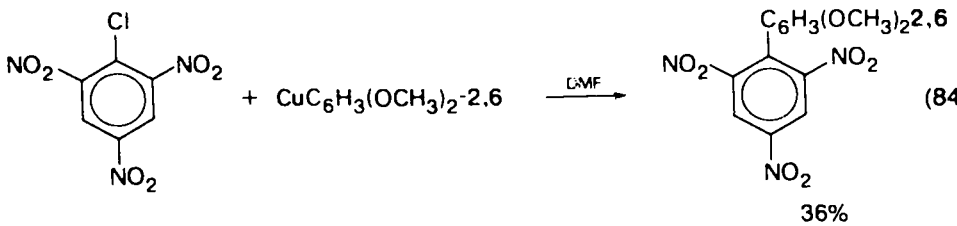




(82)[96]

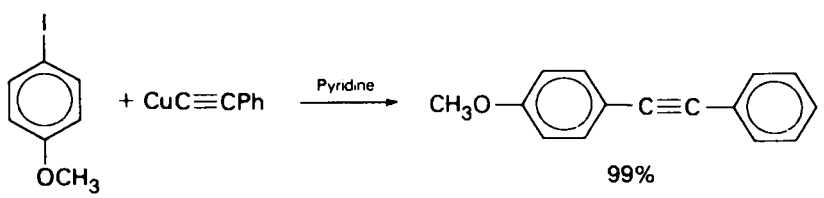


(83)[97]



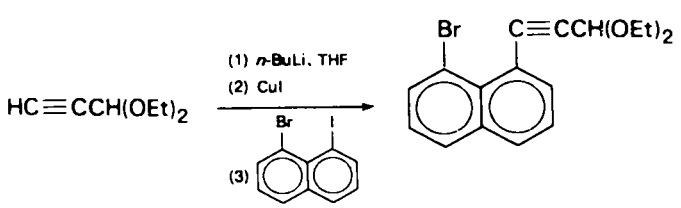
(84)[98]

Cuprous acetylides have been often used for replacement of aromatic halogen by the acetylide group. Equation (85) describes an application of the Stephens–Castro procedure in which cuprous acetylides are coupled with aromatic iodides in refluxing pyridine[90].



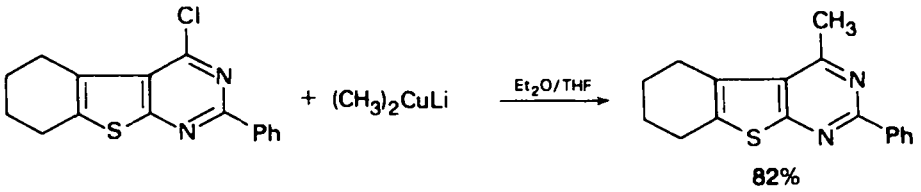
(85)

A variation on the theme (equation 86) involves the generation *in situ* of the acetylide using THF as solvent[99]:

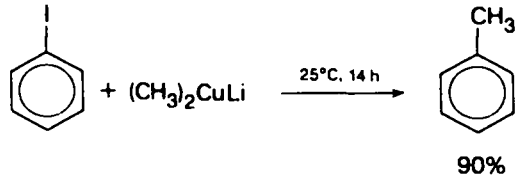


(86)

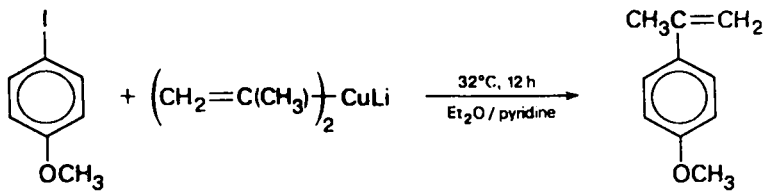
Lithium dialkylcuprates have been less investigated. A few examples are reported below:



(87)[100]

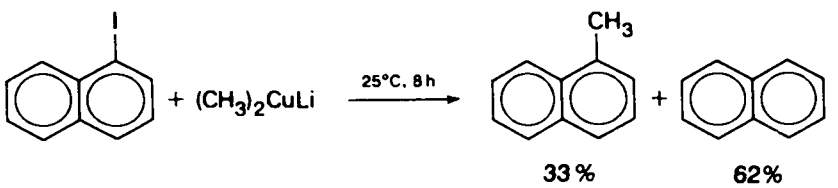


(88)[18]



(89)[101]

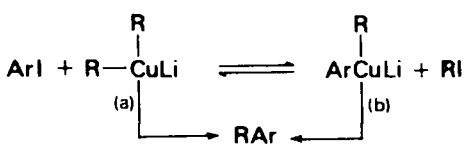
However, it appears that in unactivated substrates halogen–metal exchange is often an important competitor. For instance, 1-iodonaphthalene reacts with lithium dimethylcuprate giving a 1 : 2 ratio of the cross-coupling and the reduction products[24]:



(90)

Similar results have been observed in the reaction of iodobenzene with di-*n*-butylcuprate[12,24]

As in the case of halogenoethylenes, several mechanistic possibilities are available for the cross-coupling with the aromatic halides. Besides the direct coupling (equation 91, path a) a metal–halogen exchange could lead to a unsymmetric cuprate and an alkyl halide. These would react to give the cross-coupling product (path b):



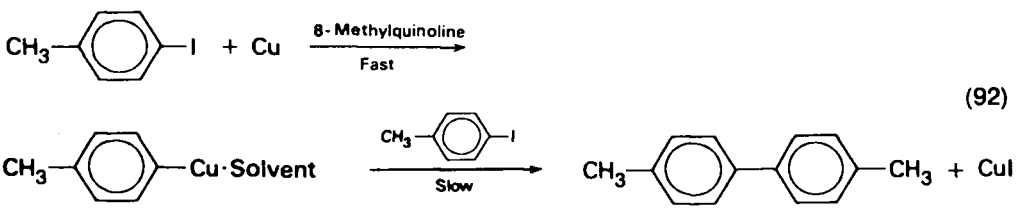
(91)

The formation of a mixed cuprate is supported by the observation that the yield of the cross-coupling product can be increased by adding an excess of alkyl halide at the end of the reaction[27]. The same result can be obtained by oxidation of the presumed intermediate[24].

In principle, for the reaction of an organocopper(I) reagent, the classical S_NAr mechanism could be considered. The isolation of Meisenheimer complexes in the reaction between alkenyl-[102] or arylcopper[98] and 1,3,5-trinitrobenzene supports such a mechanism. However, from an investigation of heteroaromatic substrates (2-halogenobenzothiazoles, halogenopyridines and halogenobenzofurazans)[103], which are known to follow such a mechanism with more typical nucleophiles, it appears that other routes are preferred. Indeed, the S_NAr mechanism was found to be of scarce (if any) importance when lithium dimethylcuprate was the reagent.

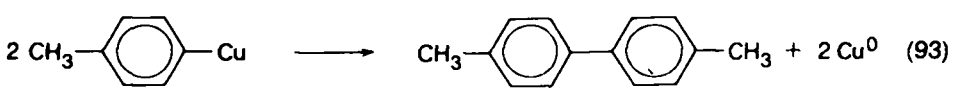
I. The Ullmann Biaryl Coupling and Related Reactions

The Ullmann reaction is a classical method for the generation of a bond between two aromatic nuclei. Most frequently, two molecular equivalents of aryl halide are reacted with one of finely divided copper to form a biaryl and copper halide. The procedure is closely related to the reactions involving organocopper(I) reagents. Indeed, the result of a mechanistic study[104] performed with *p*-iodotoluene and copper in 8-methylquinoline suggests that *p*-tolylcopper is produced and stabilized in the form of a complex with the solvent. The subsequent relatively slow reaction with *p*-iodotoluene gives 4,4′-dimethylbiphenyl:



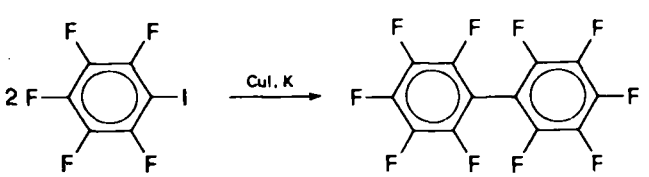
(92)

However, the self-coupling of the intermediate is considered to be an important competitor of the cross-coupling step:



(93)

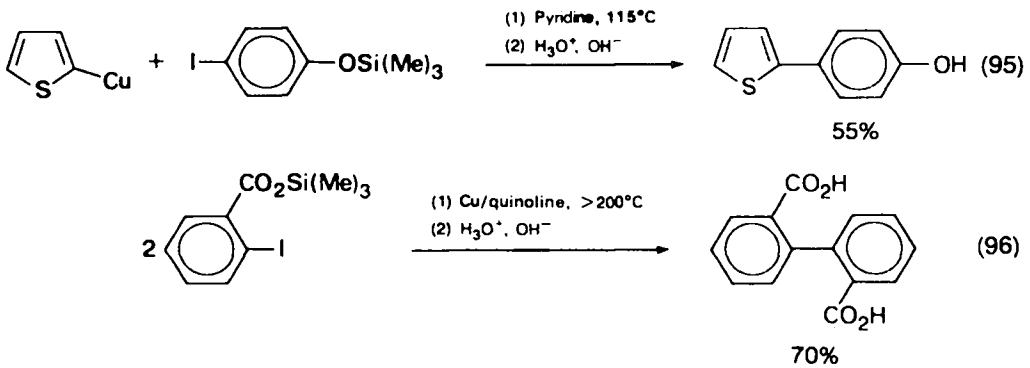
The Ullmann reaction is frequently used to prepare symmetrical and unsymmetrical biaryls, to effect ring closures at an aryl–aryl bond, and to prepare oligo-polyphenylenes. The aryl halides are activated by electronegative substituents such as nitro or methoxycarbonyl groups, particularly when these are located in the *ortho* position with respect to the halogen atom. The reaction has been extensively reviewed by several authors[105–110] and in recent years significant progress has been reported[111–116]. For instance, using an activated form of Cu powder made by the reduction of CuI with potassium, the coupling can be carried out in much milder conditions, as shown by the reaction of pentafluorophenyl iodide in 1,2-dimethoxy-ethane[111]:



(94)

Indeed, the above catalyst requires a temperature of 85 °C to give an 83% yield of decafluorobiphenyl. In a previous work the same compound was obtained in a 72% yield by carrying out the reaction at 300 °C for 10 h in a sealed tube with no solvent, using normal copper bronze[117].

Another significant advance is represented by the successful use of trimethylsilyl groups to protect the hydroxyl-, amino- or carboxyl groups present in halogenoaryl substrates[112]. Indeed, these functions are known to inhibit the formation of biaryls:

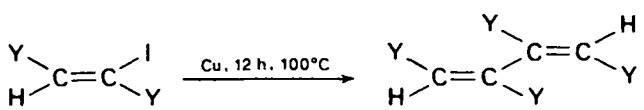


(95)

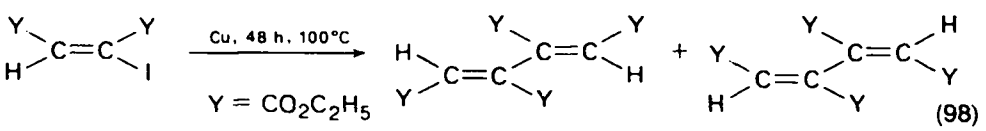
(96)

The overall yield of the Ullmann coupling is not affected significantly by this procedure due to the fact that the silylation and the desilylation steps are virtually quantitative.

The Ullmann-like coupling of alkenyl halides has been reported[118]. The use of olefins has permitted a study of the stereochemical course. Coupling of diethyl iodofumarate results in a 96% isolated yield of gas chromatographically pure *E,E*-1,2,3,4-tetracarboethoxy-1,3-butadiene, whereas the corresponding iodomaleate gives an 89% yield of pure tetraester consisting of 87% *Z,Z*-butadiene and 13% of the *E,E* isomer (equations 97 and 98). The ratio between the two products was found to increase (94:6) at 75°C.



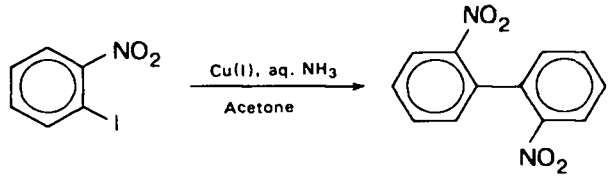
(97)



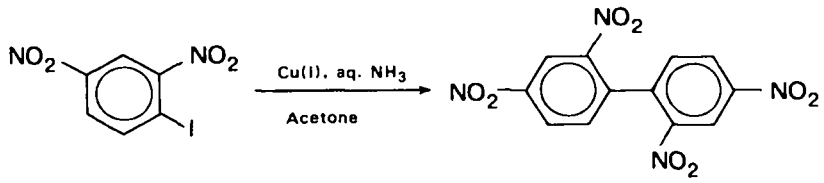
(98)

On the basis of these results vinyl–copper compounds have been suggested as intermediates. Indeed, compounds of this type are known to be fairly stable stereochemically and to couple stereospecifically with retention of configuration[11]. In the above reaction it has been suggested that an organocopper intermediate probably undergoes self-coupling rather than coupling with unreacted organoiodide.

Synthetic and mechanistic studies of the Ullmann coupling in homogeneous solution have been reported[119]. Copper(I) trifluoromethanesulphonate dissolved in equal volumes of acetone and 5% aqueous ammonia has been used as a catalyst. *o*-Iodonitrobenzene and 2,4-dinitroiodobenzene couple in a few minutes to form 2,2′-dinitrobiphenyl and 2,2′,4,4′-tetranitrobiphenyl respectively[120]:



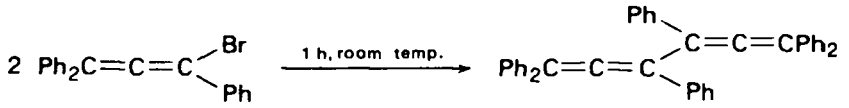
92% (99)



92% (100)

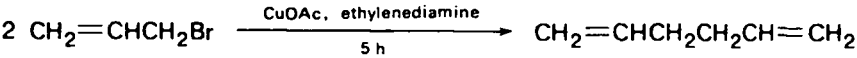
However, although the few results obtained are of considerable interest, the homogeneous procedure at the present time cannot be considered a substitute for the classical approach.

The use of Cu(I) salts has also found applications in the synthesis of diallenes[121] and dienes[122–124]. The former have been prepared in DMF with CuCl as a catalyst:



72% (101)

The same catalyst[123], or cuprous acetate in CH_3CN and in the presence of ethylenediamine, was used for the synthesis of 1,5-dienes from allyl chloride or bromide[122]:



98% (102)

III. REACTIONS OF ORGANOMETALLIC REAGENTS IN THE PRESENCE OF TRANSITION METAL CATALYSTS

A. Introduction

When the use of Cu(I) salts to modify organolithium compounds or Grignard reagents began to reveal its tremendous synthetic potential, it appeared of obvious interest to verify the similarities and differences between the organocopper(I) derivatives and the organometallic species obtained by adding Fe(II), Co(II) and Mn(II) salts to organolithium compounds in the same way as copper(I) halides are added to obtain the copper reagents.

The results obtained by Corey and Posner[125] in the cross-coupling reactions using the species obtained in this manner have shown that, generally, the copper reagents (R_2CuLi) are superior to the corresponding manganese, iron and cobalt organo-derivatives. Therefore these organometallic reagents have found little use in synthesis, with the exception of organomanganous derivatives, which, however, have been reacted most frequently with carbonyl compounds[126–129].

On the other hand, in the last decade the reactions between halides and organometallic reagents in the presence of catalytic amounts of Ni, Pd and (to a lesser extent) Fe derivatives have revealed a synthetic potential which at the moment is far from being fully exploited. This section will be devoted to these rather novel procedures, dealing first with the reactions of the most familiar type of organometallic reagents (i.e. the Grignard reagents).

B. Cross-coupling Reactions of Grignard Reagents in the Presence of Nickel Complexes

It has been known for a long time that the cross-coupling of the organic moieties of Grignard reagents and organic halides is induced by many transition metal halides. However, due to the formation of homocoupling and disproportionation products, the reaction did not find a frequent use in the synthetic field for many years[130].

A decade ago the situation began to change, mainly due to two papers on nickel-catalysed cross-coupling of Grignard reagents with organic halides, a reaction which cannot be performed in a satisfactory manner with the magnesium derivatives alone. These papers were published almost simultaneously by Corriu and Masse[131] and by Tamao, Sumitani and Kumada[132]. Corriu and Masse reported the successful cross-coupling between vinylic or aromatic halides in the presence of nickel acetylacetonate ($Ni(acac)_2$) with formation of stilbenes or terphenyls according to equations (103)–(105):

$$\underset{E}{PhCH{=}CHBr} + ArMgX \xrightarrow[Ni(acac)_2\ (0.2\%)]{Et_2O,\ 25°C} \underset{E}{PhCH{=}CHAr} \qquad (103)$$

50–75%

$$\underset{E}{ClCH{=}CHCl} + 2\ ArMgX \xrightarrow[Ni(acac)_2\ (0.2\%)]{Et_2O,\ 25°C} \underset{E}{ArCH{=}CHAr} \qquad (104)$$

40–50%

$$p\text{-}BrC_6H_4Br + 2\ ArMgX \xrightarrow[Ni(acac)_2\ (1\%)]{Et_2O,\ reflux} p\text{-}ArC_6H_4Ar \qquad (105)$$

>80%

On the other hand, in the first[132] of a series of fundamental investigations[132–137] the Kumada group reported a similar cross-coupling with a variety of aromatic and vinylic halides according to equations (106) and (107):

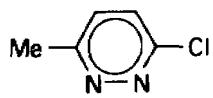
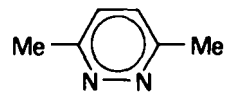
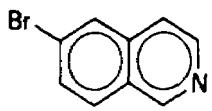
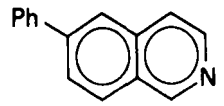
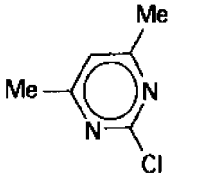
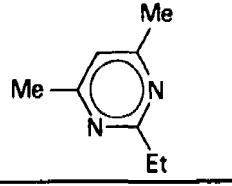
$$RMgX + ArX' \xrightarrow{NiCl_2L_2} R{-}Ar + MgXX' \qquad (106)$$

$$RMgX + R^1CH{=}CHX' \xrightarrow{NiCl_2L_2} R^1CH{=}CHR + MgXX' \qquad (107)$$

A summary of the relevant results are collected in Table 2 where a few contributions deriving from other laboratories and dealing with extension to heteroaromatic halides are also reported[138–140].

The most effective catalysts were found to be $Ni(dppp)Cl_2$ (dppp = $Ph_2PCH_2CH_2CH_2PPh_2$) for alkyl and simple aryl Grignard reagents, $Ni(dmpe)Cl_2$ (dmpe = $Me_2PCH_2CH_2PMe_2$) for alkenyl and allylic Grignard reagents, and $Ni(PPh_3)_2Cl_2$ for sterically hindered aryl Grignard reagents and halides.

TABLE 2. Cross-coupling reactions of aryl, alkenyl and heteroaromatic halides with Grignard reagents in the presence of $NiCl_2L_2$ complexes as catalysts

Grignard reagents	Organic halides	L_2	Products	Overall yield, %	References
n-PrMgBr	PhCl	dppp[a]	PhPr-*n*	94	137
i-PrMgCl	PhCl	dppp[a]	{PhPr-*i* / PhPr-*n*} (96 : 4)	89	133
MeMgI		dppp[a]		71	138
PhMgBr		dppp[a]		90	140
CH_2=$CHCH_2MgBr$	PhBr	dmpe[b]	$PhCH_2CH$=CH_2	63	137
CH_3CH=$CHMgBr$	PhBr	dmpe[b]	PhCH=$CHCH_3$	84	137
i-PrMgCl	PhCl	dmpe[b]	{PhPr-*i* / PhPr-*n*} (9 : 84)	84	133
i-PrMgCl	*p*-$CF_3C_6H_4Cl$	dmpe[b]	{*p*-$CF_3C_6H_4$Pr-*i* / *p*-$CF_3C_6H_4$Pr-*n*} (46 : 44)	100	134
i-PrMgCl	*p*-$MeOC_6H_4Cl$	dmpe[b]	{*p*-$MeOC_6H_4$Pr-*i* / *p*-$MeOC_6H_4$Pr-*n*} (6 : 65)	25	134
MesMgBr[d]	PhBr	$2PPh_3$	MesPh	96	137
PhMgBr	CH_2=CHCl	dppe[c]	PhCH=CH_2	89	132
n-$C_8H_{17}MgCl$	CH_2=CHCl	dppe[c]	*n*-$C_8H_{17}CH$=CH_2	95	132
EtMgBr		dppe[c]		74	139

[a]dppp = 1,3-bis(diphenylphosphino)propane.
[b]dmpe = 1,2-bis(dimethylphosphino)ethane.
[c]dppe = 1,2-bis(diphenylphosphino)ethane.
[d]Mes = mesityl.

The nature of the ligand in the catalyst is particularly critical in the case of the reaction of secondary alkyl Grignard reagents. At variance with the reactions of *n*-alkyl reagents, which give *n*-alkyl derivatives without any rearrangement of the alkyl group, the coupling reactions of isopropylmagnesium chloride with chlorobenzene occurs together with the isomerization of the isopropyl group to *n*-propyl. The extent of this isomerization is strongly dependent upon the nature of the phosphine ligand and of the group present on the benzene ring of the substrates[133,134]

Without going into further detail, it will suffice to say that using the $Ni(dppp)Cl_2$ catalyst it is possible to reduce the formation of *n*-propylbenzene (from chlorobenzene) to the rather low value of 4% of the product. As mentioned above, the isomerization is strongly influenced by the electronic nature of the substituent on the aromatic ring. In fact, electron-releasing substituents facilitate the isomerization to *n*-propyl derivatives, while electron-withdrawing substituents give rise to isomeric mixtures with a higher percentage of isopropyl derivatives.

A large and significant part of the work performed by the Kumada group has dealt with stereochemical problems. The reactions of *Z*-1-alkenyl Grignard reagents with aryl halides in the presence of $Ni(dmpe)Cl_2$ is accompanied by $Z \rightarrow E$ isomerization[135]. The stereoselectivity observed is strongly dependent upon the nature of aryl halide and the halide-to-Grignard reagent ratio, a higher stereoselectivity being observed with more reactive aryl halides and with greater halide-to-Grignard reagent ratios. These facts have been considered consistent with the intervention of an isomerization process involving the reagents and competing with the essentially stereoselective cross-coupling.

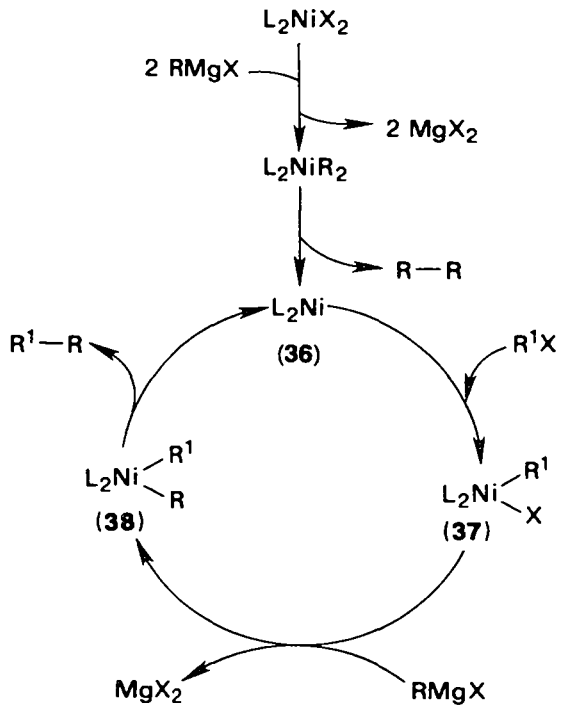
The substitution of the halogen of *Z*- and *E*-β-bromostyrene with the organic moiety of phenylmagnesium bromide occurs with retention of configuration. Inversion is only a minor component (7%) of the stereochemical pathway. However, a more complex pattern is observed in the case of *Z*- and *E*-1,2-dichloroethenes[136]. As reported in Table 3, the reactions leading to 1,2-diphenylethenes proceed with a stereospecificity dependent upon the nature of the catalyst. A low degree of stereospecificity is observed with $Ni(PPh_3)_2Cl_2$ as catalyst. On the other hand, *Z*-stilbene is the predominant isomer or the exclusive product when dppe ($Ph_2PCH_2CH_2PPh_2$) and dmpe are used respectively as ligands in the catalysts. Finally, *E*-stilbene is the prevailing product with the dppp ligand.

The analysis of this stereochemical course requires a concise presentation of the catalytic cycle which is considered[130,132] to operate in these cross-coupling reactions. As shown in Scheme 1, in an initial step a Ni(0) species (**36**) is formed by reaction of the Grignard reagent with the Ni(II) complex. The oxidative addition of the substrate halide R^1X to the Ni(0) species leads to the catalytically active complex $L_2Ni(R^1)X$ (**37**). The reaction of this complex with the Grignard reagent produces the diorganonickel complex $L_2Ni(R^1)R$ (**38**) which then reductively eliminates the

TABLE 3. Isomer ratios of stilbene formed from the reactions of 1,2-dichloroethenes with PhMgBr in the presence of $NiCl_2L_2$

	Z : *E* stilbene product ratios from	
L_2	*E*-Cl—CH=CH—Cl	*Z*-Cl—CH=CH—Cl
$(PPh_3)_2$	30 : 70	84 : 16
dppe	80 : 20	90 : 10
dmpe	99 : 1	100 : 0
dppp	26 : 74	33 : 67

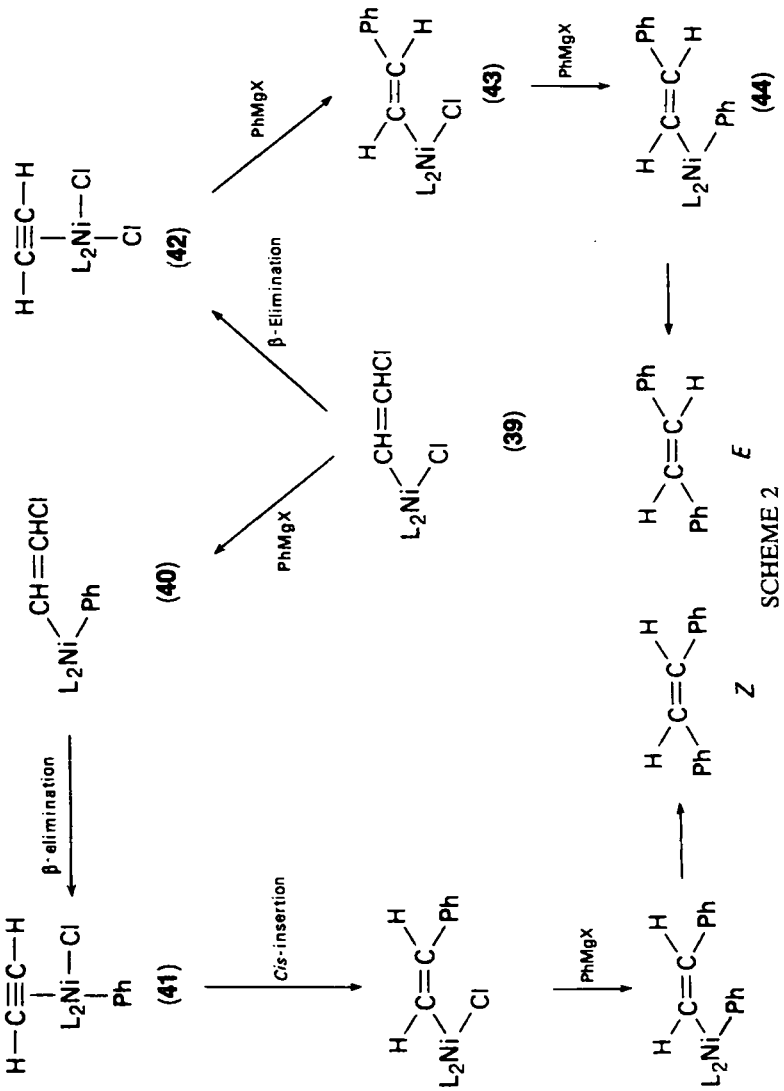
cross-coupled product R^1–R and at the same time regenerates the Ni(0) needed for the catalytic cycle.



SCHEME 1

According to Kumada and coworkers[136], Scheme 1 can be integrated to account for the stereochemical results observed with the 1,2-dichloroethenes. As shown in Scheme 2, the tendency towards forming *Z*-stilbene should arise from an elimination–addition mechanism. The *β*-elimination from the diorganonickel species **40** leads to an acetylene complex **41** which, after a *cis* insertion process and reaction with the Grignard reagent produces the *Z*-stilbene. The prevailing formation of the *E*-olefin when dppp is the ligand in the catalyst has been tentatively explained assuming that the alkenyl complex **39**, before reacting with the Grignard reagent, undergoes elimination to give the five-coordinate intermediate **42**. In this intermediate the nickel centre may be blocked by the coordinating acetylene molecule from the attack of a Grignard reagent. Consequently, the nucleophilic attack could occur on the acetylene carbon from the outside rather than on the nickel atom and this would lead to the *trans*-alkenyl complex **43**. Reaction of the latter with Grignard reagent produces the complex **44** responsible for the *E*-stilbene formation.

It is our opinion that more work is needed for a complete explanation of all the observed facts. Whenever possible, the reactions of 1,2-dichloroethenes should be divided into two sequential cross-couplings and the stereochemical course of each step should be elucidated. In this connection it is worth noting that Ratovelomanana and Linstrumelle[141], using $Ni(PPh_3)_4$ as catalyst directly were able to carry out the substitution of one halogen atom of *E*- or *Z*-1,2-dichloroethenes stereospecifically with some alkyl Grignard reagents. However, using the same Ni(0) catalyst and

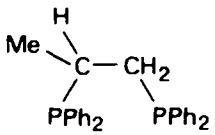

β-elimination
Cis-insertion
PhMgX
β-Elimination
(41)
(40)
(42)
(39)
(43)
(44)
Z
E

SCHEME 2

phenylmagnesium bromide, both mono- and bis-coupling products were obtained in a non-stereospecific manner[142]. All these differences require an adequate explanation. In future work it will also be important to evaluate the role of other possible mechanisms. In fact, the possibility of the intervention of both Ni(I) and Ni(III) species has been suggested recently in the formation of the cross-coupled products[143].

In spite of the stereochemical and mechanistic complexities, Grignard reagents modified by Ni complexes appear to be powerful synthetic tools. In addition to the several features presented above, it seems appropriate at this point to mention the recent work on the asymmetric cross-coupling reactions[144–151], which has already found an interesting application in the total synthesis of optically active α-curcumene[148].

Consiglio and coworkers have studied the asymmetric cross-coupling between secondary alkyl Grignard reagents and aromatic, heteroaromatic or vinylic halides in the presence of optically active nickel(II) complexes[144–146]. Using a catalyst having (+)*R*-1,2-bis(diphenylphosphino)propane (Prophos, **45**) as a ligand, optical yields appear to be dependent upon the type of the halogen present on both substrate and reagent. In the reactions between phenyl halides and *s*-butylmagnesium halides the optical yields are in the range 5–45%[145].

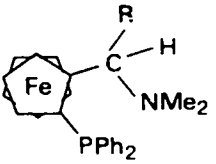


(45)

The optical purity of the 2-phenylbutane obtained from C_6H_5I has values intermediate between those observed with C_6H_5Br and C_6H_5Cl. This trend cannot be ascribed to the reactivities of the C_6H_5X systems, which follow the order $C_6H_5I > C_6H_5Br > C_6H_5Cl$. Furthermore, for all the three types of halides the optical yields decrease with the Grignard reagent used in the order *s*-BuMgI > *s*-BuMgBr > *s*-BuMgCl. Finally, the halogen of the Grignard reagent has a dramatic effect upon the absolute configuration of the product. Indeed, the *S*-enantiomer prevails when starting with *s*-BuMgCl whereas the use of *s*-BuMgBr or *s*-BuMgI leads to the predominant formation of the *R* counterpart.

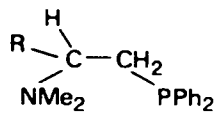
Extensive work on the asymmetric cross-coupling between vinyl bromides and Grignard reagents has been performed by the Kumada[147–151] group. The reactions between 1-phenylethylmagnesium chloride with vinyl bromide in the presence of $NiCl_2$ and chiral ligands result in the formation of optically active 3-phenyl-1-butene in high chemical yields. Optical yields depend upon the nature of the ligand used, namely (aminoalkylferrocenyl)phosphines (**46**)[147], β-dimethylaminoalkylphosphines (**47**)[149] and polystyrene-bound β-dimethylaminoalkylphosphines (**48**)[150]. The highest optical yields (94%) are obtained using *R*-*t*-Leuphos. (**47**, R = *t*-Bu) as the ligand[149].

The reaction discussed above represents an asymmetric destruction, one enantiomer of the Grignard reagent reacting faster than the other. However, it is very likely that the reagent always exists in a racemic form due to its inversion, which should be relatively fast as compared with the coupling process. When the carbanionic centre of the Grignard reagent does not coincide with the asymmetric carbon atom, the optically active olefin is formed and the unreacted Grignard reagent is partially resolved[151]. Accordingly, when an ether solution of racemic 2-phenylpropylmagnesium chloride is allowed to react with less than one equivalent of vinyl bromide in the presence of the *S*-Valphos ligand (**47**, R = *i*-Pr) and nickel chloride (equation 108), 4-phenyl-



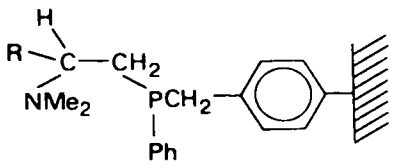
(46)

R = H, Me



(47)

R = Me, *i*-Pr, *t*-Bu, Ph, $PhCH_2$



(48)

R = *i*-Pr, $PhCH_2$

1-pentene (**49**) (7.7% enantiomeric excess of *S*-configuration) and (after carbonation and hydrolysis) 3-phenylbutanoic acid (**50**) (5.8% enantiomeric excess of *R*-configuration) are formed.

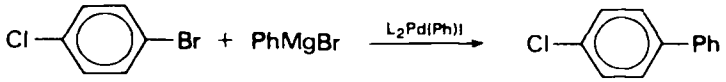
$$\begin{array}{l} Ph(Me)CHCH_2MgCl + CH_2{=}CHBr \xrightarrow[Et_2O/0°C]{L^*/NiCl_2} \\ \qquad Ph(Me)\overset{*}{C}HCH_2MgCl + Ph(Me)\overset{*}{C}HCH_2CH{=}CH_2 \\ \qquad\qquad\qquad\qquad (49) \\ \qquad\qquad \Big\downarrow \begin{array}{l}(1)\ CO_2 \\ (2)\ H_3O^+\end{array} \\ \qquad Ph(Me)\overset{*}{C}HCH_2COOH \\ \qquad\qquad (50) \end{array} \qquad (108)$$

In the above discussion, keeping within the scope of this review, our attention was focused upon the use of halides as substrates for the cross-coupling. However, in the last few years, work from several laboratories has shown that various types of enol ethers and also vinyl, aryl, heterocyclic or allyl sulphides or selenides can be used profitably as substrates and, therefore, the methodology is becoming more advantageous due to the interesting variations on this theme[152–158].

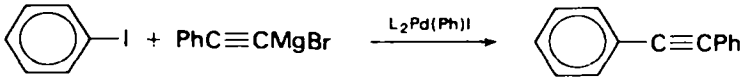
C. Cross-coupling Reactions of Grignard Reagents in the Presence of Palladium Complexes

As could be predicted from a simple consideration of Scheme 1 (Section III.B), palladium(0) and palladium(II) complexes can also be used to catalyse the cross-coupling between Grignard reagents and halides[159–166]. Indeed, the use of these catalysts has been reported for a variety of halides, including allenic and propargylic halides[159].

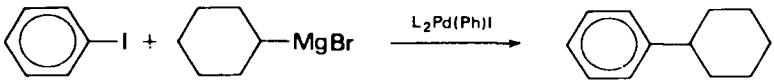
In 1976 Sekiya and Ishikawa[160] have reported the reactions of aryl, alkynyl and alkyl Grignard reagents with aryl halides in the presence of iodo(phenyl)bis(triphenylphosphine)palladium (equations 109–111).



73% (109)



84% (110)

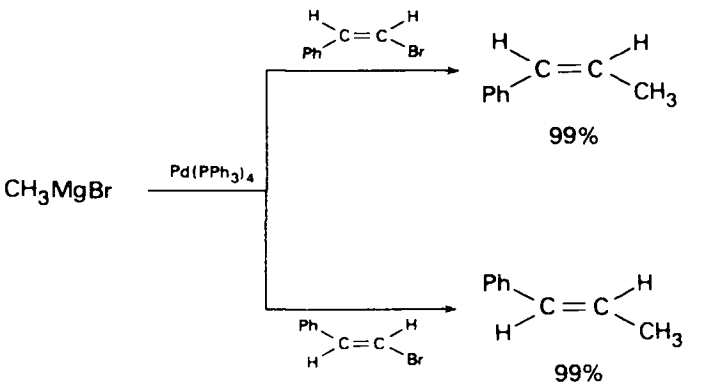


51% (111)

The mono-alkylation or mono-arylation of aromatic and heteroaromatic dihalides can be carried out successfully (with yields in the range 52–75%) in the presence of Pd catalysts having triphenylphosphine molecules or 1,4-bis-(diphenylphosphino)butane as ligands[161]. This represents an advantage with respect to the nickel-catalysed Grignard reactions[137], where a predominant formation of dialkylated product is observed even when an equimolecular amount of reagent is used.

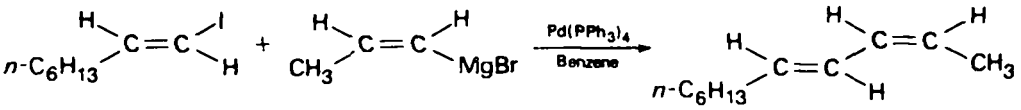
The cross-coupling of a secondary Grignard reagent, i.e. *s*-butyl magnesium chloride with bromobenzene, *E*-*β*-bromostyrene and 2-bromopropene has been found to be efficiently catalysed by dichloro[1,1′-bis(diphenylphosphino)ferrocene]palladium(II)[162]. The result is noteworthy in view of the large degree of isomerization often observed with Ni catalysts and secondary Grignard reagents[134].

An interesting feature is represented by the highly stereospecific course of the reaction between alkenyl halides and Grignard reagent. In a detailed investigation Murahashi and coworkers[163] have shown that in the presence of $Pd(PPh_3)_4$ (equation 112) the methylation of *Z*- or *E*-*β*-bromostyrene (with methylmagnesium bromide) in benzene gives *Z*- or *E*-propenylbenzenes in high yields and with a stereospecificity of 99%. Therefore, the isomeric purity of the alkenes obtained with the Pd catalyst is higher than that obtained with the Ni catalyst[136].



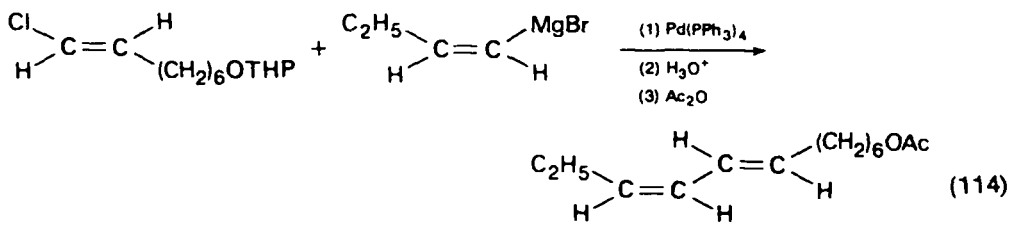
(112)

The stereospecific coupling has found several interesting applications in synthesis. In fact, the reaction between *E*-1-iodo-1-octene and *Z*-1-propenyl-1-magnesium bromide in the presence of $Pd(PPh_3)_4$ gives (2*Z*,4*E*)-2,4-undecadiene (≥97% of isomeric purity) in high yields (equation 113)[164].



87% (113)

Z-1-Butenyl-1-magnesium bromide has been coupled with *E*-8-chloro-7-octen-1-yl tetrahydropyranyl ether to give, after hydrolysis and acetylation, the sex pheromone (**51**) of *Lobesia botrana*, a major pest of European vineyards (equation 114)[141]. The preservation of the stereochemical integrity in the reagent and in the substrate makes the reaction an attractive stereospecific route to dienes.

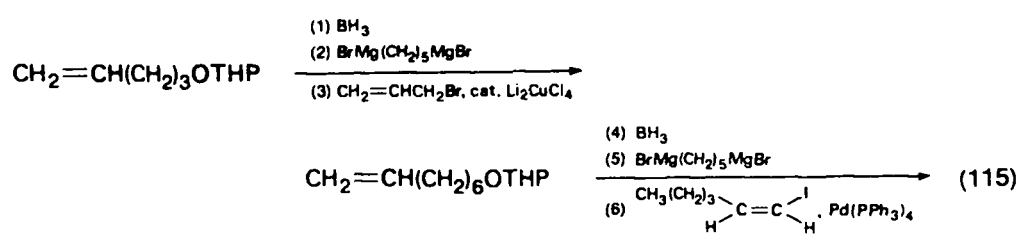


(114)

(**51**)

95%

Another application is represented by the synthesis of a sex pheromone (**52**) of the southern armyworm moth, *Prodenia eridania* (equation 115)[165]. It is worth noting that the procedure of steps 2 and 5 involves the use of pentane-1,5-di(magnesium bromide) for the selective transformation of organoboranes to the Grignard reagents[165] which are then coupled with the allyl (step 3) or the alkenyl (step 6) halide.



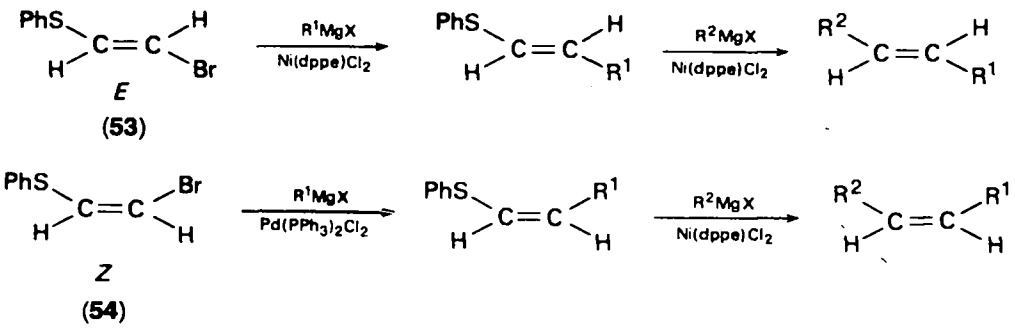
(115)

(**52**)

50%

From the results reported above it would be tempting to conclude that the palladium catalysts should be preferred with respect to the nickel catalysts. However, it seems wiser to consider both types of complex as useful and complementary. As an example of the convenient use of both Ni and Pd catalysts, it is worth reporting the results of an

investigation performed recently in these laboratories[142]. In connection with studies on highly stereoselective olefin synthesis[167], we have found that starting with *E*- or *Z*-1-bromo-2-(phenylthio)ethene and Grignard reagents in ether, two sequential cross-coupling processes take place to give the diaryl- or dialkyl-substituted ethenes. In order to obtain the unsymmetric olefins ($R^1CH{=}CHR^2$) it is only necessary to add the second Grignard reagent (R^2MgX, see Scheme 3) after completion of the reaction of the first one. The difference between the leaving group abilities of the two groups (Br > SPh) is sufficiently high that no symmetric olefins ($R^1CH{=}CHR^1$) are formed.

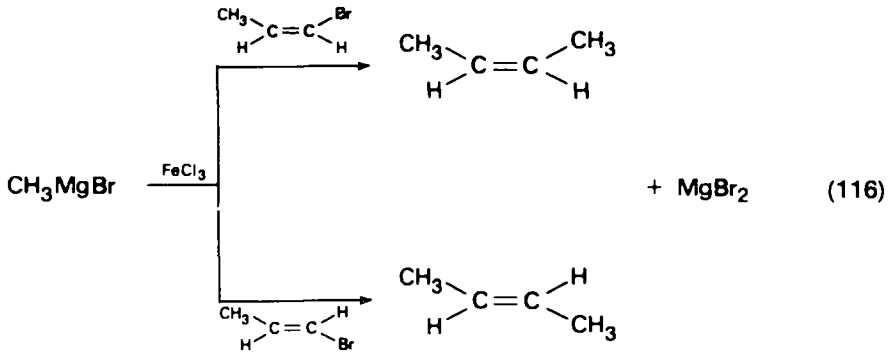


SCHEME 3

The use of a nickel catalyst, $Ni(dppe)Cl_2$, in the case of the *E*-isomer (**53**) gives a final olefin with an *E*-isomeric purity higher than 99%. In the case of the *Z*-isomer (**54**), the use of the nickel catalyst in both steps is unsatisfactory since the isomeric purity of the final olefins in the cases investigated is only 70%. A significant improvement is brought about by using a Pd(II) catalyst in the first step. (The second step does not occur at any significant rate under Pd catalysis.) Indeed, the stereoselectivity with this catalyst can reach values in the range 95–98%. The relevant data reported in Table 4 show that the combination of two types of catalytic complex and of the two leaving groups leads to a novel and general stereospecific entry to 1,2-disubstituted ethenes.

D. Iron-catalysed Cross-coupling Reactions of Grignard Reagents

1-Alkenyl halides react readily (at 0–25 °C) with Grignard reagents in a THF solution containing $FeCl_3$ as catalyst[168]. The process is stereospecific, since *Z*- and *E*-1-propenyl bromides give *Z*- and *E*-2-butene respectively (equation 116).



The yields obtained with primary alkyl Grignard reagents are in the range 65–85%. Interestingly, using tris(dibenzoylmethido)iron(III) as catalyst, it is possible to extend

TABLE 4. Sequential cross-coupling reactions of *E*- or *Z*-1-bromo-2-(phenylthio)ethene with Grignard reagents in the presence of nickel- or palladium–phosphine complexes as catalysts[142]

Substrate configuration	Step 1		Step 2		Final olefin	Overall yield, %	Product configuration	
	R^1MgX	Catalyst	R^2MgX	Catalyst			*E*, %	*Z*, %
E	PhMgBr	$Ni(dppe)Cl_2$	MeMgI	$Ni(dppe)Cl_2$	PhCH=CHMe	100	>99	<1
E	*n*-BuMgBr	$Ni(dppe)Cl_2$	*n*-BuMgBr	$Ni(dppe)Cl_2$	*n*-BuCH=CHBu-*n*	90	>99	<1
E	Ph(Me)CHMgCl	$Ni(dppe)Cl_2$	*n*-BuMgBr	$Ni(dppe)Cl_2$	Ph(Me)CHCH=CHBu-*n*	91	>99	<1
E	Ph(Me)CHMgCl	$Ni(dppe)Cl_2$	PhMgBr	$Ni(dppe)Cl_2$	Ph(Me)CHCH=CHPh	85	>99	<1
Z	PhMgBr	$Pd(PPh_3)_2Cl_2$	MeMgI	$Ni(dppe)Cl_2$	PhCH=CHMe	93	3	97
Z	*n*-BuMgBr	$Pd(PPh_3)_2Cl_2$	*n*-BuMgBr	$Ni(dppe)Cl_2$	*n*-BuCH=CHBu-*n*	72	2	98
Z	Ph(Me)CHMgCl	$Pd(PPh_3)_2Cl_2$	*n*-BuMgBr	$Ni(dppp)Cl_2$	Ph(Me)CHCH=CHBu-*n*	53	3	97
Z	Ph(Me)CHMgCl	$Pd(PPh_3)_2Cl_2$	PhMgBr	$Ni(dppp)Cl_2$	Ph(Me)CHCH=CHPh	70	4	96

the reaction to secondary and tertiary alkyl Grignard reagents without facing any difficulty connected with the isomerization process[169]. Indeed, no transformation of the isopropyl to the *n*-propyl group or of the *t*-butyl to the isobutyl group is detected. However, the yields are lower than those obtained in the case of the primary alkyl Grignard reagents, and the formation of significant amounts of alkane, alkene and homocoupling products deriving from the Grignard reagents is observed.

In order to explain the catalytic cycle it was suggested[169] that the process involves an initiation, a propagation and a termination step (equations 117–122).

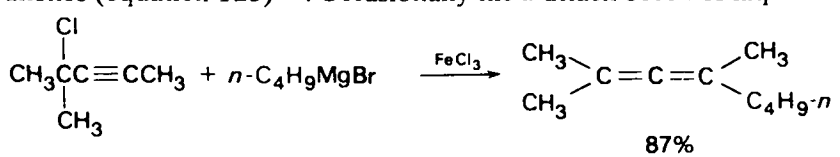
Initiation	$Fe(III) + 2\,RMgX \longrightarrow Fe(I) + R_{ox}$	(117)
Propagation	$Fe(I) + RMgX \rightleftharpoons RFe(I)^- + MgX^+$	(118)
	$RFe(I)^- + R^1Br \longrightarrow RR^1Fe(III) + Br^-$	(119)
	$RR^1Fe(III) \longrightarrow R{-}R^1 + Fe(I)$, etc.	(120)
Termination	$n\,Fe(I) \longrightarrow [Fe(I)]_n$	(121)
	$Fe(I) \xrightarrow{(ox.)} Fe(III)$	(122)

In the first step (equation 117) reduction of the iron(III) complex occurs. Alkene, alkane and alkyl dimers are the usual products of oxidation (R_{ox}) of the Grignard reagent. In the propagation step (equations 118–120) a $RFe(I)^-$ species is formed and then an oxidative addition takes place between this species and the halide. The cross-coupled product is formed in the reductive elimination (equation 120).

An alternative scheme to be considered for the cross-coupling is different only in the propagation step. According to such a mechanism, the substitution process requires the reduced iron species to effect substitution by a coordination mechanism, with no oxidation or reduction of the iron (equations 123 and 124)[169].

Propagation	$Fe(I) + R^1Br \rightleftharpoons Fe(R^1Br)$	(123)
	$Fe(R^1Br) + RMgX \longrightarrow R{-}R^1 + MgXBr + Fe(I)$, etc.	(124)

Propargyl chlorides react with Grignard reagents in the presence of an iron catalyst to give allenes (equation 125)[170]. Occasionally the α-attack becomes important. Thus,



87% (125)

non-terminal tertiary propargyl chlorides form only allenes with primary and secondary alkyl Grignard reagents. However, a 1 : 1 mixture of alkyne and allene is produced when they react with MeMgI.

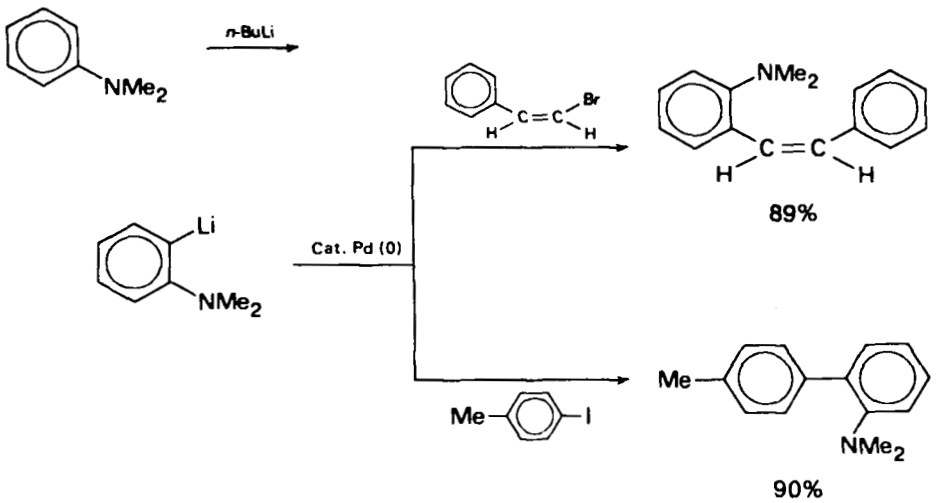
The proposed mechanism considers a catalytic cycle involving low valence state transition metal species similar to those proposed by Tamura and Kochi[168].

E. Cross-coupling Reactions of Organolithium Compounds in the Presence of Palladium or Nickel Complexes

Murahashi and coworkers[163] have reported that alkenyl halides undergo alkylation, arylation and vinylation at room temperature in benzene and in the presence of a catalytic amount of $Pd(PPh_3)_4$. Other Pd catalysts, including the commercial

$Pd(PPh_3)_2Cl_2$ complex, can also be successfully employed. Good yields are obtained in most cases and the reaction occurs with a high degree (98–100%) of retention. Therefore, the process compares rather well with the analogous cross-coupling discussed above, which involves Grignard reagents.

Besides alkenyl halides, aryl halides can be also used. The examples reported below deal with the two types of halides, and both cases emphasize the advantage presented by the lithium reagents which can be prepared by metallation of relatively acidic substrates (equation 126).



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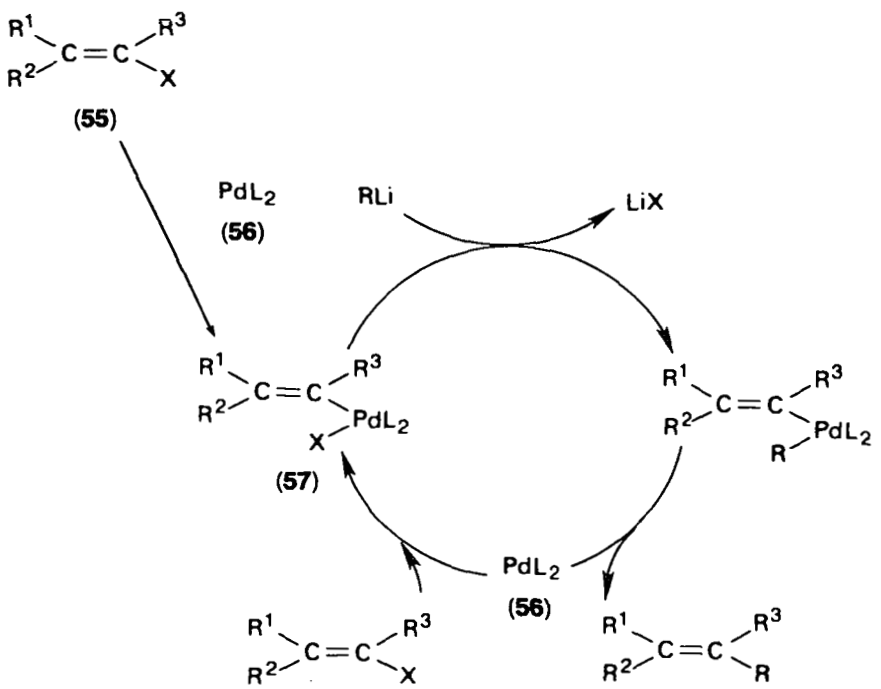
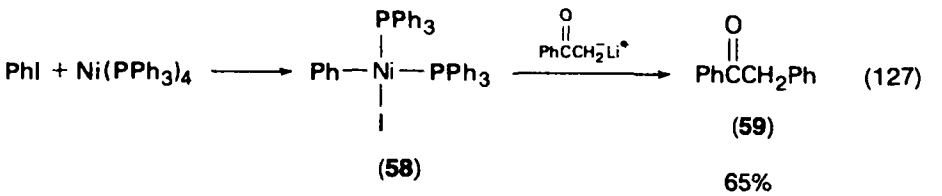


SCHEME 4

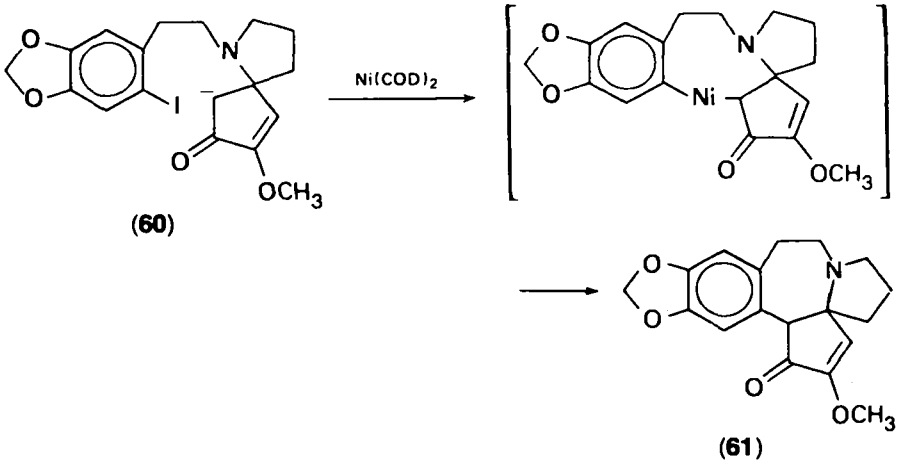
A catalytic cycle, such as that discussed in Scheme 1 for the Ni catalysts and Grignard reagent, has been suggested to operate in the case of lithium derivatives and the Pd catalysts. The process reported in Scheme 4 for an alkenyl halide starts with an oxidative addition of the substrate (**55**) to zero-valent palladium (**56**). Then the resulting alkenylpalladium intermediate (**57**) begins the catalytic reduction–oxidation cycle.

Ni(0) complexes have been found to be effective catalysts in similar cross-coupling reactions. Thus the phenylnickel iodide complex (**58**), formed from iodobenzene and $Ni(PPh_3)_4$, reacts with the lithium salt of acetophenone to give benzyl phenyl ketone (**59**) (equation 127)[171]. The procedure has been applied to the synthesis of cephalo-



(127)

taxinone (**61**) starting with the iodide **60** in the presence of bis(1,5-cyclooctadiene)nickel ($Ni(COD)_2$) as catalyst (equation 128)[171]. The reduction of the carbonyl group of **61** forms cephalotaxine[172], which, after esterification, is very active against lymphoid leukaemia.



(128)

F. Cross-coupling Reactions of Organozinc Compounds in the Presence of Nickel or Palladium Catalysts

The reactions of organic halides with organozinc derivatives in the presence of Ni or Pd catalysts have already found several useful applications in organic synthesis. For instance, a general and mild procedure for the preparation of unsymmetrical biaryls and diarylmethanes has been reported[173]. The arylzinc chloride can be prepared by reaction of the corresponding aryllithium or Grignard reagents and zinc chloride, whereas the benzylzinc derivatives can easily be obtained from benzyl bromide and Zn powder.

As shown in equation (129) either $Ni(PPh_3)_4$ or $Pd(PPh_3)_2Cl_2$ can be used as catalyst. In the latter case the presence of diisobutylaluminium hydride (DIBAL) is required to reduce Pd(II) to Pd(0).

$$RZnX + ArX' \xrightarrow[Pd(PPh_3)_2Cl_2 + DIBAL]{Ni(PPh_3)_4 \text{ or}} R{-}Ar \qquad (129)$$

$R = Ar$ or $ArCH_2$; $X = Br, Cl, Ar$; $X' = Br, I$

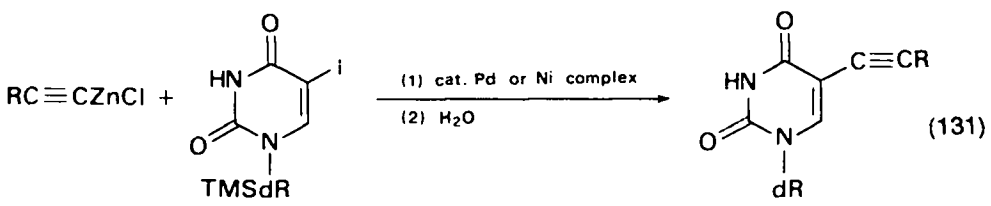
Actually, several reactions of the organozinc derivatives could also be accomplished with Grignard reagents. However, the advantage in using organozinc compounds is the possibility of carrying out, with high yields, the cross-coupling with substrates having functional groups sensitive to the Grignard reagents (e.g. methyl *p*-bromobenzoate, *p*-bromobenzonitrile and *p*-iodonitrobenzene).

The use of an alkynylzinc reagent in the reaction with aryl halides permits a general synthesis of terminal and internal arylalkynes (equation 130)[174].

$$RC{\equiv}CZnCl + ArX \xrightarrow{Pd(0)} RC{\equiv}CAr \qquad (130)$$

$R = H$, alkyl or aryl; $X = Br, I$

The same type of reagent has been employed in the cross-coupling with a silylated 5-iodo-2′-deoxyuridine (**62**) to give, after the deprotection step, 5-alkynyl-2′-deoxyuridines (**63**) (equation 131)[175]. These are interesting compounds in view of the antiviral and antitumoural properties of the C-5 substituted 2′-deoxyuridine system.



(131)

(**62**) (**63**)

dR = deoxyribose; TMSdR = *O*-bis(trimethylsilyl)deoxyribose

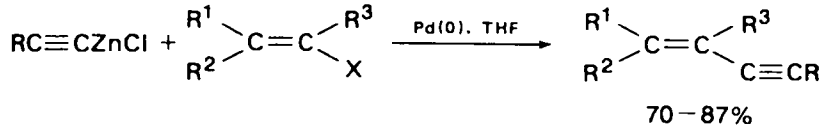
In addition, the cross-coupling reaction involving aryl halides was carried out successfully with the Reformatsky reagent. The arylation was performed in the presence of $Ni(PPh_3)_4$, in HMPA/Methylal (dimethoxymethane) as solvent[176] (equation 132). The procedure has been suggested as an alternative to other methods of synthesizing arylacetic derivatives which are vegetal hormones and anti-inflammatories[177,178].

$$ArX + BrZnCH_2CO_2Et \xrightarrow[HMPA/Methylal\ (1:1)]{Ni(PPh_3)_4\ (10\%)} ArCH_2CO_2Et + ZnBrX \qquad (132)$$

$X = Br, Cl, I$

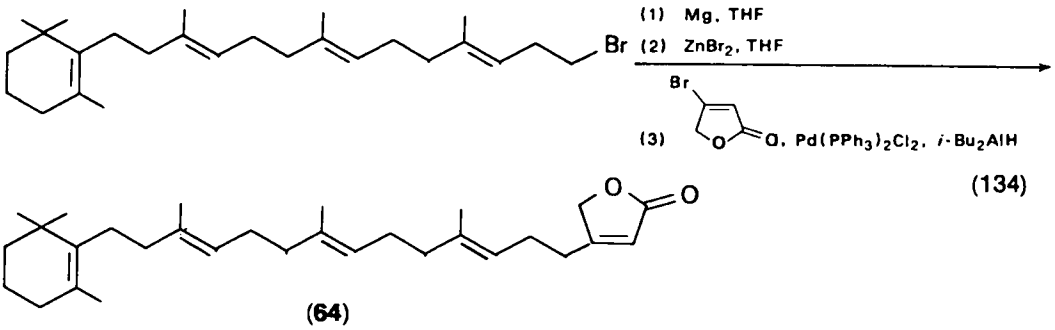
Alkenyl halides can undergo cross-coupling with the organozinc derivatives in the presence of Pd or Ni catalysts. The reactions of alkynyl, homopropargylic and homoallylic zinc compounds represent a useful route to conjugated enynes (equation 133)[179], 1,5-enynes and 1,5-dienes[180].

The reaction between homoallylic zinc compounds and β-halogeno-α,β-unsaturated carbonyl derivatives has proven to be well suited for the selective synthesis of butenolides and furans of terpenoid origin. The validity of the procedure is best illustrated by the final step of the synthesis of the mokupalide **64** (equation 134)[181].



(133)

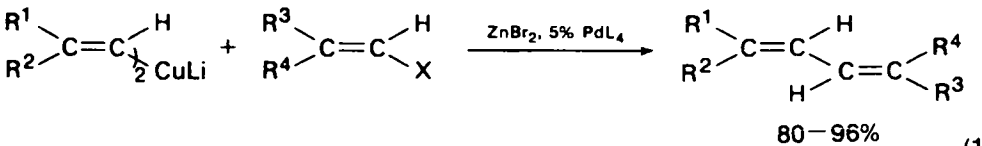
$R = R^2 = H$, alkyl; $R^1 = H$, alkyl or CO_2Me; $R^3 = H$; X = Br, I



(134)

(64)

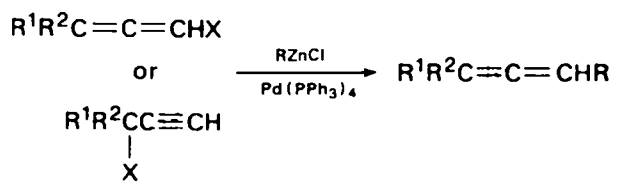
Recently it has been reported[182] that alkenylzinc derivatives can be formed from the corresponding copper(I) compounds obtained by following the Normant procedure[31]. Their reactions with alkenyl halides afford a method of synthesis of 1,3-dienes with a very high stereospecificity (>99%) (equation 135). The importance of the procedure can be better appreciated when one considers that the same product cannot be obtained by direct coupling of the organocopper reagent with alkenyl halides. Indeed, a few cases[42,164,183] are known of alkenyl cuprate–alkenyl halide coupling and the observed stereoselectivity and/or yields do not reach the high vaules of the procedure involving the zinc derivatives.



(135)

$R^1 = R^4 = H$, alkyl; R^2 = alkyl; R^3 = H, alkyl, Ar; X = Br, I

Organozinc compounds have been also used in the coupling with propargylic and allenic halides according to equation (136)[184]. The process is obviously similar to the Pd(0)-catalysed reaction of Grignard reagents[159]. However, a comparison between the $PhMgBr/Pd(PPh_3)_4$ and $PhZnCl/Pd(PPh_3)_4$ systems reveals that, in the first case, the cross-coupling reaction with the allenic halide (e.g. PhCH=C=CHX) is accompanied by a substantial amount of halogen–metal exchange leading to the allenic Grignard reagent (PhCH=C=CHMgX).



(136)

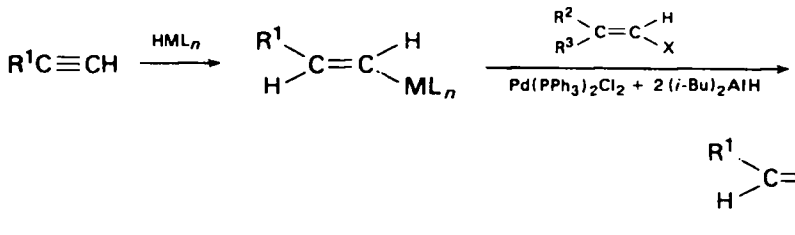
G. Cross-coupling Reactions of Organoaluminium or Organozirconium Compounds in the Presence of Nickel or Palladium Catalysts

Trialkyl or trialkynylaluminium compounds react with tertiary halides or secondary alkylsulphonates to give cross-coupling products. Alkenylalanes react only with the latter type of substrate[185–188]. The scope of these reactions has been broadened to a large extent by the use of Ni or Pd catalysts. Indeed, a convenient synthesis of internal alkynes[189] can be carried out by the nickel-catalysed reaction of alkylalanes with alkynyl halides (equation 137).

$$R_3Al + R^1C{\equiv}CBr \xrightarrow[\text{Pentane, } 25°C]{Ni(mesal)_2} R^1C{\equiv}CR \qquad (137)$$

R = alkyl; R^1 = alkyl, aryl; Ni(mesal)$_2$ = bis(*N*-methylsalicylaldimine) nickel

Furthermore, alkenylalanes[190], which can easily be obtained by hydroalumination of alkynes, react with alkenyl halides in the presence of the $Pd(PPh_3)_2Cl_2 + 2\ (i\text{-}Bu)_2AlH$ system as catalyst to give dienes in a highly stereoselective manner (equation 138).

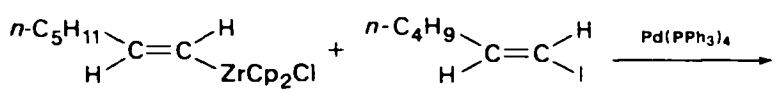


(138)

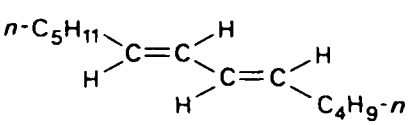
ML_n = Al (*i*-Bu)$_2$; R^1 = alkyl; R^2 = H, alkyl or CO_2Me; R^3 = H, alkyl; X = I, Br

The hydroalumination procedure is not compatible with various common oxygen functional groups in the R^1 group and this represents a severe limitation. A significant improvement can be brought about by the use of the hydrozirconation procedure, which can tolerate certain ether functionalities such as —OEt or —OTHP groups. The *E*-1-alkenylzirconium derivative can be reacted with alkenyl halides according to equation (138) ($ML_n = ClZrCp_2$) to give 1,3-dienes[191] stereoselectively. The application of the procedure to a few specific cases is reported in equations (139)–(142).

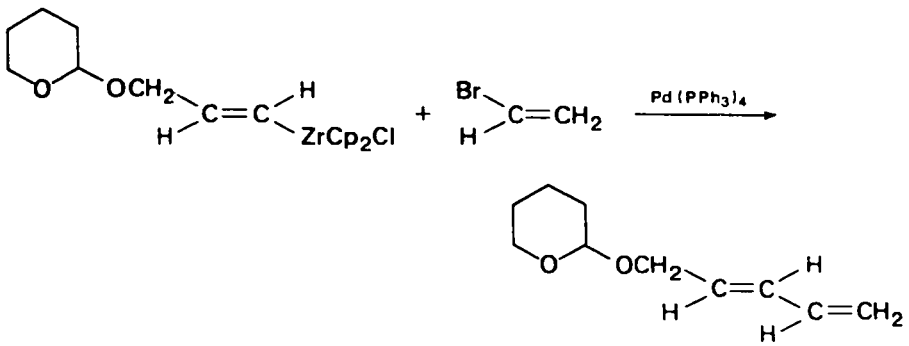
Equation (142) shows the possibility of adopting the same procedure for the arylation[192] of the organozirconium compounds. It is worth noting that $Ni(PPh_3)_4$ can be used for the arylation process. However, in the alkenyl–alkenyl coupling leading to dienes the use of palladium catalysts appears to give the final product in higher yields.[191]



(139)

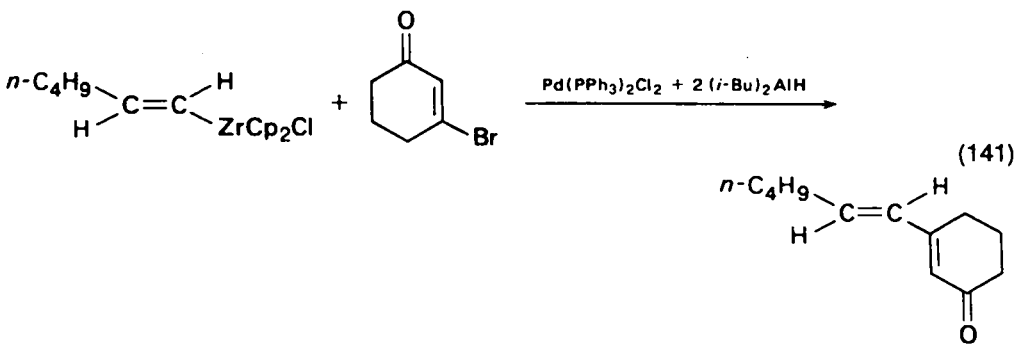


91%



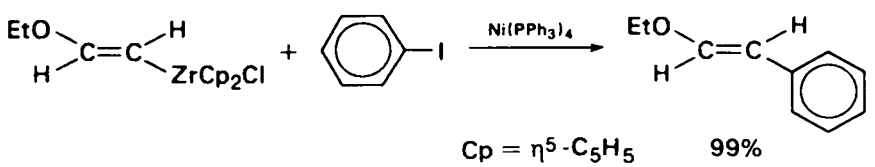
(140)

77%



(141)

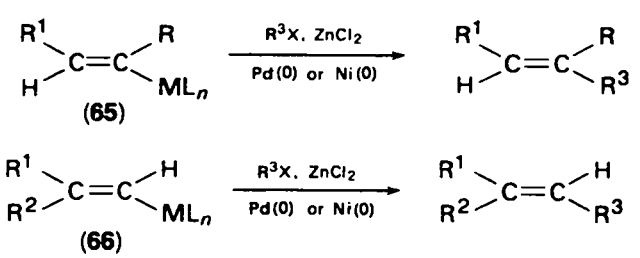
60%



(142)

Cp = η^5-C_5H_5 99%

Furthermore, Negishi and coworkers[193,194] have been able to promote the reactions, otherwise unsuccessful, of alkenyl, aryl and alkynyl halides with alkenylaluminium or zirconium compounds of the type **65** and **66** by adding, other than Pd or Ni catalysts, metal salts containing Zn or Cd. The procedure provides a general method of synthesis of trisubstituted olefins (equation 143).



(143)

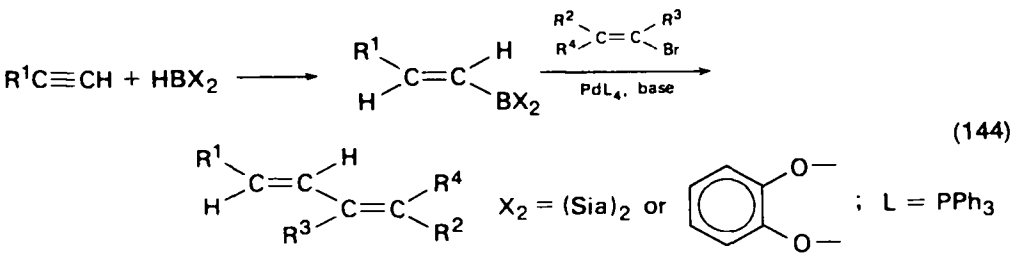
(65) **(66)**

ML_n = Al(*i*-Bu)$_2$ or $ZrCp_2Cl$; R = R^1 = R^2 = alkyl; R^3 = alkenyl, aryl or alkynyl; X = Br, I

H. Cross-coupling Reactions of 1-Alkenylboranes in the Presence of Palladium Complexes

Among the boron compounds, organoborates are known to couple[195] directly with highly reactive halides (e.g. methyl iodide and allyl bromide). In Section II.E we have seen the use of copper(I) salts to modify some boron compound, thus enabling them to undergo the cross-coupling reactions[74].

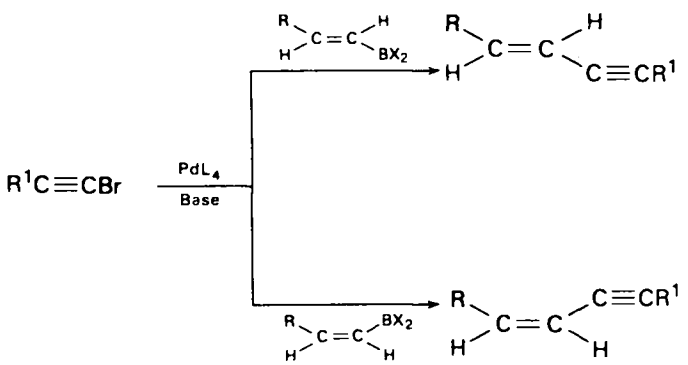
In the presence of $Pd(PPh_3)_4$ the reaction of an equimolar amount of *E*-1-hexenyldisiamylborane with *E*-1-bromo-2-phenylethene in THF gives the cross-coupled product, *E*,*E*-1-phenyl-1,3-octadiene, in a yield of only 2%. However, the yield is dramatically increased (to 59%) by addition of an excess of 2 N aqueous sodium hydroxide. The yield is even higher (80%) with *E*-1-hexenyl-1,3,2-benzodioxaborole. Retention is observed in the reagent and in the substrate. Consequently a procedure according to equation (144) leads to *E*,*E*-dienes with an isomeric purity in the range 96–100%[196].



(144)

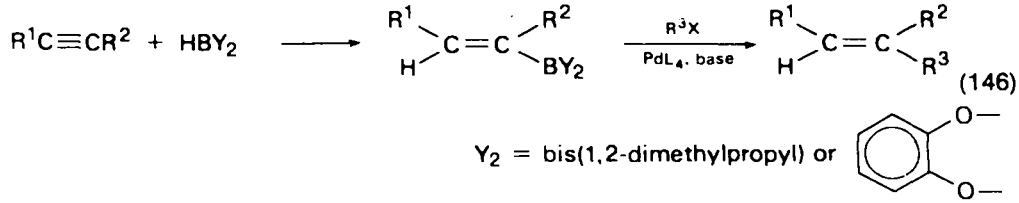
The versatility of the procedure is shown by the fact that *Z*,*Z* and *Z*,*E* conjugated alkadienes can be also obtained. The first isomer is obtained in the reaction of *Z*-1-alkenylboranes with *Z*-1-alkenyl bromide, whereas the second isomer can arise using a reagent and a substrate having different configurations[197].

Z- or *E*-enynes can easily be formed by using alkynyl halides as substrates (equation 145)[196,197].



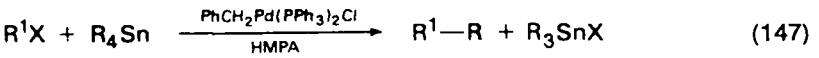
(145)

The scope of the method is not restricted to the synthesis of conjugated dienes or enynes. Indeed, the *E*-1-alkenylboranes, readily obtainable via hydroboration of acetylenes, have been reacted with aryl, allylic or benzylic halides to yield arylated alkenes, 1,4-alkadienes or allylbenzenes in good yields (equation 146)[198,199].

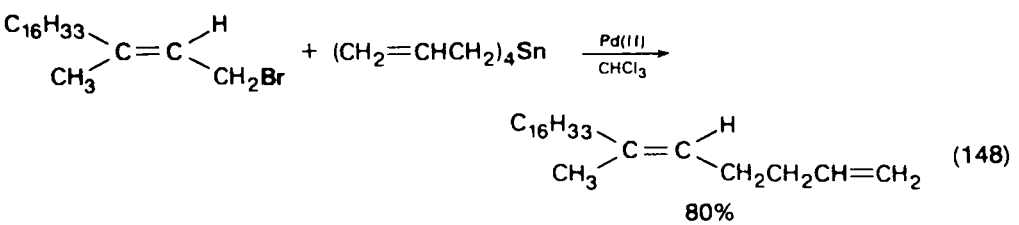


I. Cross-coupling Reactions of Tetraorganotin Compounds in the Presence of Palladium Catalysts

Palladium complexes catalyse the coupling of tetraorganotin compounds with benzyl and aryl halides[200,201]. In a detailed investigation, benzylchlorobis(triphenylphosphine)palladium(II) was found to be the reagent of choice for the reactions which were carried out in HMPA (equation 147).

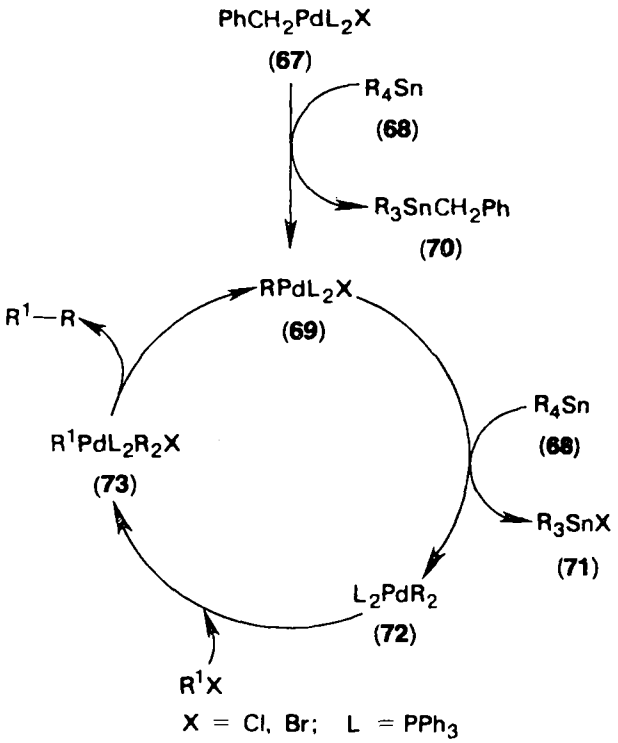


A large variety of organotin compounds can be made and therefore it is possible to effect methylation, butylation, vinylation, arylation and benzylation of benzyl and aromatic halides, The yields are in the range 78–100%, with the exception of the tetrabutyl case which, with benzyl bromide, gives only 42% of amylbenzene. Recently[202] the procedure has been employed to prepare 1,5-dienes by reacting tetraallyltin or allyltributyltin with allyl bromides in the presence of Pd(II) and/or $ZnCl_2$ as a catalyst (equation 148).



Various functional groups, including the ketone function, are not affected by the reaction, and this represents an advantage with respect to Grignard or organolithium compounds. A possible mechanism is reported in Scheme 5.

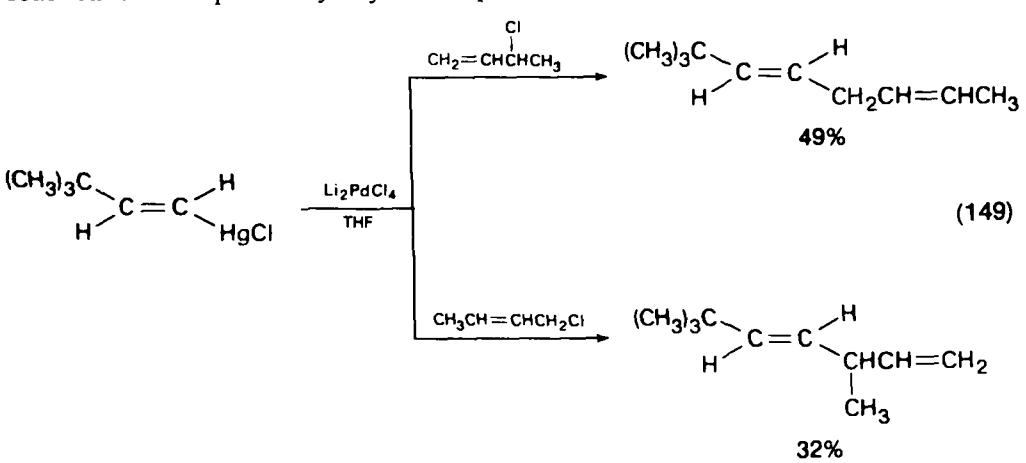
The catalyst benzylhalogenobis(triphenylphosphine)palladium(II) (**67**) undergoes transmetallation with the tetraorganotin compound (**68**) replacing the benzyl group rather than the halogen[200] and forming the organohalogenobis(triphenylphosphine)palladium(II) (**69**) together with benzyltriorganotin (**70**). The complex **69** reacts with the tetraorganotin (**68**) rather than with the more reactive **70** since the first is present in large excess. (However, the reaction between **69** and **70** plays a major role in an alternative catalytic cycle valid only for the benzyl halides and not reported here for the sake of simplicity.) The halogen–alkyl (or aryl) exchange between **68** and **69** yields the dialkylpalladium complex (**72**). This gives the palladium(IV) complex (**73**) by oxidative addition of an organic halide R^1X. Reductive elimination of **73** leads to the formation of the cross-coupled product $R^1—R$ and to the regeneration of complex **69**.



SCHEME 5

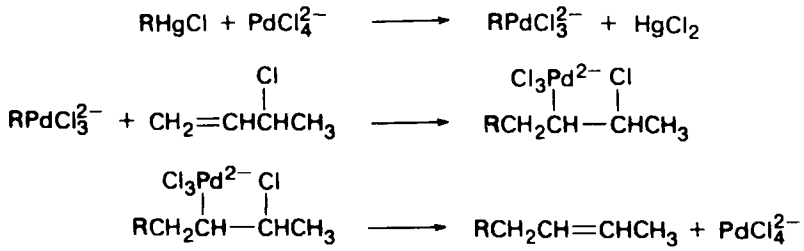
J. Cross-coupling Reactions of Organomercuric Halides in the Presence of Palladium Complexes

Arylmercurials[203] can be coupled with allylic halides by using palladium chloride and lithium chloride as catalysts in the presence of 10–30% of cupric chloride. Allylaromatic compounds are formed in 31–87% yields. Under similar conditions vinylmercurials lead to dienes[204]. As shown in the specific case of equation (149) the reaction is accompanied by allylic transposition.



(149)

This is explained by the suggested mechanism which involves addition of an organopalladium species to the olefin, followed by elimination leading to the cross-coupled product (see Scheme 6).

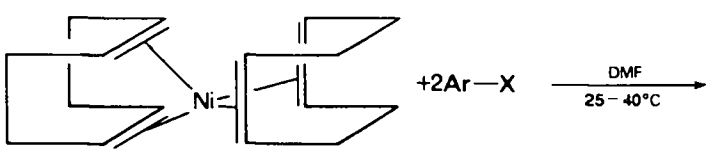


SCHEME 6

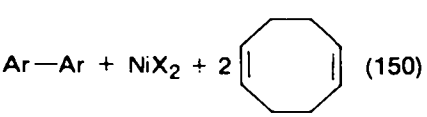
Due to the fact that the method requires the use of an organometallic compound as the starting reagent and a transition metal species as catalyst, we have considered it convenient to deal with the reaction in this section. However, it is worth noting that the process represents a mechanistic analogy with other reactions involving organopalladium compounds as intermediate (see Section V).

IV. SELF-COUPLING OF ARYL OR ALKENYL HALIDES BY MEANS OF NICKEL(0) COMPLEXES

Bis(1,5-cyclooctadiene)nickel(0) (**74**) reacts with a variety of aryl halides at moderate temperature in DMF to produce biaryls, nickel dihalide and 1,5-cyclooctadiene (COD) according to the following equation[205]:



(**74**)

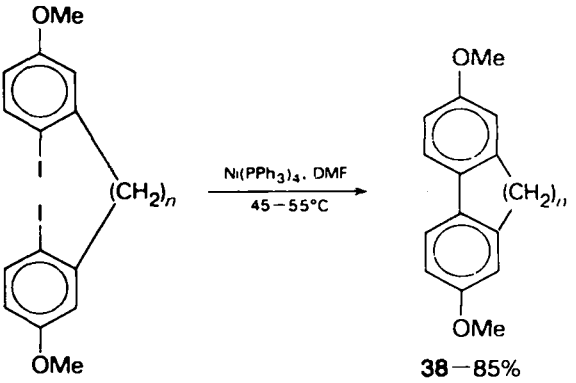


(150)

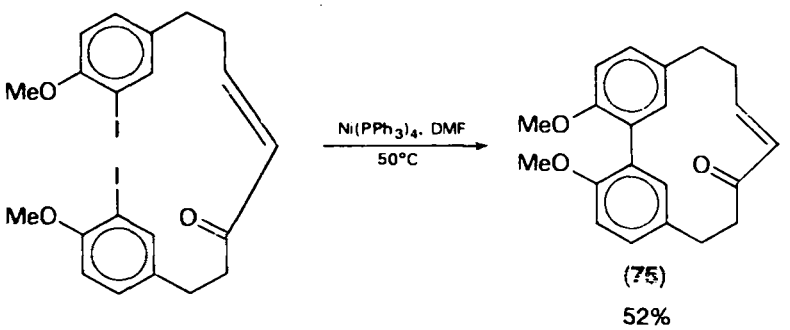
In most of the reported cases good yields are observed and functional groups such as ketone, aldehyde, ester and nitrile are tolerated by this procedure. As shown by the example in equation (151), by using a suitable substrate the coupling can also occur intramolecularly to give a variety of carbocyclic rings (bridged biphenyls[206]).

The method is successful for preparing functionalized rings, including compound **75**, a key intermediate in the synthesis of alnusone, a natural *meta*-bridged biphenyl[207]. However, the presence of acidic functional groups (e.g. hydroxyl, carboxylic acid) leads to the reduction of the carbon—halogen bond at the expense of the coupling reaction. Furthermore, both 2- and 4-nitrobromobenzene fail to react under the usual conditions.

In order to avoid the use of sensitive complexes which are conventionally prepared by cumbersome techniques[208], a procedure has been devised which involves the generation *in situ* of tris(triphenylphosphine)nickel(0) by reduction of bis(tri-

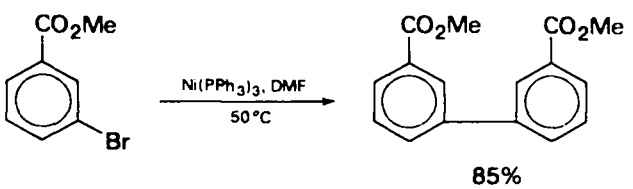


(151)



(152)

phenylphosphine)nickel(II) dichloride with zinc in the presence of triphenylphosphine[209]. The $Ni(PPh_3)_3$ complex thus formed is treated with aryl halides in DMF to give biaryl in good to excellent yields (equation 153):



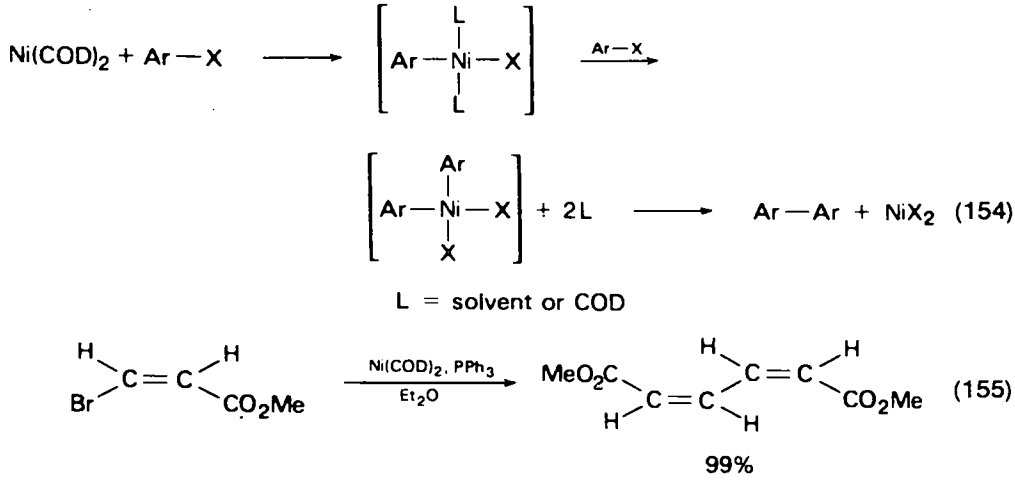
(153)

Although both the above-mentioned procedures employ stoicheiometric amounts of nickel, Kumada and coworkers[210] have recently reported that aryl coupling can be carried out with catalytic amounts (~10%) of nickel(II), using zinc powder as the ultimate reductant.

The mechanism of biaryl formation suggested by Semmelhack and coworkers[205,206] involves the oxidative addition of two molecules of aryl halides to the zero-valent nickel. The subsequent reductive elimination leads to the coupling of the coordinated aryl groups (equation 154).

However, for a related process in which aryl halides are coupled with preformed nickel(II) complexes of the type *trans*-$ArNiX(PEt_3)_2$, Tsou and Kochi[143] have proposed a radical chain mechanism involving paramagnetic nickel(I) and arylnickel(III) species as key reactive intermediates in the propagation steps.

Vinyl halides[209,211] can also undergo symmetric coupling in a stereoselective manner by reaction with Ni(0) complexes (equation 155).



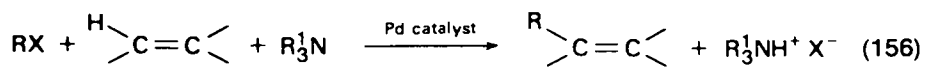
L = solvent or COD

99%

V. REACTIONS OF HALIDES WITH ALKENES OR ACETYLENES IN THE PRESENCE OF PALLADIUM CATALYSTS

A. Reactions with Alkenes

Fundamental work, mainly performed by Heck[212] during the last decade, has permitted the discovery and the development of a useful synthetic procedure which formally leads to the substitution of an olefinic hydrogen with the organic residue of a halide (equation 156).

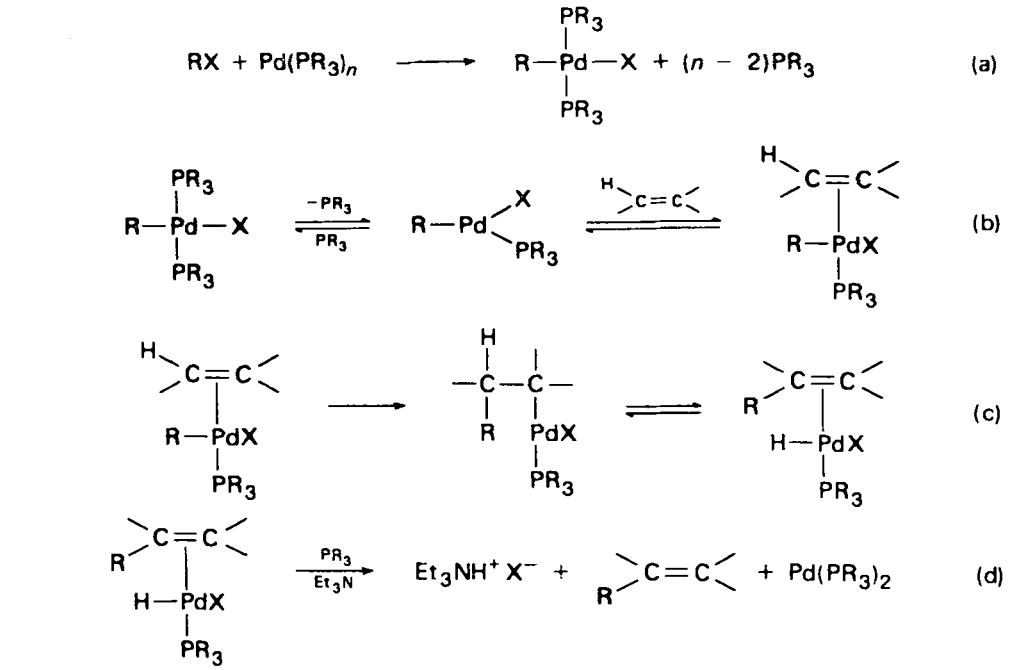


A convenient way of carrying out the reactions involves the use of a slight excess of the olefin with respect to the organic halide, a slight excess of the amine, usually triethylamine, 1 mol% of palladium acetate and 2 mol% of a triarylphosphine, usually tri-*o*-tolylphosphine. Under the reaction conditions, the palladium acetate–phosphine complex formed initially is reduced to the palladium(0)–phosphine catalyst. A plausible mechanism (Scheme 7) involves: (a) the oxidative addition of the halide to the Pd(0) complex; (b) coordination of the olefin to the Pd(II) complex; (c) insertion of the olefin and elimination of 'HPdX' to form an olefin π complex with the hydridopalladium group; (d) a dissociation step to give the substituted olefin.

Although electronic effects can play a significant role in some instances, steric effects are found to be generally dominating. Thus, the organic group of the halide will end attached to the less substituted carbon atom of the double bond regardless of the polarization of the olefin. Relevant data supporting this conclusion for the reactions of bromobenzene with various olefins are reported in Table 5[213].

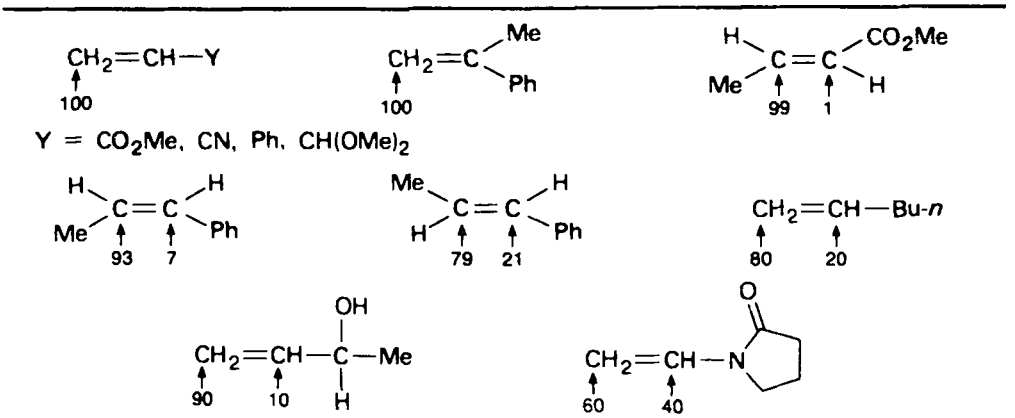
When 1,2-disubstituted alkenes are used, information on the stereochemical course can be obtained. The results are best explained in terms of a *syn* addition of the organopalladium followed by a *syn* elimination of 'HPdX'[214]. The stereochemical course of the reaction is depicted in a simplified manner in Scheme 8.

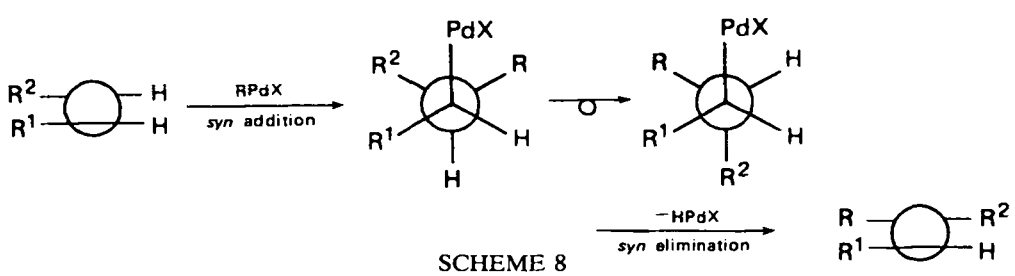
Thus, bromobenzene reacts with *Z*-1-phenyl-1-propene producing 73% of *Z*-1,2-diphenyl-1-propene, while the *E*-isomer gives 79% of the *E*-1,2-diphenyl-1-propene (equation 157).



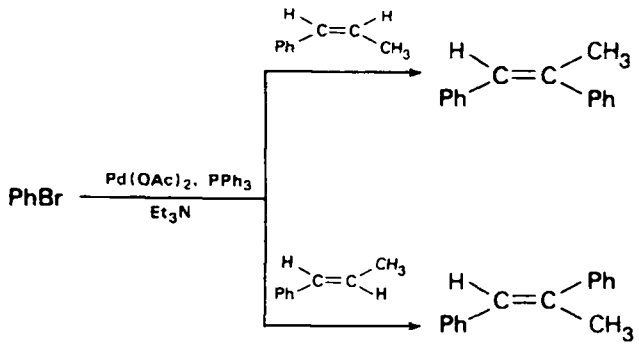
SCHEME 7

TABLE 5. Regioselectivity in the palladium-catalysed arylation of olefins with bromobenzene



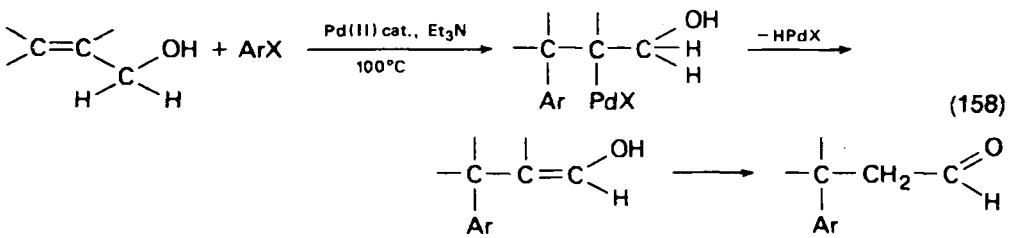


SCHEME 8

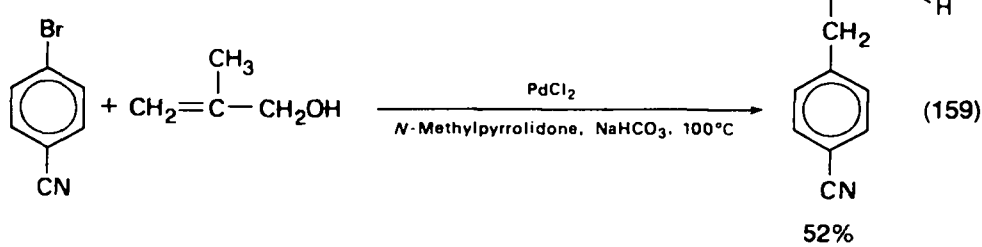


(157)

Mono-, di- and trisubstituted ethenes can be used as olefinic substrates; however, the rate of the reaction decreases with increasing substitution. An interesting course (equation 158) is followed with allylic alcohols, where the reductive elimination occurs toward the alcoholic carbon, thus leading to carbonyl compounds as final products[215–223]. A specific case is presented in equation (159).



(158)

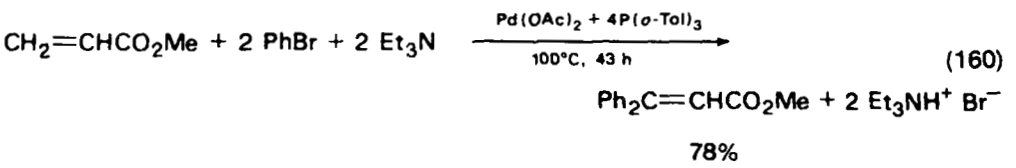


(159)

Generally, aryl[214–217,224–232], heterocyclic[218–223,232–234], benzylic[224] and vinylic[232,235,236] iodides and bromides can undergo the reaction with olefins in the presence of a Pd catalyst. In some cases (e.g. benzylic compounds[224] and tropone derivatives[237]) chlorides have also been used. A limitation is represented by the fact that the only halides which can be used under the reaction conditions are those which are not prone to undergo β-elimination of HX.

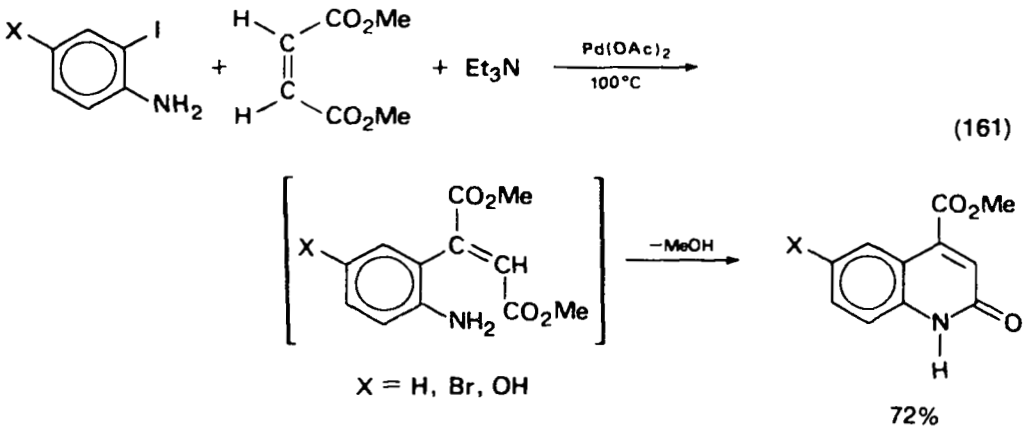
An extensive study has been performed by reacting aryl halides with methyl acrylate[225] and as a result a wide variety of substituents on the organic halides appear to be tolerated by the procedure.

The versatility of the arylation process is further illustrated by the diarylation of olefins[229] (equation 160).



(160)

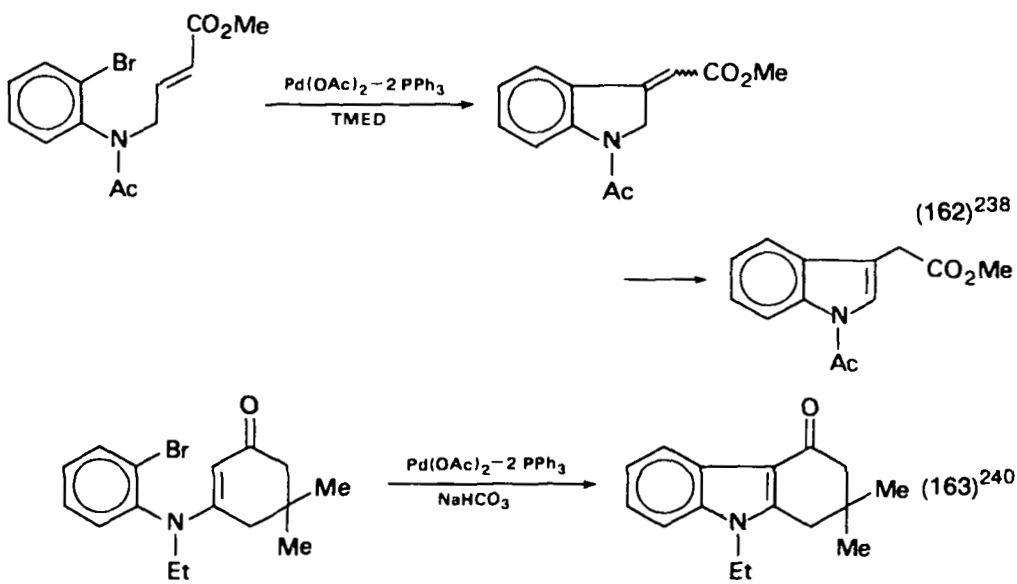
This process can be carried out in combination with a ring closure to form 2-quinolones[229] (equation 161).



(161)

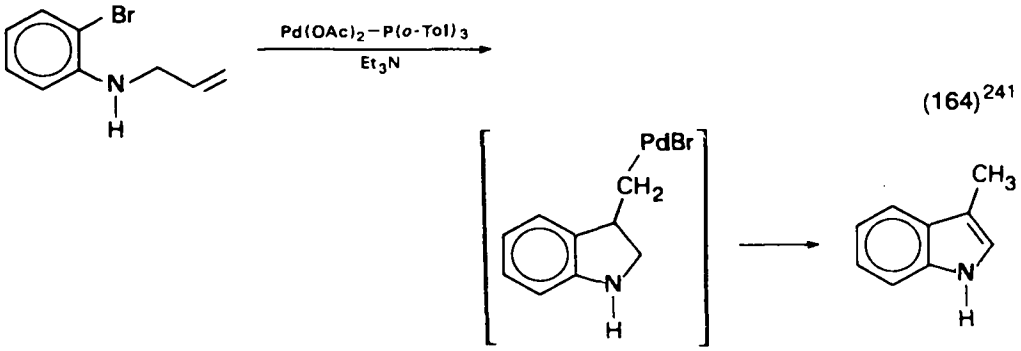
It can also lead to intramolecular cyclization with formation of heterocyclic systems[238–242] (equations 162–165).

It is noteworthy that cyclizations similar to that reported in equations (162), (164) and (165) have been carried out successfully using a Ni(0) rather than a Pd(0) catalyst and have been employed in the synthesis of natural compounds[243–245].

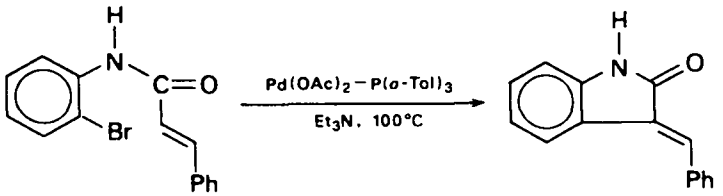


(162)[238]

(163)[240]

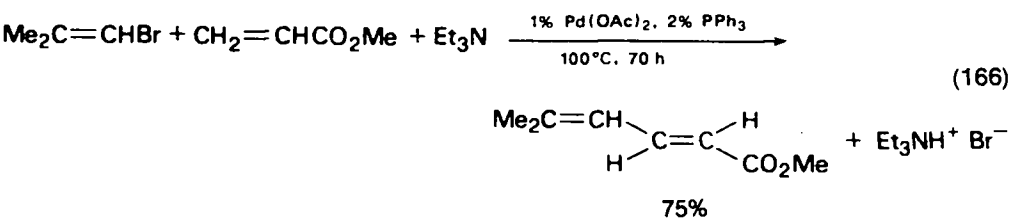


(164)[241]



(165)[242]

The reactions between vinylic halides and methyl acrylate are similar to those of the aryl halides. Thus 2-methyl-1-bromo-1-propene leads to methyl *E*-5-methyl-2,4-hexadienoate[235] (equation 166):



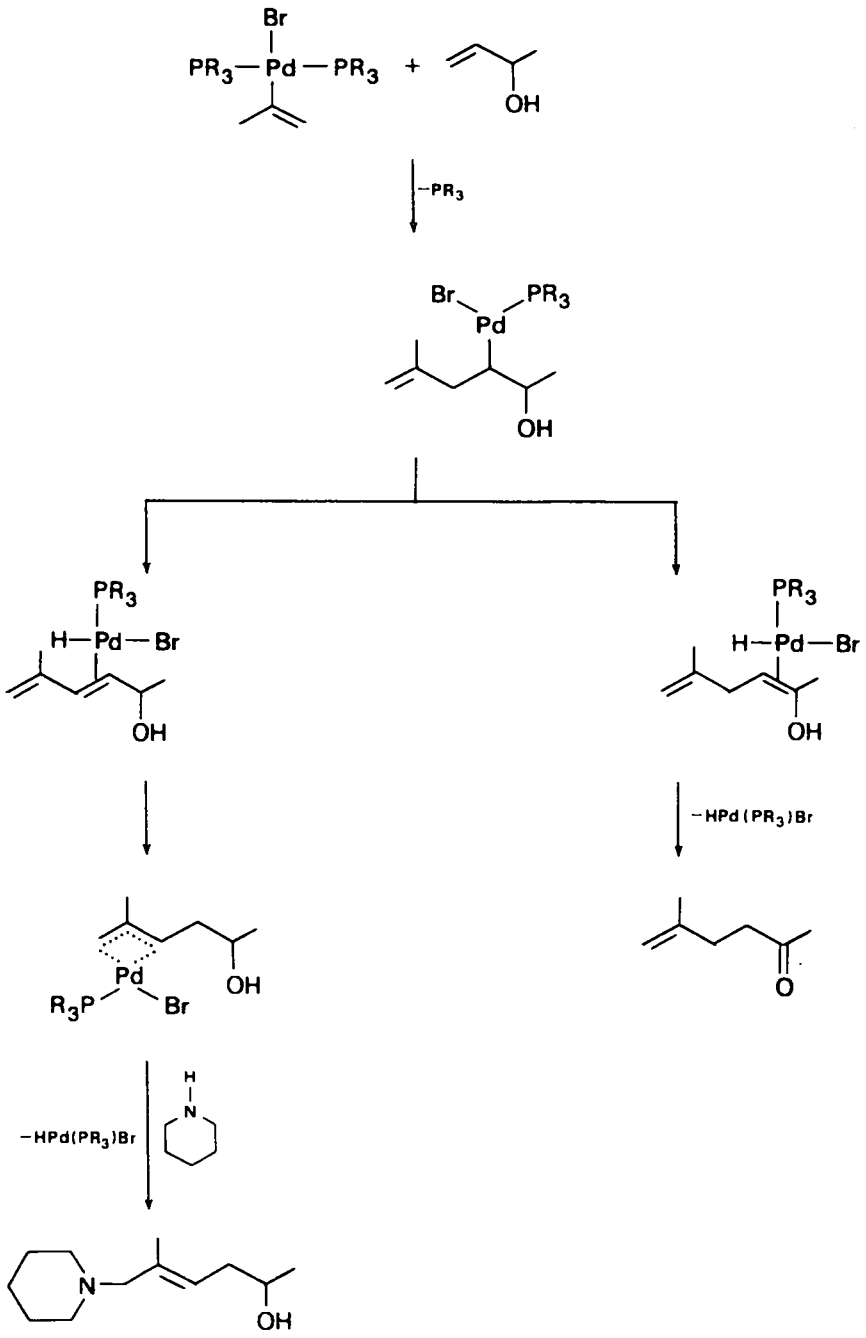
(166)

75%

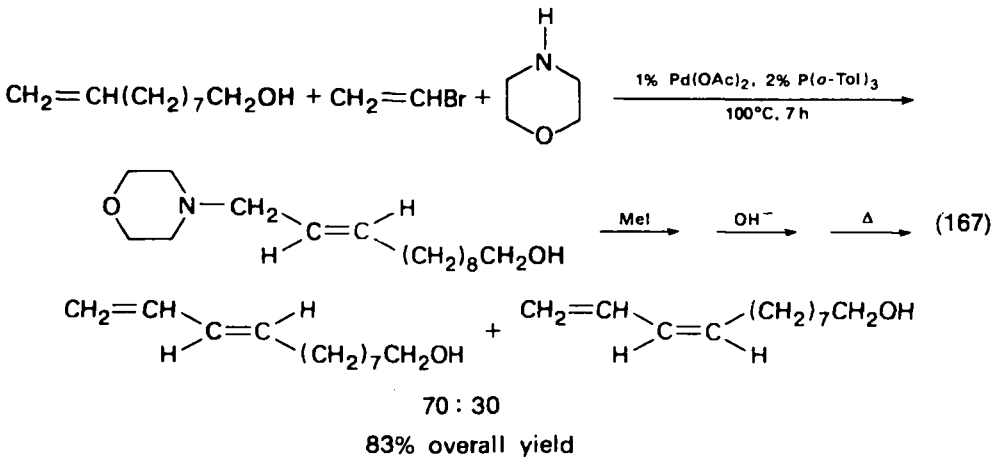
A low stereoselectivity is observed in the reaction of *E*- or *Z*-1-bromo-1-hexene with methyl acrylate due to the formation and isomerization of intermediate π-allylic complexes which involve the double bond originally present in the organic halide[235].

A limitation of the reaction with vinylic halides is represented by the fact that the strongly electron-withdrawing carboxyl group is required on the organic substrate. In an attempt to find experimental conditions which would permit carrying out the reaction between 2-bromopropene and 3-buten-2-ol, piperidine was used as a base[236]. Incorporation of the amine was found to occur and 33% of 5-methyl-6-piperidino-4-hexen-2-ol together with 63% of 5-methyl-5-hexen-2-one were isolated. The two different products arise because two possibilities are open for the elimination of palladium hydride: towards the alcoholic carbon and in the opposite direction (Scheme 9). In the latter case a π-allylic intermediate can be formed and can then undergo nucleophilic attack by the secondary amine.

The amine incorporation has been transformed into a synthetically useful process[231,236,246]. An interesting application is represented by the synthesis of the 9,11-dodecadien-1-ol, precursor of the pheromone of the red bollworm moth, starting with readily available materials to obtain 12-morpholino-10-dodecen-1-ol in 82% yield. Hoffman degradation of the compound gives a 70 : 30 mixture of the *E*- and *Z*-dienols[212], the first being, as an acetate, the biologically active isomer (equation 167).



SCHEME 9

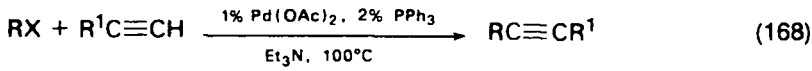


(167)

B. Reactions with Acetylenes

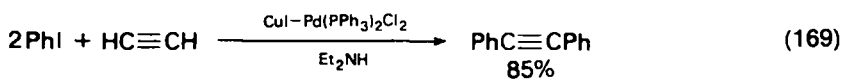
Acetylenes are involved in two different types of reaction with halides in the presence of palladium catalysts. The course followed by the reaction depends upon the nature of the halides and of the catalytic system.

The process of more general validity, reported by Dieck and Heck[247], is formally similar to the reactions of halides with olefins, since in the final product one hydrogen atom of the acetylene will be substituted by the organic part of the halide. Even the conditions are generally similar to those used previously in the palladium-catalysed olefin substitution reactions, except that the amine is used as a solvent (equation 168).



(168)

Analogous results have been obtained by Cassar[248], who carried out the reaction in DMF and in the presence of tetrakis(triphenylphosphine)palladium(0) as catalyst and sodium methoxide or phenoxide as base. Furthermore, Hagihara and coworkers[249] have reported the same substitution reaction catalysed by palladium complexes in the presence of a co-catalyst, i.e. cuprous iodide. With this modified procedure the reaction proceeds under milder conditions (room temperature) giving more satisfactory results for the direct synthesis of symmetrically disubstituted acetylenes from acetylene gas (equation 169)

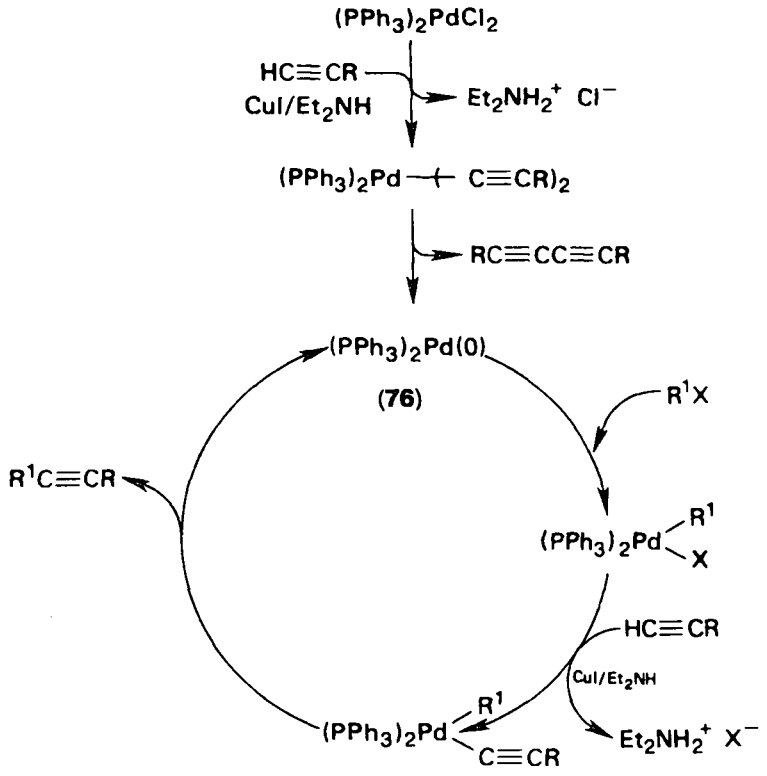


(169)

A likely mechanism for the latter process is reported in Scheme 10[249].

Alkynylation of the starting catalyst followed by reductive elimination of a diacetylene produces a Pd(0) complex (**76**). Oxidative addition of the organic halide and CuI/Et_2NH-catalysed alkynylation gives the palladium complex **77**. This generates the Pd(0) catalyst through the reductive elimination of the formal substitution product.

A similar scheme could also be considered for the reaction carried out in the conditions employed by Dieck and Heck and by Cassar, except for the alkynylation



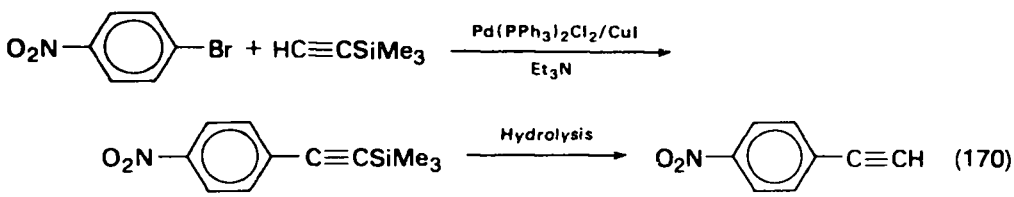
R = H, Ph, CH_2OH; R^1 = aryl, alkenyl, pyridyl

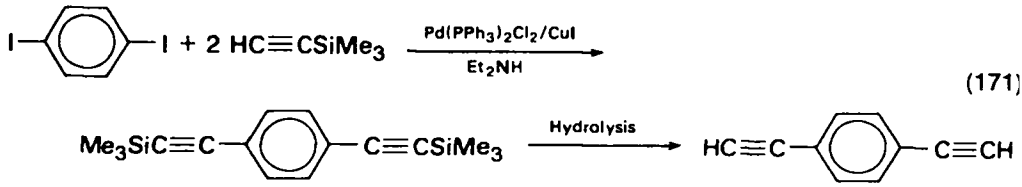
SCHEME 10

process, where presumably an acetylide anion produced by interaction of the acetylene with the base (methoxide, phenoxide or triethylamine) could be operating.

Aryl[247–250], vinyl[141,247–249] and heterocyclic[247,249–255] halides can be used. Most frequently, since unsubstituted acetylene is employed in the coupling, disubstituted acetylenic compounds are the final products. However, the arylation of trimethylsilylacetylene followed by hydrolysis leads to ethynylarenes[250] (equation 170). Starting from dihalogeno derivatives, the same procedure affords diethynylarenes (equation 171).

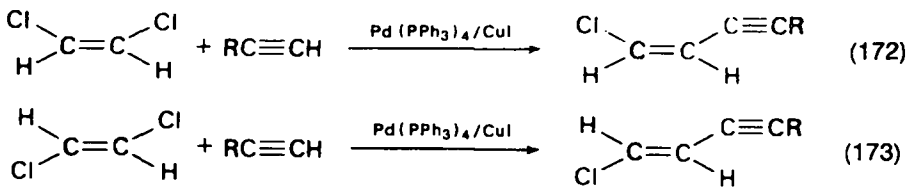
The reaction with alkenyl halides occurs with retention of configuration. Thus when *Z*- or *E*-1,2-dichloroethylene is treated with terminal acetylenes in the presence of *n*-butylamine together with catalytic amounts of tetrakis(triphenylphosphine)-





(171)

palladium(0) and copper iodide, 1-chloro-1-en-3-ynes are formed in yields in the range 65–100% and an isomeric purity higher than 99% (equations 172 and 173)[141].



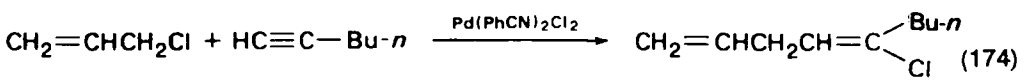
(172)

(173)

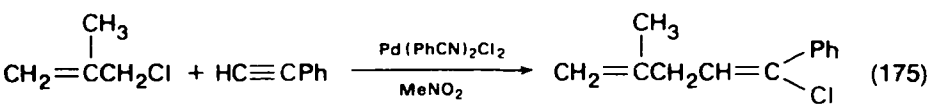
R = n-C_5H_{11}, CH_2OTHP, CH_2OAc, CH_2SMe

In other cases the yields of the coupling reaction of aliphatic 1-alkynes with *Z*- or *E*-1-halogeno-1-alkenes are rather low due to the reaction of the alkenyl halides with Et_2NH[256]. In the synthesis of 1,3-enynes of general formula $CH_2{=}CH{-}C{\equiv}CR^1$, $CH_2{=}C(R){-}C{\equiv}CR^1$ and $RCH{=}CH{-}C{\equiv}CR^1$ (R = alkyl; R^1 = alkyl, $(CH_2)_nOH$), better results are obtained when the coupling reaction is carried out under phase transfer conditions, employing a benzene solution of 1-alkyne and alkenyl halide, diluted aqueous NaOH as base, $(PhCH_2)Et_3NCl$ as a phase transfer agent, and $Pd(PPh_3)_4$–CuI as a catalyst. The method has been employed to prepare some pure insect sex pheromone components or their precursors in high overall yields. Distinct advantages are presented in terms of simple procedure and low cost with respect to the methods involving either the use of organometallic derivatives of 1-alkynes[257] or the catalytic substitution of acetylenic hydrogen[249].

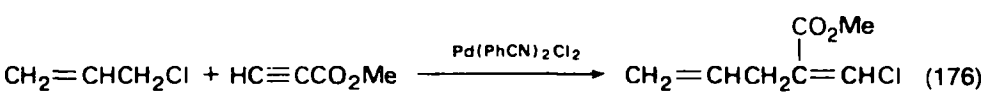
The second type of reaction involving acetylenes has been reported by Kaneda and coworkers[258] and represents a process in which an allylic halide adds to the triple bond of a monosubstituted acetylene, disubstituted acetylene or acetylene itself. The $Pd(PhCN)_2X_2$ complex is the most active catalyst. Chlorides or bromides can be used together with $Pd(PhCN)_2Cl_2$ or $Pd(PhCN)_2Br_2$ respectively. It is worth noting that the reaction between phenylacetylene and allyl iodide in the presence of $Pd(PhCN)_2I_2$ does not take place. A few specific examples are illustrated by equations (174)–(178).



(174)



(175)



(176)

$$CH_2{=}CHCH_2Cl + HC{\equiv}CCO_2H \xrightarrow{Pd(PhCN)_2Cl_2} CH_2{=}CHCH_2\underset{\displaystyle CO_2H}{\overset{\displaystyle |}{C}}{=}CHCl \quad (177)$$

45%

$$CH_2{=}CHCH_2Cl + HC{\equiv}CCH_2OH \xrightarrow{Pd(PhCN)_2Cl_2}$$

$$CH_2{=}CHCH_2CH{=}\underset{Cl}{\overset{CH_2OH}{C}} + CH_2{=}CHCH_2\underset{Cl}{\overset{CH_2OH}{\overset{|}{C}}}{=}\underset{Cl}{\overset{H}{C}} \quad (178)$$

As can easily be appreciated from the cases reported above, alkyl or phenyl substituents lead to products in which the new carbon–carbon bond formation has occurred at the carbon bearing the hydrogen atom (equations 174 and 175). The reverse addition is observed for compounds having electron-withdrawing substituents (equations 176 and 177), whereas a mixture of the two possible products is observed for the propargylic alcohol (equation 178). Mixtures of products deriving from the two orientations are also formed when 1,2-disubstituted acetylenes are used (equation 179).

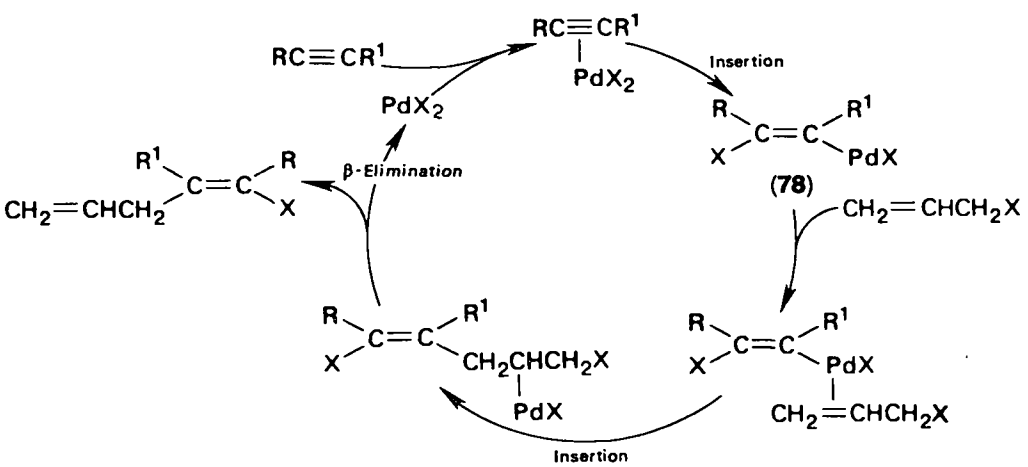
$$CH_2{=}CHCH_2Cl + EtC{\equiv}CPh \xrightarrow{Pd(PhCN)_2Cl_2}$$

$$CH_2{=}CHCH_2\underset{Cl}{\overset{Et}{\overset{|}{C}}}{=}\underset{Cl}{\overset{Ph}{C}} + CH_2{=}CHCH_2\underset{Cl}{\overset{Ph}{\overset{|}{C}}}{=}\underset{Cl}{\overset{Et}{C}} \quad (179)$$

In contrast to substituted acetylenes, the reaction of acetylene itself with allyl chloride gives a cotrimer 1-chloro-1,3,6-heptatriene besides the codimers *E*- and *Z*-1-chloro-1,4-pentadienes (equation 180).

$$CH_2{=}CHCH_2Cl + HC{\equiv}CH \xrightarrow{Pd(PhCN)_2Cl_2}$$

$$CH_2{=}CHCH_2CH{=}CHCl + CH_2{=}CHCH_2CH{=}CHCH{=}CHCl \quad (180)$$



SCHEME 11

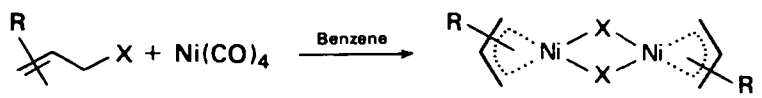
The insertion–elimination mechanism reported in Scheme 11 has been suggested as operating in the codimerization process. Insertion of acetylene into a Pd–halogen bond occurs first and subsequently an allyl halide inserts into a palladium–vinyl bond. Elimination of PdX_2 and formation of a codimer completes the catalytic cycle.

In the case of the unsubstituted acetylene the successive insertions of acetylene and allyl halide into the Pd–vinyl bond of intermediate **78** lead to the cotrimer. The stereochemistry of the codimers depends upon the type of attack leading to the palladium vinyl bond, the *Z*- or the *E*-codimer being formed with a *cis* or a *trans* attack respectively. Although in the case of the addition of allyl bromide to 1-hexyne in the presence of $Pd(PhCN)_2Br_2$ the product has a *Z* geometry, it is worth noting that the addition of 'PdX' across double or triple bonds depends on subtle factors[259].

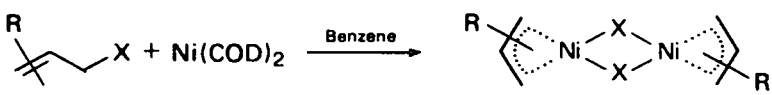
VI. REACTIONS INVOLVING π-ALLYLNICKEL COMPLEXES

A. Cross-coupling Reactions of π-Allylnickel Complexes with Halides

The π-allyl (or η^3-allyl) ligand is a very common carbon ligand. A wide variety of allylmetal compounds have been prepared by the general procedure first used to obtain bis-π-allylnickel[260]. However, in the chemistry of π-allylnickel complexes the simple bis(π-allyl)nickel(0) has not found the large number of applications which have been uncovered for the π-allylnickel(I) halides. These are prepared in high yields by the reaction of allylic halides with nickel(0) complexes (nickelcarbonyl or bis(cyclooctadiene)nickel) in non-polar solvents such as benzene (equations 181 and 182).



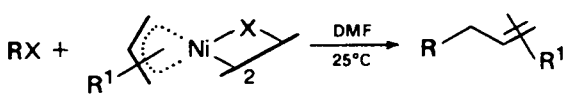
(181)



(182)

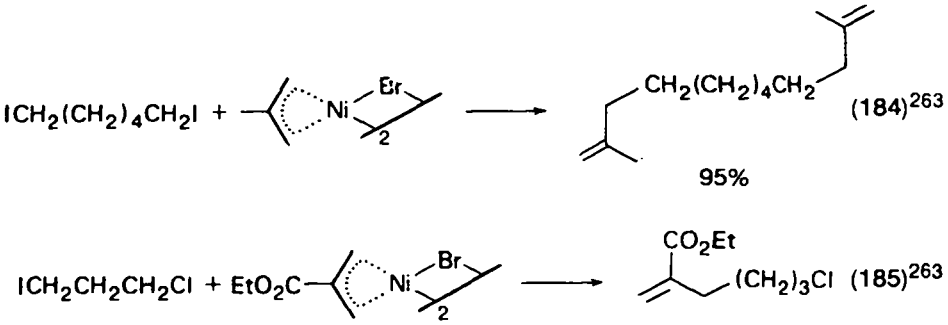
When $Ni(CO)_4$ is used the reagents are heated in benzene[261]. On the other hand, a lower temperature (−10°C) can be employed with the $Ni(COD)_2$ complex[262] and this represents an advantage when thermally sensitive complexes must be prepared. The π-allyl complexes are usually isolated in high yields as red to red-brown crystalline solids, which are air-sensitive in solution, but stable for several years in the absence of air.

π-Allylnickel halides react with primary and secondary alkyl, aryl and vinyl halides (usually bromides or iodides) in DMF or other coordinating solvents such as HMPA and *N*-methylpyrrolidone according to equation (183)[263].

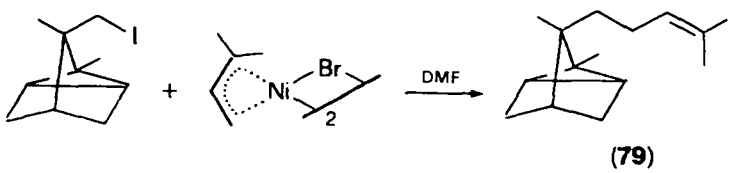


(183)

A wide variety of functional groups, including ester, amide, nitrile and hydroxyl, are tolerated by the reaction. If two identical halogen atoms are present in the substrate, they will both undergo substitution by the allyl residue (equation 184) whereas iodine can easily be replaced without affecting a C—Cl bond present in the molecule (equation 185).

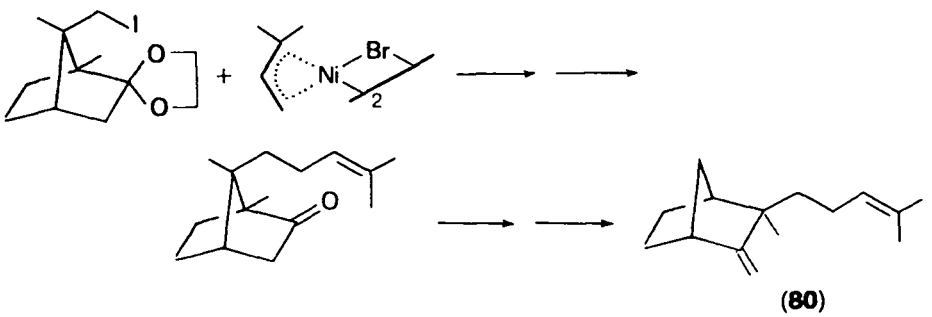


When the two terminal carbons of the allyl system are not equivalent, the coupling will occur at the least substituted position. This is illustrated by the synthesis of α-santalene[263](**79**) (equation 186) and β-santalene[264](**80**) (equation 187).



(186)

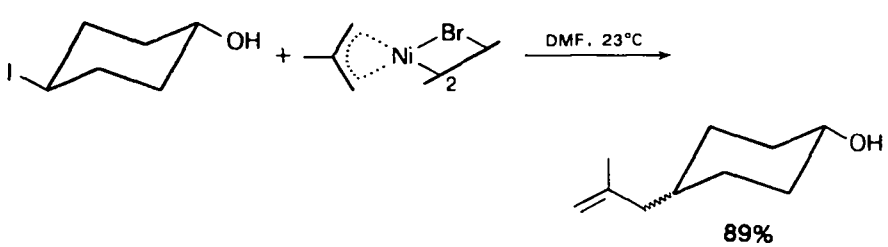
(**79**)



(187)

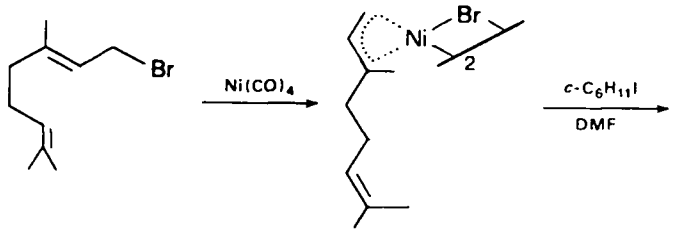
(**80**)

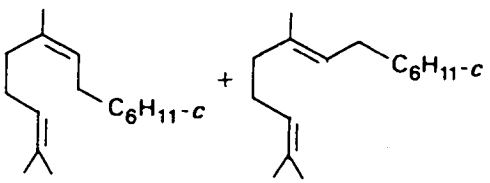
The configuration of the starting allyl halides or of the halide substrates is not maintained during the reactions and mixtures of isomeric products are formed[263,265] (equations 188–190). The example reported in equation (190) also demonstrates the usefulness of the 2-methoxyallylnickel complex for the introduction of the acetonyl group into the substrate.



(188)[263]

89%

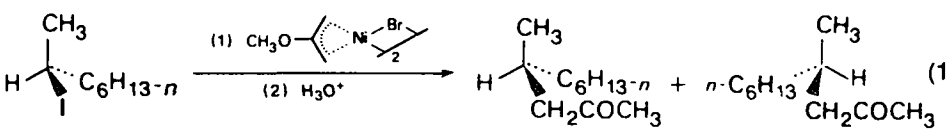




(189)[263]

(40%) (60%)

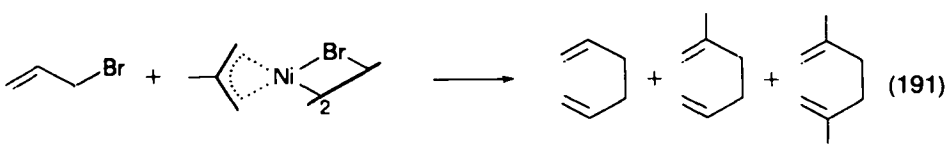
60% overall yield



(190)[265]

50% 50%

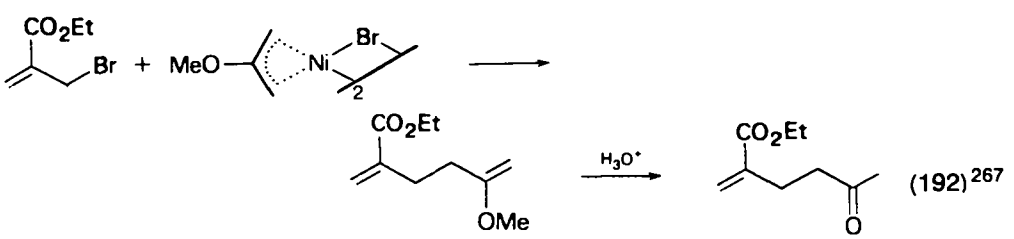
The reaction with allyl halides is complicated by the exchange between the allyl ligand and the allyl halide. For example, the reaction between π-(2-methallyl)nickel bromide and allyl bromide leads to almost a statistical distribution of all three possible products in a 95% yield[266] (equation 191).



(191)

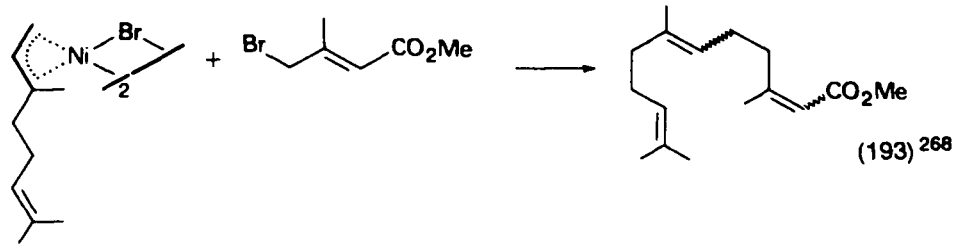
22% 53% 25%

However, a good selectivity is observed when an electron-withdrawing substituent is present on either one of the reacting allyl systems (equations 192 and 193)[267,268].



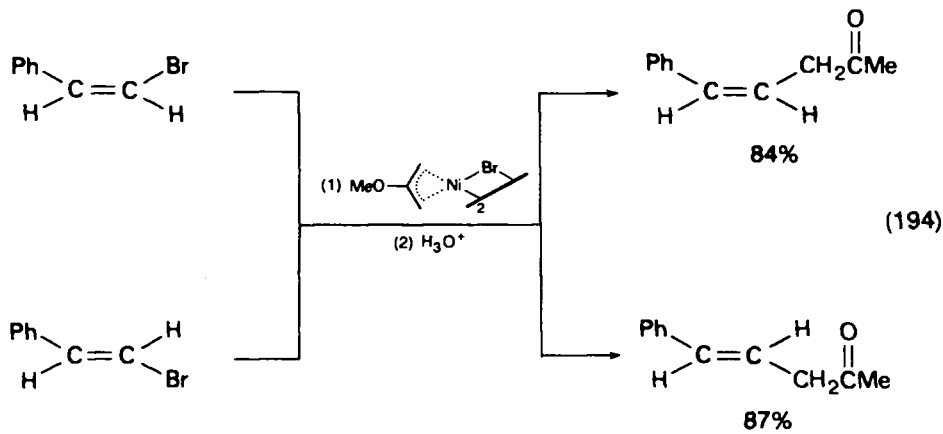
(192)[267]

84%



(193)[268]

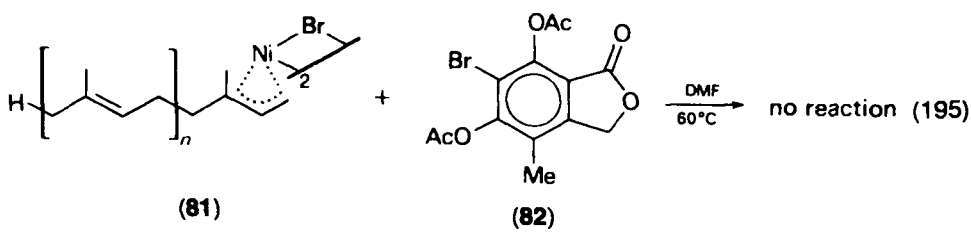
Z- or *E*-β-bromostyrenes react with the 2-methoxyallylnickel complex to give *Z*-5-phenyl-4-penten-2-one or the corresponding *E*-isomer respectively, following a course of retention of configuration (equation 194)[267].



(194)

Such a stereochemical course appears to be in sharp contrast to that observed in the reaction with alkyl halides.

The reaction of π-allylnickel halides with aromatic halides appears to be sensitive to steric effects. Thus the complex **81** does not react with the aromatic bromide **82** having two acetate groups in positions *ortho* to the bromine (equation 195). Upon heating at 60–65°C for 48–60 h thermal dimerization of the complex occurs and bigeranyl or squalene are formed[269].

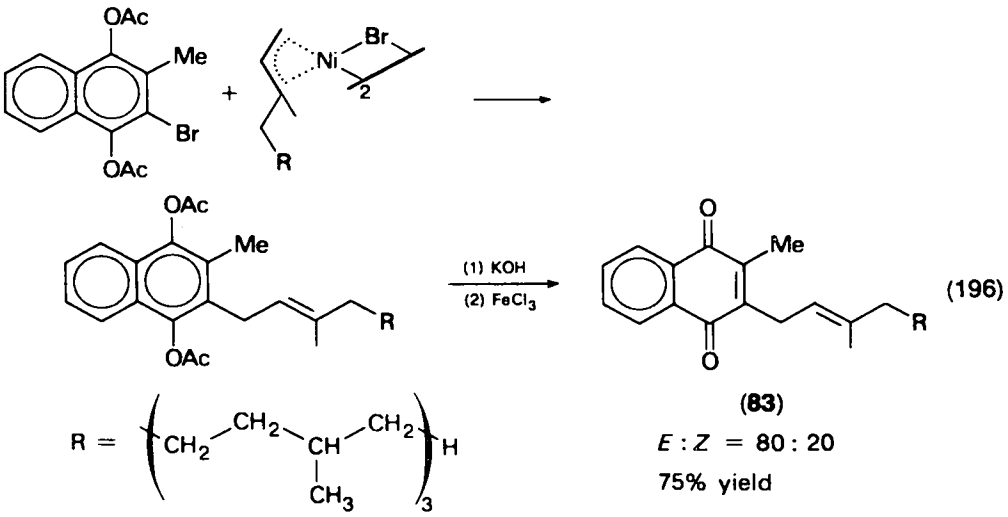


(81) (82)

$n = 1, 2$

In spite of this sensitivity to steric effects the reaction of π-allylnickel complexes with aryl halides has been employed successfully in the synthesis of a variety of natural compounds which include vitamins K_1 and $K_{2(5n)}$[270,271], coenzyme Q_1[272,273], 6'-acetonylpapaverine[267], monomethyltocols[274], isocoumarins, dihydroisocoumarins and isoquinolones[275]. The sequence used for the synthesis of vitamin K_1 (**83**),

isocoumarins (**84**) and dihydroisocoumarins (**85**) are reported in equations (196) and (197).

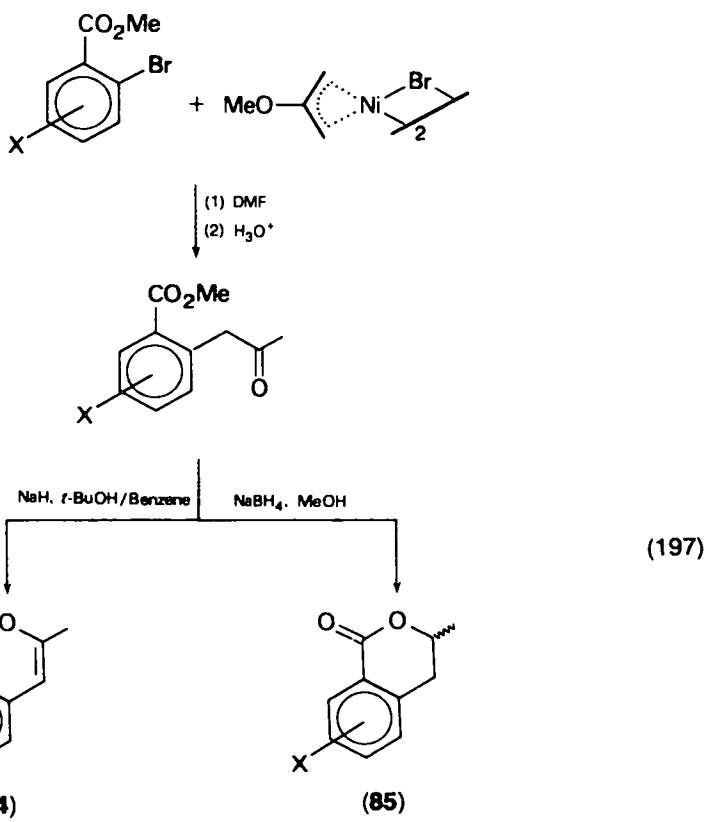


(196)

(**83**)

$E:Z$ = 80 : 20

75% yield

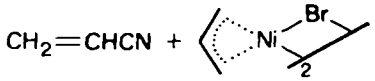


(197)

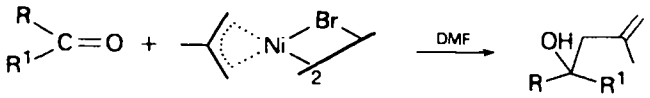
(**84**) (**85**)

X = H, 6-Cl, 6, 7-di-OMe

The behaviour of the π-allylnickel complexes discussed above could be easily explained in terms of a 'nucleophilic character' of the organometallic compound which on reacting with the electrophilic substrate would lead to the cross-coupled products. Results in support of this view could also be taken from the reactions of the same complexes with other 'electrophilic' substrates such as activated olefins, which undergo Michael-type addition[276] (equations 198), and aldehydes or ketones, which react with these complexes to give homoallylic alcohols[277] (equation 199).



$$CH_2{=}CHCN + \text{[allyl-Ni-Br}_2\text{]} \longrightarrow CH_2{=}CHCH_2CH_2CH_2CN \qquad (198)$$



$$R^1(R)C{=}O + \text{[allyl-Ni-Br}_2\text{]} \xrightarrow{DMF} \text{OH, R, R}^1\text{-substituted product} \qquad (199)$$

However, on the basis of results which will be presented below, it has been proposed that the reactions of π-allylnickel complexes with halides follow a radical chain mechanism[265].

A possible initiation step (Scheme 12) involves one-electron transfer from the nickel complex to the organic halide with production of the corresponding radical ion (step a). Formation of a halide ion and a radical (step b) is followed by the reaction of the latter with the organometallic complex to give the allylation product and NiBr· (step c). Interaction between this species and the substrate leads to the radical ion necessary for the chain propagation sequence. The chain propagation steps (b) and (c) are similar to those proposed by Kornblum and coworkers[278], and by Russell and Danen[279] for the reaction of nitro carbanions with *p*-nitrobenzyl chloride.

$$RX + [(allyl)NiBr] \longrightarrow RX^{-\cdot} + [(allyl)NiBr]^{+\cdot} \qquad (a)$$

$$RX^{-\cdot} \longrightarrow R^{\cdot} + X^{-} \qquad (b)$$

$$R^{\cdot} + [(allyl)NiBr] \longrightarrow R{-}allyl + NiBr^{\cdot} \qquad (c)$$

$$NiBr^{\cdot} + RX \longrightarrow RX^{-\cdot} + NiBr^{+} \qquad (d)$$

SCHEME 12

Alternatively, the radical chain-type oxidative addition, reductive elimination sequence of steps (c), (d) and (e) of Scheme 13 could be considered to operate. A similar oxidative addition of free radicals has been proposed by Osborn and coworkers[280].

The racemization observed in the case of the reaction of *S*-(+)-2-iodooctane (equation 190) is in agreement with the radical mechanism. Furthermore,

$$R^{\cdot} + [(allyl)NiBr] \longrightarrow [R(allyl)NiBr]^{\cdot} \qquad (c)$$

$$RX + [R(allyl)NiBr]^{\cdot} \longrightarrow R^{\cdot} + [R(allyl)NiBrX] \qquad (d)$$

$$[R(allyl)NiBrX] \longrightarrow R{-}allyl + NiBrX \qquad (e)$$

SCHEME 13

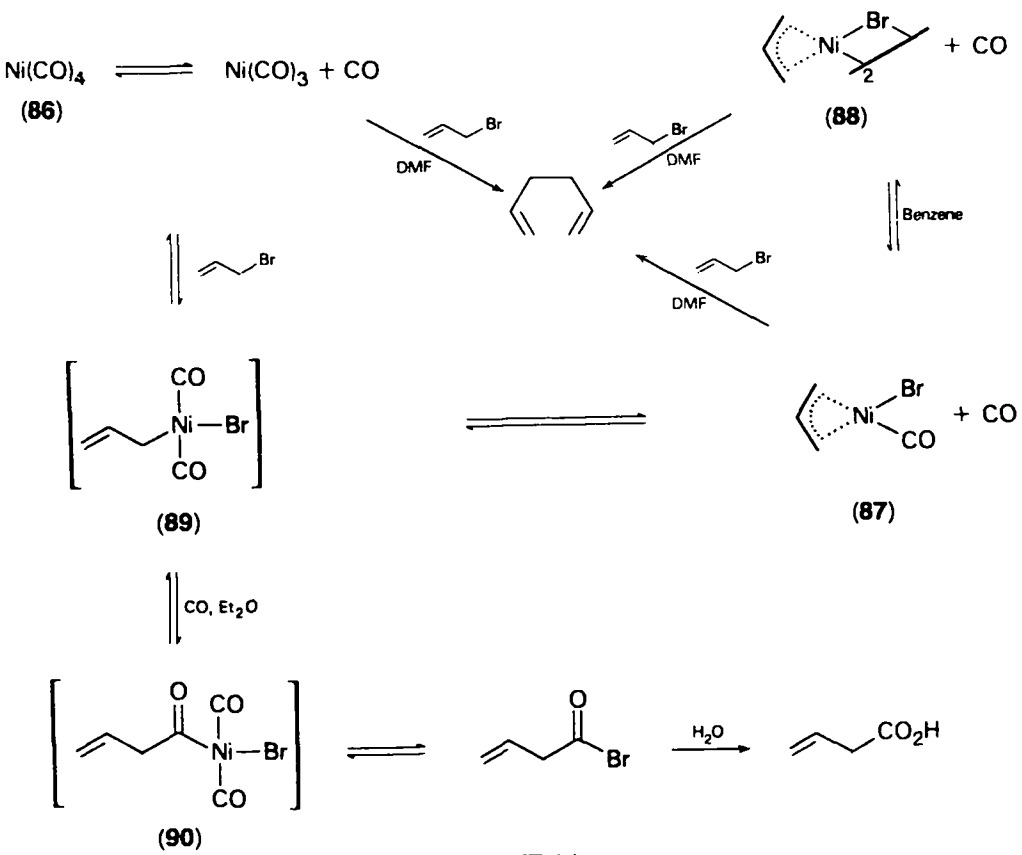
m-dinitrobenzene (a potent radical anion scavenger[278,279]) has been found to inhibit this reaction as well as the reactions of π-(2-methallyl)nickel bromide with 2-iodooctane, iodobenzene, β-bromostyrene and even with the highly reactive methallyl bromide. Finally, in order to reconcile the intervention of radicals with the retention of configuration observed in the case of β-bromostyrene[267], it is necessary to assume that the radicals involved are able to maintain the original configuration by interacting with the metal. Indeed, free vinyl radicals are known to undergo isomerization very easily[53,281].

B. Self-coupling Reactions of Allyl Halides by Means of Nickel Tetracarbonyl

The coupling between two molecules of allyl halide can occur without the preliminary preparation of a π-allylnickel complex. Indeed, the synthesis of 1,5-hexadiene by reaction of allyl chloride with nickel carbonyl was reported in 1943[282].

The reaction (equation 200) usually requires highly polar coordinating solvents (e.g. DMF) and temperatures in the range 25–50°C[266,283,284].

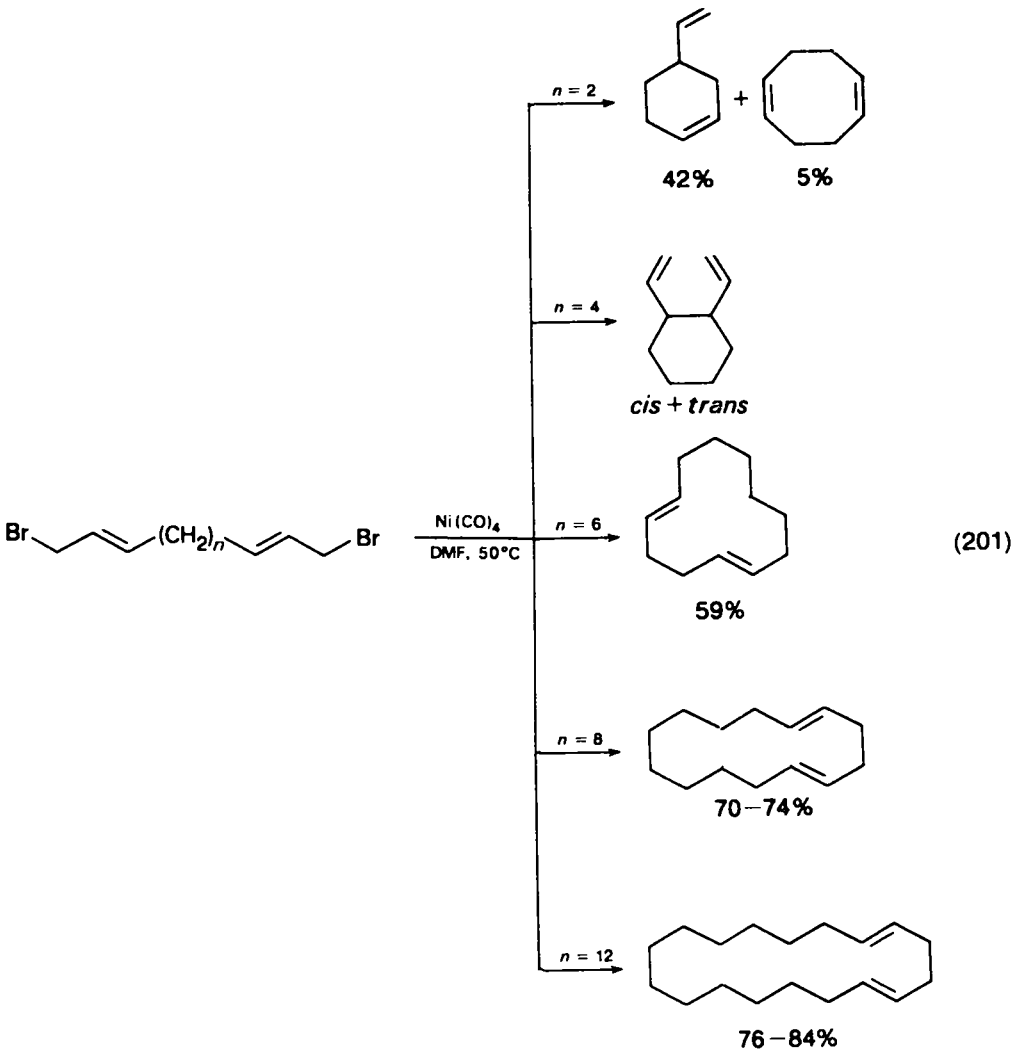
$$2\,CH_2{=}CHCH_2X + Ni(CO)_4 \longrightarrow CH_2{=}CHCH_2CH_2CH{=}CH_2 + NiX_2 + 4\,CO \quad (200)$$



SCHEME 14

The intermediacy of a π-allylnickel complex which reacts with a second molecule of halide should be responsible for the coupling[266]. A critical role is played by the solvent. As we have already seen, the use of a non-polar solvent affords the isolation of the π-allylnickel halide complex, whereas in a highly polar solvent the reaction leads to the coupling. Furthermore, it is known that the course of the reaction can be completely changed using solvents of moderate polarity (e.g. Et_2O) and, more importantly, by increasing the carbon monoxide pressure[285]. In this case carbonylation products are formed. All the observed facts can be explained according to Scheme 14[266,283–285].

The loss of one CO molecule from $Ni(CO)_4$ (**86**) creates a vacant coordination site, thus permitting the reaction with the halide and the formation of a π-allylnickel(bromo)carbonyl complex (**87**) which can be detected spectroscopically (ν_{CO} 2060 cm^{-1}). Dimerization of **87** accompanied by the loss of carbon monoxide, leads to the π-allylnickel halide complex **88**. This can be isolated in non-polar solvents whereas in polar solvents the coupling with allyl halide occurs. The same



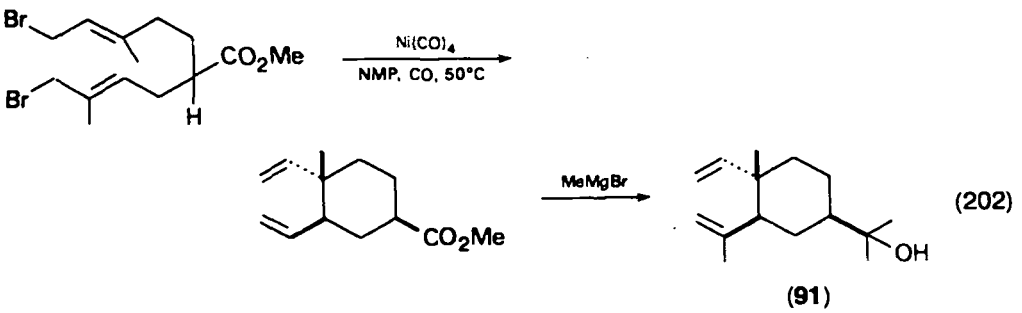
(201)

coupling can be also obtained by the π-allylnickel(bromo)carbonyl complex (**87**). The reversibility of the steps leading to the nickel complex is supported by the fact that the action of CO on the bis-π-allylnickel bromide complex (**88**) can lead to the π-allylnickel(bromo)carbonyl complex (**87**) and eventually to the same allyl bromide, which undergoes the coupling in the reaction conditions.

As reported in Scheme 14, a σ-allylnickel complex (**89**) should be the precursor of the π-allylnickel(bromo)carbonyl (**87**). The σ-complex (**89**) in solvent of moderate polarity and in the presence of CO undergoes a migratory insertion reaction to produce an acylmetal complex (**90**) and finally the carbonylation product (e.g. an acid in the presence of water or an ester in the presence of alcohol). While the synthetic usefulness of the carbonylation procedure will be discussed in a subsequent section (Section VIII.B), the example reported in equation (201) clearly demonstrates the importance of the coupling of allyl halides by treatment with $Ni(CO)_4$, particularly in the formation of medium or large rings[286]. When $n = 6, 8, 12$ the cyclization product is mainly (95–98%) the *E*,*E* isomer.

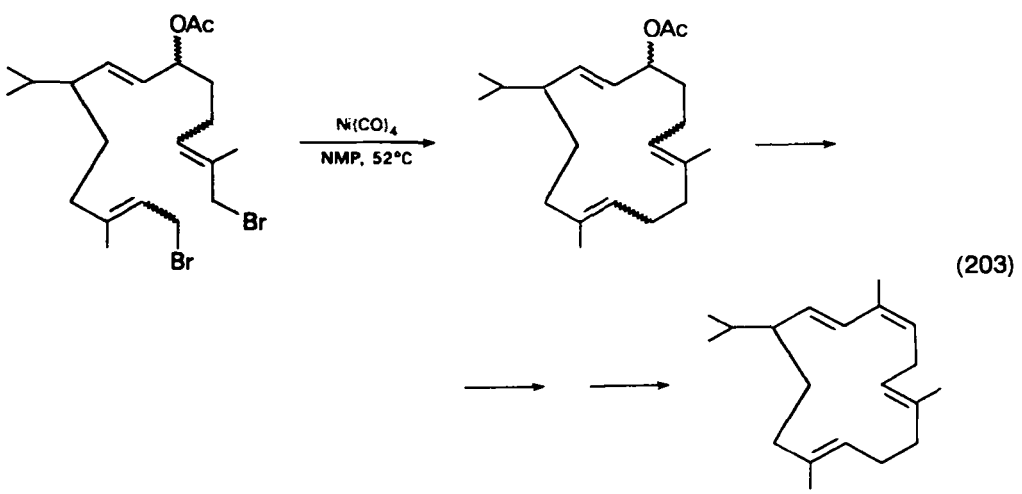
The reaction has found a number of applications in the synthesis of natural compounds which include D,L-elemol (**91**), (±)-cembrene (**92**) and humulene (**93**) (equations 202–204)[287–291], where the solvent is *N*-methylpyrrolidone (NMP).

The importance of a double bond in attaining the proper geometry for the cyclization is illustrated by the examples reported in equations (205) and (206)[292].



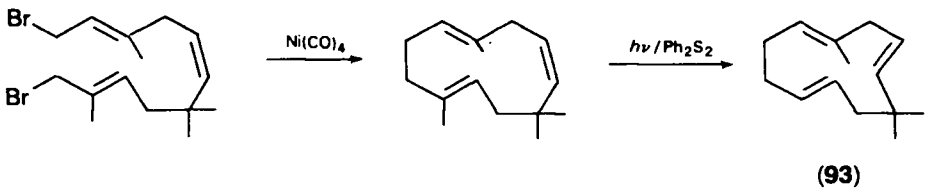
(202)

(91)



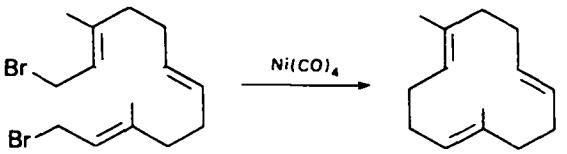
(203)

(92)



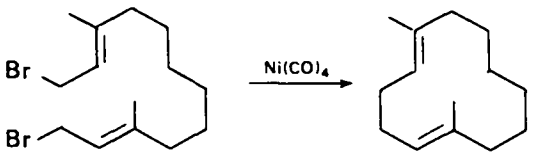
(204)

(93)



(205)

68%

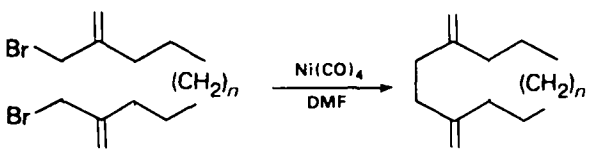


(206)

(94) 4%

Indeed, the lack of the central double bond in the starting material (**94**) can be considered responsible for the much lower yield observed.

While the synthesis of large ring methylenecycloalkanes can be easily carried out[293], the production of systems with exocyclic double bonds is more difficult than the formation of rings with endocyclic double bonds. The reaction requires high dilution conditions, and satisfactory yields are obtained in the case of large rings (equation 207).



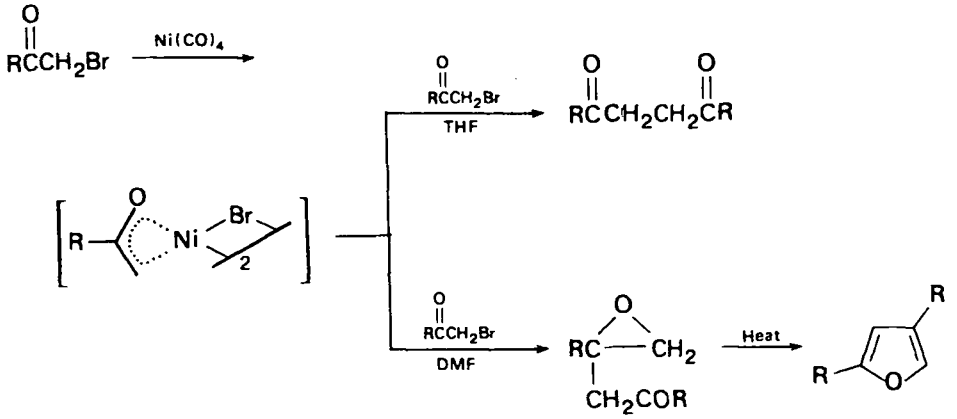
(207)

$n = 4$ 0% yield

$n = 6, 8, 12$ 20–60% yield

C. Reactions Involving π-Oxyallylnickel Complexes

α-Haloketones can be considered as the oxygen analogues of allyl halides. Thus, a similar behaviour of the two classes of compounds is found with nickel carbonyl[294,295]. We have seen above that the π-allylnickel complex generated from the allyl halide and $Ni(CO)_4$ can react with a carbon–halogen bond and with a carbonyl group. In the α-haloketone series the behaviour observed can be explained in terms of an oxyallylnickel species giving these two types of reactions depending upon the solvent used. The reaction at the carbon–halogen bond of another molecule occurs in THF, whereas a β-ketoepoxide is produced in DMF. When the latter compound is heated above 130°C, a dehydration reaction leads to a 2,4-disubstituted furan (equation 208).

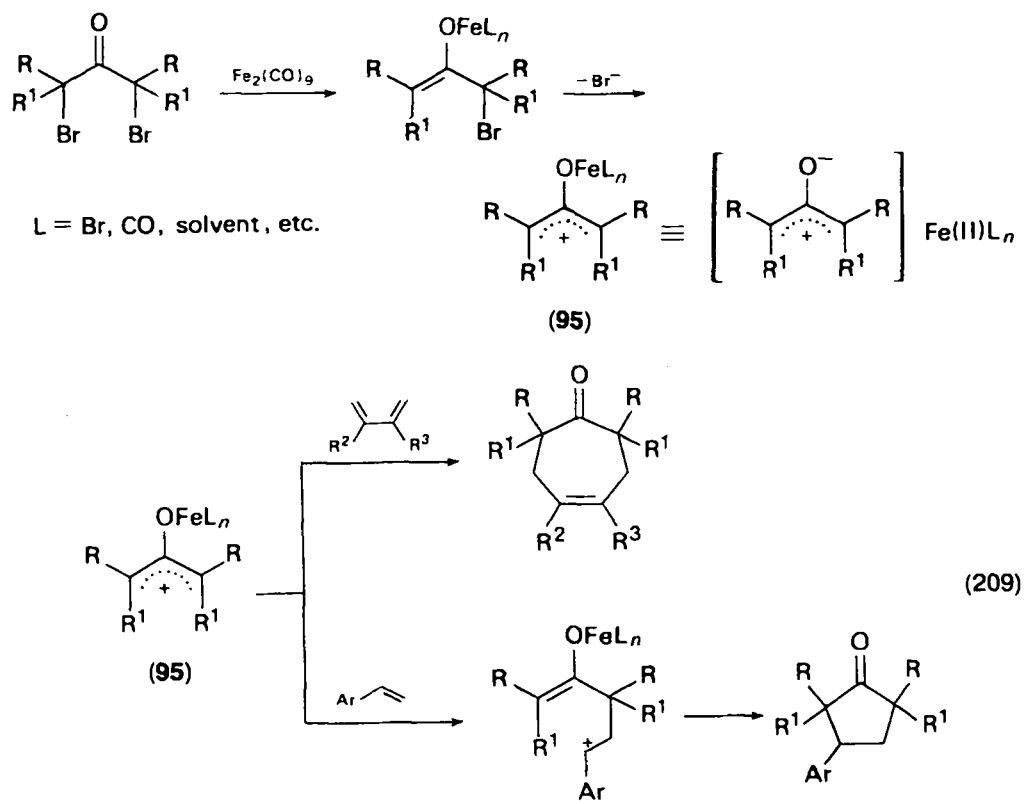


(208)

VII. REACTIONS WITH IRON CARBONYLS

A. Cyclocoupling of α,α′-Dibromoketones

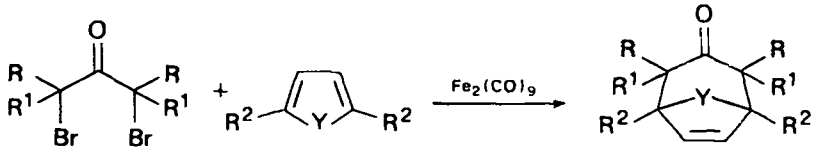
In a series of papers[296–309] Noyori and coworkers have developed a synthetic methodology which is based upon the reactions between α,α′-dibromoketones, iron carbonyls and 1,3-dienes or aryl olefins. In this manner a 3 + 4 → 7 or a 3 + 2 → 5 cyclocoupling process occurs according to equation (209).



(209)

In both types of process a key intermediate is represented by the iron-stabilized oxyallyl cation (**95**), which, as shown in equation (209), is formally a dipolar species. This intermediate is generated from a Fe^{2+}-stabilized α-bromoenolate which in turn can be produced by a two-electron reduction of the dibromoketone with the zero-valent iron or by oxidative addition of the halide to the iron complex[310] followed by a change into a more stable structure[297]. the oxyallyl cation can react with dienes or alkenes giving cyclocoupling products.

As expected for the $\pi^2 + \pi^4$ cycloaddition process with the diene substrates[298,299], systems with a fixed suitable geometry such as furan or cyclopentadiene are very good receptors of the intermediate allyl cation (equation 210).



(210)

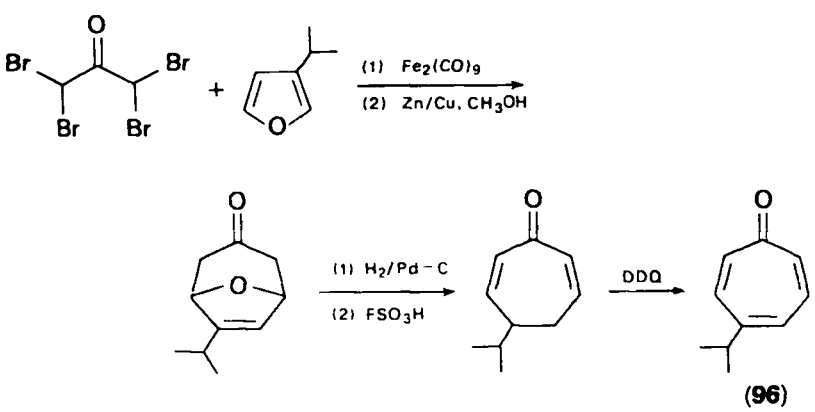
The reaction with heterocyclic systems having more aromatic character, such as thiophene and *N*-methylpyrrole, has been found to give products of electrophilic substitution at the five-membered ring. Other difficulties involve the failure of the cycloaddition with the simple α,α′-dibromoacetone and with the dibromides of other methyl ketones. However, in these cases the difficulty can be overcome by starting with tri- or tetrabromoketones and carrying out the dehalogenation of the cyclic product with a Zn/Cu couple in methanol.

The 3 + 4 → 7 cyclocoupling procedure has found a number of applications in the synthesis of natural compounds including α- and β-thujaplicins[300], nezukone[300], tropane alkaloids[301] and in an interesting route leading to C-nucleosides[302]. The syntheses of nezukone (**96**) and tropine (**97**) are reported below as illustrative examples (equations 211 and 212).

At variance with the 3 + 4 → 7 cyclocoupling, which can be regarded as a concerted $(\pi^2 + \pi^4)$ cycloaddition, the reaction between the allyl cation and olefins[303] represents a thermally forbidden $(\pi^2 + \pi^2)$ process, according to the orbital symmetry rules, and it is expected to follow a stepwise mechanism, with an orientation controlled by the stability of the zwitterionic intermediates[304,305].

The sequence reported in Scheme 15 has been proposed to explain the mechanism.

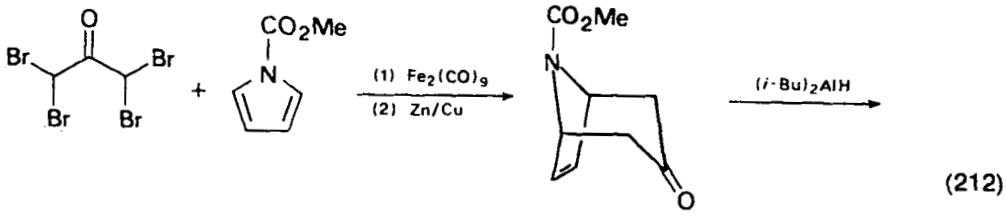
Electrophilic attack of the oxyallyl species **98** on the olefinic substrate produces



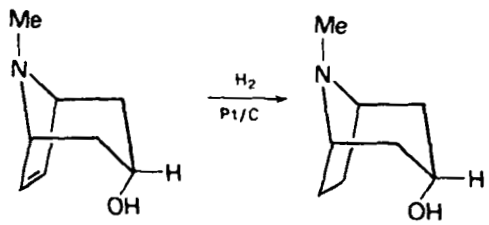
(211)

(**96**)

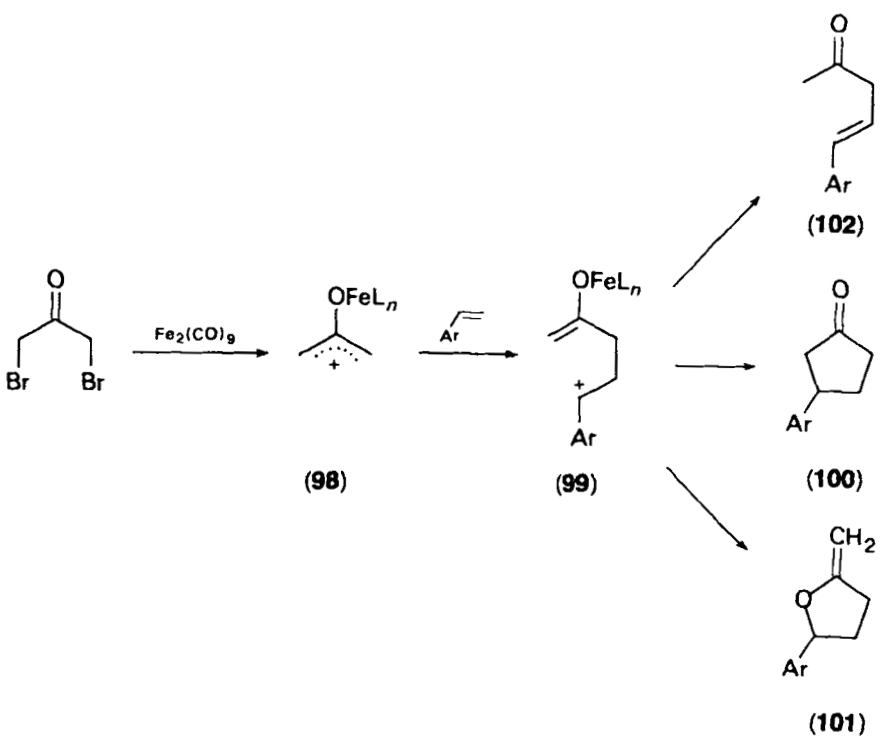
DDQ = 2,3-dichloro-5,6-dicyano-*p*-benzoquinone



(212)



(97)

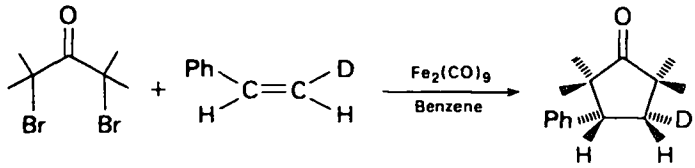


(98) (99) (100) (102) (101)

SCHEME 15

the intermediate **99**. The ring closure of this intermediate leads to the cyclopentanone **100**. Minor competing pathways are also possible. Thus ring closure can occur at the oxygen terminus. **99** → **101**, whereas a prototropy from the zwitterionic intermediate leads to the open chain unsaturated ketone **102**. This can be envisaged as a result of an electrophilic olefinic substitution by the oxyallyl cation.

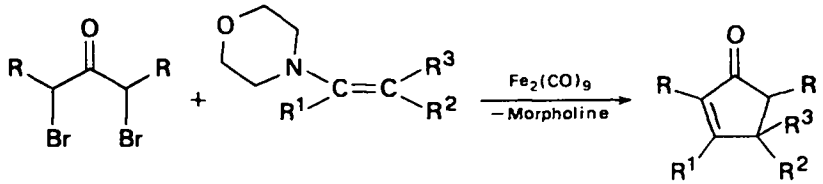
In spite of the stepwise nature of the process, the reaction with *Z*-β-deuteriostyrene (equation 213) was found to follow a stereospecific course[306], thus leading to the suggestion that free rotation in the oxyallyl cation is prevented by charge transfer or coulombic attraction between the enolate and the cationic centre.



(213)

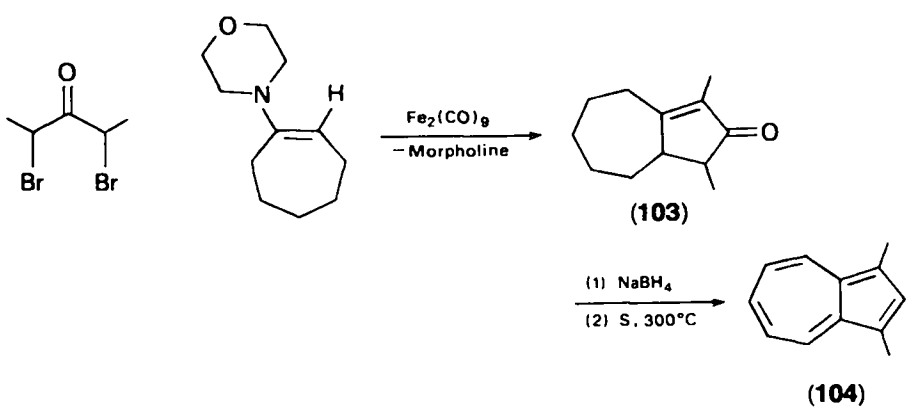
The observed course can also be explained by assuming a quite rapid bond formation between the charged termini.

Interesting variations on the theme and applications to the synthesis of specific compounds have been reported[307,308]. Thus the reaction with an enamine and elimination of the amine moiety takes place readily to produce a cyclopentenone[307] (equation 214).



(214)

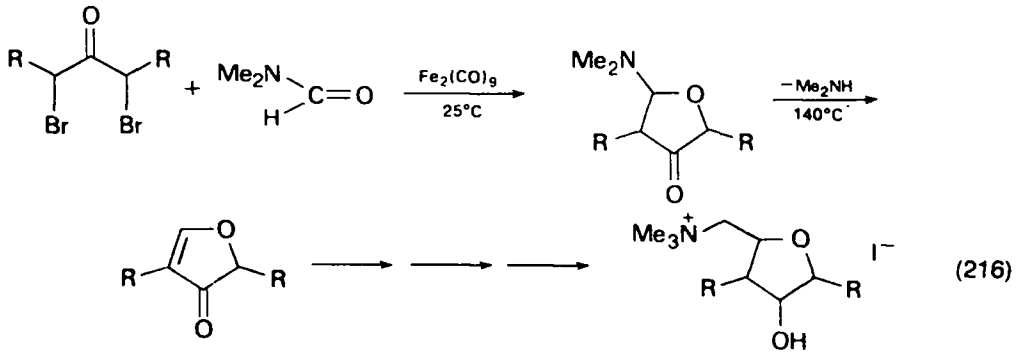
The procedure can be applied successfully to the synthesis of the azulene **104** using cycloheptanone enamine as the substrate to produce the bicyclo[5,3,0]decenone **103**. Reduction of the ketone and treatment with sulphur to effect dehydration and dehydrogenation gives the azulene **104** (equation 215).



(215)

(104)

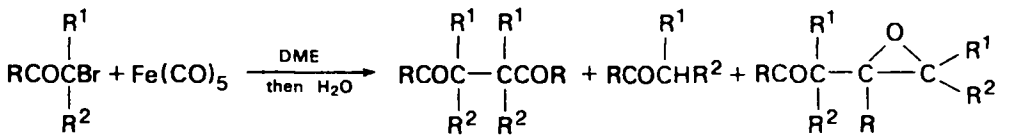
The carbon–oxygen double bond of carboxamides can also react with the oxyallyl complex to give 3-(2*H*)-furanones after elimination of dimethylamine (equation 216). The method was applied successfully to the synthesis of 4-methylmuscarine[309].



(216)

B. Reactions of α-Haloketones

Besides the product of reductive dehalogenation, the reactions of α-haloketones with $Fe(CO)_5$ give 1,4-diketones and β-epoxyketones, thus showing a behaviour similar to that observed when $Ni(CO)_4$ is used[310] (equation 217).



(217)

In order to explain the observed products, which are formed in variable amounts depending upon the conditions, the mechanism shown in Scheme 16 was proposed.

The first step is represented by an oxidative addition of the α-haloketone to $Fe(CO)_5$ to give **105**. This compound can lose carbon monoxide to form **106**, which can then be converted to the monoketone **107** by cleavage of the iron—carbon bond (addition of water), and to the 1,4-diketone **108** and/or the β-epoxyketone **109** by reaction with α-haloketone. It is also possible that **105** reacts directly with additional α-haloketone to give the coupled product **108** or with H_2O to form a monoketone **107**.

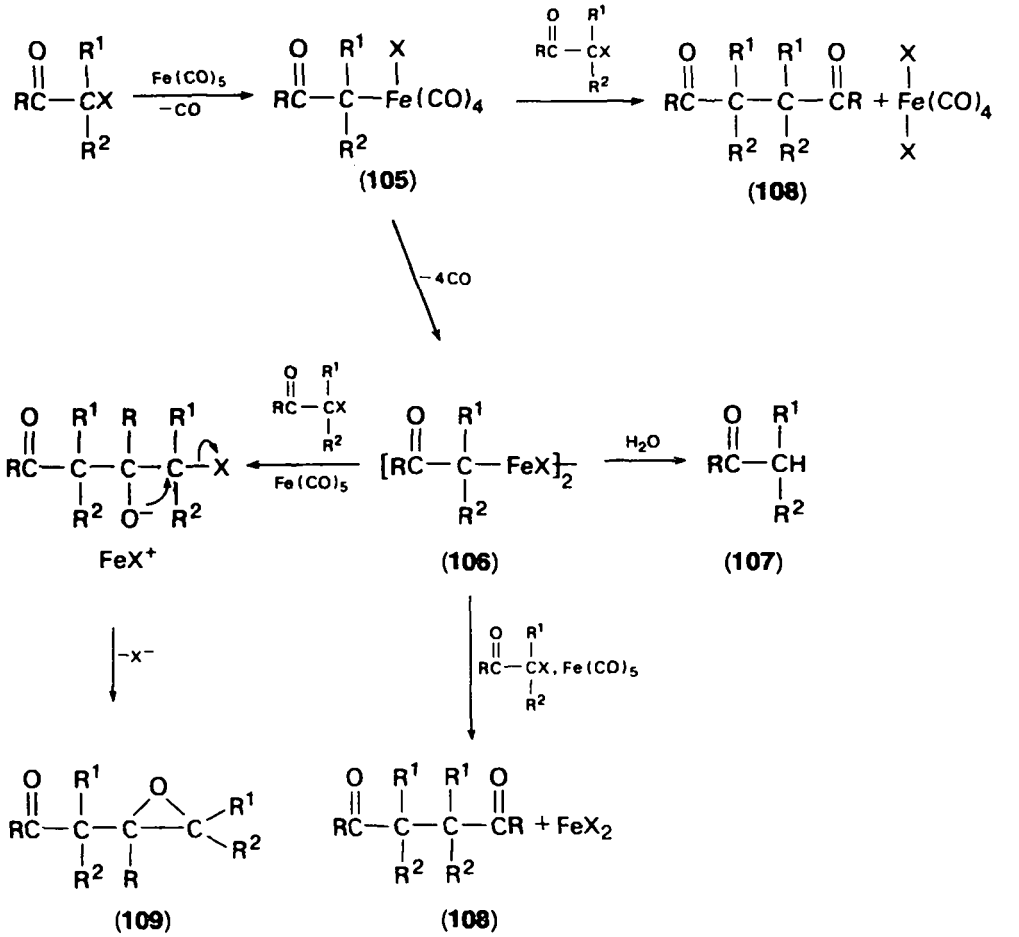
C. Reactions of Geminal Dihalides

Iron carbonyls are able to effect the coupling of *gem*-dihalides according to the following equation:

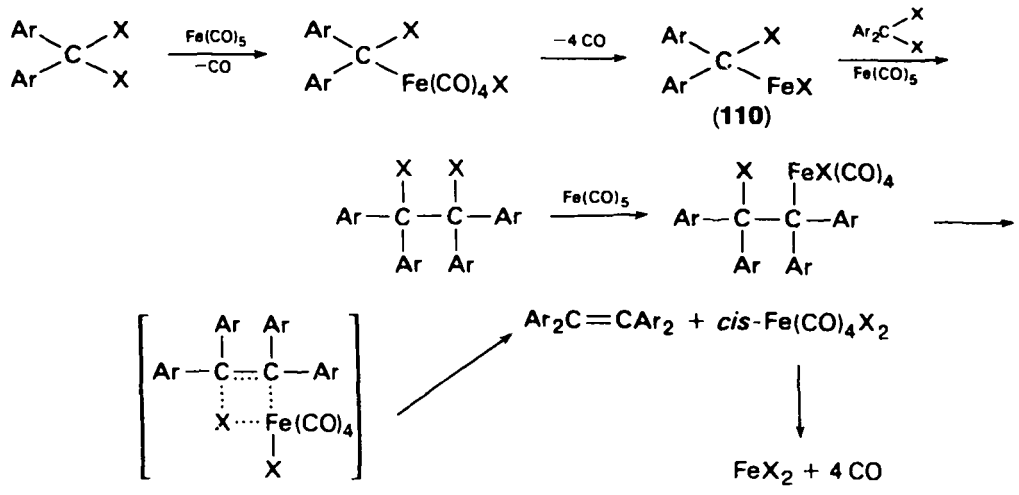
$$2\,Ph_2CCl_2 + 2\,Fe(CO)_5 \longrightarrow Ph_2C{=}CPh_2 + 2\,FeCl_2 + 10\,CO \qquad (218)$$

The formation of carbenes and their coupling to give the olefinic products has been considered a mechanistic possibility[311]. However, a different reaction sequence has been proposed by Alper and Keung[310] (Scheme 17).

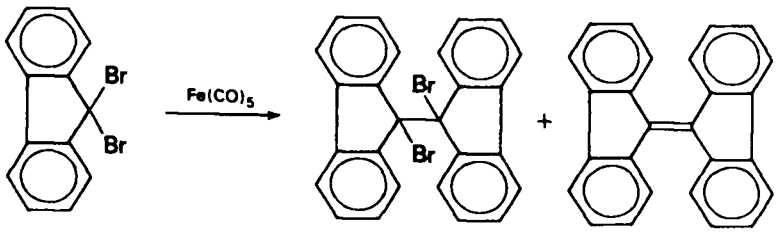
As a support for the mechanism (which is rather similar to that discussed for the coupling of α-haloketones in Scheme 16), it is worth noting that in the reaction of dichlorodiphenylmethane a purple-red complex (probably the halogen-bridged dimer of **110**) and *cis*-dichlorotetracarbonyliron are isolated. Furthermore, treatment of 9,9-dibromofluorene with $Fe(CO)_5$ in refluxing benzene gives the alkene and 9,9'-dibromobisfluorenyl (equation 219).



SCHEME 16



SCHEME 17



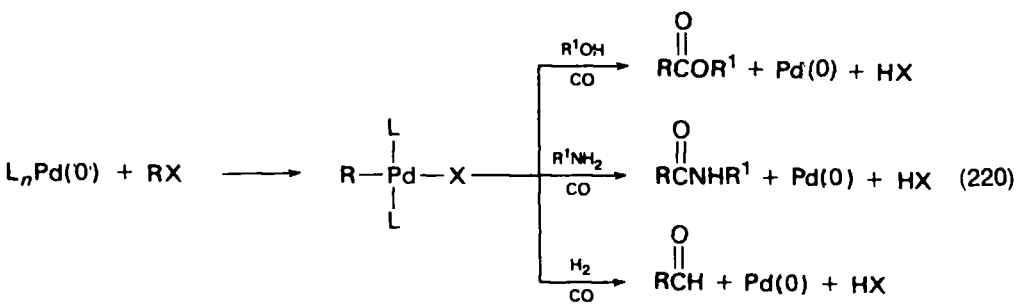
(219)

VIII. CARBONYLATION REACTIONS

A. Carbonylation with CO in the Presence of Palladium Catalysts

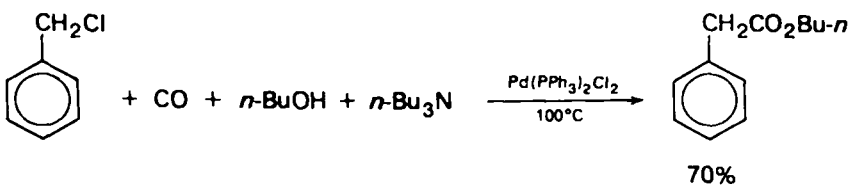
The complex arising from the oxidative addition of the aryl, benzyl, vinyl and heteroaromatic halides to a Pd(0) complex in an atmospheric pressure of carbon monoxide can undergo a variety of synthetically useful transformations.

Esters[312,313], amides[314] or aldehydes[315] are formed in the presence of methanol, primary or secondary amines or hydrogen, respectively, according to equation (220).



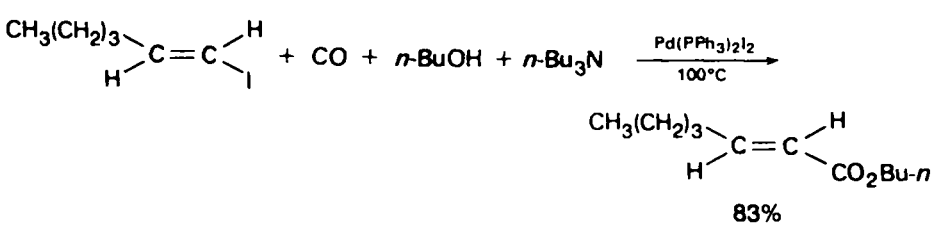
(220)

Dihalobis(triphenylphosphine)palladium(II) complexes, which are presumably reduced under the reaction conditions to a Pd(0) species by CO or H_2, are generally used as catalysts and a strongly basic tertiary amine is added to neutralize the hydrogen halide formed in the reaction. The use of the tertiary amine can be avoided in the formation of the amide when the primary or secondary amine employed is a sufficiently strong base. The reaction tolerates a variety of functional groups and shows appreciable to high stereospecificity with *Z*- and *E*-vinylic halides. A few specific cases are reported below (equations 221–226).



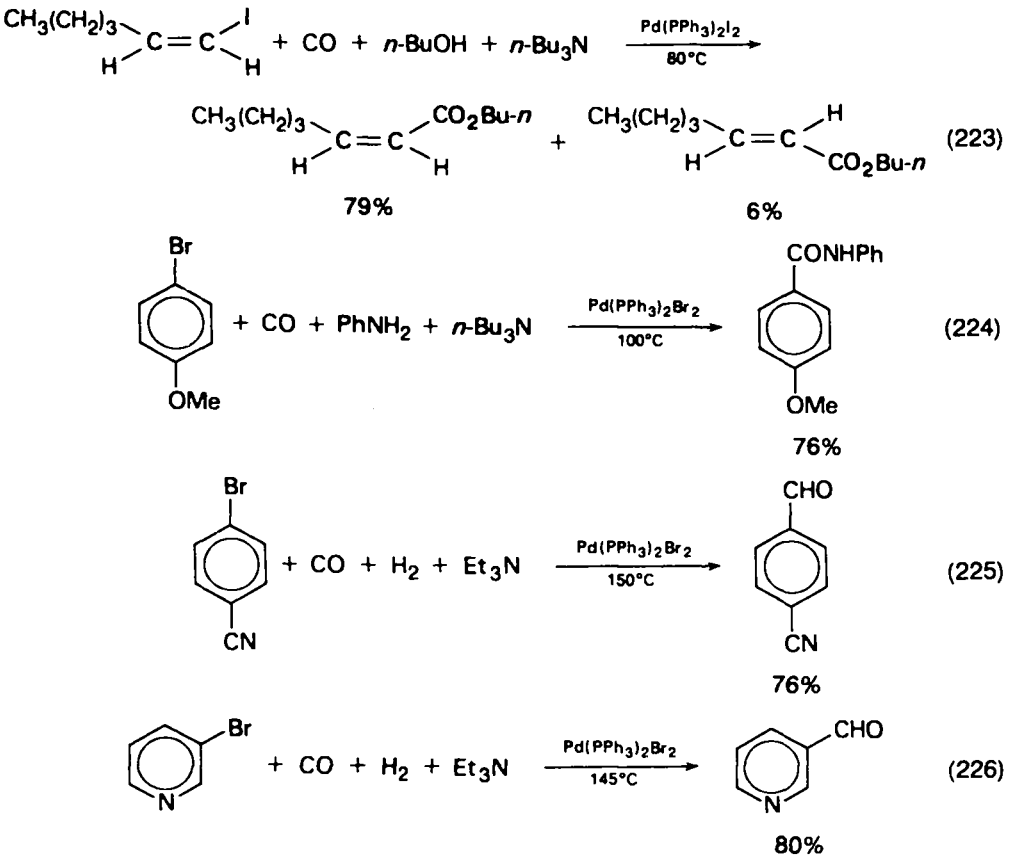
(221)

70%

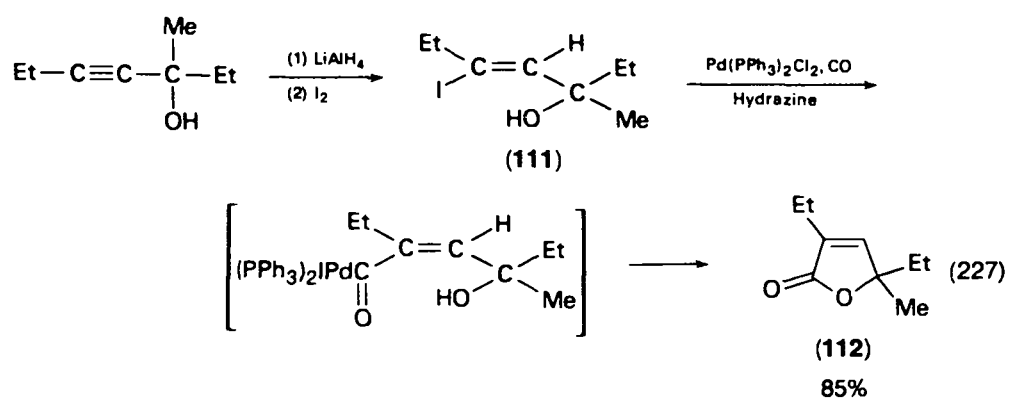


(222)

83%

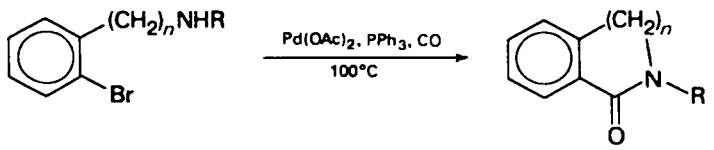


Interesting applications of this process to the synthesis of some heterocyclic systems have also been reported. A specific case is shown in equation (227), where the *Z*-vinyl iodide **111** produced from a propargyl alcohol is transformed into $\Delta^{\alpha,\beta}$-butenolide **112**[316].



Moreover, five-, six- and even seven-membered benzolactams can be produced in good yields from the corresponding *o*-bromo(aminoalkyl)benzenes[317]. The process,

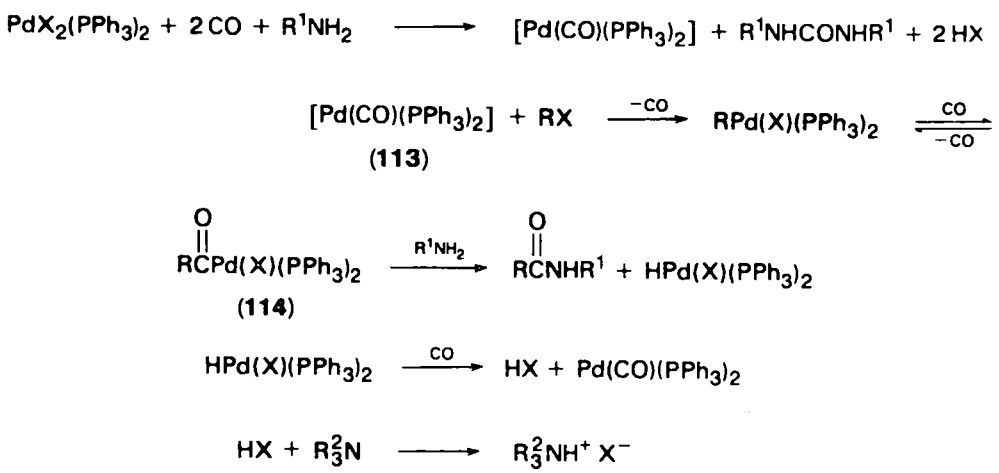
which is depicted in equation (228), has been successfully applied to the total synthesis of sendaverine[318], an alkaloid which is of interest in connection with the biogenesis of the protoberberines[319].



(228)

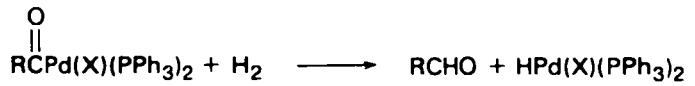
$n = 1-3$ 40–65%

A possible mechanism for the formation of amides is reported in Scheme 18, where the key steps are the oxidative addition of the halide to the palladium(0) complex **113** and subsequent formation of the acylpalladium intermediate **114**, which would give the amide upon reacting with the amine.



SCHEME 18

A similar scheme could also be envisaged for the ester formation, whereas the reduction of the acylpalladium intermediate **114** with H_2 could account for the aldehyde formation (equation 229).

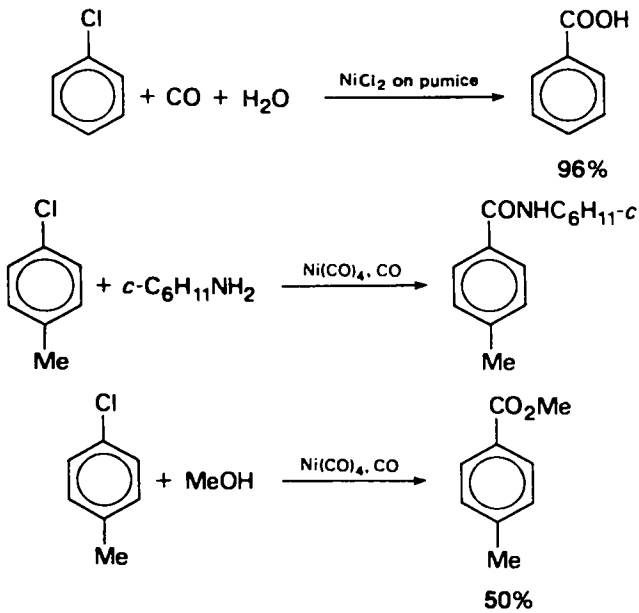


(229)

B. Carbonylation with CO in the Presence of Nickel Catalysts

Carbonylation of aryl halides under CO pressure in the presence of a transition metal has been thoroughly investigated[320]. Simple heterogeneous catalysts such as $NiCl_2$ on pumice[321], NiI_2 on SiO_2[322] or an homogeneous catalyst such as $Ni(CO)_4$ have been used. A variety of carbonylation products can be obtained. The formation of aromatic acids in the presence of water, esters in the presence of alcohols and amides in the presence of amines is reported in equations (230)–(232).

Nakayama and Mizoroki[325–327] have pointed out the importance of the presence of a base in the carbonylation of aryl halides under CO pressure. Using nickel acetate as



catalyst the yield rises from 1% in the absence of KOAc to 90% in the presence of a stoicheiometric amount of KOAc. It is very likely that the HBr formed acts as an inhibitor and therefore the carbonylation reaction is accelerated by the removal of the acid.

The carbonylation of allyl halides with CO in the presence of $Ni(CO)_4$ has been thoroughly investigated[284,328]. Due to its relationship to the other processes involving π-allyl complexes, the reaction which occurs according to equation (233) has been introduced in Section VI.B.

$$R_2C{=}\overset{R}{\overset{|}{C}}{-}\overset{R}{\overset{|}{C}}HX + CO + R^1OH \xrightarrow{Ni(CO)_4} R_2C{=}\overset{R}{\overset{|}{C}}{-}\overset{R}{\overset{|}{C}}HCO_2R^1 + HX \qquad (233)$$

R^1 = H or alkyl; X = Cl, Br, I

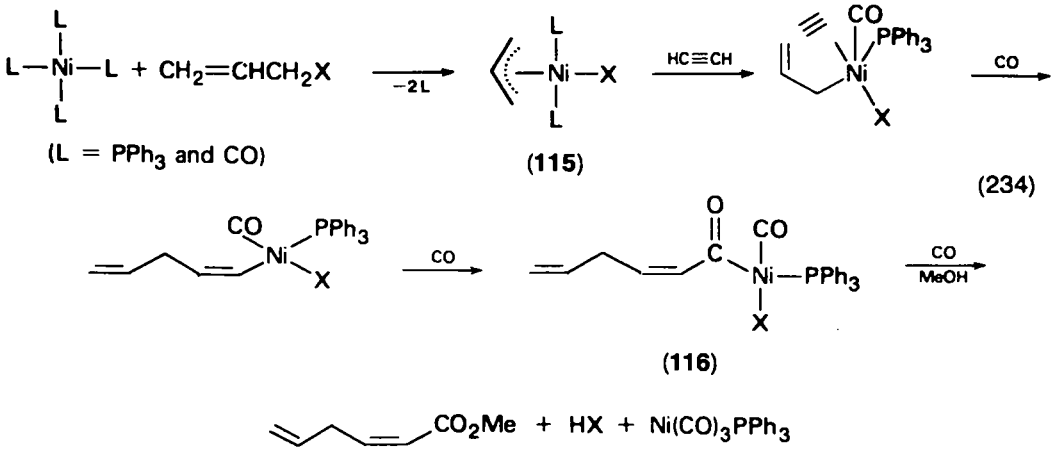
Depending upon the product desired, the reaction requires the use of an alcohol or H_2O/acetone mixtures. Unsaturated acid chlorides can also be obtained, provided that an inert solvent is used[266,283–285]. Insertion of unsaturated species can also be achieved and this is discussed below (Section VIII.C).

C. Carbonylation of π-Allylnickel Complexes with CO Accompanied by Insertion of Olefins or Acetylenes

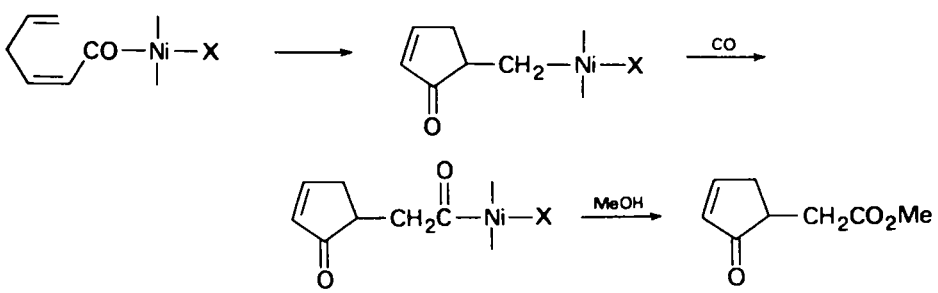
Chiusoli and coworkers have reported a series of reactions in which the carbonylation of π-allylnickel complexes occurs together with the insertion of unsaturated species such as alkynes or alkenes[284,328].

A variety of products are formed depending upon the starting materials and reactions conditions[329–332]. The reactions of the unsubstituted acetylene (equations 234 and 235) or ethylene (equation 236) are reported below as examples.

Insertion of acetylene and CO can follow two different courses depending on whether methanol or an inert solvent is used. According to equation (234) the



complex **115** derived from the oxidative addition of the allyl halide to the zero-valent nickel complex can insert acetylene and CO to give **116**, which after reaction with MeOH produces methyl *Z*-2,5-hexadienoate. A ring closure process can be followed when the reaction is carried out with a low concentration of methanol in inert solvent (equation 235). The formation of the cyclopentenone ring can be represented as an addition of the acylnickel end to the terminal double bond.

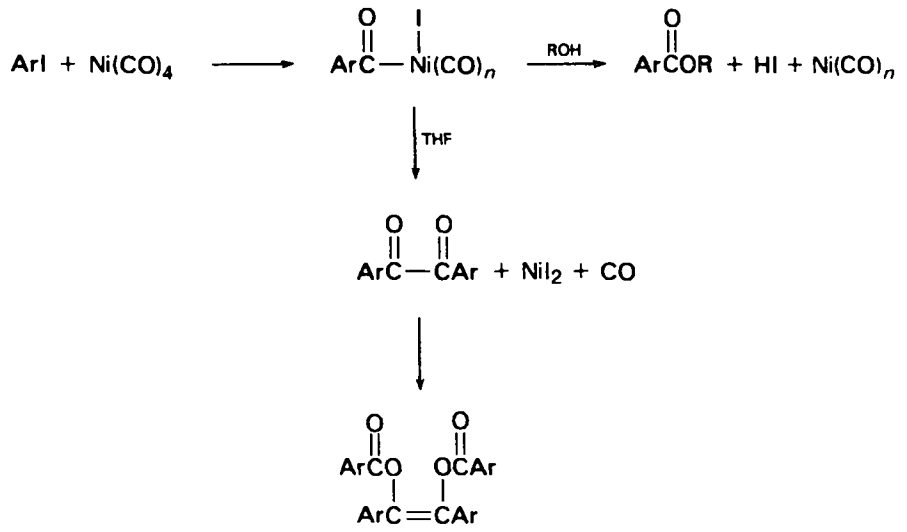


Ethylene itself, under a pressure of 20–30 atm, reacts at 40 °C with tetracarbonyl nickel in a methanolic solution of allyl chloride to give methyl 5-hexenoate (equation 236). The yields are in the range 40–60%. However, a variety of by-products are formed.

$$CH_2{=}CHCH_2Cl + CH_2{=}CH_2 + CO + CH_3OH \xrightarrow{\text{Ni complex}} CH_2{=}CHCH_2CH_2CH_2CO_2CH_3 + HCl \quad (236)$$

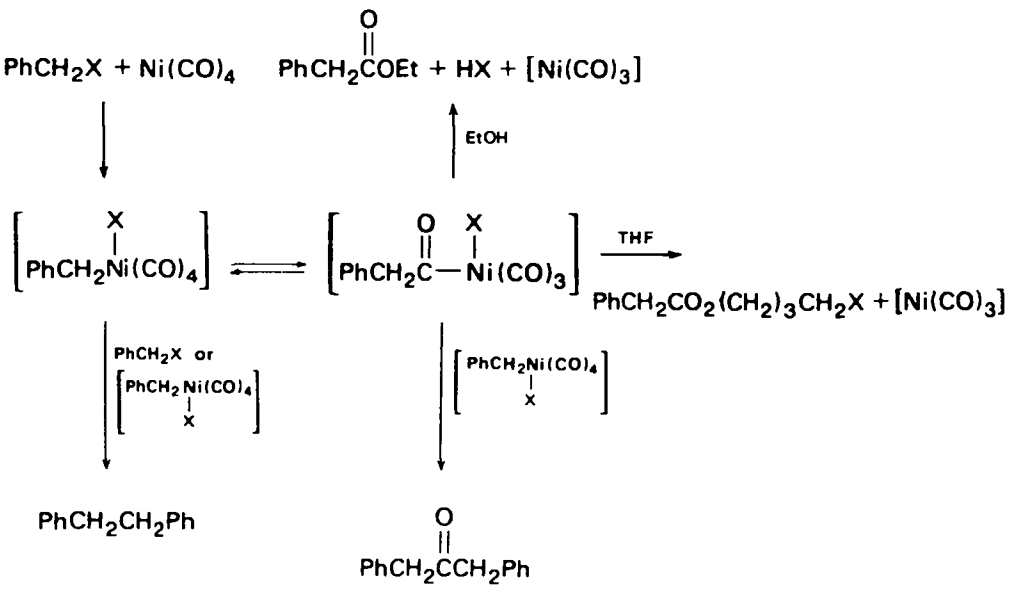
D. Carbonylation with Metal Carbonyls

Carbonylation of aryl iodides can be also carried out using only $Ni(CO)_4$[333]. The products obtained depend upon the nature of the solvent, aromatic esters or benzils being formed in alcohol or in aprotic solvents, respectively. When hindered iodides are used, enediol diesters are also formed in addition to the benzils (Scheme 19). Aryl chlorides and bromides and alkyl halides do not react with nickel carbonyl under these conditions.



SCHEME 19

The reaction of benzyl halides with $Ni(CO)_4$ in various solvents was studied by Tsutsumi and coworkers[334]. The relative amounts of the products (e.g. esters, 1,2-diphenylethane or dibenzyl ketone) depend upon the nature of the solvent and of the leaving group. The origin of the observed products is reported in Scheme 20. Furthermore, products derived from Friedel–Crafts type reactions (i.e. diphenylmethane and dibenzylbenzene) are formed in benzene. In THF the fission of the tetrahydrofuran ring occurs to give the 4-halogeno-*n*-butyl ester of phenylacetic acid.

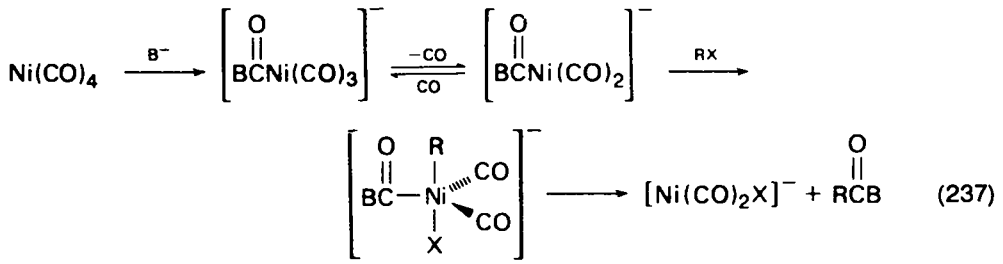


SCHEME 20

Besides the Ni complexes a variety of other metal carbonyls have been used in the carbonylation reaction. For instance, iodobenzene and benzyl halides[335,336] react with $Fe_3(CO)_{12}$ to give benzophenone or symmetrical aryl-substituted acetones, respectively.

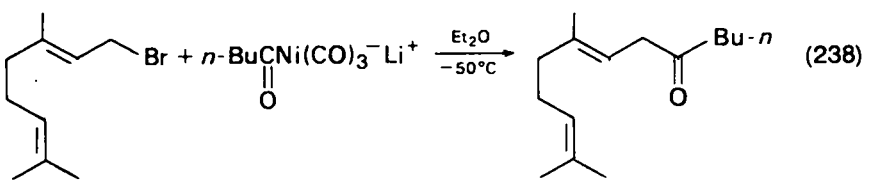
E. Carbonylation with Metal Carbonyl Anions

By treatment of metal carbonyls with bases such as organolithium compounds or alkoxide ions, carbonyl metallate anions are produced. These complexes are quite strong nucleophiles and quite reactive in oxidative addition reactions. Accordingly, they react with halides, leading to a variety of interesting products. In the case of the reaction of $Ni(CO)_4$ with a base (B^-) the metal carbonyl anions should have the $[BCONi(CO)_3]^-$ structure and the reactions can be explained according to a mechanism which involves an oxidative addition step[283] (equation 237).

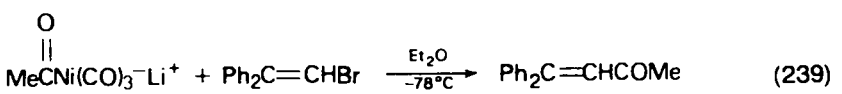


(237)

Thus allyl and vinyl halides react with the complexes derived from alkyllithium and nickel carbonyl giving ketones[283] (equations 238 and 239). In the allyl system the geometry of the halide is maintained during reaction.

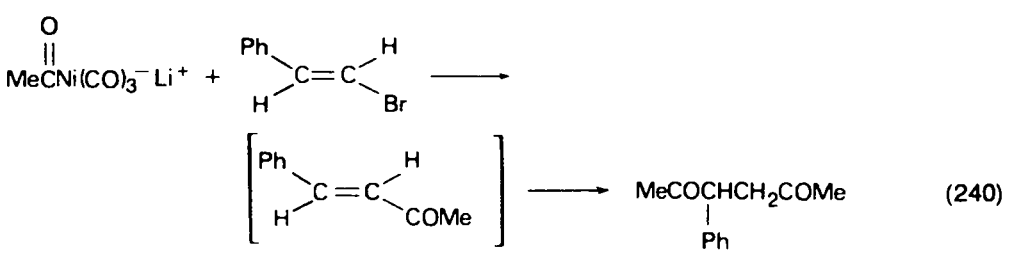


(238)



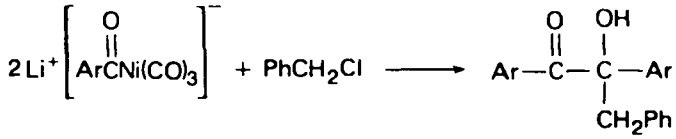
(239)

In some cases the first reaction is accompanied by a second addition. 1,4-Diketones are formed from *E*-β-bromostyrene (equation 240) and this is expected on the basis of the ability of the acylnickel carbonylate to add to unsaturated systems[337,338].



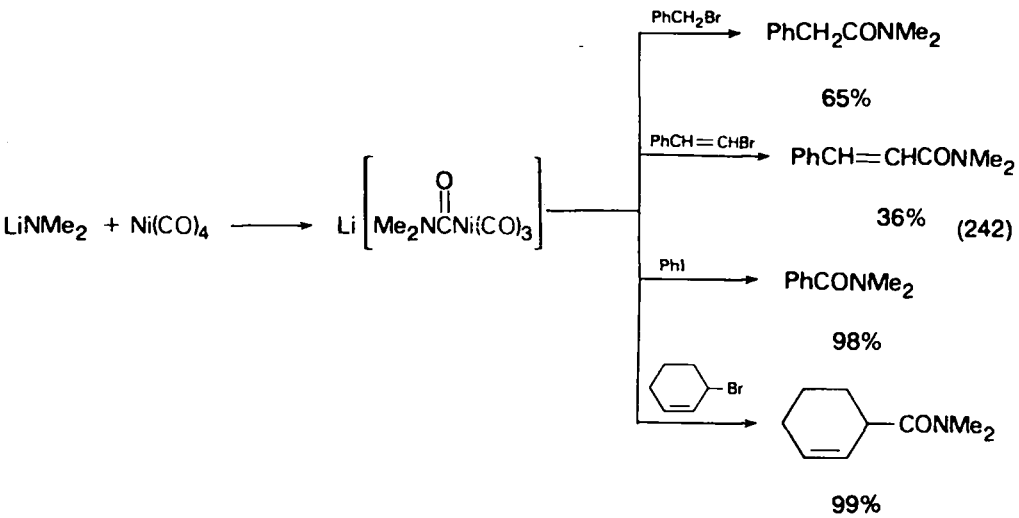
(240)

In the case of the ketone derived from the reaction with benzyl chloride the second attack occurs at the carbonyl group[339] (equation 241).



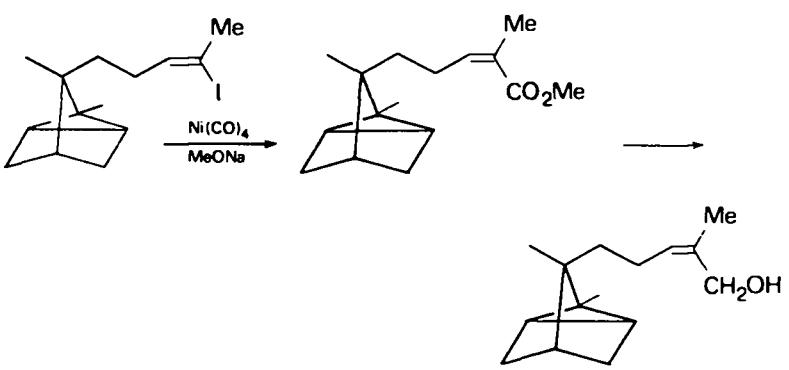
(241)

The reaction of lithium amides with $Ni(CO)_4$ leads to lithium carbamoyltricarbonylnickelates[340,341], from which amides can be formed upon treatment with organic halides[341] (equation 242).



(242)

Allyl bromides, vinyl bromides and aryl iodides react with sodium alkoxide–nickel carbonyl complexes[342]. The carbonylation has been successfully applied to the key step of the stereospecific synthesis of α-santalol (**117**) (equation 243)[343].



(243)

(**117**)

The reactivity of these complexes depends upon the nature of the alcohol. Thus, simple primary alkyl halides, which do not react with the $MeO^-/Ni(CO)_4$ complex, are able to produce the corresponding *t*-butyl esters with the $t\text{-}BuO^-/Ni(CO)_4$ complex.

Cassar and Foà[344] have reported the successful carbonylation of aryl bromides and chlorides using the $Ca(OH)_2/Ni(CO)_4$ system in dipolar aprotic solvents under 1 atm carbon monoxide. A catalytic cycle is achieved in these conditions, with an anionic nickel carbonyl complex acting as a catalyst.

The reaction between organolithium derivatives and iron pentacarbonyl leads to lithium acyltetracarbonylferrates, which by analogy with the corresponding nickel complexes are able to react with alkyl halides to give unsymmetrical ketones[345]. In the case of benzyl bromide the reaction leads to a ketone which can be easily isolated (equation 244) without undergoing the second addition observed with the acyl nickel carbonylate.

$$Li[p\text{-}MeC_6H_4COFe(CO)_4] + C_6H_5CH_2Br \longrightarrow p\text{-}MeC_6H_4COCH_2C_6H_5 \quad (244)$$

67%

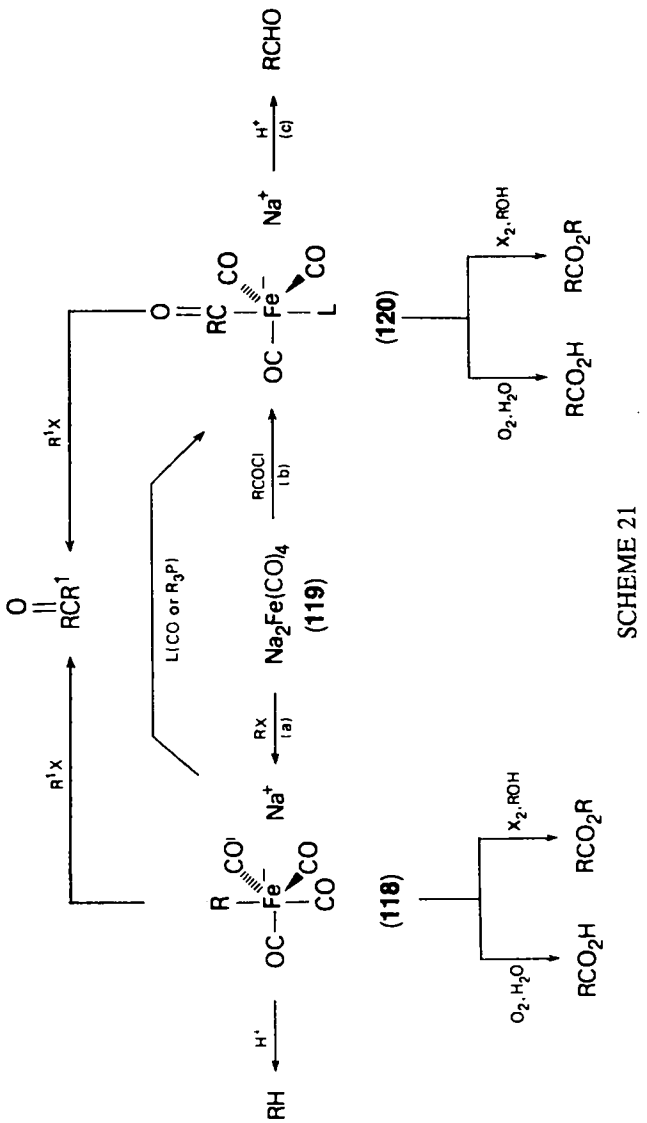
Among the iron complexes derived from iron carbonyls, the alkali tetracarbonylferrates are the most useful for organic synthesis. The use of disodium tetracarbonylferrate, $Na_2Fe(CO)_4$, has been developed by Cooke and Collman[346,347]. The complex can be prepared by reduction of $Fe(CO)_5$ either with sodium amalgam in THF or with sodium benzophenone ketyl in dioxane (equations 245 and 246).

$$\underset{\text{orange}}{Fe(CO)_5} \xrightarrow[THF]{Na(Hg)} \underset{\text{red–yellow}}{Na_2Fe(CO)_4} \quad (245)$$

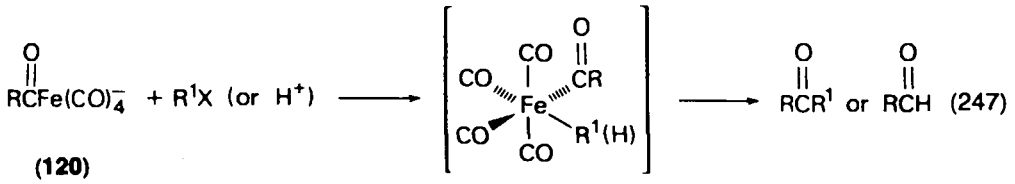
$$\underset{\text{orange}}{Fe(CO)_5} + \underset{\text{deep blue}}{Na} \xrightarrow[PhCOPh]{\text{Dioxane, 100°C}} \underset{\text{white}}{Na_2Fe(CO)_4 \cdot 1.5\text{-dioxane}} \quad (246)$$

The second procedure is very practical, leading to a pure and more soluble solvate and can easily be scaled up. However, the use of large quantities of $Na_2Fe(CO)_4$ represents a problem, due to its extreme oxygen sensitivity, which makes the complex spontaneously inflammable in air. As outlined in Scheme 21, the use of $Na_2Fe(CO)_4$ permits the conversion of aliphatic halides (or sulphonates) to aldehydes[346], asymmetric ketones[348], carboxylic acids[349], esters[349] or amides[349].

As shown in Scheme 21, the anionic alkyl- and acyliron(0) complexes **118** and **120** are the key intermediates in various reactions[347]. Formation of the saturated d^8 complex **118** can be considered an oxidative addition of the coordinatively saturated starting d^{10} complex **119**, or equivalently an S_N2 attack performed by the same complex. Substrate reactivities ($CH_3 > RCH_2 > RR^1CH$; vinyl and aryl inert), leaving group effects ($I > Br > OTs > Cl$), kinetics (second order) and stereochemistry (inversion in step a) are those which are usually observed for S_N2 processes. The acyl complex **120** can be formed by migratory insertion from the complex **118** in the presence of excess of CO or added triphenylphosphine. Alternatively disodium tetracarbonylferrate can be reacted with acyl chlorides to give complex **120**. Upon reacting with acetic acid or with alkyl halides, **120** produces aldehydes or ketones, respectively. The conversion of acyliron(0) complex **120** into aldehydes or ketones could involve a six-coordinated iron(II) complex (**121**)


O
RCR¹
R¹X
L(CO or R₃P)
RX
(a)
Na₂Fe(CO)₄
(119)
RCOCl
(b)
RC CO
OC—Fe—L
CO
Na⁺
H⁺
(c)
RCHO
R CO'
OC—Fe—CO
CO
H⁺
RH
(118)
(120)
X₂, ROH
RCO₂R
O₂, H₂O
RCO₂H

SCHEME 21



(120) (121)

(equation 247). The mechanism for the production of ketones directly from complex **118** as well as of the oxidative cleavages producing acids or their derivatives are less clear[347].

Independently from the mechanistic details, the reaction with the carbonylferrate represents a valid synthetic tool and this conclusion is fully supported by the specific examples of equations (248)–(251), which, among other features, show that the procedure is tolerated by functional groups which would be attacked by the more reactive magnesium or lithium reagents.

$$Cl(CH_2)_6Br \xrightarrow[(2)\ AcOH]{(1)\ Na_2Fe(CO)_4,\ THF,\ CO} Cl(CH_2)_6CHO \quad 82\% \qquad (248)^{347}$$

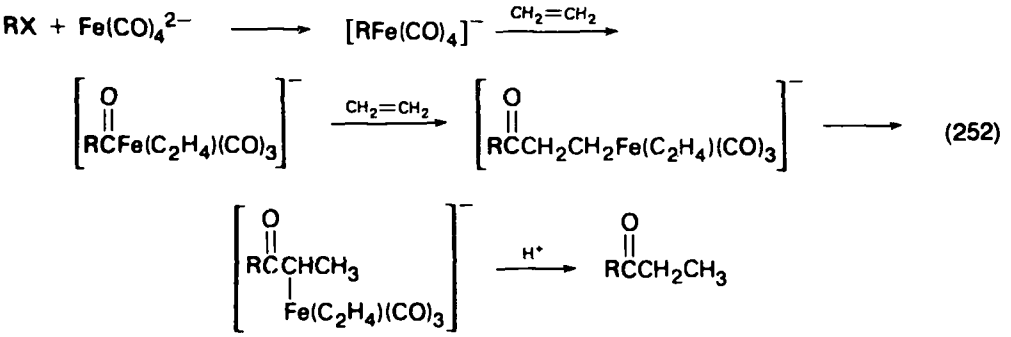
$$EtO_2C(CH_2)_4Br \xrightarrow[(2)\ EtI]{(1)\ Na_2Fe(CO)_4,\ N\text{-methylpyrrolidone}} EtO_2C(CH_2)_4\overset{O}{\overset{\|}{C}}Et \quad 74\% \qquad (249)^{348}$$

$$n\text{-}C_5H_{11}COCl \xrightarrow[(2)\ EtI]{(1)\ Na_2Fe(CO)_4,\ THF-HMPA} n\text{-}C_5H_{11}\overset{O}{\overset{\|}{C}}Et \quad 87\% \qquad (250)^{348}$$

$$n\text{-}C_{12}H_{25}Cl \xrightarrow[(2)\ O_2,\ H_2O]{(1)\ Na_2Fe(CO)_4,\ N\text{-methylpyrrolidone}} n\text{-}C_{12}H_{25}CO_2H \quad 84\% \qquad (251)^{349}$$

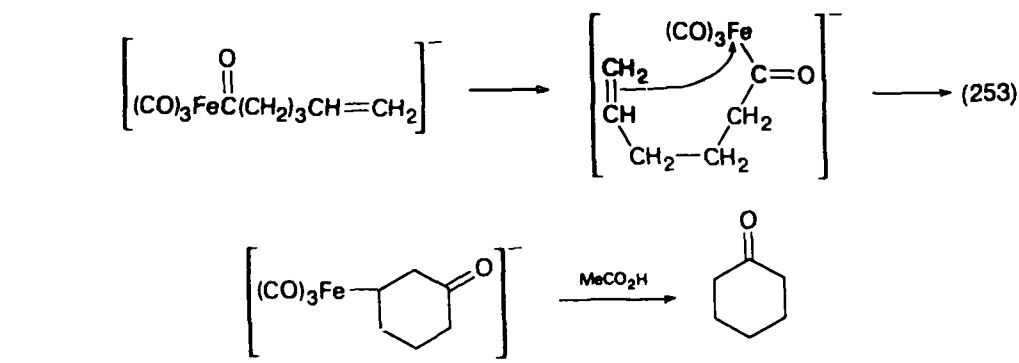
However, the process also has some limitations. In fact the pK_b value for $Na_2Fe(CO)_4$ is near that of OH^- and this causes a tendency to promote elimination. Thus, only primary halides can be satisfactorily employed. Secondary tosylates are preferred over secondary halides and tertiary substrates cannot be used. Furthermore, the alkylation of the alkyl or acyl intermediates **118** or **120** usually requires a primary iodide. Allylic halides cannot be employed due the formation of stable 1,3-diene–$Fe(CO)_3$ complexes rather than of the alkyliron(0) intermediate **118**. Finally, the conversion **118** → **120** fails for alkyl groups bearing adjacent electronegative groups. This represents a restriction of the scope of the aldehyde synthesis. However, the difficulty can be overcome by employing the acid chloride route [(b) followed by (c)[350] (Scheme 21)][347].

Extensions of this procedure have also been reported. Thus insertion of ethylene into the acylmetal bond of an acyliron(0) complex followed by a rearrangement to an α-metalloketone leads to conversion of organic halides to ethyl ketones[351] (equation 252).



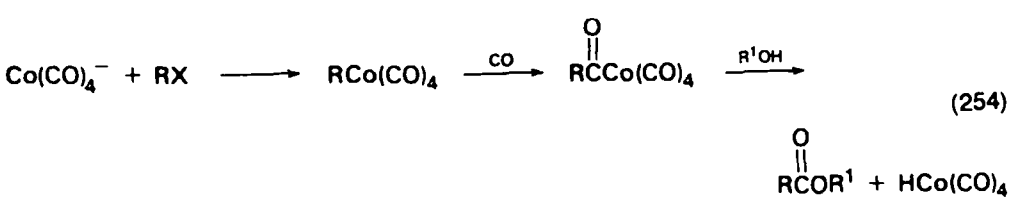
(252)

Reactions between $Na_2Fe(CO)_4$ and γ-ethylenic bromides or tosylates having a terminal double bond produce cyclic ketones by intramolecular insertion of the terminal olefins into the iron–carbon bond[352] (equation 253).



(253)

Organic halides can be also transformed into esters by means of sodium tetracarbonylcobaltate[353]. In fact, reduction with Na/Hg or disproportionation of $Co_2(CO)_8$ with base leads to the d^{10} cobalt(0) complex. This is able to react with halides which usually undergo the S_N2 process (e.g. 1°, 2°, allyl and benzyl halides and α-halogenoesters) as shown in equation (254).

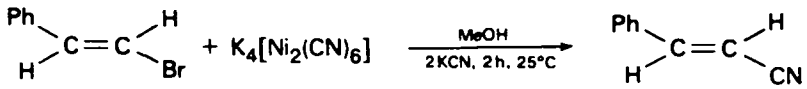


(254)

An intermediate alkylcobalt tetracarbonyl is formed which under one atmosphere of CO leads to the acylcobalt tetracarbonyl. This gives the ester after treatment with alcohol. Carrying out the reaction in the presence of a tertiary amine, the $HCo(CO)_4$ produced can be transformed into $Co(CO)_4^-$, thus accomplishing a catalytic process.

IX. CYANATION REACTIONS

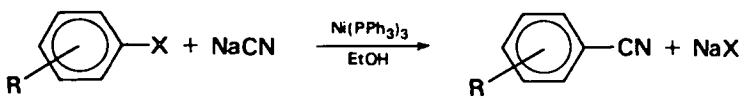
Cyanation of vinyl or aryl halides can be carried out with several complexes. Vinyl halides react with potassium hexacyanodinickelate, $K_4[Ni_2(CN)_6]$ to give α,β-unsaturated nitriles (equation 255)[342].



(255)

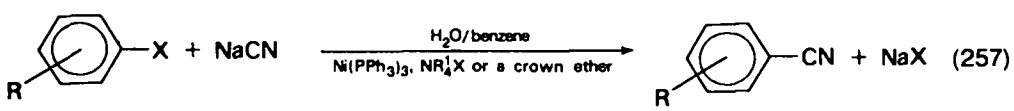
For the cyanation of *Z*- and *E*-β- and α-bromostyrenes, pentacyanocobaltate complexes have been also used[354]. Compared with the cyanation of β-bromostyrene by CuCN[355], $K_4[Ni_2(CN)_6]$ + KCN[342] or $Pd(PPh_3)_4$ + KCN[356], this method seems more convenient and gives excellent yields and selectivity under milder conditions.

Cyanation of various non-activated aryl iodides and bromides can be carried out with KCN and Pd(II) acetate[357] or tetrakis(triphenylphosphine)palladium(0)[358] as catalysts. The same reaction has been shown to occur also with NaCN in the presence of $Ni(PPh_3)_3$ or σ-$ArNi(PPh_3)_2Cl$ as catalysts under very mild conditions (equation 256)[359].



(256)

Furthermore, these nickel-catalysed cyanations can be conveniently carried out under phase transfer conditions, using both liquid–liquid and solid–liquid techniques[360]. The first technique (equation 257) gives better yields and a higher catalyst turnover. The procedure appears to be very useful both on a laboratory scale and for industrial production.



(257)

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CHAPTER **27**

Dihalocyclopropanes

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I. INTRODUCTION

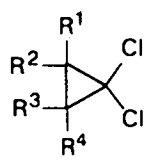
The term 'dihalocyclopropane', or to give a specific example 'chlorofluorocyclopropane', as used in this chapter always means 1,1-dihalocyclopropane (*gem*-dihalocyclopropane), e.g. 1-chloro-1-fluorocyclopropane (*gem*-chlorofluorocyclopropane). 1,2-Dihalocyclopropanes are regarded as rather unimportant and are relatively unstudied.

The first dihalocyclopropane was described more than 90 years ago[1]. However, this class of compounds was considered exotic for about 60 years. In 1950 Hine[2] confirmed a proposal of Geuther given in 1862[3], that dichlorocarbene ($:CCl_2$) is an intermediate in the basic hydrolysis of chloroform. Formation of $:CCl_2$ proceeds via the trichloromethyl anion, further hydrolysis leads to CO and formate (equation 1).

$$\begin{aligned} HCCl_3 + HO^- &\rightleftharpoons CCl_3^- + H_2O \\ CCl_3^- &\rightleftharpoons :CCl_2 + Cl^- \\ :CCl_2 &\xrightarrow{HO^-,\,H_2O} HCO_2^- + CO \end{aligned} \qquad (1)$$

Doering's experimental generation of $:CCl_2$ from $HCCl_3$ under anhydrous conditions with subsequent addition to olefins opened the way for a simple synthesis of dichlorocyclopropanes[4] (equation 2).

$$HCCl_3 + R^1R^2C{=}CR^3R^4 \xrightarrow{t\text{-BuOK}} \text{dichlorocyclopropane} \qquad (2)$$



Due to their accessibility dihalocyclopropanes have been investigated in some detail during the last 25 years, and a number of excellent reviews have been published[5–13]. The primary literature surveyed for this review consists mainly of articles from 1967–1980.

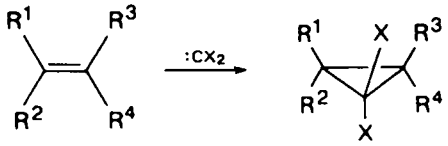
II. SYNTHESIS OF DIHALOCYCLOPROPANES

A. General Remarks

The first dihalocyclopropanes synthesized were dichloro and dibromo derivatives[4]. Chlorofluoro- and bromochlorocyclopropanes from mixed haloforms[14] and difluorocyclopropanes[15] followed. Dihalocyclopropanes derived from all possible

combinations of halogens have now been synthesized. Accessibilities and yields of these dihalocyclopropanes are strongly dependent on the method of generation of dihalocarbene. On the other hand, all these methods have been used for synthesis of dichlorocyclopropanes, the most important dihalocyclopropanes.

The formation of dihalocyclopropanes always proceeds by addition of $:CX_2$ (or :CXY) to olefins (equation 3).



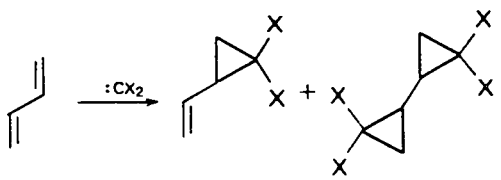
(3)

It has been shown that $:CX_2$ generated from various precursors is always the same 'free' $:CX_2$, and not an organometallic intermediate[16–18].

Some fundamental details of this reaction postulated by the first investigators have now been completely confirmed. Thus, formation of dihalocyclopropanes is stereospecific. Pure *cis* and pure *trans* olefins give *cis* and *trans* dihalocyclopropanes, respectively[19–23] (see equation 3).

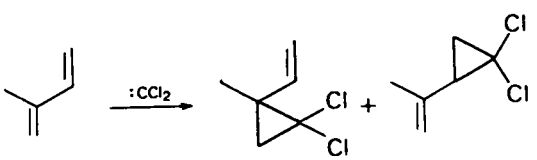
Dihalocarbenes were found to be electrophilic towards simple alkenes, reacting most rapidly with the most highly alkylated olefins[19,24]. Relative reactivity measurements were carried out by using competition experiments[19,21]. Moss investigated the carbenic selectivity in cyclopropanation reactions in detail[24–31] and verified a theory of carbene addition reactions[27,30,31]. Moreover, the influences of cyclopropyl substituents[32], large steric hindrance[33,34], charge distribution[35], solvent[36] and temperature[37] have been studied.

Dihalocarbenes add to 1,3-dienes to give vinyldihalocyclopropanes and tetrahalobicyclopropyls[20,38–43] (equation 4).



(4)

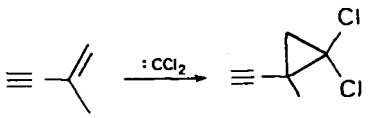
Generally 1,4-addition does not take place (for cheletropic 1,4-additions and homo-1,4 additions of dihalocarbenes to olefins see elsewhere[44–49]). If two different substituted double bonds are available for reaction, the addition of dihalocarbene usually takes place at the most nucleophilic bond[41] (equation 5).



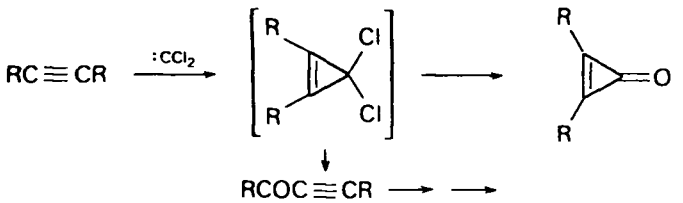
98 : 2 (5)

Reaction of enynes with dihalocarbenes proceeds via attack of $:CX_2$ on the olefinic double bond, leaving an unchanged triple bond[50,51] (equation 6).

With acetylenes themselves the reaction with dichlorocarbene is usually sluggish. The primary products, dichlorocyclopropenes, are partially hydrolysed during the reaction to give α,β-acetylenic ketones, cyclopropenones, and subsequent products[52–57] (equation 7).

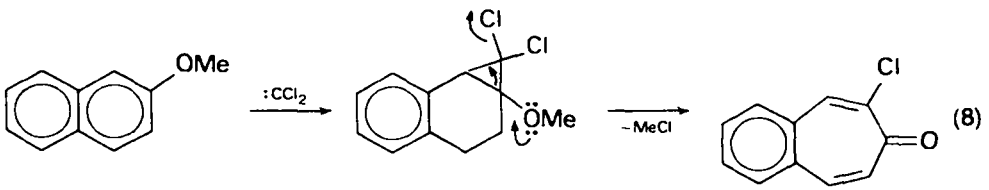


(6)



(7)

Reactions of dihalocarbenes with aromatic double bonds are mostly very slow, in many cases accompanied by rearrangement with ring expansion and loss of hydrogen chloride or other small molecules[14,58–61] (equation 8).



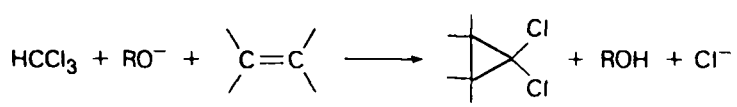
(8)

This type of reaction is discussed in more detail in Sections II.B–E.

B. By Use of Alkoxides

1. Sources of dihalocarbenes

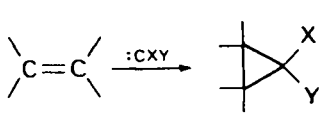
The formation of dichlorocyclopropanes from chloroform, an alkoxide and an olefin is a good preparative procedure[4], widely used for more than 15 years. Potassium *t*-butoxide is the base of choice. Other alkoxides have been applied occasionally[62–66], but usually with lower yields (equation 9; see also equations 1–3).



(9)

Inert solvents (benzene[60,61], *n*-hexane[67]) may be used. Reactions have frequently been conducted in excess olefin as the solvent, when the yields of dichlorocyclopropanes are considerably improved. The presence of *t*-butanol has no influence in some cases[68], but has been reported to be harmful in others[69].

Dibromocyclopropanes (**1**) have been synthesized similarly in good yield[4,20,22,59]. Diiodocyclopropanes (**2**) were at first believed to be too unstable for isolation[70], but they may be isolated readily, and in several cases distilled unchanged[71,72]. Some mixed dihalocyclopropanes (**3**, **4**) have been reported[14,73] (equation 10), but they are synthesized more conveniently by other methods (see Section II.C–F). Difluorocyclopropanes could not be obtained by HX elimination from HCF_2X[11].



(**1**) X, Y = Br
(**2**) X, Y = I
(**3**) X = Cl; Y = Br
(**4**) X = Cl; Y = F

(10)

Other sources of $:CCl_2$ are alkyl trichloroacetates and related compounds. Basic cleavage of trichloroacetates with alkoxide leads to the trichloromethyl anion (equation 11), which reacts as shown formerly.

$$Cl_3CCOOR + R'O^- \rightleftharpoons Cl_3C\underset{\displaystyle O^-}{\overset{\displaystyle OR}{\overset{|}{\underset{|}{C}}}}OR' \rightleftharpoons Cl_3C^- + ROCOOR' \qquad (11)$$

The yields of dichlorocyclopropanes are excellent, regardless of the base used (*t*-BuOK, EtONa, MeONa)[74,75]. Excess olefin and excess pentane have served as solvents. The dialkyl carbonate formed may be separated from the product by extraction with sulphuric acid, or by distillation.

Alkyl dichlorofluoroacetate and sodium methoxide have been used as starting materials for the synthesis of chlorofluorocyclopropanes[76,77] (equation 12).

$$Cl_2FCCOOR + \text{C=C} \xrightarrow{MeO^-} \text{Cl, F} \qquad (12)$$

Hexachloroacetone readily yields $:CCl_2$ in an aprotic medium on treatment with a base such as sodium methoxide[78,79]. The methyl trichloroacetate formed in the first step may react with MeONa to give more $:CCl_2$ (equation 13), but the second step is not utilized effectively.

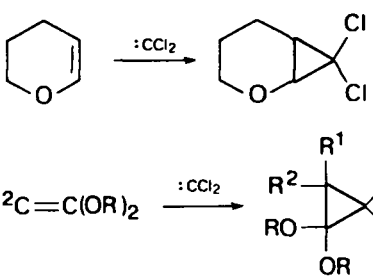
$$Cl_3CCOCCl_3 + MeO^- \longrightarrow Cl_3COOMe + Cl_3C^- \qquad (13)$$

sym-Difluorotetrachloroacetone has been described as a source of :CClF[80].

2. *Role of substrate*

Many substituted ethylenes have been used as starting materials for preparation of dihalocyclopropanes (see Table 1) according to the methods described above. Normally, the yield is moderate to good. Ethylene itself did not react with $:CCl_2$ by this procedure[19]. Dienes, trienes and so on gave the monoadducts preferentially; the yields of products by a further addition of $:CX_2$ are considerably lower[21,39,40,62,81–84] (see equations 4, 5).

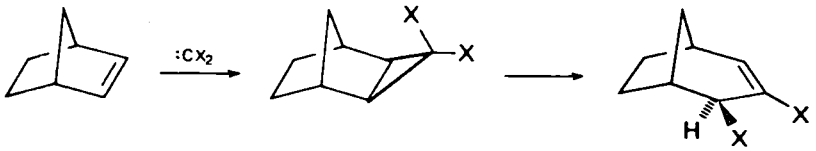
Some vinyl ethers such as dihydropyran[85] (equation 14), 2*H*-1-benzopyran and 4*H*-1-benzopyran[86] react with $:CCl_2$ to give the dichlorocyclopropanes.



(14)

Ketene acetals are suitable substrates for the formation of alkoxydichlorocyclopropanes[87] (equation 14). In some cases the primary adducts are isolable at low temperatures, but subsequent reactions take place easily[67,87,88].

Ring strain is another reason for spontaneous rearrangement. Thus, addition of $:CCl_2$ to norbornene leads to a tricyclic adduct, isolated by some authors[89,90], whereas



(15)

others reported immediate formation of the rearranged product[91,92] (equation 15; see also Section IV.D.1).

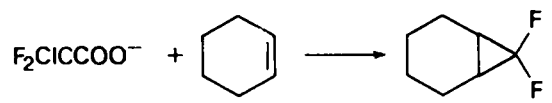
Most benzene derivatives are inert towards $:CX_2$ generated by the alkoxide method, but some aromatic compounds which approach olefinic character were found to be susceptible to attack by $:CCl_2$[14,58–61,93] (see equation 8).

C. By Thermolysis of Trihaloacetates

The reaction of trichloroacetic acid to give chloroform and carbon dioxide on heating with various bases, first observed 100 years ago[94], was shown to be a first-order reaction of the carboxylate anion, forming carbon dioxide and a trihalomethyl anion[95] (equation 16).

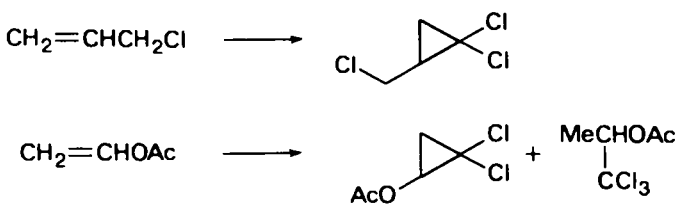
$$X_3CCOO^- \longrightarrow CO_2 + X_3C^- \longrightarrow :CX_2 + X^- \qquad (16)$$

This thermal decomposition of salts of trichloroacetic acid in aprotic solvents (preferably dimethoxyethane) under reflux in the presence of an olefin is an excellent method for preparation of dichlorocyclopropanes[38,96]. Sodium trichloroacetate is a cheap technical product. From difluorochloroacetate in the presence of cyclohexene the difluorononcarane can be obtained in good yield[15] (equation 17).



(17)

The thermolysis method is of special interest in the preparation of adducts of carbene acceptors that are sensitive to bases. Allyl chloride afforded 59% yield of the dichlorocyclopropane[38], while from vinyl acetate two products were obtained, dichlorocyclopropyl acetate and (1-trichloromethyl)ethyl acetate, the latter by addition of Cl_3C^- to the double bond[38] (equation 18).



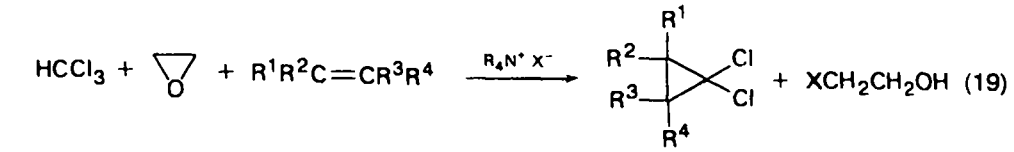
(18)

Some steroid acetates were converted to the dichloro- and difluorocyclopropanes[97].

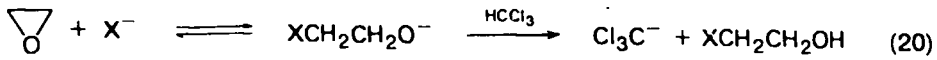
D. By Use of Ethylene Oxide

1. *Primary adducts*

The reaction mixture of chloroform, olefin, ethylene oxide and a quaternary ammonium salt at 130–170°C in a pressure vessel yields dichlorocyclopropanes[98,99] (equation 19).



The mechanism proceeds via attack of a soluble anion on ethylene oxide, forming an alkoxide anion which is capable of eliminating a proton from chloroform (equation 20).

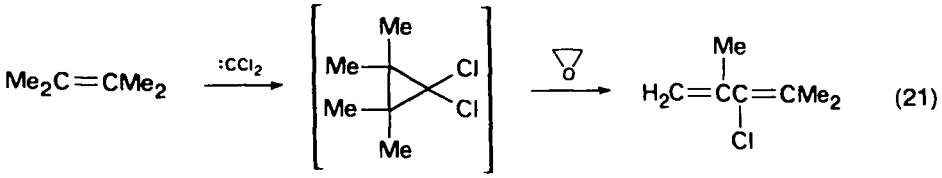


The concentration of the ammonium salt should be low, and therefore the reaction medium is neutral. All reagents are cheap, and the procedure is simple, even on an industrial scale. The main disadvantage is the relatively high temperature, which is responsible for subsequent reactions (see Section II.D.2).

Many olefins[99] and diolefins[42] were converted to the dichlorocyclopropanes. Normally the yields of diolefin bis-adducts were considerably higher than those obtained via other procedures. The ethylene oxide method has been successfully used for the preparation of chlorofluoro-[99,100] and difluorocyclopropanes[99] from the industrially available haloforms $HCCl_2F$ and $HCClF_2$.

2. *Subsequent reactions*

There are many cases in which the primary adducts are unstable under the reaction conditions of the ethylene oxide method. Thus, at 150°C tetramethylethylene gave only a chlorodiene by elimination of hydrogen chloride[101] (equation 21).



Depending on the reaction temperature, trimethylethylene yielded either the dichlorocyclopropane or the chlorodiene, or a mixture of both. The dibromo compounds are even more sensitive to this ring cleavage[101,102].

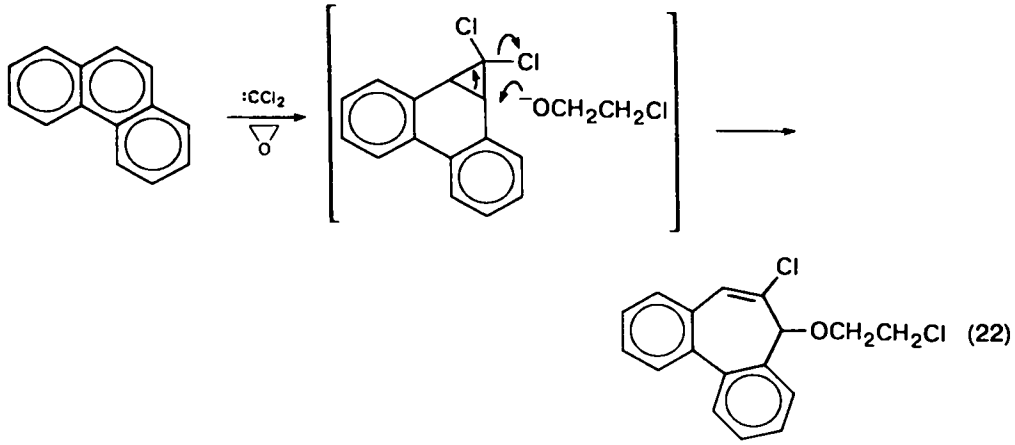
Highly substituted chlorofluoro- and difluorocyclopropanes react with ethylene oxide during their preparation to yield a complex mixture[103].

Whereas different types of secondary products were obtained from acetylenes[55], naphthalene, anthracene and phenanthrene gave ring enlargement compounds by nucleophilic attack on the primary adduct by chloroethoxide ion[104] (equation 22).

Alkylated aromatic hydrocarbons (e.g. 2,3-dimethylnaphthalene) react with low to moderate yields to give spirononatrienes[105,106]. Evidence for the mechanism (equation 23) is given by certain experiments[106].

Alkoxydichlorocyclopropanes (stable products synthesized from vinyl ethers and $:CCl_2$ according to Sections II.B and C) are normally unstable in the presence of ethylene oxide at elevated temperatures. Ring cleavage by alkoxide leads to acetals[107,108] (equation 24).

This reaction is useful for the preparation of α-fluoro-α,β-unsaturated aldehydes (from $HCCl_2F$)[109] (see also Section IV.D.5).



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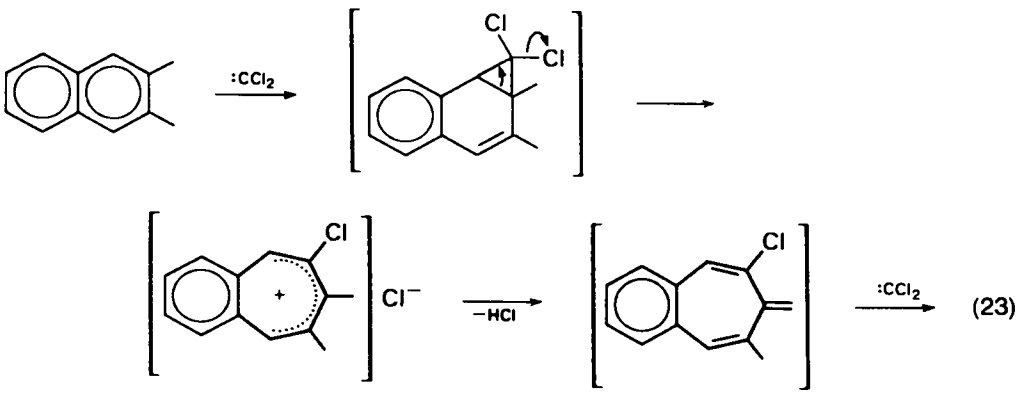
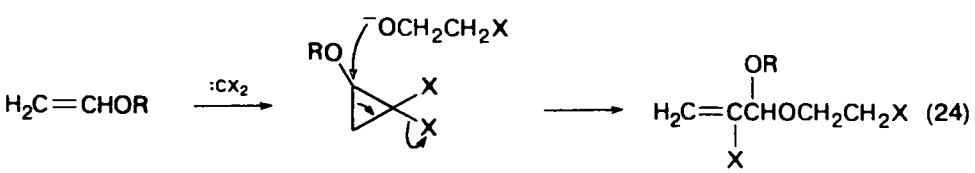


(23)



(24)

E. By Phase Transfer Catalysis

1. Dichlorocyclopropanes

In phase transfer catalysis (PTC) a substrate in an organic phase reacts chemically with a reagent present in another phase which is usually aqueous or solid. Reaction is achieved by means of a transfer agent; this agent or catalyst is capable of solubilizing or extracting inorganic and organic ions, in the form of ion pairs, into the organic

media[110]. This method has been very important for the synthesis of many types of organic compounds during the last 10 years, not only for preparation of dihalocyclopropanes. Therefore, some surveys[111–113], and books[13,114,115] have been published. The Dehmlows' excellent monograph[13] contains about 1400 references and is most useful for the practising organic chemist.

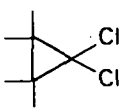
Contrary to Doering's result[4] that only 0.5% of dichloronorcarane was formed when cyclohexene is reacted with chloroform and aqueous potassium hydroxide, Makosza obtained dichlorocyclopropanes in good yields when carrying out the reaction of olefins with chloroform and strong aqueous bases *in the presence of a catalyst*, usually benzyltriethylammonium chloride[116]. The multistep process is shown below (equation 25) and involves deprotonation at the interphase, thus forming the trichloromethyl anion, an equilibrium reaction with a quaternary ammonium salt to form an unstable tetraalkylammonium trichloromethylide which is transferred to the organic phase, decomposition to dichlorocarbene and tetraalkylammonium chloride, and irreversible addition of dichlorocarbene to an olefin.

$$HCCl_3 + HO^- Na^+ \rightleftharpoons CCl_3^- Na^+ + H_2O$$

$$CCl_3^- + [X^- NR_4^+] \rightleftharpoons [CCl_3^- NR_4^+] + X^-$$

$$[CCl_3^- NR_4^+] \rightleftharpoons [Cl^- NR_4^+] + :CCl_2 \qquad (25)$$

$$:CCl_2 + \rangle C{=}C \langle \longrightarrow$$



The PTC method ('Makosza's method') is now by far the most convenient procedure for preparation of dichlorocyclopropanes. All reagents are cheap, the reaction and work-up are very simple, the yields are commonly superior to those obtained with other methods, and subsequent reactions are minimized. Only with very base-sensitive substrates are the essentially neutral reactions (Sections II.C and F) preferred. Best results were obtained with excess chloroform used as both solvent and reagent, concentrated sodium hydroxide, 1 mol% of catalyst relative to olefin, and a temperature ranging from about 0°C to reflux[113]. For reaction of 1 equiv. of dichlorocarbene to give the monoaddition product with a polyolefin, molar amounts of chloroform are used with methylene chloride as a solvent. The influence of a catalyst[117–120], optimization experiments[121] and side reactions[122,123] have all been investigated in detail.

Solid sodium[124] and potassium hydroxide[125], or potassium carbonate[126], have also been used successfully under PTC conditions. An improved PTC version of the trichloroacetate method allows the use of base-sensitive substrates or the generation of thermolabile products[127,128].

The total number of simple alkyl- and/or aryl-substituted dichlorocyclopropanes prepared by Makosza's method[34,52,116,117,119,127–137] is very high. Sterically hindered alkenes can also be converted, but normally with lower yield[33,34,138,139]. Severe steric hindrance might be a limitation for dichlorocyclopropane formation, even under drastic conditions[33,34,52]. For example, tetraphenyl (**5**)[33], tetrabenzyl (**6**)[34] and triphenylmethylethylene (**7**)[34] did not react at all (equation 26).

In a few cases rearrangement may occur under the reaction conditions, preferably with polycyclic bridged[140–146] or extremely highly substituted alkenes[34] (equation 27).

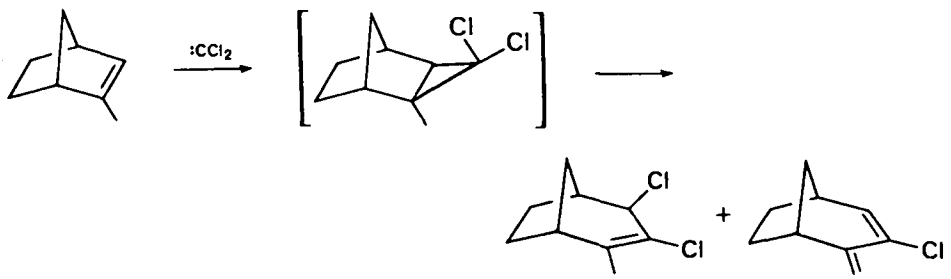
Multiple additions of dichlorocarbene to systems with more than one double bond can readily be achieved, although the yields of the higher adducts[43,52,118,139,147–161] are

$$R^1_2C{=}CR^1R^2 \xrightarrow[PTC]{:CCl_2} \not\rightarrow \quad (26)$$

(5) $R^1 = R^2 = Ph$

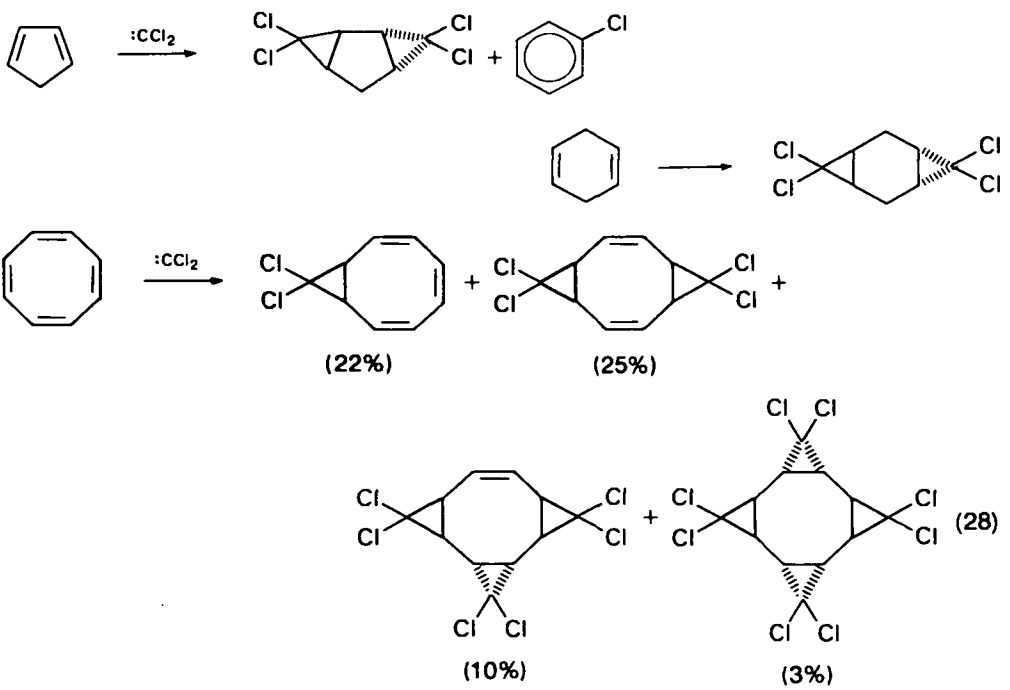
(6) $R^1 = R^2 = PhCH_2$

(7) $R^1 = Ph;\ R^2 = Me$



(27)

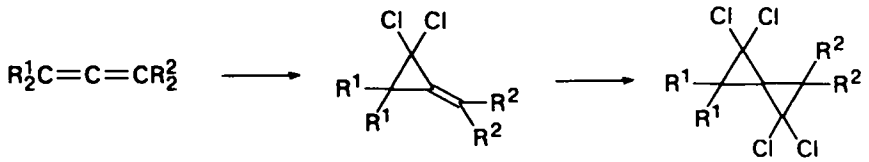
generally lower in value, because the system is deactivated towards further attack by the electron-withdrawing effect of the chlorine atoms. However, in contrast to all other methods, the second addition of dichlorocarbene to a monoadduct is so fast that even the cyclopentadiene bis-adduct is isolable in high yield[43,147]. Some further examples[43,52,156,157] are shown in equations (28).



(28)

For steric reasons many cyclic dienes give only one bis-adduct. Acyclic dienes normally react to give two isomers: the *meso* and D,L forms. Configuration determination is possible from dipole moment measurements[43,162] or by high resolution ^{1}H-NMR spectra[43].

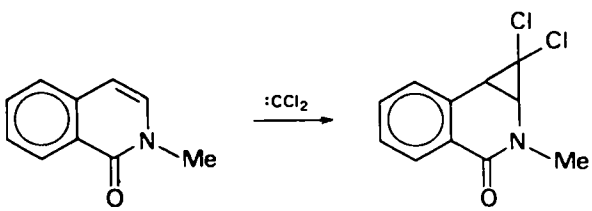
Spiro-linked dichlorocyclopropanes are normally formed from allenes and cumulenes[52,163–168] (equation 29), although sometimes rearrangements can occur[163,164].



(29)

The superiority of the PTC method has also been shown by reaction of acetylenes to form cyclopropenones[56,169] (see also equation 7), and by conversion of aromatic hydrocarbons. Whereas indene[170,171] (see also equation 8), phenanthrene[172,173] and pyrene[147] yield normal primary adducts, only rearrangement products could be isolated from naphthalene[173], alkoxynaphthalenes[174–176], and biphenylene derivatives[177]. Spirononatrienes from alkylated aromatics (see equation 23) have been obtained in relatively high yields[105,106]. Surprisingly, polymethylnaphthalenes lead to the isolation of unchanged bis-adducts and heptafulvenes[178].

Dichlorocyclopropanes from heterocyclic compounds are described as stable only in a very few cases[179–181] (equation 30).

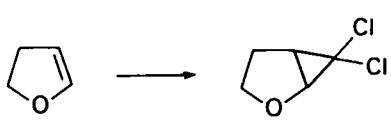


(30)

(82%)

Subsequent reactions normally take place under the prevailing reaction conditions[106,182,183].

Dihydroheterocyclics give the bicyclic dichlorocyclopropanes in good yields[182,184–187] (equation 31).

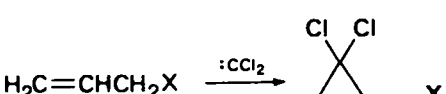


(31)

(72%)

Similarly, acyclic enol ethers and esters[188–192], and enamines[193–196], react with dichlorocarbene. Some adducts rearrange easily under the reaction conditions.

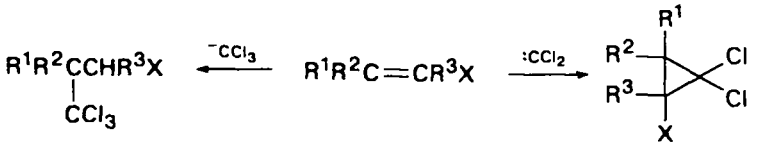
The presence of functional groups such as those in allyl derivatives does not influence the formation of dichlorocyclopropanes[197–205] (equation 32).



(32)

X = Br, Cl, OH, OR, OCOR

Because the PTC system provides both CCl_3^- and $:CCl_2$, reaction with electron-deficient double bonds leads to two different types of product[206-211] (equation 33).

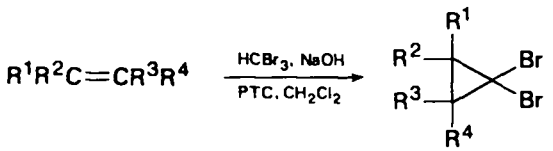


$$X = CN,\ COR,\ CO_2R \tag{33}$$

The ratio of the two products is dependent on the nature of X, the degree of substitution, and the reaction conditions. Sometimes subsequent reactions may occur[206,208].

2. Other dihalocyclopropanes

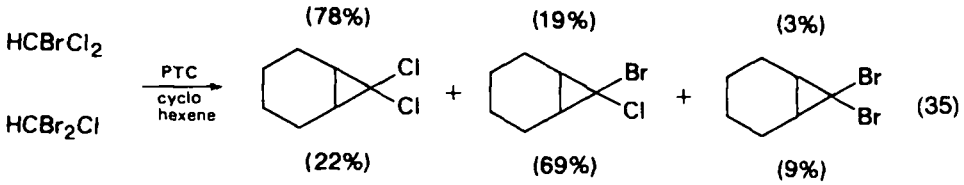
a. Dibromocyclopropanes. Preparation of dibromocyclopropanes by the PTC method is very similar to that of dichlorocyclopropanes (equation 34).



(34)

The best reaction conditions are as follows: twofold excess of bromoform to alkene, methylene chloride as solvent, long reaction time, room temperature, and vigorous stirring. Using this procedure, a large number of olefins have been converted to the relevant dibromocyclopropanes[52,212-217]. Many bis-adducts to diolefins are reported[52,158,212,214,218-222], and with functionalized olefins the corresponding dibromocyclopropanes can be similarly prepared[186,190,197,202,217,223-234]. Due to the increased reactivity of bromo compounds in comparison to the chloro derivatives, fast subsequent and side reactions[122,141,182,226,235,236] and/or decreased yields are sometimes to be expected.

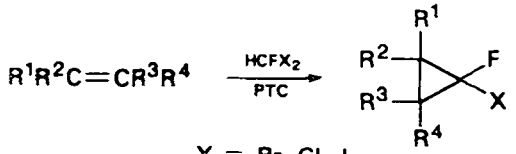
b. Bromochlorocyclopropanes. Halogen exchange processes of the haloform reagents under PTC conditions lead generally to mixed dihalocyclopropanes from mixed haloforms[237] (equation 35).



(35)

The extent of exchange and the yields are dependent on the olefinic substrate and the catalyst used[123]. Dibenzo-18-crown-6 has been found to give the highest yield of bromochlorocyclopropanes together with the best selectivity[238].

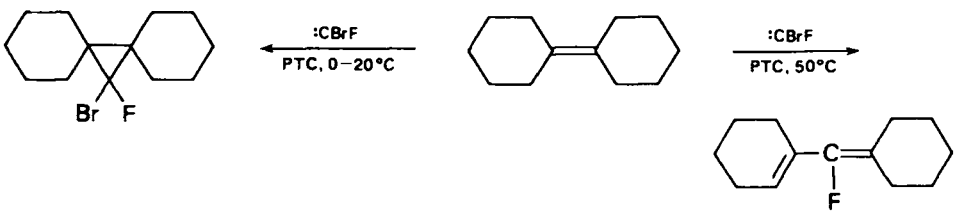
c. Difluoro-, chlorofluoro-, bromofluoro- and iodofluorocyclopropanes. Whereas difluorocyclopropanes have been obtained by PTC only with extremely low yields[239], chlorofluoro-, bromofluoro- and iodofluorocyclopropanes are readily formed (equation 36). Fluorine exchange has never been observed.



X = Br, Cl, I (36)

In particular, synthesis of chlorofluorocyclopropanes with commercially available dichlorofluoromethane is easy[239–246]. The reaction proceeds at 0°C using either a condenser cooled to −30°C or a pressure vessel.

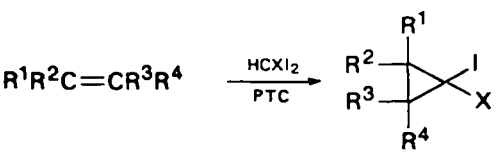
Similarly, reaction of dibromofluoromethane[247] with olefins in methylene chloride gives the interesting bromofluorocyclopropanes[239,248–250]. Under the same reaction conditions, highly substituted olefins yield either bromofluorocyclopropanes or fluorodienes exclusively[34] (equation 37), the product depending solely on the reaction temperature.



(37)

The generation of fluoroiodocyclopropanes from fluoroiodomethane under PTC conditions was surprising because Makosza claimed a catalyst poisoning effect by iodide ion[251]. However, various fluoroiodocyclopropanes have been reported[252,253]. They are stable compounds, in some cases separable into the isomers[253].

d. Chloroiodo-, bromoiodo- and diiodocyclopropanes. Using methylene chloride as a solvent chloroiodo- and diiodocyclopropanes have also been prepared from chlorodiiodomethane[254] or iodoform with moderate yields[253,255] (equation 38).

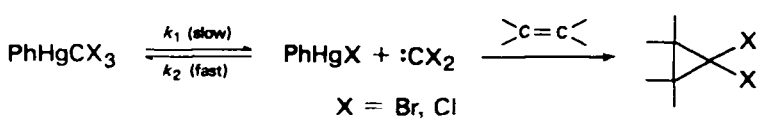


X = Cl, I (38)

The alkyldiiodocyclopropanes made by the PTC method are rather unstable, probably due to very sensitive by-products[253] (see also Baird[71]). Aryl compounds are more stable[255]. The synthesis of bromoiodocyclopropanes has also been considered[256] (equation 38, X = Br), but never tried. These compounds have been prepared from dibromocyclopropanes[256] (see Section IV.A.2).

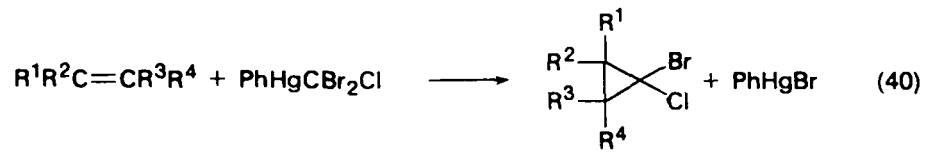
F. By Phenyl(trihalomethyl)mercury

Phenyl(trihalomethyl)mercury compounds react with olefins to give dihalocyclopropanes in high yield (equation 39).



X = Br, Cl (39)

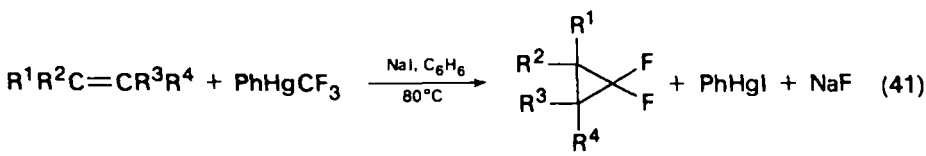
Based on observations of some prior authors that phenyl(trichloromethyl)mercury decomposes when heated at 150°C to give phenyl mercuric chloride, Seyferth and coworkers found this reaction to be an excellent source for dichloro- and dibromocarbenes, yielding the respective dihalocyclopropanes when carried out in the presence of olefins[257–260]. This procedure does not involve trihalomethide ion as an intermediate, nor does it require basic reaction conditions. Seyferth's route allows the preparation of dihalocyclopropanes from olefins which contain base-sensitive functional groups (allyl isocyanate, dimethylvinylchlorosilane)[260], which react with trihalomethide ion (acrylates, crotonates)[260], or which are only poor nucleophiles (ethylene, stilbene)[260]. The reaction is carried out in benzene solution at reflux temperature. Under these reaction conditions phenyl(trichloromethyl)mercury needs 36–48 h for a maximum yield, but phenyl(tribromomethyl)mercury needs only 2 h[260]. Elimination of phenyl mercuric bromide is highly favoured over elimination of phenyl mercuric chloride. Therefore, dichlorocyclopropanes are prepared more conveniently either from phenyl(bromodichloromethyl)mercury[259,260], or from phenyl(trichloromethyl)mercury, in the presence of sodium iodide[16], involving a halogen exchange with elimination of phenyl mercuric iodide[261]. A clean elimination of phenyl mercuric bromide allows preparation of bromochlorocyclopropanes from phenyl(dibromochloromethyl)mercury in high yields and with excellent purity[262,263] (equation 40).



(40)

Main disadvantages of the mercurial route are the high toxicity of mercury compounds and the cost of the reagents. The delicate synthesis of the mercury organic reagents has been simplified by PTC[264].

Undoubtedly the most important application of Seyferth's method is in the preparation of difluorocyclopropanes[265]. Phenyl(trifluoromethyl)mercury[266,267] has been used in the presence of sodium iodide to facilitate the transfer of difluorocarbene to olefins (equation 41)[268,269], forming difluorocyclopropanes in excellent yields.



(41)

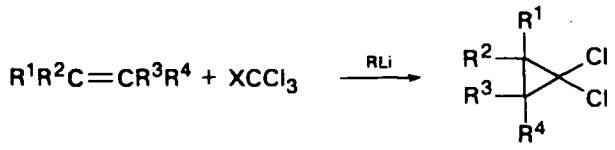
Chlorofluoro-[270,271] and bromofluorocyclopropanes[272,273] have been similarly prepared by the mercurial route.

G. By Other Methods

All the methods for the synthesis of dihalocyclopropanes discussed above (Sections II.B–F) have important synthetic value (especially the PTC method – see Section II.E), or at least they have been used for a long period. The following methods possess only limited value, or they are mere curiosities.

1. Via organometallic compounds

Some polyhalogenated methanes when treated with methyl- or butyluthium in the presence of excess olefin give dihalocyclopropanes[274]. Bromo- and iodotrichloromethanes are better suited than carbon tetrachloride (equation 42).



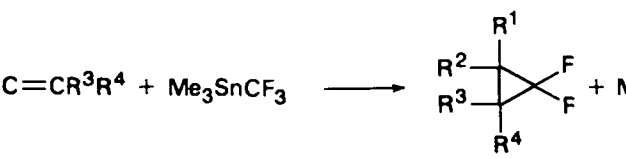
$$R^1R^2C{=}CR^3R^4 + XCCl_3 \xrightarrow{RLi} \text{(cyclopropane)} \qquad (42)$$

X = Br, Cl, I; R = Me, Bu

Other bases were also used[275,276]. The most important application of the alkyllithium route is its use for the synthesis of monochlorocyclopropanes[23,277].

Isolated lithium trihalomethides as precursors for dihalocyclopropanes have particularly been used for mechanistic studies[278–281]. Treatment of carbon tetrachloride with titanium chloride (where the titanium exhibits a low valency state) resulted in the formation of dichlorocyclopropanes in good yield[282].

Difluorocyclopropanes have been prepared by thermolysis of trimethyl(trifluoromethyl)tin at 150°C in the presence of olefins[265,283–287] (equation 43).



$$R^1R^2C{=}CR^3R^4 + Me_3SnCF_3 \longrightarrow \text{(difluorocyclopropane)} + Me_3SnF \qquad (43)$$

Under the same conditions, acetylenes give difluorocyclopropenes[284–286,288].

2. Miscellaneous

Thermolysis of trichloromethylsilicon trichloride at 250°C[289], reaction of anhydrous sodium hydroxide with chloroform in tetraglyme[290], PTC with epoxides instead of olefins[291], decarboxylation of free trichloroacetic acid in dimethyl formamide (DMF)[292], retro carbene transfer under irradiation from dichlorocyclopropanes to olefins[293], and Diels–Alder synthesis with tetrachlorocyclopropene[294] are some examples of procedures for the synthesis of dichlorocyclopropanes under special conditions. Photolysis and pyrolysis of difluorodiazirine in the presence of olefins will both lead to difluorocyclopropanes[295].

III. NMR SPECTRA OF DIHALOCYCLOPROPANES

A. ^{1}H-NMR Spectra

As has been well known for a long time, the shielding of hydrogen nuclei in three-membered rings is anomalous. A methylene group in cyclopropane (δ = 0.22 p.p.m.) is shielded to a much greater extent than is the methylene group in propane (δ = 1.33)[298–300]. Substitution with two halogen atoms affords a downfield shift of 1.0–1.5 p.p.m. as indicated by 1,1-dichlorocyclopropane (δ = 1.49)[99]. The order of

TABLE 1. Selected dihalocyclopropanes prepared from olefins

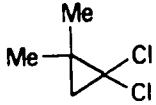
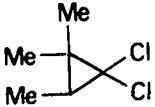
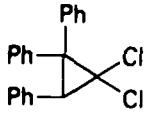
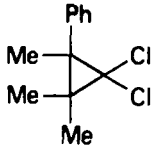
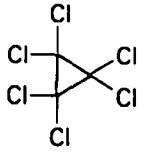
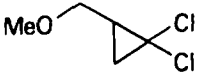
Product	Method[a]	Yield, %	Reference
1. *Dichlorocyclopropanes*			
	D.1 F.2	8 65	99 260
	D.1	26	99
	B.1 B.2	65 76	4 75
	B.1 E.1 E.2	66 60 97	4 116 121
	B.1 E.2	16 76	4 121
	E.2	33	121
	B.1 E.1 F.2	74 80 80	296 116 263
	B.1 E.1 F.2	0 96 90	52 52 260
	E.1	80	52
	E.2	91	34
	F.1 F.2	74 83	260 260
	E.2 F.2	80 76	204 260
	E.2	83	203
	E.1 F.2	0[b] 85	206 263
	E.1	71	116
	F.2	86	263

TABLE 1. (*continued*)

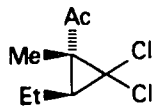
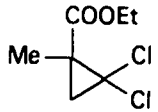
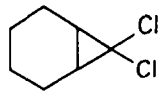
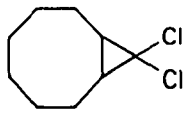
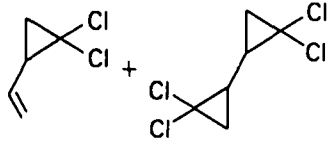
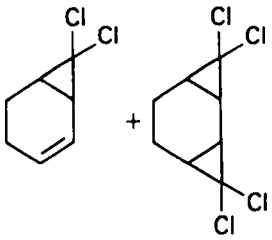
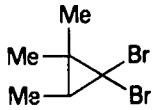
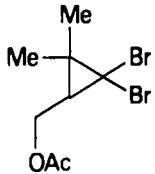
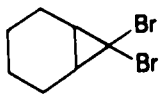
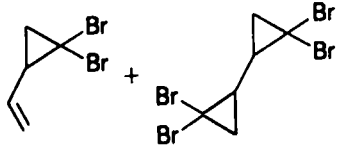
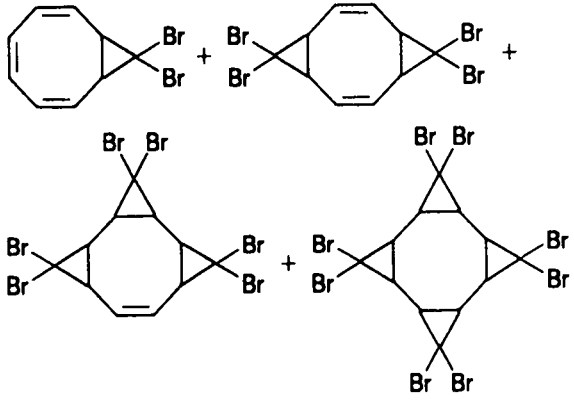
Product	Method[a]	Yield, %	Reference
	E.1	50	202
	E.1	85	206
	E.1	82	136
	B.1	59	4
	C.1	65	38, 96
	D.1	78	99
	E.1	72	116
	E.2	97	121
	E.2	98	130
	F.4	91	16
	G.1	91	274
	D.1	73	99
	F.4	98	16
 *meso*, D,L mixture[c]	B.1	51 + trace	39, 40
	D.1	44 + 16	42
	E.1	Trace[d] + 66	43
	F.2	58 + 10	260

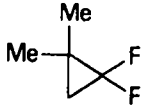
TABLE 1. (*continued*)

Product	Method[a]	Yield, %	Reference
	B.1	33 + 0	297
	E.2	Trace + 97[e]	43
2. *Dibromocyclopropanes*			
	B.3	66	21, 22
	E.3	73	212
	E.3	81	213
	B.3	14	21
	E.3	61	214
	E.3	89	213
	B.3	75	4, 21
	E.3	72	212
	E.3	92	215
	F.5	88	257
	B.3	40 + 9	41

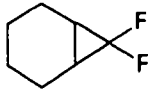


E.3	38 + 25 + 1 + 0.3	158

3. *Difluorocyclopropanes*

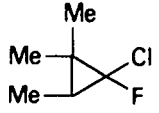


D.2	13	99
G.2	71	295

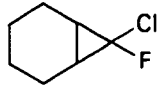


C.2	11	15
D.2	29	99
F.6	83	269
F.7	89	287

4. *Chlorofluorocyclopropanes*

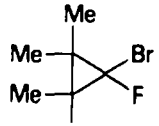
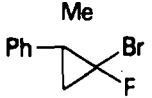
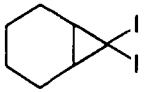


E.4	43	240



B.4	24	14
D.3	45	99
E.4	58	239
F.8	84	271

TABLE 1. (*continued*)

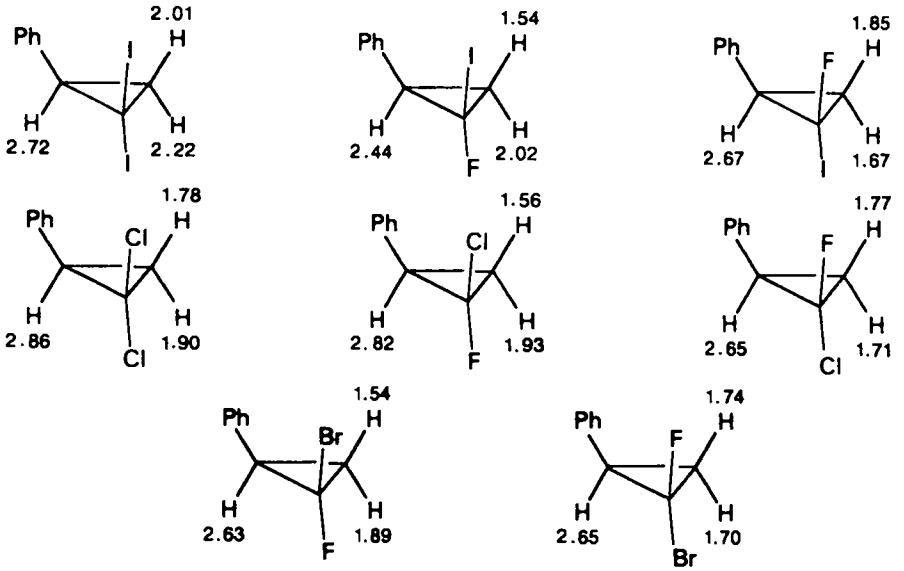
Product	Method[a]	Yield, %	Reference
5. *Bromofluorocyclopropanes*			
	E.5	70	248
	E.5	84	249
6. *Fluoroiodocyclopropanes*			
	E.6	60	252
7. *Diiodocyclopropanes*			
	E.7	20	255
	B.5 E.7	34 –[f]	71 254

[a]The methods are indicated in agreement with the subheadings in Section II as follows:

B.1: $HCCl_3$, *t*-BuOK
B.2: Cl_3CO_2Et, NaOMe
B.3: $HCBr_3$, *t*-BuOK
B.4: $HCCl_2F$, *t*-BuOK
B.5: HCI_3, *t*-BuOK
C.1: Refluxing of Cl_3CCO_2Na in DMF
C.2: As C.1, with ClF_2CCO_2Na
D.1: $HCCl_3$, ethylene oxide, quaternary ammonium salt, about 170 °C
D.2: As D.1, with $HCClF_2$
D.3: As D.1, with $HCCl_2F$
E.1: $HCCl_3$, PTC, non-optimized conditions
E.2: $HCCl_3$, PTC, optimized conditions
E.3: $HCBr_3$, PTC
E.4: $HCCl_2F$, PTC
E.5: $HCBr_2F$, PTC, in CH_2Cl_2
E.6: As E.5, with $HCFI_2$
E.7: As E.5, with HCI_3
F.1: $PhHgCCl_3$
F.2: $PhHgCBrCl_2$
F.3: $PhHgCl_2I$
F.4: $PhHgCCl_3$, NaI
F.5: $PhHgCBr_3$
F.6: $PhHgCF_3$, NaI
F.7: Me_3SnCF_3, NaI
F.8: $PhHgCCl_2F$
G.1: $CBrCl_3$, BuLi
G.2: Irradiation of difluorodiazirine

[b]4,4,4-Trichlorobutyronitrile (72%) as isolated product.
[c]See also Kuhn and coworkers[43].
[d]Relationship between mono- and bis-adduct is strongly dependent on molar ratio of $HCCl_3$ to diene. With a large excess of $HCCl_3$ almost no monoadduct remains; with molar amounts or a slight excess in CH_2Cl_2 a maximum yield of monoadduct can be obtained.
[e]Large excess of $HCCl_3$, only *anti* isomer.
[f]Not determined.

the downfield shift is I > Br ≈ Cl > F. A comparison of some dihalocarbene adducts to styrene may illustrate this[249,253]:

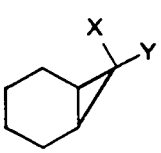


Furthermore, it is well known that the *cis* H–H coupling constants (7–12 Hz) are larger than the *trans* coupling constants (4–9 Hz); the geminal coupling constants are about 4–8 Hz[298–300]. Fluorine-containing dihalocyclopropanes exhibit more complex ^{1}H-NMR spectra by the additional H–F coupling. The *cis* H–F coupling constants (11–20 Hz) are larger than the *trans* coupling constants (4–12 Hz)[301–303]. Their values depend on the electronegativities of the groups vicinal to the fluorine atom[249,253].

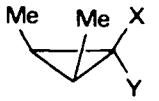
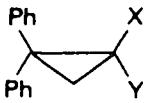
High resolution ^{1}H-NMR investigation allows both conformation assignment of substituted dihalocyclopropanes[304] and configuration determination (*meso*- and D,L) of tetrahalobicyclopropyls[43].

B. ^{13}C-NMR Spectra

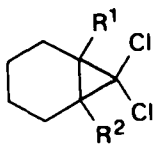
1,1-Dichlorocyclopropane absorbs at 56.1 and 21.5 p.p.m.[305], thus exhibiting shifts for the α- and β-carbons, respectively, of 59.0 and 24.4 p.p.m. from cyclopropane. These shifts are essentially twice those found for a single chlorine[306]. The order of downfield shift is F > Cl > Br > H > I[307]. Some examples are given below:



X	Y	δ[CXY], p.p.m.	Reference
H	H	10.3	308
I	Br	11.3	256
Br	Br	40.5	308, 309
Cl	Br	51.8	309
Br	Cl	58.2	309
Cl	Cl	67.5	308, 309
F	Br	85.2	309
Br	F	97.1	309
F	Cl	95.7	309
Cl	F	101.7	309

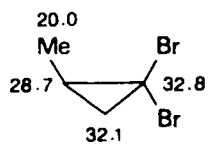
	X	Y	δ[CXY], p.p.m.	Reference
	Br	Br	40.1	310
	Cl	Br	51.5	310
	Br	Cl	57.6	310
	Cl	Cl	67.1	310
	Cl	I	13.4	311
	Cl	Cl	64.6	311
	F	I	59.9	311

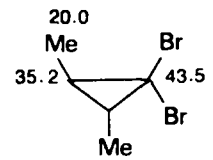
Generally, the expected downfield shift has been found with increasing degree of substitution of the dihalocyclopropanes[34,308,310,312].

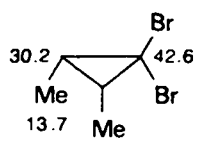


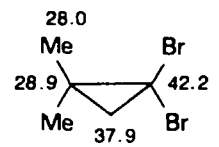
R^1	R^2	δ[CCl_2], p.p.m.	Reference
H	H	67.4	34
Me	H	73.1	34
Me	Me	78.1	34

Within groups of compounds having the same degree of substitution, the pattern shows only small differences[312]:









The ^{13}C–^{19}F coupling constants have been measured for a few cyclopropane systems[34,306]. In tetrachloro-1,1-difluorocyclopropane, J_{CF} is 313 Hz, while J_{CF} = 304–309 Hz in some bromofluorocyclopropanes[34].

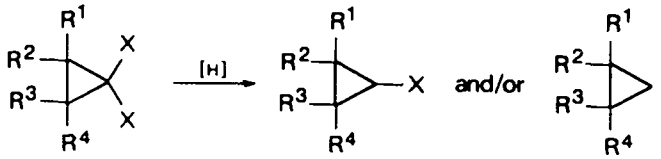
IV. REACTIONS OF DIHALOCYCLOPROPANES

A. Substitution Reactions

Reactions of dihalocyclopropanes are possible either with conservation of the cyclopropane ring or with ring cleavage. Substitution of the halogen atoms by hydrogen or alkyl groups, unaccompanied by ring rupture, proceeds normally via radical intermediates, four-centre transition states, or halogen–metal exchange. So called substitutions by nucleophiles are discussed in connection with eliminations.

1. Reductive dehalogenation

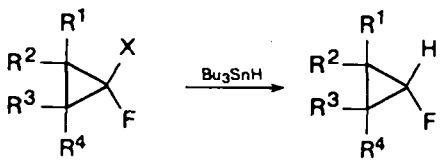
Hydrogenolysis of dihalocyclopropanes leads to monohalocyclopropanes or cyclopropanes, according to the reagents and conditions[313] (equation 44).



(44)

Complete substitution of halogen by hydrogen can be effected by sodium in alcohol[4,314] or in liquid ammonia[315], by lithium/*t*-butanol in dimethoxyethane (DME), tetrahydrofuran (THF), or ether[106,316–319], by some complex hydrides[320–322], or by catalytic hydrogenation over Raney nickel in methanolic potassium hydroxide[323]. The reaction sequence, addition of dihalocarbene and removal of the halogen atoms leading to the respective cyclopropanes are especially interesting in cases where direct Simmons–Smith reaction failed[324].

More important are methods for selective reduction of dihalo- to monohalocyclopropanes. Most popular as reagent is tri-*n*-butyltin hydride introduced by Seyferth[325]. Diiodo-[70,253], and dibromocyclopropanes can be reduced in good yield at temperatures below 40°C[230,325–330]; dichlorocyclopropanes require temperatures of *ca.* 140°C[325,331]. This radical reaction[332] gives a mixture of isomers in most of the cases where there is a possibility of forming *cis* and *trans* isomers[325]. The *cis/trans* ratio which has been determined[70] is dependent on steric factors, but not in a simple manner[325]. Tributyltin deuteride is useful for deuterium labelling among cyclopropanes[333]. When two molar equivalents of tributyltin hydride are used the dihalocyclopropanes are converted to the cyclopropanes[325,331]. The order of facility of dehalogenation is I > Br > Cl > F. Therefore, bromochlorocyclopropanes are reduced to chlorocyclopropanes[325]. More useful are the reductions of bromofluoro- and chlorofluorocyclopropanes to fluorocyclopropanes[334] with retention of configuration (equation 45).



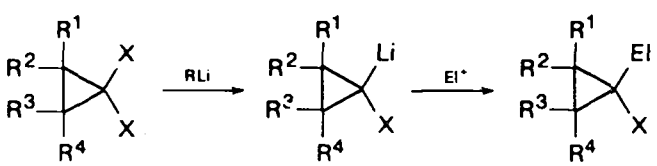
(45)

X = Br, Cl

Higher yields are available with sodium in liquid ammonia[335,336], or with lithium aluminium hydride[337]. Further selective monoreductions have been described with Grignard reagents[338–340], complex hydrides[341], zinc/acetic acid[342,343], zinc/alcoholic potassium hydroxide[344], zinc/copper couple[345], aluminium amalgam[346], butyllithium and subsequent treatment with methanol[347–349], and *O,O*-diethyl-α-lithiomethylphosphonate[350], as well as photochemically[351] and electrochemically[352].

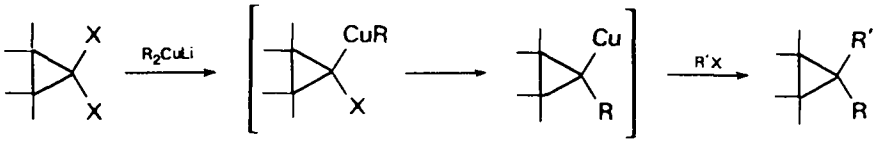
2. Substitution via 1-lithio-1-halocyclopropanes

Halogen–metal exchanges between dihalocyclopropanes and alkyl lithium at low temperatures occur easily to give lithium carbenoids which generally are nucleophilic enough to react with various electrophiles[353] (equation 46).



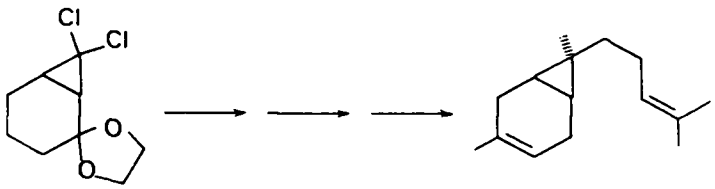
(46)

Alkylation with alkyl halides (El = alkyl, equation 46) leads to 1-alkyl-1-halocyclopropanes[354–356]. Dialkylation reactions with lithium dialkylcuprate proceed similarly via a copper(I)carbenoid intermediate[357,358] (equation 47).



(47)

Thus, in a one-pot procedure, dialkylcyclopropanes with various R and R′ groups can be synthesized[359]. This sequence is found to be stereochemically controllable and is successfully applied to sesquicarene synthesis[360] (equation 48).

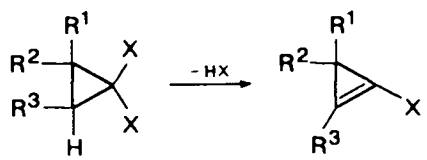


(48)

Other examples for the reaction of 1-lithio-1-halocyclopropanes with electrophiles have been shown by treatment with iodine to give bromoiodocyclopropanes[256] (see Section II.E.2d), with carbon dioxide to give ·carboxylic acids[353, 361–363], with *N*-methylformanilide to give aldehydes[363], with aldehydes to give secondary alcohols[364], and with dimethyl(methylene)ammonium iodide to give dimethylaminomethylcyclopropanes[365].

B. Elimination and Elimination/Addition

β-Elimination of hydrogen halide from α-halocyclopropanes bearing at least one cyclopropyl hydrogen atom should lead to halocyclopropenes (equation 49).



(49)

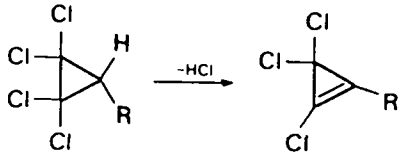
However, there are only a few examples of this reaction in which stable halocyclopropenes have been isolated. Usually subsequent or side reactions are involved.

1. Perhalocyclopropenes

The most stable halocyclopropene is tetrachlorocyclopropene (equation 49; R^1, R^2, R^3, X = Cl), readily prepared from pentachlorocyclopropane by treatment with concentrated potassium hydroxide at 90°C[366].

Tetrachlorocyclopropene is an interesting starting material, giving other perhalocyclopropenes by halogen exchange with boron, antimony and potassium halides[366–368] by a mechanism involving trihalocyclopropenylium salts[369]. Recently, some substitution[370] and cycloaddition reactions[371] have been published.

Similarly, substituted tetrachlorocyclopropanes react with solid potassium hydroxide in benzene to give functionalized perchlorocyclopropenes[372] (equation 50).



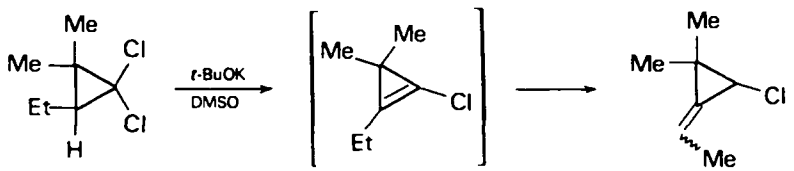
(50)

R = CO_2H, CO_2R, CHO, COR'

2. *Monochlorocyclopropenes and subsequent products*

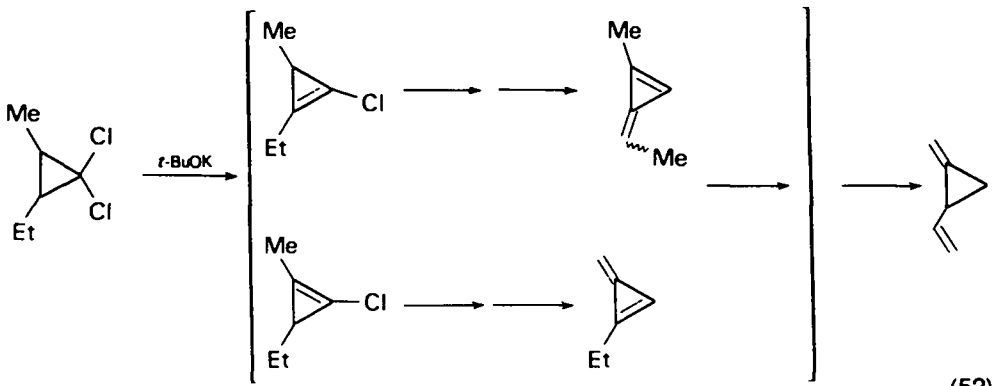
Alkali-induced elimination reactions of alkyl- or aryl-substituted dichlorocyclopropanes (equation 49, R^1, R^2, R^3 = H, alkyl, aryl; X = Cl) offer simple routes to chlorocyclopropenes which are stable only under certain conditions. Thus, a second elimination of hydrogen chloride, isomerization, and nucleophilic addition of the base used must be excluded. The *t*-butyl derivative[373] (equation 49, R^1, R^2 = Me; R^3 = *t*-Bu) and even better some phenyl chlorocyclopropenes[374,375] (equation 49; R^1, R^2 = various substituents; R^3 = phenyl) have been prepared and characterized. Monobromocyclopropenes, extremely reactive with water, have been obtained in solution from bulky substituted dibromocyclopropanes[376].

Isomerization of cyclopropenes to alkylidenecyclopropanes takes place in all cases where substituent R^3 (see equation 49) allows hydrogen migration. A simple example is given by the isolation of the ethylidenecyclopropane (equation 51) from a complex mixture[377].



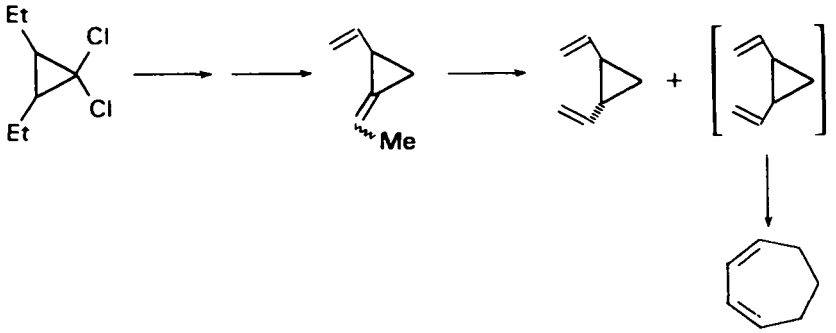
(51)

The reaction proceeds more efficiently when a second hydrogen chloride elimination is possible to give vinyl(alkylidene)cyclopropanes[377] (equation 52).



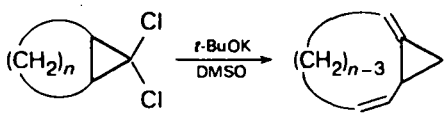
(52)

Dichlorodiethylcyclopropane allows isomerization of the initial product to divinylcyclopropanes. The *cis* isomer spontaneously undergoes Cope rearrangement and subsequent isomerization to give 1,4-cycloheptadiene[377,378] (equation 53). This sequence has been used for a synthesis of dictyopterene A and C'[379].



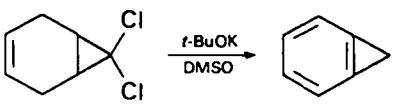
(53)

The bicyclo[n.1.0]alka-1,n-dienes (n = 5–10) have been synthesized from dichlorobicyclo[n.1.0]alkanes[380] (equation 54). Their thermal stability depends on the ring size.



(54)

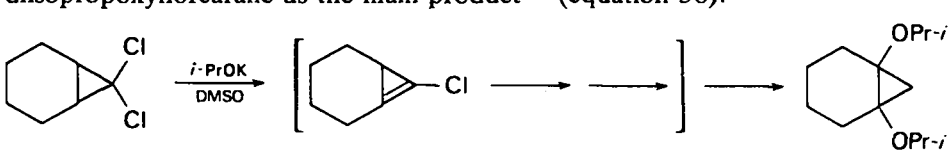
Consequently, dichloronorcarene reacts with t-BuOK in DMSO to yield benzocyclopropene[381] (equation 55).



(55)

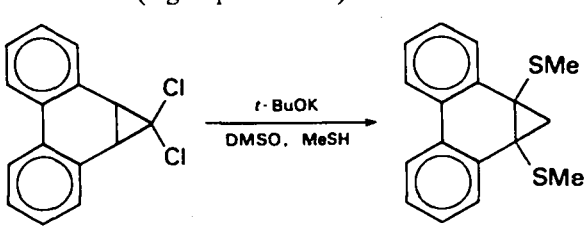
Benzocyclopropene exhibits remarkable thermal stability despite the high strain energy associated with this ring system. Synthesis and chemistry of benzocyclopropene is discussed in detail[382]. Cyclopropa[a]arenes synthesized from various dichlorocyclopropanes are highly reactive. Tar-like substances and solvent reaction products have been isolated, but despite this, reaction pathways could be elucidated[171,383–388].

If the elimination reaction occurs with a base which may also play the role of a nucleophile, an addition reaction takes place after the elimination. The first example was shown by the reaction of dichloronorcarane with potassium isopropoxide to give diisopropoxynorcarane as the main product[389] (equation 56).



(56)

A similar reaction with potassium t-butoxide in DMSO gave a mixture of toluene, o-xylene and some other aromatic hydrocarbons[390,391]. In the presence of nucleophiles such as thiols, an addition reaction to the cyclopropene intermediate leads to substituted cyclopropanes[389,392,393] (e.g. equation 57).



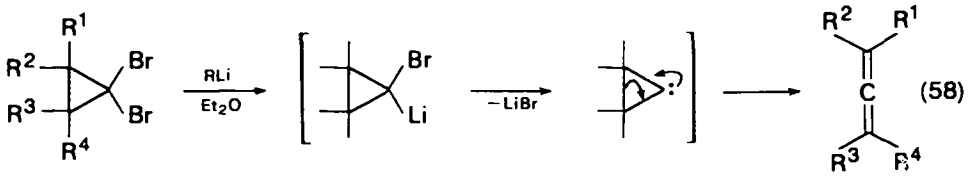
(57)

The mechanism of these elimination–addition reactions in DMSO[394] and some non-polar media[395] has been elucidated.

C. Carbenoid Reactions

1. Allene synthesis

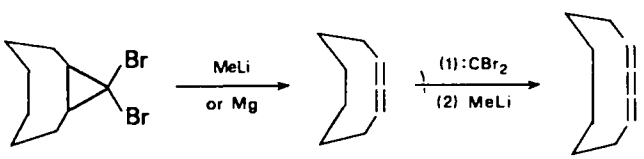
Dibromocyclopropanes can usually be converted into the corresponding allenes by treatment with a lithium alkyl in ether or hexane[396–399] solution. Yields are often high, and this represents one of the best general methods for the preparation of acyclic and cyclic allenes. The mechanism of this process involves initial lithiation followed by elimination of lithium bromide. The carbene thus obtained can then collapse as indicated to give the allene (equation 58). Products other than allenes are sometimes obtained (see below, Section IV.C.2), and their formation may also be rationalized in terms of intermediates shown in equation (58).



(58)

Various types of allenes have been prepared with different alkyl, cycloalkyl, and aryl substituents[168,396–401], including functional groups[402–404]. Similarly, cumulenes[405–407] can be obtained from adducts of dibromocarbene to allenes, and diallenes[399, 408–410] from bis-adducts to dienes. Contamination of the allenes thus obtained with acetylenes has been observed only under special conditions[400,411]. Generally, the allene synthesis is also possible from dichlorocyclopropanes with butyllithium. However, the yields are lower and some side products occur[399]. Other reagents, such as magnesium in ether[412,413], sodium on alumina[414], zinc salts[415], chromium(II) salts[416,417], and copper(I) salts[418], have been used in the reactions with dibromocyclopropanes to give allenes, but with minor success. Only the reaction with chromium(III) chloride/lithium aluminium hydride in anhydrous DMF gave allenes in high yield[419].

Cyclic allenes with the allene group situated in a ring larger than eight-membered appeared to be relatively stable. Thus, cyclonona-1,2-diene was obtained as the sole product in 93% yield from 9,9-dibromobicyclo[6.1.0]nonane with methyllithium[399,420]. A second analogous step allows conversion to cyclodeca-1,2,3-triene[421] (equation 59).



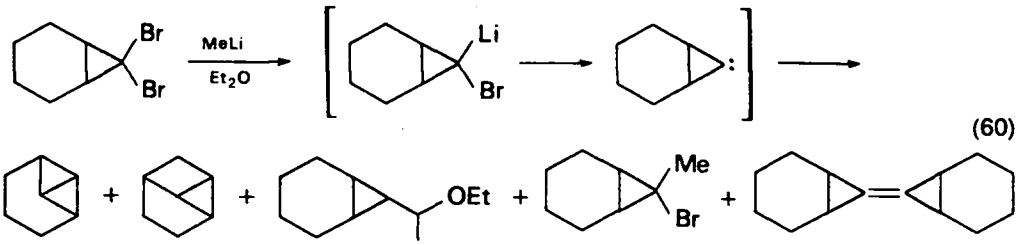
(59)

Preparation of larger cyclic allenes proceeds similarly[422].

2. Products other than allenes

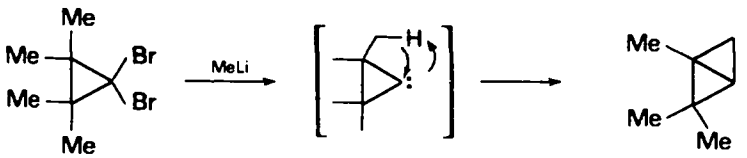
The normal reaction of the cyclopropylidene, ring opening to produce the allene (equation 58), can be suppressed if the allene is made sufficiently strained, and if pathways for carbene insertion or addition reactions are available. Thus, the reaction of dibromonorcarane with methyllithium generates a carbene which undergoes intra-

molecular insertion into C—H bonds, intermolecular insertion into the solvent ether, alkylation, or reaction with the lithiated species to give the dimer[423–425] (equation 60).



(60)

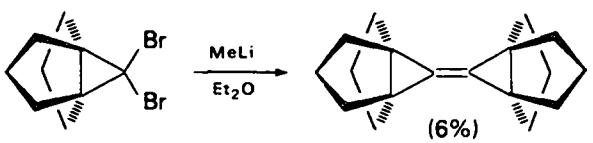
Skattebøl found[399] that dibromotetramethylcyclopropane gave no tetramethylallene on treatment with methyllithium, and it was jointly discovered[426,427] that 1,2,2-trimethylbicyclo[1.1.0]butane is formed (equation 61).



(61)

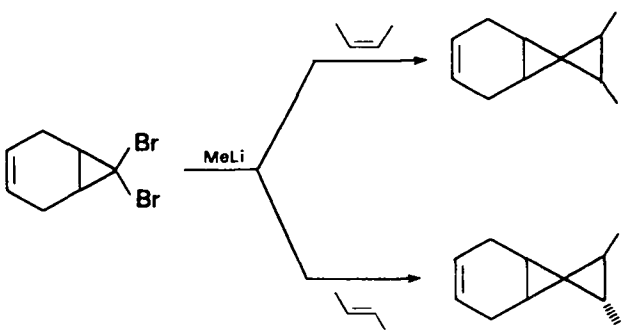
This finding was expanded to cover other tetrasubstituted dibromocyclopropanes[428–433]. Some trisubstituted[434] and bulky disubstituted[435,436] dibromocyclopropanes gave mixtures of allenes and bicyclobutanes. Competitive insertion reactions starting from bicyclic cyclopropylidenes lead to mixtures of tricyclic compounds[437–439]. Cyclopropylidenes also gave insertion products into O—H[440] and N—H[441] bonds, and into C—H bonds adjacent to oxygen[442] and nitrogen[441].

The dimerization reaction has recently been used for preparation of extremely highly substituted olefins[443–445] (equation 62).



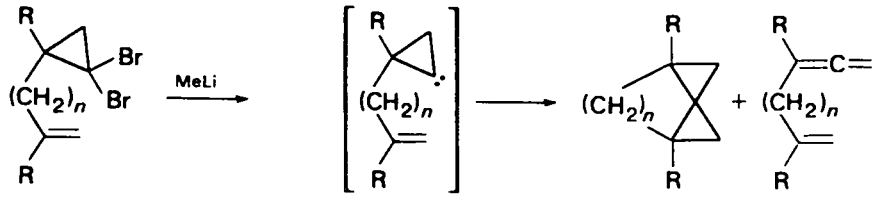
(62)

The carbene formed by reaction of dibromocyclopropanes with methyllithium can be trapped by intermolecular reaction with an olefin[446] (equation 63).



(63)

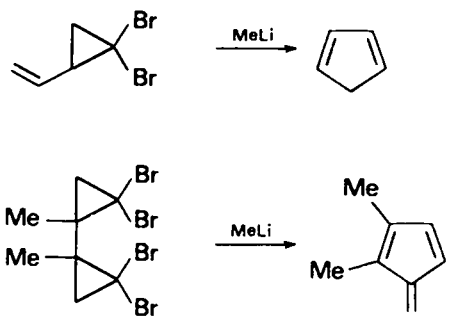
Monoadducts of dibromocarbene to dienes possess in addition a reaction pathway on treatment with methyllithium. The carbenoid intermediate is able to give an intramolecular addition to the double bond, forming a tricyclic compound[447] (equation 64).



(64)

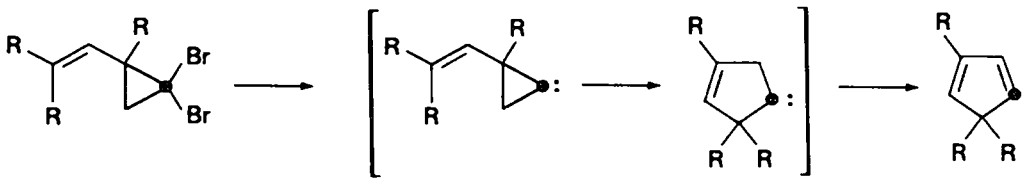
R = H, Me; n = 2, 3

This route opened a way for synthesis of some spiro compounds[448,449]. Dibromo(vinyl)cyclopropanes (see equation 64; n = 0), however, react with methyllithium to give cyclopentadienes as the main products together with small amounts of allenic compounds[450]. Bis-adducts to 1,3-dienes give fulvenes (equation 65) together with other products[450,451].



(65)

The mechanism has been carefully studied by labelling experiments[452] (equation 66).



(66)

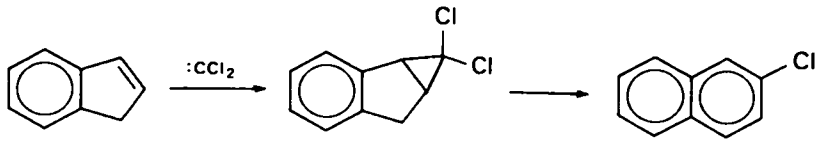
This vinylcyclopropylidene to cyclopentylidene rearrangement was investigated in detail both mechanistically[453] and synthetically for preparation of condensed cyclopentadienes[454,455] and pentalene derivatives[456–458]. Monoadducts of dibromocarbene to cyclic dienes and alkenyl cycloalkenes gave complex mixtures of the products described above[459,460].

D. Cyclopropyl–Allyl Ring Opening Reactions

1. Thermal rearrangement

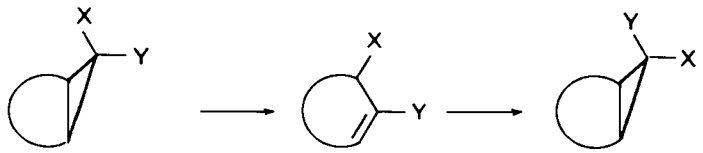
Soon after they became accessible[4], it was apparent that certain dihalocarbene adducts of cyclic olefins were thermally unstable[461]. Parham[14,59] found that the indene adduct rearranged readily to give 2-chloronaphthalene (equation 67).

On the other hand, many dihalocyclopropanes, both monocyclic and bicyclic, are very stable to heat. The ease of rearrangement depends on stereochemical and elec-



(67)

tronic factors, and also on ring size[462]. Many observations on bicyclic[85,92,462–468] and tricyclic[469–473] systems suggested that the *endo* disposition of the leaving group was a crucial factor in the facilitation of this rearrangement (equation 68).

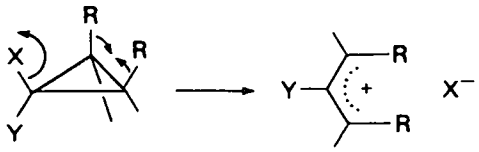


(68)

endo, thermally unstable — *exo*, thermally stable

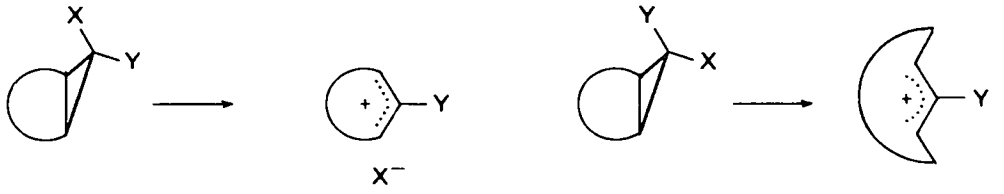
X = preferred leaving group

A theoretical treatment of this problem[474,475] has led to the conclusion that the concerted rearrangement of a cyclopropyl to an allyl carbonium ion should proceed by a stereospecific disrotatory process such that the groups *trans* to the leaving group (X^-) rotate outwards and those *cis* to it rotate inwards, as the C—X bond begins to break[476] (equation 69).



(69)

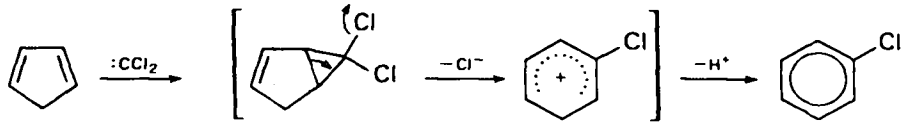
This prediction, also verified with monocyclic systems[477,478], has a stereochemical consequence for the rearrangement of bicyclic dihalocyclopropanes. *Endo* derivatives lead to *cis*- and *exo* derivatives to *trans*-substituted allyl carbonium ions (equation 70).



(70)

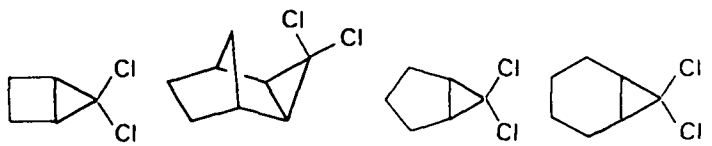
Therefore, on grounds of ring strain, only *exo* derivatives of a large ring system would be expected to undergo facile rearrangement[462]. Furthermore, the rate of rearrangement depends on the availability of the halide to give an anion, and on the stability of the allylic cation. There are many experiments which show that dichlorocyclopropanes require more drastic conditions than the corresponding dibromo derivatives[68,462,479–481]. Fluoride ion is a very poor leaving group in the present context[482–484]. The order of the leaving groups has the expected dependence, i.e. Br > Cl > F.

A number of electronic factors affect the stability of the intermediate allylic carbonium ion[88,479,481,483–485]. Most representative might be the addition of dichlorocarbene to cyclopentadiene to give chlorobenzene via an unstable monoadduct and comparatively stable cation[486] (equation 71).



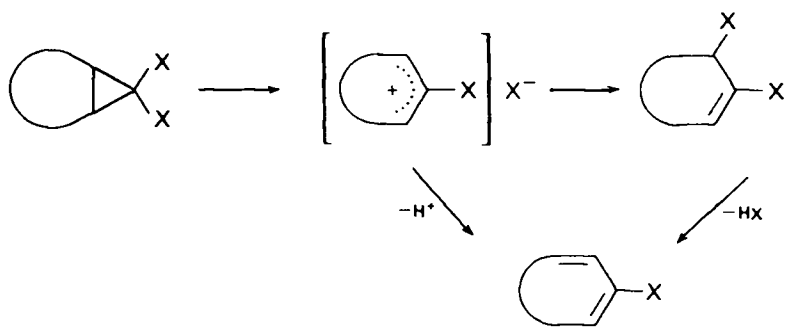
(71)

The ring-size effect makes the dichlorocarbene adduct to cyclobutene completely unstable, even at 0°C[487]. The next higher homologues are more stable, in the order indictated by equation (72)[92]. The stability of the dichlorocarbene adducts to norbornene lies between that of cyclobutene and cyclopentene[89–92].



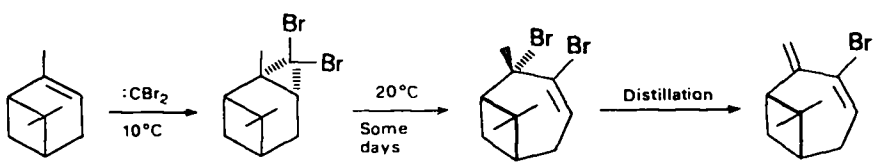
(72)

The allylic cation generally can be attacked by the halide anion to give a haloallyl halide, or a halodiene can be formed by loss of a proton (equation 73). Reactions in the presence of a nucleophile are discussed in Section IV.D.5.



(73)

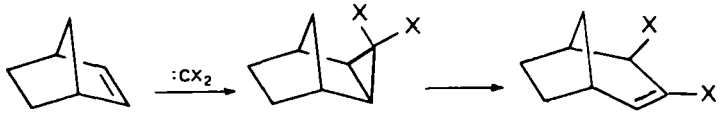
The reaction pathway normally depends on thermal conditions[68,85,479] and on the stability of end-products[14,59]. Heating in quinoline facilitates the ring opening reaction[479]. An example of the successive isolation of all three reaction products is given by addition of dibromocarbene to α-pinene[488] (equation 74).



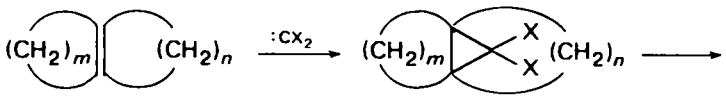
(74)

Norbornene undergoes addition of dihalocarbene exclusively on the *exo* side. Significantly, the adduct rearranges to *exo*-3,4-dihalobicyclo[3.2.1]oct-2-ene[469] (equation 75).

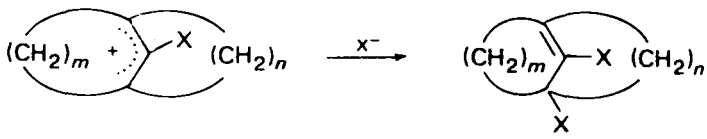
Addition of dihalocarbene to the internal double bond of a bicyclic system leads to a propellane which is opened to a bridgehead olefin (equation 76).



(75)



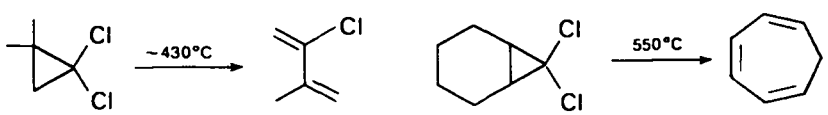
(76)



Three different possibilities result under these circumstances: (1) with $m, n \geq 3$, the propellanes are thermally stable unless heated in polar solvents[34,489–491]; (2) with $m = 4, n = 2$, the primary adduct shows only limited stability, forming a dimer of the bridgehead olefin[491,492]; (3) with $n \geq 6$ the rearranged bridged compounds are stable. This sequence has been utilized for the synthesis of meta-cyclophanes and related compounds[493–501].

The rearrangement of a hydroxy-substituted dichlorocyclopropane has been used for a tropinone synthesis[502].

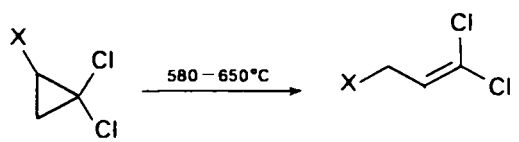
Pyrolysis reactions of dichlorocyclopropanes in a flow system at 400–500°C lead either to 2-halodienes[101] or to trienes[503,504], depending on the starting material and the reaction conditions (equation 77).



(77)

Decomposition of chloroform at 400–500°C in the presence of olefins leads to chlorodienes[505].

Dichlorocyclopropanes unable to eliminate hydrogen chloride isomerize under pyrolytic conditions[506] (equation 78).

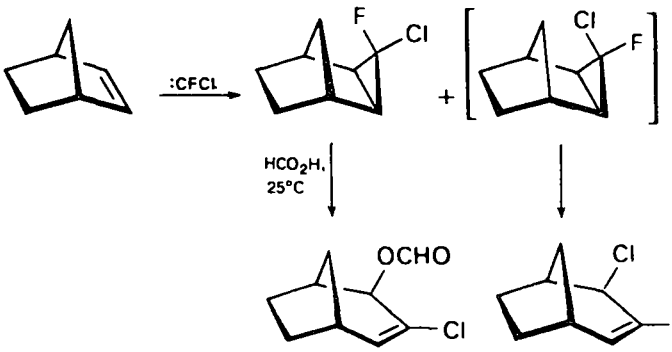


(78)

X = Cl, CF_3

2. Proton assisted

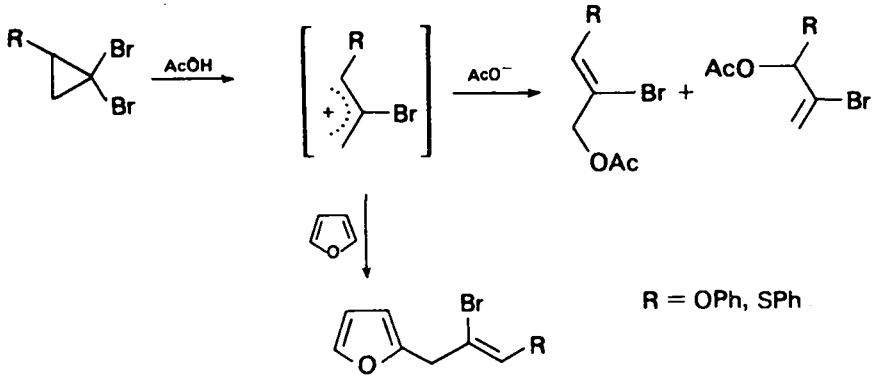
Addition of chlorofluorocarbene to norbornene gives an isomeric mixture of the very unstable *endo* chloro isomer, isolable only as a rearrangement product, and a thermally stable *endo* fluoro isomer. This derivative undergoes ring opening at room temperature with anhydrous formic acid to yield the *exo* formate[507] (equation 79).



(79)

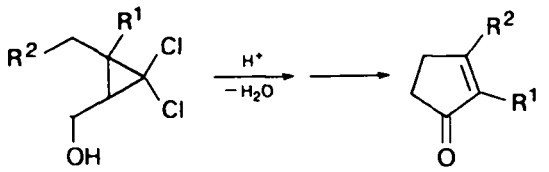
This pseudo-first-order reaction proceeds by protonation at the fluorine atom and subsequent cleavage of the C—F bond synchronous with ring opening and addition of the formate[507]. Such a concerted mechanism competes generally with the free allyl cation mechanism[469,508].

Solvolysis of dibromocyclopropanes in boiling acetic acid in the presence of a large excess of furan resulted in a mixture of bromoallyl acetates and an allyl-substituted furan, indicating an electrophilic attack on the allyl cation on the furan ring[509] (equation 80) (see also Friedel–Crafts reactions, Section IV.D.4).



(80)

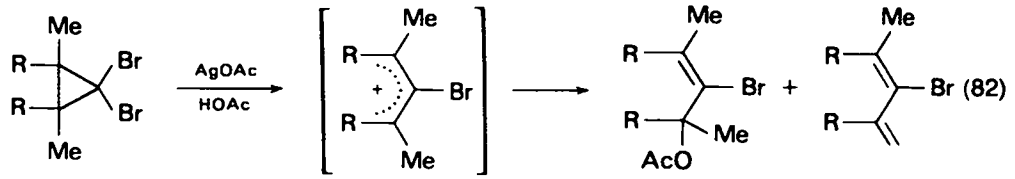
Treatment of (3,3-dialkyl-2,2-dichlorocyclopropyl)methanols with hydroboric acid at 100°C leads to 2-cyclopentenones[199,510,511] (equation 81). The mechanism involves several steps[511].



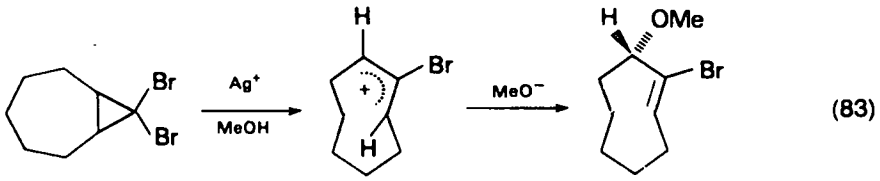
(81)

3. *Silver ion assisted*

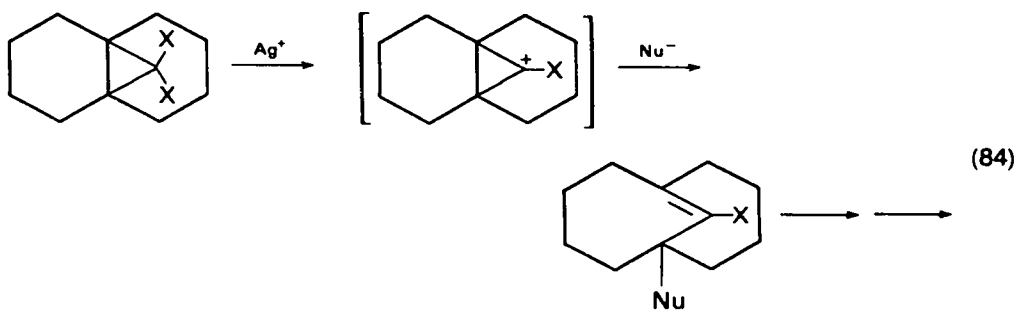
The bond cleavage of a C—X bond and the cyclopropyl–allyl ring opening reaction of dihalocyclopropanes is facilitated in the presence of silver salts. Monocyclic dibromocyclopropanes afford an open chain allyl cation which either can be attacked by the anion of the silver salt or can eliminate a proton[512]. The higher the degree of substitution the larger will be the amount of diene (equation 82).



Bromofluorocyclopropanes give the fluoroallyl derivatives by bromide elimination[249]. Bicyclic dihalocyclopropanes are attacked from the *exo* side, for stereochemical reasons. Therefore, a *trans* allylic cation is formed yielding *trans* cycloalkenes[513–519] with a ring size of at least eight carbon atoms[518] (equation 83).

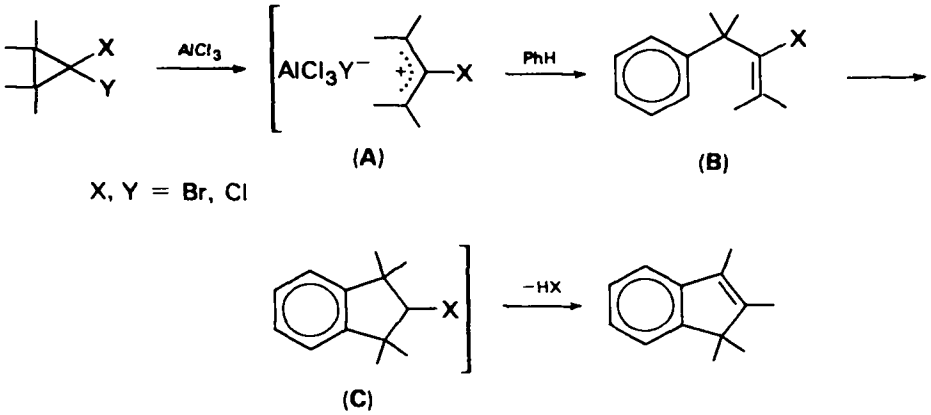


In addition to silver acetate[512] and perchlorate in alcohols[517] or aqueous acetone[516], silver tosylate[516], fluoride[515] and trifluoroacetate[520] have been used. In the presence of boron trifluoride this type of reaction is strongly accelerated[521]. Reaction of the intermediate allylic cation with nitriles leads to substituted amides[252,522]. Solvolysis of alkoxydihalocyclopropanes with silver salts/alcohol affords α,β-unsaturated ketones[523,524]. Silver ion-assisted solvolysis of dibromopropellane in methanol or aqueous acetone is a complicated procedure. Depending on the solvolysis conditions and the ring system, various reaction products can be isolated such as dimethoxypropellanes[525,526], ring enlarged unsaturated ketones[489,525–529], cyclodecanone derivatives[528–532], and others[527–532]. Product analysis and ^{13}C-labelling experiments give results which are consistent only with a bridgehead olefin mechanism[530,531] (equation 84).



4. *Lewis acid assisted*

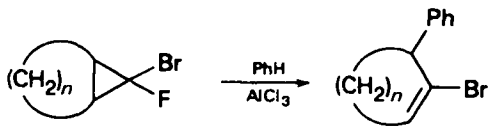
Buddrus[533,534] and Skattebøl[535] independently found that dichloro- or dibromocyclopropanes react with aromatic hydrocarbons in the presence of aluminium chloride or ferric chloride to give indenes. The mechanism proposed involves ring opening to the chloroallyl cation **A**, electrophilic attack leading to **B**, intramolecular reaction with formation of a chloroindane **C**, and finally dehydrohalogenation accompanied by Wagner–Meerwein rearrangement[534,535] (equation 85).



(85)

Evidence for the mechanism was presented in the reactions of bromofluorocyclopropanes (X = Br, Y = F) by trapping intermediates of types **B** and **C**[536].

Bicyclic dichlorocyclopropanes are less suited for Friedel–Crafts reactions. With only a few exceptions[136,537], polymeric material has normally been isolated[136,538]. Bicyclic bromofluorocyclopropanes react with benzene and aluminium chloride to give bromocycloalkenylbenzenes[136] (equation 86). With toluene, xylene and anisole, subsequent reactions occur[136].

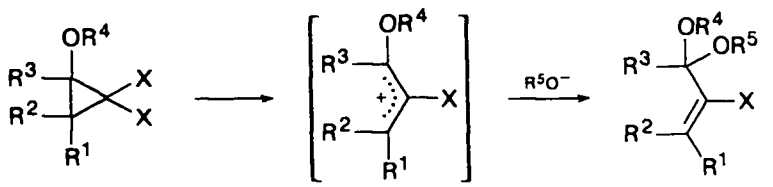


(86)

n = 4, 5, 6

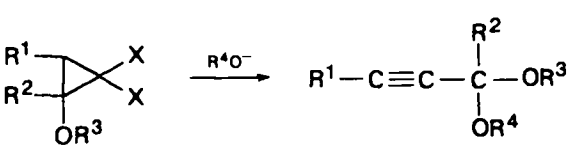
5. *Nucleophile assisted*

The cyclopropyl–allyl rearrangement mentioned above readily proceeds with alkoxy-substituted dihalocyclopropanes. The additionally stabilized allyl cation can easily be trapped by alcohols or alkoxides as nucleophiles to give unsaturated acetals[539,540] (equation 87).



(87)

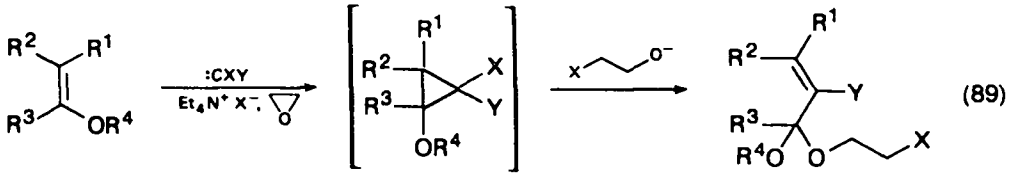
In some cases, preferably with strong bases such as potassium *t*-butoxide, further elimination could be observed, yielding propargyl aldehyde acetals[539,541] (R^2 = H), or propiolic acid *ortho* esters[542] (R^2 = OR^3) (equation 88).



(88)

Basic ring opening of acyloxydichlorocyclopropanes in the presence of hydrazine leads to pyrazoles[543, 544].

As briefly discussed in Section II.D.2, the adducts of dihalocarbene to enol ethers are not stable in the presence of ethylene oxide. Therefore, reaction of enol ethers with dihalocarbene generated by the ethylene oxide method leads to unsaturated acetals in a one-pot reaction[107–109] (equation 89).



(89)

X = Br, Cl; Y = Br, Cl, F

These acetals have been used synthetically for many subsequent reactions[108], e.g. for the first synthesis of α-fluoroacrolein[109] (R^1, R^2, R^3 = H; Y = F). Repeated dichlorocarbene addition to cyclic enol ethers, acetal formation and subsequent elimination provides a homologation reaction to medium sized ring systems[107,108,545]. Morpholine-assisted ring opening leads to mixtures of halodiene and *N*-allyl substituted morpholines[540,546,547].

Some ring opening reactions of bicyclic dihalocyclopropanes with potassium *t*-butoxide involve cyclopropene intermediates[395,548,549]. Bis-adducts with cyclohexadiene give complex product mixtures[550–552]. Other nucleophiles such as malonates can either react according to the elimination–addition mechanism[549] (see also Section IV.B.2) or with an allylic cation[249].

V. ACKNOWLEDGEMENTS

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CHAPTER **28**

Photoelectron spectra of organic halogen compounds

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I. INTRODUCTORY REMARKS: PHOTOELECTRON SPECTROSCOPY TODAY AND SCOPE OF THIS REVIEW

The early tempestuous years of photoelectron spectroscopy–comprising the development of the method[2–5], commercial production of high-resolution

spectrometers and measurement of the ionization patterns of thousands of molecules[2–9]–have now been superseded by a period of reflection about practical application[1,10,11]. Based on the experience gathered, it is now feasible, for example, to optimize gas-phase reactions 'visually' in a flow tube, including those which are heterogeneously catalysed[10,12,13], with the aid of continuously recorded PE spectra: the ionization patterns, i.e. the 'molecular fingerprints' of the reactants, give way to those of the products. It is the purpose of this report on the photoelectron (PE) spectra of the also industrially important class of halogen compounds to elaborate upon the 'reading' of the 'individual molecular band patterns', and to demonstrate that in the daily use of photoelectron spectra there are no more particular difficulties involved than are met in the investigation of infrared frequencies or mass spectroscopic fragments.

As a second facet, it should be pointed out that this technique, low energy photoelectron spectroscopy, is intimately connected with the variety of bonding problems in molecules. The method, developed in the past decade[2,14], provides easily accessible and detailed information on cation states. However, the assignment of the spectra and their interpretation can be achieved only by applying carefully the tools of modern quantum chemistry. The procedures required depend on the individual problem and range from simple Hückel-type approximations[6] to calculations beyond the Hartree–Fock limit[7,15,16].

The PE spectra of halogen compounds comprise representatives of nearly every element in the periodic table. Obviously, many investigations have not been stimulated by purely spectroscopic interest, but rather by the incentive to compare chemically related compounds. Therefore, this review will follow the arrangement in the periodic table, starting with sections on saturated group IVB halides and on halogen-substituted open-chain and cyclic π systems.

Three introductory sections, all of them with accent on halogen compounds, intend to familiarize the reader with (i) PE spectroscopic information on radical cation states (Section II), (ii) the assignment of the ionization patterns by comparison of equivalent radical cation states of chemically related compounds (Section III), and (iii) the discussion of PE spectra, choosing as examples small prototype halogen compounds (Section IV).

Organic halogen derivatives are covered predominantly. Nevertheless, some inorganic molecules had to be included for obvious reasons: many of them are smaller in size and of higher symmetry, which leads to more transparent effects and also to simplification of the PE spectroscopic interpretation, while the results can easily be transferred to related organic and organometallic derivatives.

Whenever possible and appropriate, the chemist's point of view has been emphasized in the discussions. Therefore, neither special experimental techniques in electron spectroscopy or adjacent fields nor computational studies of the molecules discussed have been covered extensively in this chapter. Conclusions, dependent on differing actual assignment of the PE spectra, are marked at such; however, completeness in repeating all the literature arguments has not been the aim of this chapter.

There are, of course, already numerous valuable reviews available on photoelectron spectroscopy in general and on some of its special aspects. In addition to those already quoted[2–11], there are more books available[17–20], partly dealing with related topics not included here, e.g. ESCA[21–23] or vacuum UV spectroscopy[24].

A legion of reviews has covered general aspects[25–29] or more special topics like the PE spectra of inorganic[30] or organic[31] compounds, or the compounds of certain elements like B (N)[32], P[33] or S[34] or containing certain substituent groups like —CN[35]. Furthermore, collections of contributions, which sometimes prove to be quite useful,

are found in the published lectures of the 1969 Royal Society seminar[36], the proceedings of the Asilomar Conference in 1971[37], and in the *Faraday Discussions* covering the Brighton meeting in 1972[38].

Summarizing, photoelecton spectroscopy has been developed within its past 20 years into a spectroscopic technique which is particularly valuable for real-time gas analysis in flow systems[1,10,11]. An essential contribution to this status originates from the intimate relationship to chemical bonding[6,7], leading to the well documented assignment of the PE spectroscopic fingerprints of thousands of molecules and allowing for their identification and characterization[1–37].

II. INFORMATION FROM PHOTOELECTRON SPECTRA OF HALOGEN COMPOUNDS

Photoelectron (PE) spectra of the 'electron-rich' halogen compounds generally display needle-like ionization bands which are assigned to radical cation states with predominant 'halogen lone pair' character. This review, therefore, will start with these characteristic features and discuss them in separate sections under headings like vibrational fine structure, Jahn–Teller distortion or spin–orbit coupling. The spectroscopic information is augmented by correlation with results from quantum chemical calculations via the famous Koopmans' theorem[2–7]. These correlations between measured and calculated data are enormously useful in assigning the PE spectra and in rationalizing the otherwise incomprehensible wealth of spectroscopic information on the radical cation states.

A. Principle of Measurement and Some Experimental Details

Photoelectron spectroscopy uses the photoionization of a neutral species M to its cation M^+,

$$M + h\nu \rightarrow M^+ + e^-, \tag{1}$$

to determine the ionization potential of M (IE(M)),

$$IE(M) = h\nu - E_{kin}(e^-), \tag{2}$$

from the difference of the photon energy $h\nu$ and the kinetic energy (E_{kin}) of the ejected electron. If, as is usual, a helium(I) discharge lamp is chosen as a source of (monochromatic) photons with $h\nu = 21.21$ eV, all ionization potentials up to 21.21 eV can be measured by counting the emitted electrons of specific kinetic energy. By way of illustration, Figure 1 displays the He(I) PE spectrum of the eight valence electron molecule hydrogen bromide: three of the expected four ionizations occur within the 21.21 eV measurement range.

The ionization energies are energy differences between the ground state of a neutral molecule M and the ground state or excited states of its radical cation M^+ generated in the photoionization process (equation 1). In general, vibrational and rotational excitations take place simultaneously, giving rise to PE bands of different shape and sometimes exhibiting fine structure (Figure 1). Other features in the PE spectra may arise from instability of the cation generated towards dissociation (Figure 1: vanishing vibrational fine structure of band ③), other electronic effects, such as spin–orbit coupling in the resulting doublet states with non-zero orbital angular momentum (Figure 1: bands ① and ②), and so on. Although a detailed discussion of the underlying general spectroscopic principles[3,4,39] would be beyond the scope of a review for the chemist, some of the more frequently observed features in He(I) PE spectra of halogen compounds have to be dealt with in the following because of their importance

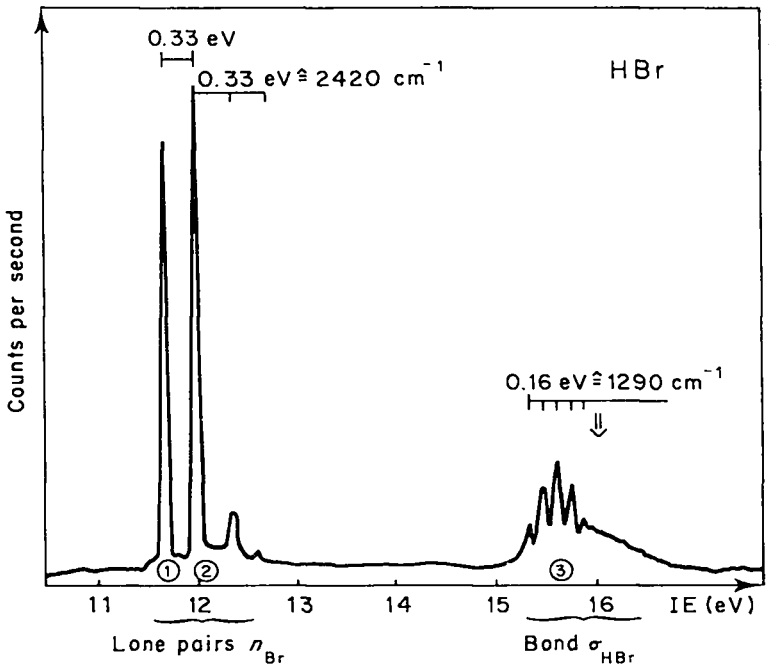


FIGURE 1. He(I) PE spectrum of HBr.

in spectroscopic assignment. Just to round off the illustrative hydrogen bromide example, the unequivocal assignment given in Figure 1 is based on the vibrational fine structures (HBr; 2560 cm^{-1}, HBr^+; 2420 cm^{-1}, i.e. non-bonding electron ejected, and 1290 cm^{-1}, i.e. bonding electron removed), on the spin–orbit coupling of the lowest HBr^+ states as well as on the loss of fine structure in the higher energy flank of the 15.6 eV band due to predissociation.

Since the PE spectrometer design has been covered in some earlier reviews[2–4,14], in the following the attention will be focused on the quality of the data measured.

The primary information plots the kinetic energy of the photoelectrons (equation 2) versus their number ejected per energy interval (see Figure 1: differential PE spectrum). Since most of the compounds investigated will slightly affect the electrostatic analyzer, a calibration of the energy scale is absolutely necessary. In a recommended standard procedure, at least two gases such as argon with IE_n = 15.755 eV/15.933 eV[40], xenon with IE_n = 12.127 eV/13.433 eV[40] or especially for the low energy region methyl iodide with IE_n = 9.538 eV/10.165 eV[39] are measured simultaneously with the sample (IE_n is the ionization energy). Deviations from linearity of the energy scale, which would require more than the usual two calibrations, do not seem to be critical in routine work.

Standard 'good' resolution seems to about 20 meV for 5 eV electrons, but fortunately resolutions near 10 meV are becoming more and more common[41]. The reproducibility, if judged from data by different workers, is better than 0.02 eV for sharp needle-like peaks, whereas broad PE bands with unresolved vibrational fine structure introduce larger uncertainties; the determination of the maximum–or even worse, of the onset–is liable to differ by ±0.15 eV if determined by different workers. The resolution increases for electrons of low kinetic energy, and therefore resonance lines of the heavier noble gases have been used in high precision work[41].

Other extensions of measurement techniques concern the use of a He(II) discharge lamp to determine higher valence electron ionization potentials, heated inlet systems allowing PE spectra of less volatile compounds to be recorded, and special procedures or devices to handle or to generate sensitive or unstable species[3,11].

B. Radical Cation States: Vibrational Fine Structure

The PE spectroscopic ionization process starts in general from the electronic and vibrational ground state of a neutral species and leads to the ground state or to some electronically and/or vibrationally excited state of the molecular cation. Therefore the second PE spectroscopic ionization potential refers to the first electronically excited cation state and not as in atomic spectroscopy to the removal of a second electron. In addition, the resulting molecular cation is often left in vibrationally excited states, giving rise to vibrational fine structure of PE bands, the intensity pattern of which can be rationalized by the Franck–Condon principle[3,4,39,42] (Figure 2).

Within the limits of the Born–Oppenheimer approximation[15,16,39] the intensity of the vibrational peaks is given by the Franck–Condon factors, i.e. the overlap integrals between the vibrational wave functions of the initial and final states, provided that the

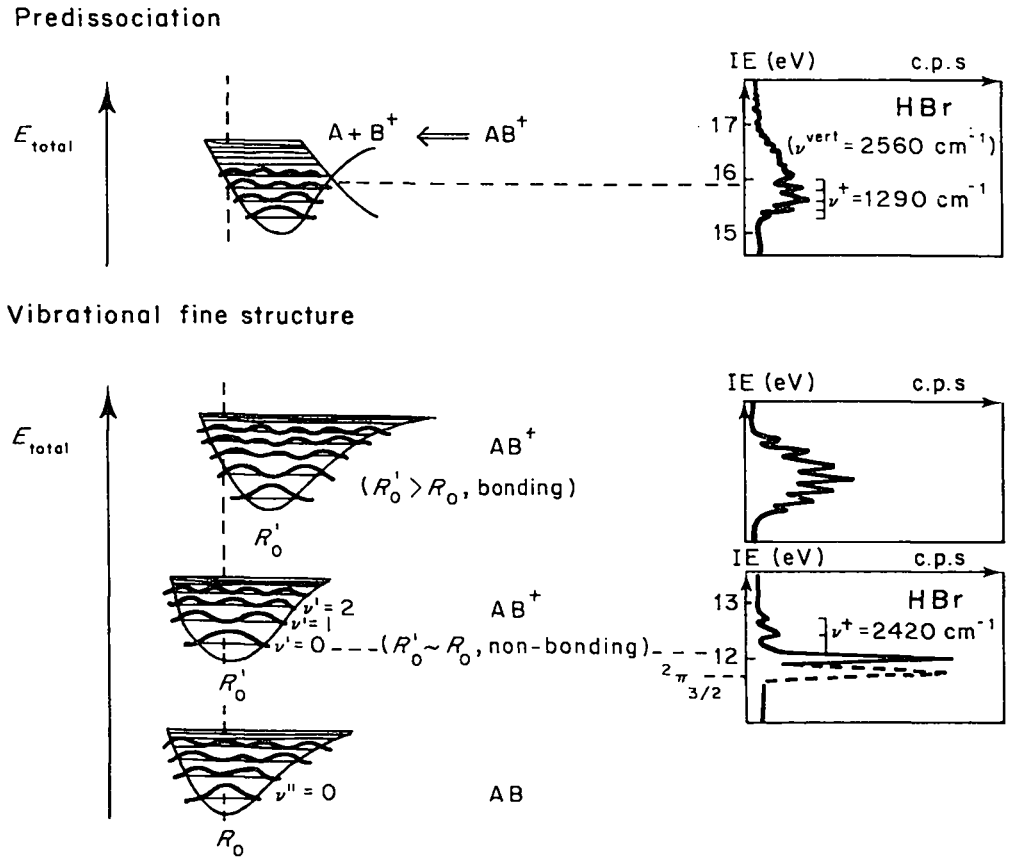


FIGURE 2. Vibrational fine structure of PE bands and Franck–Condon principle (see Figure 1, HBr).

electronic transition moment does not vary significantly over the range of the PE band. Classically, this can be looked upon as corresponding to electronic transitions with fixed internuclear distances. Sharp and unsymmetrical band envelopes with most of the intensity in the $v'' = 0 \rightarrow v' = 0$ transition result if the equilibrium nuclear distance remains approximately constant upon ionization. Significant differences in molecular equilibrium geometries show up in broad symmetrical band envelopes with progression frequencies v^+ changed relative to vibrations v of the neutral molecule.

No fine structure at all is observed for dissociative cation states, while predissociation broadens the vibrational levels (Figure 2). It has to be pointed out, however, that most PE bands of polyatomic molecules unfortunately do not exhibit vibrational fine structure, because spectrometer resolution is hardly sufficient to resolve numerous overlapping progressions.

The geometry of cations can be determined if 'spectroscopic' Franck–Condon factors are available. The procedure is straight forward for diatomics, whereas for larger molecules more complex problems result: The corresponding PE bands usually show only one or two vibrational progressions, and, on the other hand, reliable normal coordinates are needed. Some attempts for compounds X—C≡N[43], X—C≡C—H[44] or $F_2C{=}S$[45] suggest that the force field is either of critical importance[46] or without much influence[44], somewhat depending on the precision required[47]. 'Larger' bond length changes amount to about 10–40 pm.

A corollary of the Franck–Condon principle states that either only totally symmetric vibrational modes can be excited, or double quanta of non-totally symmetric ones[18,48].

Ionization energies are quoted either as 'adiabatic' or as 'vertical'[3,4]. The adiabatic ionization energy corresponds to the energy difference between the lowest vibrational level of the cation and the neutral molecule, i.e. to the difference between the minima of the respective potential surfaces. Therefore, 'adiabatic' usually refers to the energy of the first vibrational peak, if this is not due to a 'hot band', i.e. an ionization of vibrationally excited molecules. A striking example is given by I_2, with only the fourth vibrational peak at 9.311 eV being interpreted as the $v'' = 0 \rightarrow v' = 0$ transition[49]. The $0 \rightarrow 0$ transitions are sometimes hard to discover in the PE spectra: their intensity often decreases considerably if large changes in equilibrium geometry occur. In contrast, the 'vertical' ionization energy (IE^{vert}) is defined as the energy difference between the two potential surfaces taken at the minimum of the ground state (Figure 2). It is generally approximated either by the PE band maximum or by the value of its most intense vibrational peak. More correctly[50–52], the first moment

$$IE^{vert} = \frac{\sum_n IE_n \cdot I_n}{\sum_n I_n} \tag{3}$$

should be used, with the summations running over all n vibrational peaks of intensity I_n within one band. The two definitions for vertical ionization differ only for unsymmetrical PE bands, and then by about one vibrational spacing.

Changes in geometry or vibrational frequencies upon ionization are frequently related to the 'bonding properties' of the ionized electron: removal of a non-bonding electron leaves the vibrational frequency unchanged, ejection of a bonding one decreases – and of an antibonding one increases[2] – the vibrational frequency in the cation relative to that of the neutral molecule[3,4]. The relevance of structural distortions is less obvious: Ionization of a strongly bonding electron will also increase the equilibrium bond length in the cation, but in some cases near-constancy of the vibrational frequency has been reported, e.g. for $F_2C{=}S$[45,53], although the Franck–Condon factors suggest a large geometry change. It also should be noted that,

within the electron pair repulsion model[54], 'lone pair' electrons determine angles, and correspondingly bending modes are observed upon their ionization. Altogether, the question of 'bonding properties' of electrons originates from the interpretation of vibrational frequency changes. In cases where fine structure is lacking, arguments often resort to the band envelope, and, for example, a needle-like one is considered to indicate the ionization of a non-bonding electron (Figure 2).

Notwithstanding all the complications discussed above, vibrational fine structure and sometimes even the band shape definitely are of considerable help in assigning and interpreting the PE spectra.

C. Degenerate Ionic States: Jahn–Teller Distortions

Electronically degenerate states are unstable with respect to distortions of the molecule which remove the degeneracy. This so-called Jahn–Teller effect[55] is often encountered in PE spectroscopy when ionizations lead to degenerate ionic states. The coupling of electronic and nuclear motion produces a complex vibrational pattern, which is usually dominated by a long progression in a degenerate mode, the excitation of which would be forbidden otherwise. This Jahn–Teller active vibration leads – if the effect is strong enough – to a permanent distortion of the ion. In case of insufficient resolution of vibrational sub-bands, the Jahn–Teller effect can still be recognised by either PE band split or by emerging shoulders on their high energy flanks. Both characteristics can be illustrated by the PE spectrum of CBr_4[56,57] (Figure 3).

Ionization of the eight p-type bromine lone pairs of CBr_4 gives to $^2T_1$, $^2T_2$ and ^2E states, which, due to spin–orbit coupling (see Section D), yield the following cation states (in double group notation; see reference 39): $^2G_{3/2} + {}^2E_{1/2}$, $^2G_{3/2} + {}^2E_{5/2}$ and

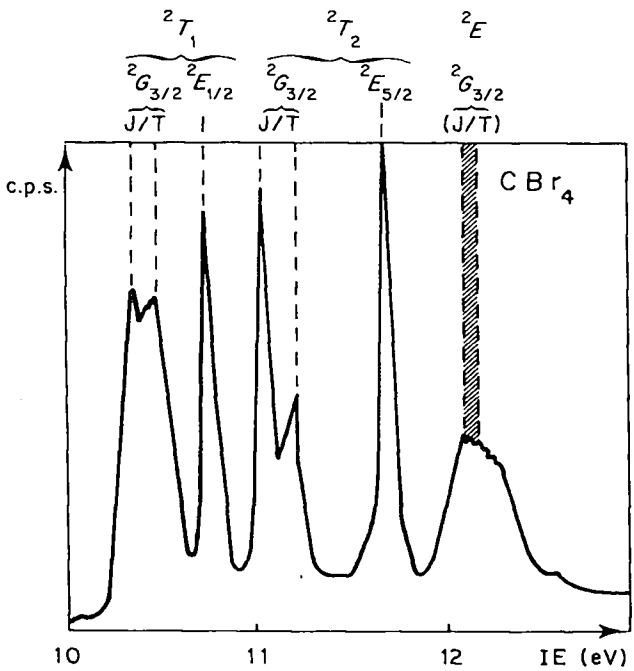


FIGURE 3. PE spectrum of CBr_4 from 10 to 12.5 eV with assignment (J/T = Jahn–Teller effect).

$^2G_{3/2}$. The $^2G_{3/2}$ components of $^2T_1$ and $^2T_2$ are clearly split by Jahn–Teller distortion of the radical cation $CBr_4^{+\cdot}$; the band belonging to $^2G_{3/2}$ (^2E) seems broadened. As in CBr_4, the Jahn–Teller effect is often connected to splitting by spin–orbit coupling. When both effects are of similar magnitude, the intensity distribution within a PE band can be seriously affected, and intensity borrowing via vibronic interaction has been demonstrated, e.g. for the first PE band of CH_3Br[58].

D. Degenerate Ionic States: Spin–Orbit Coupling

Spin–orbit coupling plays an important role in the PE spectroscopic assignment and interpretation of bromine and iodine compounds especially.

Normally, the final states in PE spectroscopy are doublet states. If their 'orbital' angular momentum is different from zero, an interaction between the orbital and spin angular momenta takes place. This spin–orbit coupling can remove degeneracies, e.g. the double degenerate $^2\Pi$ state of HBr^+ splits into $^2\Pi_{3/2}$ and $^2\Pi_{1/2}$ states, and the corresponding PE bands (Figure 1) are separated by $12.01 - 11.68 = 0.33$ eV[2–4]. This interaction clearly represents a relativistic effect, dealt with for atoms in the familiar $\vec{L} \cdot \vec{S}$, $\vec{j} \cdot \vec{j}$, or intermediate coupling schemes, depending on the magnitude of the spin–orbit interaction, being smaller or greater than, or comparable to, the electrostatic interaction[59].

The strength of the spin–orbit interaction is characterized by the coupling constant $\mathcal{J}_A$, which increases down the periodic table and with the charge of the atom. For the halogens, the split between spin–orbit coupled atomic states amount to 0.050 eV for F, 0.109 eV for Cl, 0.457 eV for Br and 0.943 eV for I[40]. From these values the following typical coupling constants $\mathcal{J}_A$ have been derived[60]: 0.07 eV for Cl, 0.30 eV for Br, 0.63 eV for I and 0.73 eV for I^+. Comparing these splits with the achievable PE spectroscopic resolution (Section II.A), observation of spin–orbit coupling effects are expected only for molecules containing atoms like Br, I, Hg, Pb, etc.

Spin–orbit coupling of degenerate cation states with non-zero angular momentum is not usually incorporated into simple MO theory, which therefore fails to predict the number of PE bands for bromine or iodine compounds, for example. However, the correspondence via Koopmans' theorem (cf. Section II.E) can be re-established easily by introducing so-called double or spinor groups, the character tables for which are to be found, for example, in reference 39. In these extended point groups, the spin part of the doublet states transforms as $E_{1/2(g)}$. The direct product of the species of the spatial and of the spin part of the wave function yields the symmetries of the final states, or – at the orbital level – of the spin orbitals. For example, the states resulting from bromine lone pair ionization of H_3CBr are, in C_{3v}' point group notation, $E \times E_{1/2} = E_{3/2} + E_{1/2}$.

For a $^2\Pi$ state, the spin–orbit splitting Δ will be roughly proportional to the atomic spin–orbit coupling constant $\mathcal{J}_A$, and to the square of the heavy atom (A) coefficient c_{JA} in the singly occupied molecular orbital J:

$$\Delta \sim c_{JA}^2 \cdot \mathcal{J}_A. \tag{4}$$

According to this first-order treatment, for instance in the PE spectrum of XeF_2 (Figure 4), spin–orbit coupling is expected only for the $^2\Pi_u$ states, because the π_g orbitals, which represent any doubly degenerate $^2\Pi_g$ state, cannot contain any $5p_{Xe}$ contribution for symmetry reasons[61].

An additional condition for spin–orbit coupling requires that the respective degenerate molecular orbitals contain contributions from two different orbitals of the heavy atom: therefore, for example, no first-order spin–orbit splitting will be expected for the doubly degenerate $^2\Pi$ state of BI_3, represented by the $\pi(1e'')$ molecular

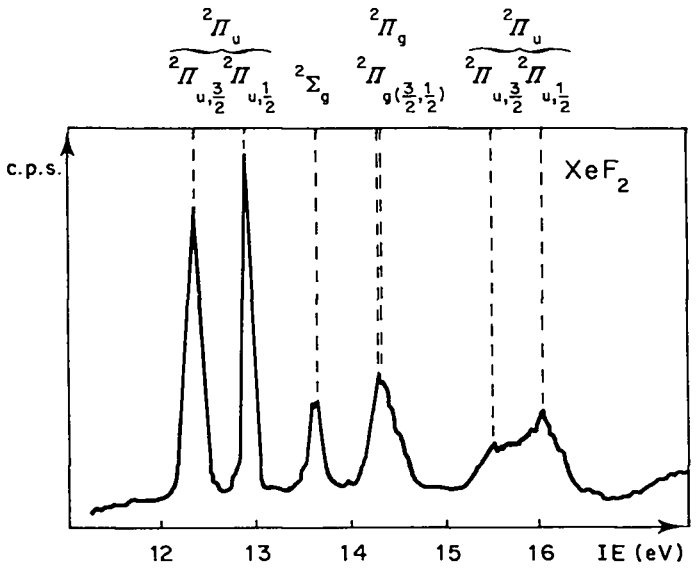


FIGURE 4. Helium(I) PE spectrum of XeF_2 from 11 to 17 eV with assignment.

orbitals, which are solely composed of the iodine p_π orbitals perpendicular to the molecular plane[62]. The first-order perturbation relationship (equation 4) has also been used for an estimate of the π atomic orbital coefficients in halogenoacetylenes based on the PE spectroscopically observed spin–orbit splittings[63].

The competition between spin–orbit interaction and (hyper)conjugation was first investigated[64] in the PE spectra of alkyl bromides (Figure 5) and the MO model developed (Figure 5) was subsequently applied to alkyl iodides[65], allyl halides[66] and iodoethylenes[67].

Figure 5 gives an explanation of why spin–orbit splitting remains nearly constant within many alkyl bromides, in spite of a considerable n_{Br}/σ_R mixing, proven by the vibrational fine structure observed[64]. Strong hyperconjugative interaction in cyclopropyl bromide affects predominantly the bromine lone pair in the ring plane, the corresponding first PE band is flattened and pushed to 9.66 eV, increasing the split to $\Delta = 0.75$ eV (Figure 5). The resonance integral β_{RX} permits the following MO classification: for $\beta_{RX} \sim \mathcal{J}_A$, a $\sigma_R(a'')$ orbital of an R group with C_s symmetry will interact with the $e_{3/2}$ and the $e_{1/2}$ spin orbital, since both contain $n_x(a'')$ contributions; for large β_{RX} the spin–orbit interaction will be quenched.

In molecular systems, which belong to symmetry point groups without ($n \geqslant 3$)-fold axis C_n, no degeneracies occur and, consequently, no splitting of degenerate states can be observed. However, spin–orbit interaction will be dominant as long as the coupling constant $\mathcal{J}_A$ remains of the same order of magnitude as the energy differences produced by the electrostatic interaction.

In view of the large iodine coupling constant $\mathcal{J}_I = 0.63$ eV, PE spectra of iodine compounds should yield evidence for those second-order effects. The iodine molecule itself forms an illustrative example[68], showing two different lone pair ionization energy differences of 0.63 and 0.79 eV[69] (Figure 6).

The MO model (Figure 6) offers a straightforward rationalization of different iodine lone pair splittings: the double group $D'_{\infty h}$ permits interaction between the $e_{1/2}$ compo-

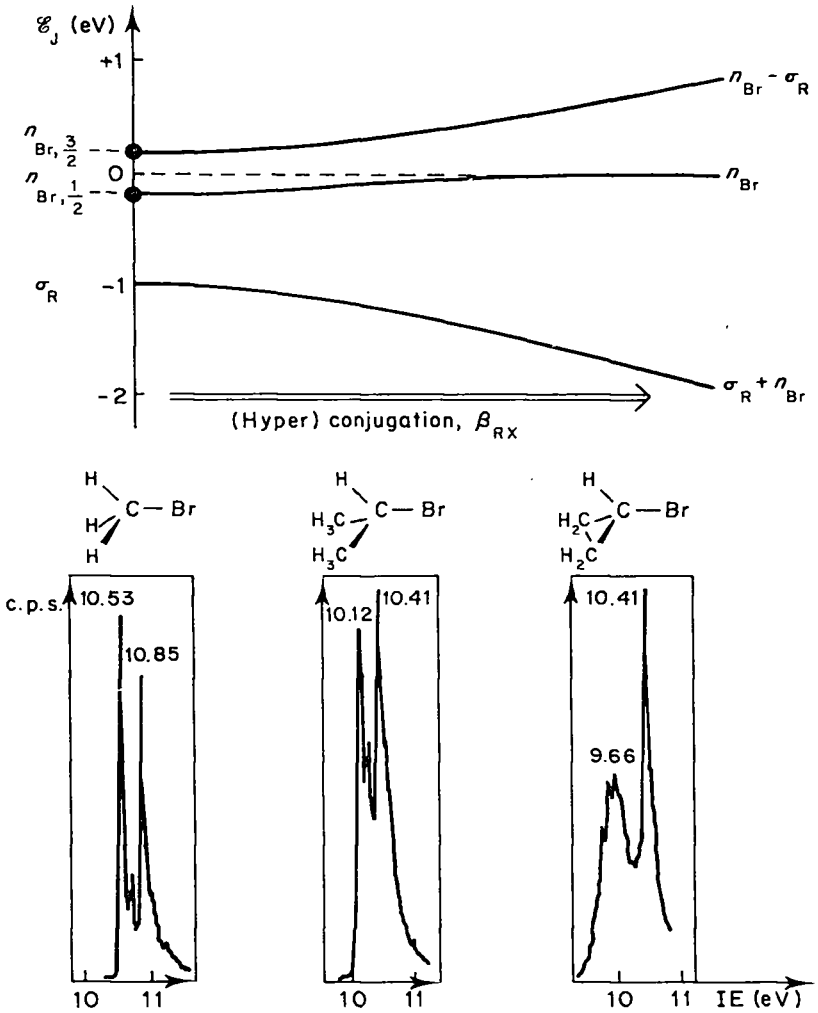


FIGURE 5. Spin–orbit coupling versus the (hyper)conjugation model[64], as exemplified for the lone pair ionization PE bands of alkyl bromides.

ments of the π and σ spin orbitals. Due to retained inversion symmetry all g/u-interactions are forbidden. The spin–orbit induced mixing between each the $e1/2g$ and the $e1/2u$ orbitals causes shifts of approximately 0.05 eV to 0.1 eV[68].

For larger molecules of low symmetry, such simple arguments have to be replaced by some consistent method of calculation. The several attempts undertaken so far have some features in common but differ in others. The main points of elaboration include the following:

(i) *Spin–orbit operator*. Although more exact expressions are available, in PE spectroscopic publications use has been made exclusively of

$$H_{SO} = \sum_n \sum_A \mathcal{J}_A(r_{An}) \vec{l}_{An} \vec{s}_n \tag{5}$$

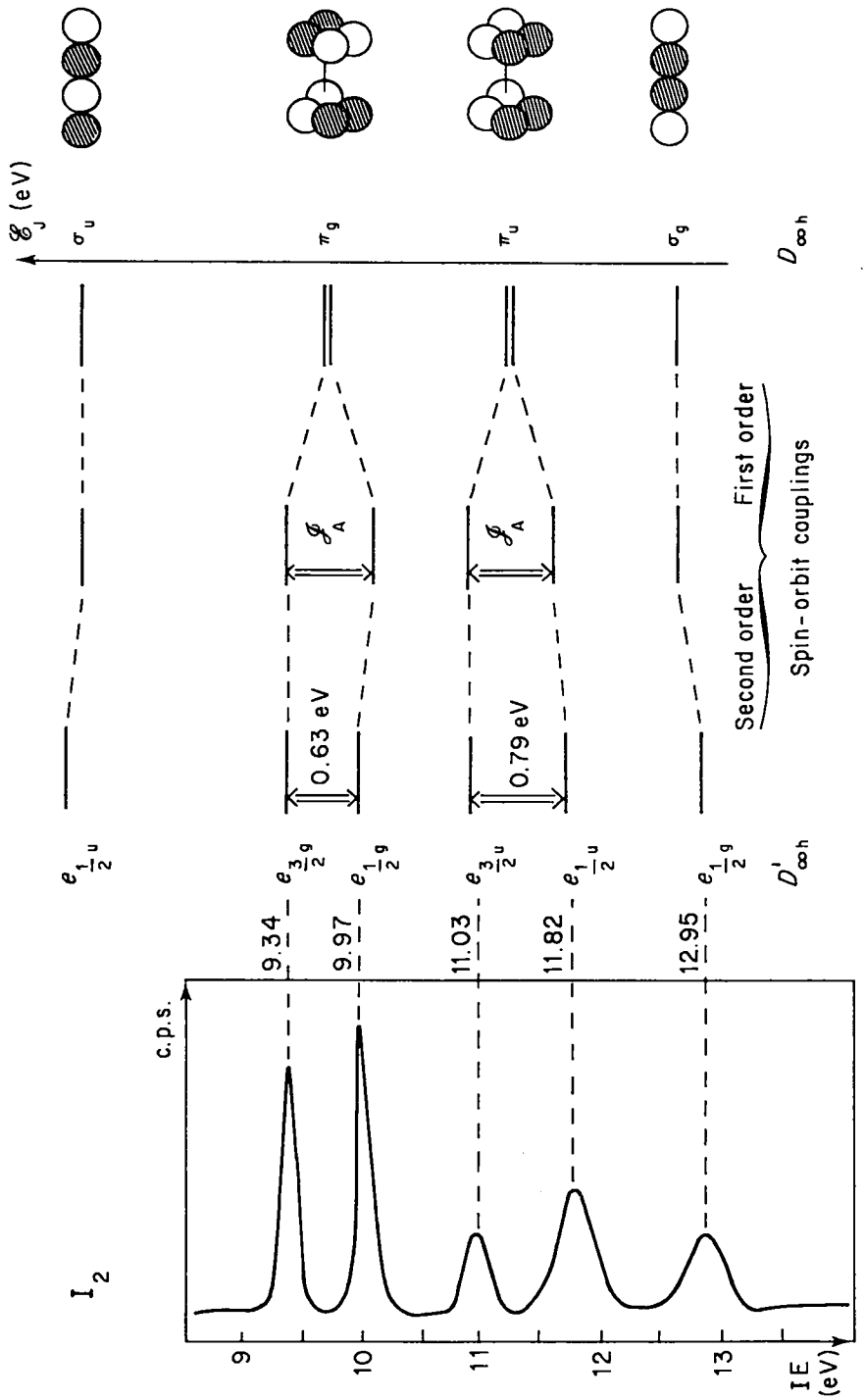


FIGURE 6. PE spectrum of I_2 from 9 to 14 eV[69,70] and its interpretation by first- and second-order spin–orbit coupling[68].

with the summation running over the n electrons and A nuclei. All the treatments at some stage replace integrals over $\mathcal{J}_A(r_{An})$ by atomic spin–orbit coupling constants. For atoms, the operator H_{SO} reduces to the one used in the Slater–Condon theory of atomic spectra[59].

(ii) *Calculation procedures*. Two different approaches have been employed: a configuration interaction procedure, which after solving the Hartree–Fock equations includes the spin–orbit operator H_{SO} as, for instance, in references 56, 57, 71, 72, or alternatively, introduction of H_{SO} in the effective Hamiltonian[62] of the original Koopmans' derivation[73]. The latter method advantageously retains the conceptually simple relationship between orbital energies and ionization potentials embodied in Koopmans' theorem (Section II.E). Both approaches are equivalent, if the configuration interaction procedure is restricted to singly excited configurations[74].

(iii) *Coupling constants*. In the PE spectra of noble gases, the observed $^2P_{3/2}/^2P_{1/2}$ is just 3/2 times the coupling constant of the atomic cation. Therefore, use of the coupling constants of the atomic cations, $\mathcal{J}_A+$, has been recommended[62]. Theoretically more attractive is an interpolation between $\mathcal{J}_A$ and $\mathcal{J}_A+$, with the actual value depending on the final charge on atom A[72,75]. Higher order effects have often been hidden due to use of $\mathcal{J}_A$ instead of $\mathcal{J}_A+$, the difference $\mathcal{J}_A+ - \mathcal{J}_A$ being of the same magnitude as second-order effects.

In conclusion, it should be pointed out that higher order effects become most important in compounds R–X, where lone pair n_X ionizations are close in energy to the ionization out of the R–X bond, e.g. in inorganic halides like HgI_2 [76,77] or BI_3 [62,78], PE ionization energies of molecules exhibiting higher order effects can be approximated numerically by calculations only if the non-relativistic energies are already reasonably well reproduced. To improve semi-empirical calculation procedures, experimental ionization energies have often been introduced as parameters into computer programs, which subsequently calculate spin–orbit interactions. All the above attempts to consider spin–orbit coupling correctly in MO models are well worth the effort, because this is one of the tools in assigning and interpreting PE spectra, especially of bromine and iodine compounds[79–81].

E. Radical Cation States and Molecular Orbitals

In the preceding sections MO arguments have been repeatedly applied in the rationalization of PE spectra (see, for example Figures 5 and 6). And, in fact, the chemist's interest in PE spectroscopy is mainly due to Koopman's theorem[73], which allows us to equate negative ionization potentials with the energies of (canonical) SCF orbitals of Hartree–Fock quality (ε_n^{SCF}):

$$IE_n = -\varepsilon_n^{SCF}. \tag{6}$$

Thus the total energy differences between cation states can be related to differences between ground state orbital energies: the PE spectrum can be thought of 'as if displaying the MO level diagram for a molecule' (Figure 7).

Koopmans' theorem can be proved rigorously, provided that (i) only one Slater determinant is used for the cation and the neutral molecule, respectively and that (ii) the orbitals in both determinants are the same canonical SCF orbitals for the neutral closed shell molecule. Koopmans' theorem further states that the ionization energies given by equation (6) are 'best' in a variational sense; i.e. it makes sense to describe ionization as a simple removal of an electron out of a canonical orbital[82]. As a corrollary, one can state that only ionizations out of an orbital would be observed if the

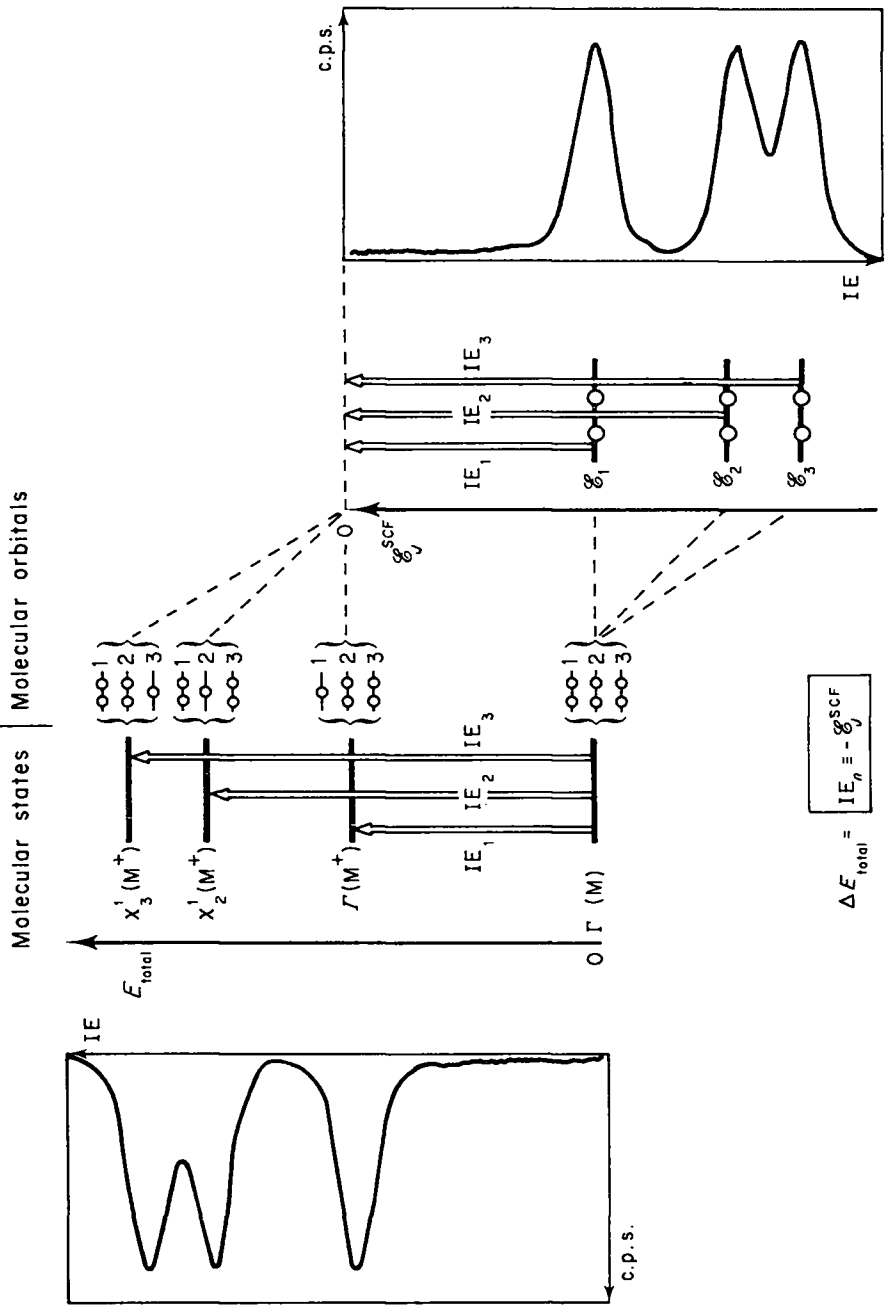


FIGURE 7. Correlation of radical cation states with molecular orbitals via Koopman's theorem[73].

restrictions (i) and (ii) held exactly: 'shake up' (ionization and simultaneous excitation) 'shake off' (double ionization) processes would be rigorously forbidden[15].

Deviations from Koopmans' theorem are expected whenever the above restrictions prove to be too severe. The accompanying energy changes can best be discussed using the idea of correlation (E_{corr}) and relaxation (E_{rel}) energies (Figure 8).

The SCF energy of the ground state (E_{SCF}) differs from the 'true' experimental energy by the correlation energy, E_{corr}. The Koopmans' theorem energy of the cation, E_{KT}^{+}, is reached by subtracting the orbital energy from E_{SCF}. E_{KT}^{+} is, however, not the SCF energy of the cation. If the orbitals are allowed to relax, a lower energy, E_{SCF}^{+} is reached. This latter energy still differs from the true cationic energy, E_{exp}^{+}, by the correlation energy, E_{corr}^{+}. Consequently, one obtains

$$IE_{exp} - IE_{KT} = (E_{corr} - E_{corr}^{+}) - E_{rel}^{+}, \tag{7}$$

taking all energies as positive quantitities. Since correlation energies often correlate with the number of electrons in a system -2 eV per electron pair might be an approximate value – the correlation part in equation (7) tends to cancel the relaxation contribution[26,83]. Consequently, Koopmans' theorem (equation 6) often holds fairly well, even if correlation and relaxation effects are substantial.

Figure 8 also suggests cases where Koopmans' theorem is liable to break down. One has to look for systems where E_{corr}^{+} tends to be larger than E_{corr}, thus preventing a cancellation. Such a situation is realized in molecular systems like F_2, where many valence electrons occupy almost all of the valence orbitals: there is not much space for an electron to avoid others, whereas removal of an electron to form the cationic species enlarges this easily accessible region, and one might expect the correlation energy, *per electron*, to be larger in the cation than in the neutral molecule. This is the

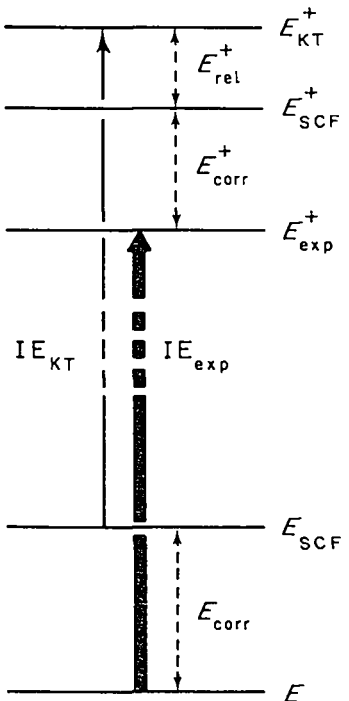


FIGURE 8. Partitioning of energies, showing cancellation of correlation and relaxation effects.

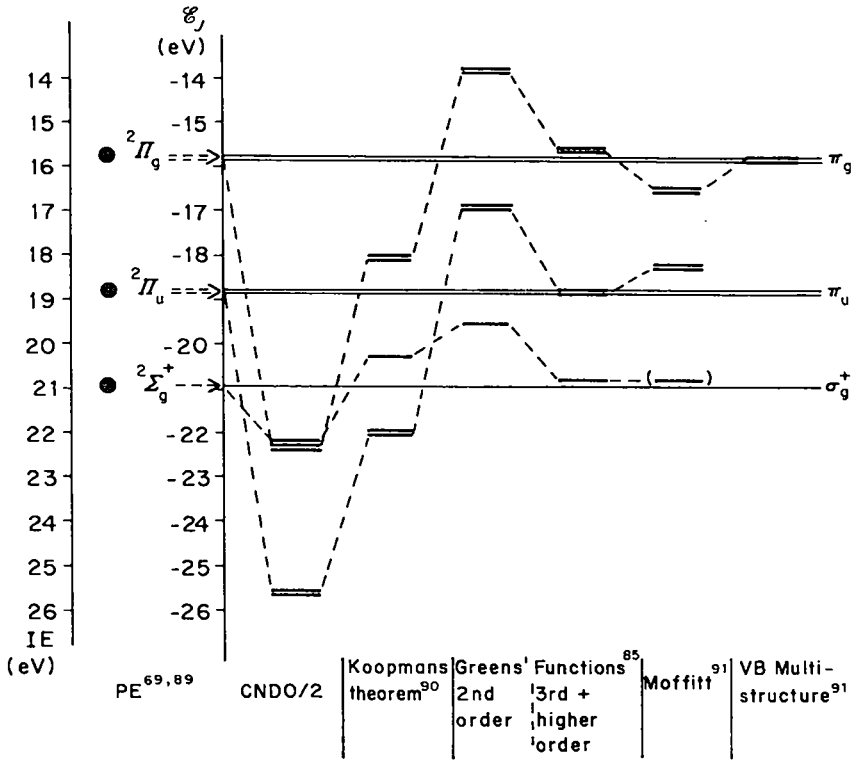


FIGURE 9. Vertical ionization energies of the F_2 molecule (●) compared with results from various calculations.

picture emerging from more sophisticated calculations[84–88]. Indeed, the breakdown of Koopmans' theorem has been demonstrated for F_2 (Figure 9).

The F_2 cation state sequence observed (Figure 9) is not reproduced via Koopmans' theorem by an *ab initio* SCF calculation, which – although of 'near Hartree–Fock' quality – yields the 'wrong' orbital sequence $\pi_g < \sigma_g^+ < \pi_u$. The CNDO/2 results – representative for semi-empirical SCF methods – predict the even worse order $\sigma_g^+ < \pi_g < \pi_u$ (Figure 9). Because 'breakdowns' of Koopmans' theorem are often difficult to prove experimentally, it should be noticed that the $^2\Pi_u$ assignment of the 18.8 eV PE band of F_2 has been provided by an analysis of the $F_2^+ {}^2\Pi_g \leftarrow {}^2\Pi_u$ emission band[92].

What can be done to go beyond Koopmans' theorem? Feasible in principle, for instance, are separate calculations for the ground state of the neutral molecule as well as for the individual molecular cation states and subsequent subtraction of calculated total energies[88]. But high quality calculations are required, which involve long computational times. Another approach investigated starts from Koopmans' theorem and avoids subtracting two large, nearly identical numbers by means of a perturbation expansion. Using techniques from many-body theory, some second-order corrections were quite encouraging, but in more critical cases higher order terms had to be included (cf. Figure 9), rendering this method impractical for routine work also.

To add also some more optimistic facets, it must clearly be pointed out that Koopmans' theorem provides the basis for the understanding and crosslinking of the enormous amount of PE spectroscopic data. Thus, by using Koopmans' theorem the number of PE bands can be easily predicted for low energy PE spectra. And, most important, comparison between PE spectra of different molecules – probably the best method of assignment (see Section III) – is done preferentially on the MO level.

III. ASSIGNMENT OF PE SPECTRA BY COMPARING EQUIVALENT RADICAL CATION STATES OF CHEMICALLY RELATED MOLECULES

The results of PE spectroscopy not only contribute to our knowledge of radical cation states but render possible a better appreciation of bonding in molecules due to fruitful symbiosis provided by Koopmans' theorem (equation 6). In spite of its possible failures and the quality of calculation actually required (see Section II.E) this link between ionization potentials and SCF eigenvalues also allows one to correlate experimental data on the basis of simple models. The fundamental concepts of symmetry, overlap and orbital perturbation, derived by comparing chemical experience and theory, in return create an order in the vast collection of otherwise solitary facts. It is the possibility of being able to determine simultaneously all ionization potentials of molecules and to 'quasi' read off via Koopmans' theorem orbital energies that make PE spectroscopy suitable for the construction and testing of molecular orbital schemes.

Sometimes, even simple Hückel-type MO models[5,6] help in understanding and correlating PE spectroscopic data. These methods are at best a faint reflection of the rigorous SCF method, not specifying the exact nature of the basis functions and including just one diagonalization in order to get the symmetry properties right. Their surprising success, which will also be obvious from this review, can be traced back to the undefined nature of their basis functions and matrix elements. Of course, intuition and experience derived from numerous PE spectroscopic investigations help. As a few examples will illustrate in the following, this procedure at the same time leads to an assignment of PE spectra by chemical comparison.

A. Example 1: Assignment of the Butadiene π Ionizations Making Use of the Perfluoro Effect and the Distortion of Hexafluorobutadiene

The PE spectra in Figure 10 demonstrate in a largely self-explanatory way (i) the π interaction on coupling of two ethylene units; (ii) proof of the butadiene π_1, π_2, σ_1 sequence[94] by fluorine σ inductive lowering with the π ionization nearly unaffected due to counteracting $n_F \rightarrow \pi$ back bonding; and (iii) the sterically induced twisting around the central bond in the hexafluoro derivative, as evidenced by the reduced π split.

Vibrational fine structures support the π assignment, and the π ionizations allow one to deduce MO parameters, e.g. for butadiene the resonance integral $\beta_\pi = -1.22$ eV[94]. The perfluoro effect demonstrated turns out to be a general means of distinguishing σ and π ionizations (see, for example, references 26, 53, 95–97) and the dihedral angle of the hexafluorobutadiene molecule has been confirmed by electron diffraction[93]. Thus comparison of chemically related molecules based on MO arguments concerning interactions, substituent effects and geometry-induced perturbations, not only covers numerous independent observations but also cements the PE spectroscopic assignment.

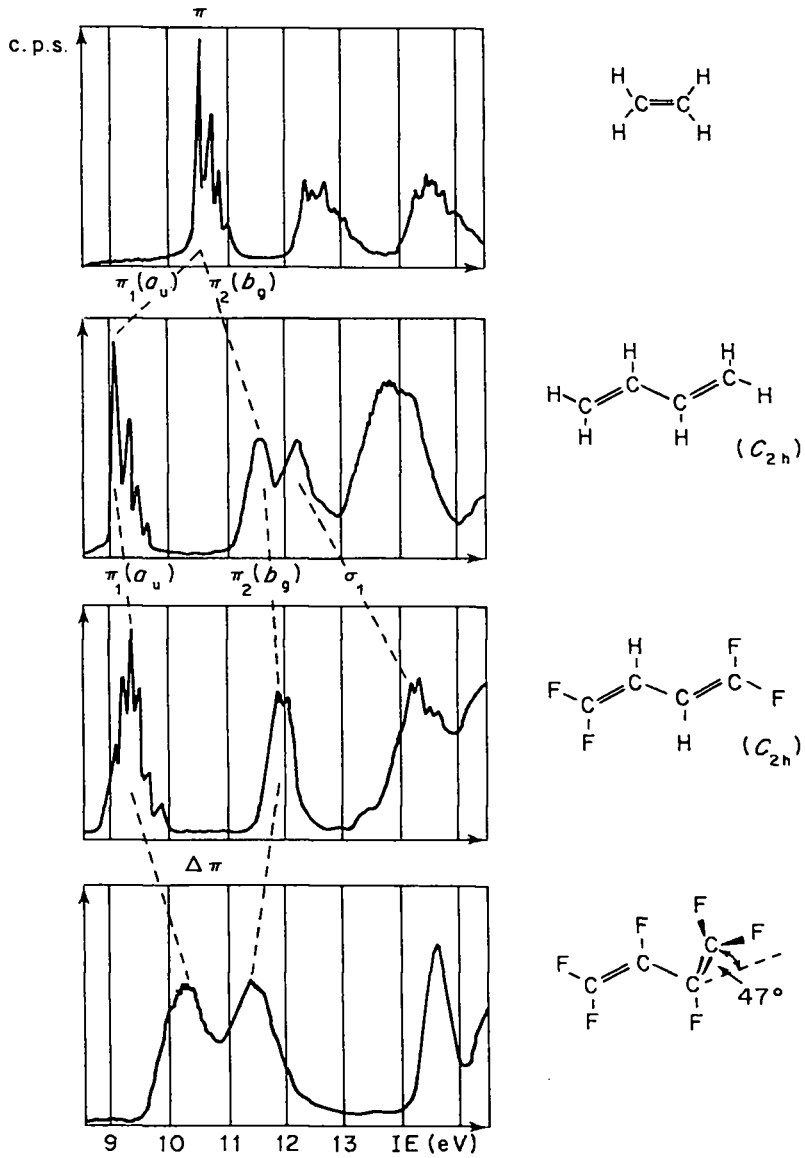


FIGURE 10. Comparison of the 9–13 eV PE spectra of ethylene[2], butadiene[94] and its 1,1,4,4-tetrafluoro- and hexafluoro-derivatives[93].

B. Example 2: Correlations across the Periodic Table[3,4,7,51]

Figure 11 displays two correlations, which include hydrogen halides: Figure 11(a) shows an isoelectronic comparison along the main quantum number $n = 3$ which has been constructed by consecutively pulling protons out of the argon nucleus to form hydride bonds[7,51], and Figure 11(b) follows the hydrogen halides down the group[51,98].

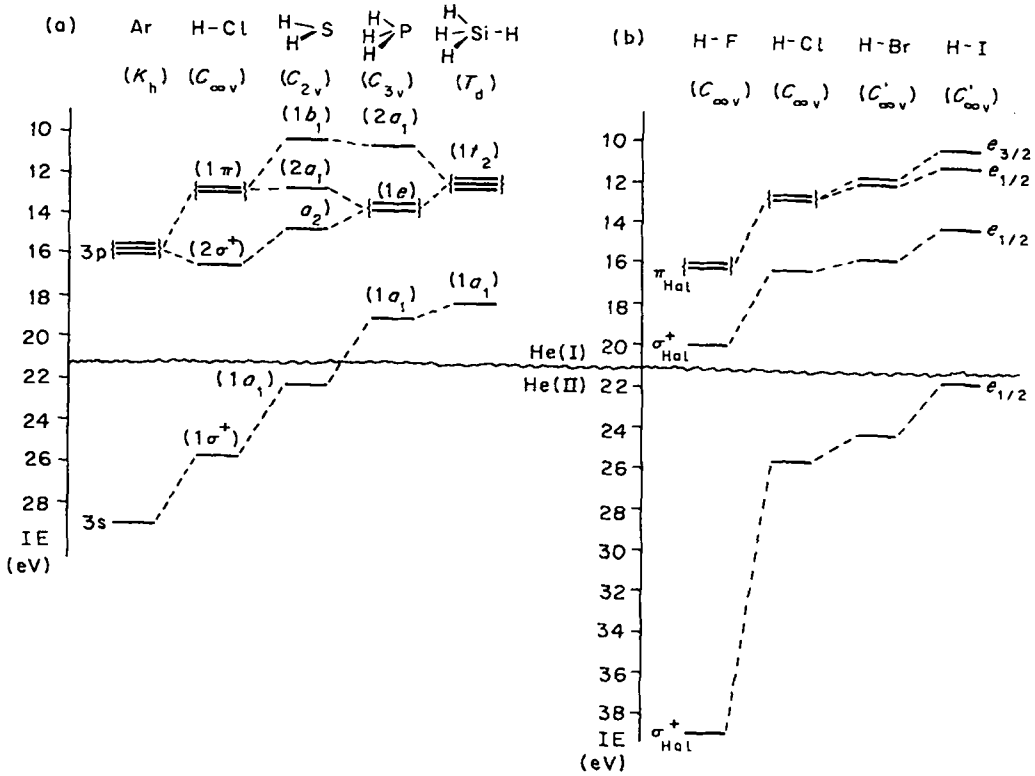


FIGURE 11. Correlation of ionization energies for (a) eight valence electron species EH_n of main quantum number $n = 3$ elements and (b) hydrogen halides.

Both correlations in Figure 11 clearly demonstrate how individual radical cation states of different molecules can be dealt with, using qualitative molecular orbital (QMO) models based on symmetry considerations. Choosing, for example, H_2S, the only system in Figure 11(a) without any degeneracy, group theory yields the orbital symmetries $\Gamma = 2a_1 + 1a_2 + 1b_1$. Moving along the QMO correlation lines (i) establishes $(1b_1)$ as sulphur lone pair in between $n_{Cl}\,(1\pi)$ and $n_P\,(2a_1)$; (ii) both n_S and σ_{SH} contributions are suggested by the adjacent $n_{Cl}\,(2\sigma^+)$ and $\delta_{HP}\,(1e)$; (iii) the $(1a_2)$ coming next must be σ_{SH} bonding according to the relationship $\sigma_{HCl}\,(2\sigma^+) \ldots \sigma_{HP}\,(1e)$; and finally (iv) the $(1a_1)$ found outside the helium(I) measurement range, as are most other s-type ionizations, largely represents $3s_S$. In this connection it has to be mentioned that perturbation theory predicts increasing mixing between symmetry-equivalent orbitals if their energetic distance decreases. Energy estimates for QMO basis orbitals can be derived advantageously from correlations of the type shown in Figure 11(b): accordingly, for example, the halogen lone pairs are ionized around 10 eV (n_I) to 16 eV (n_F), or the s-type ionizations are all found outside the helium(I) region with $IE(\sigma_F^+) = 39.9$ eV (!) documenting the extreme fluorine effective nuclear charge (see Figure 9). If Z_{eff} decreases, the ionization centre of gravity rises, and sum rules for either all ionizations[99] or, separately, s- or p-type ones[100] might be applied.

Reasoning along the above lines, QMO models based on symmetry and PE ionization energies can, for example, suggest the number of PE bands to be observed

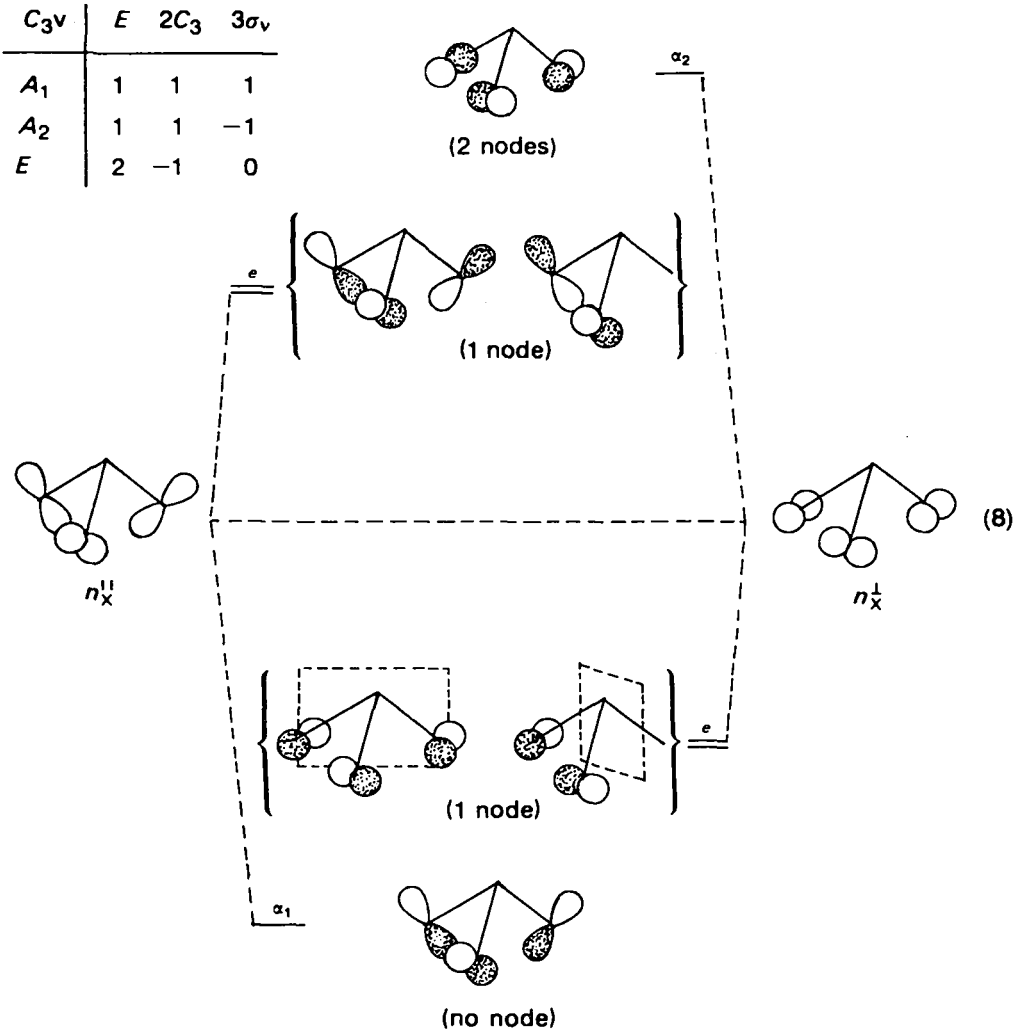
in characteristic energy intervals, facilitate the comparison of chemically related compounds and allow one to assign their PE spectra by means of perturbation arguments.

C. Example 3: Resemblances in the PE Spectra of H_3P, F_3P and F_3PO[7,33,101]

To exemplify further the usefulness of QMO correlations, Figure 12 presents the PE spectra of three C_{3v} phosphorus compounds and their seemingly complicated (?) assignment.

Again, understanding is facilitated by PE spectroscopic comparison. Starting with the H_3P orbitals already discussed (Figure 11 (a)), H/F substitution should increase all ionization energies in F_3P due to the high effective nuclear charge of F (Figure 11(b)), affecting most the σ_{PF} orbitals because of their high F contributions. In addition, every F ligand possesses two p-type lone pairs n_F, which according to QMO should split as follows[33]:

C_{3v}	E	$2C_3$	$3\sigma_v$
A_1	1	1	1
A_2	1	1	−1
E	2	−1	0



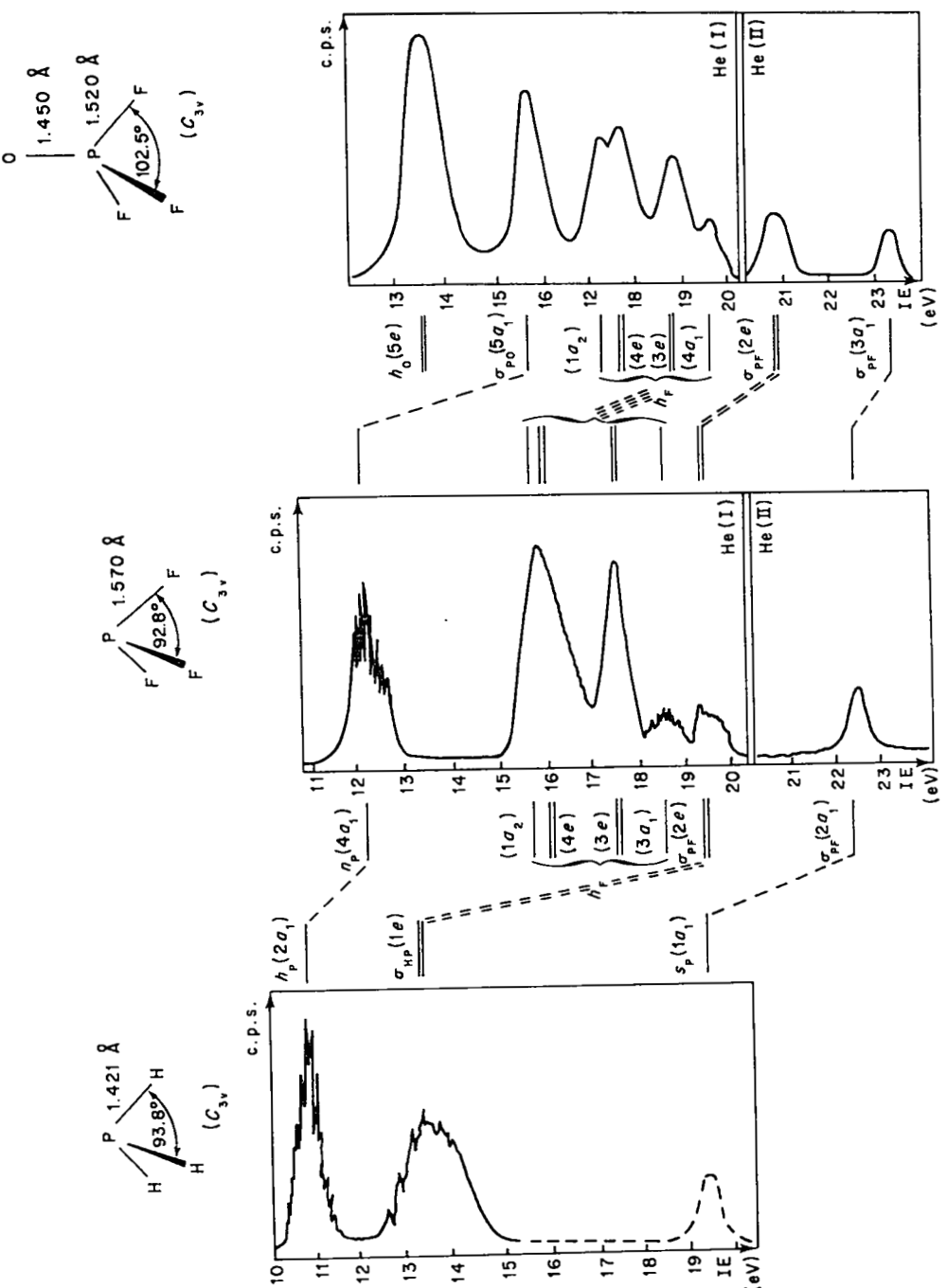


FIGURE 12. PE spectra of H_3P, F_3P and F_3PO together with their *ab initio* SCF supported assignments.

The F_3PO PE spectrum shows four bands in an approximate intensity ratio 1:2:2:1 resolved between 17 and 19.5 eV, which are accordingly assigned to the fluorine lone pair ionizations. Taking into account the renewed increase in ionization potentials resulting from oxygen addition to the n_P lone pair forming a σ_{PO} bond, most of the assignment proposed in Figure 12 has been covered. To continue with some details: for example, the rather high oxygen lone pair ionization energy $IE(n_O) = 13.52$ eV relative to H_2O with $IE(n_O) = 12.61$ eV[2] can be explained by strong back bonding P—O, in full agreement with the exceptionally large PO force constant of F_3PO ($f_{PO} = 11.38$ mdyn/Å: see reference 33). Angle opening and bond lengthening on adduct formation $F_3P \rightarrow F_3PO$ can be traced back to charge redistribution caused by the oxygen σ acceptor properties[33], which already showed up in the high energy shifts of the PE bands. The missing ionizations from $2s_O$ and $2s_F$ electrons are expected only at much higher energy (Figure 11(b)).

Considering that F_3PO contains a total of 32 valence electrons, the above interpretation of its radical cation states by using symmetry-adapted QMO models and PE spectroscopic comparison with other C_{3v} phosphorus molecules[33,101,103] – and the confirmation thereof by *ab initio* SCF calculations[102] – can hardly be surpassed in the simplicity of the argumentation.

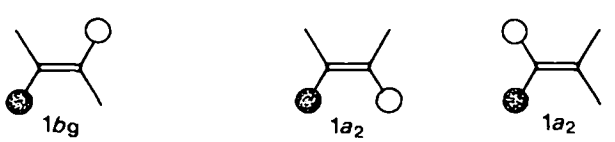
D. Example 4: Dichloroethylene Ionizations Used for PE Spectroscopic π Parametrization Based on an Internal Reference Orbital[6,104]

The three-step procedure is illustrated by Figure 13: the QMO basis functions of symmetries $\Gamma(C_{2h}) = 1a_g + 2a_u + 1b_g + 1b_u$, which are constructed in step 1 from π and lone pair n_{Cl} orbitals, mix according to their symmetry type in step 2, and the resulting QMO scheme is parametrized by comparison with the *trans*-dichloroethylene PE spectrum in step 3.

The parametrization procedure (Figure 13) is based on only a few essentials. Most important, there is only one – and therefore interaction free – occupied QMO of b_g symmetry, which consequently constitutes an internal reference α_{Cl}. The predominant split, $\Delta\pi$, can be directly determined by $IE_5(\pi_3) - IE_4(\pi_2)$. Subtracting $\Delta\pi$ from IE_1 yields $\alpha^{Cl}_{C=C}$, the basis π_{CC} orbital energy of *trans*-1,2-dichloro substituted ethylene. The difference to the corresponding value for unsubstituted ethylene $\alpha^{H}_{C=C}$ may be interpreted as an inductive effect $-I_{Cl}$. Finally, by solving the second-order determinant containing $\alpha^{Cl}_{C=C}$ and α_{Cl} (Figure 11), the resonance integral β_{CCl} is obtained[6,104]. In addition, σ admixture to the n_{Cl} combinations $4b_u$ and $5a_g$, i.e. so-called 'through bond' shifts[105], $\Delta IE(\sigma_{1,2})$, can be defined relative to the internal standard $\pi_2(1b_g)$.

Continuing along the above lines, numerous relationships offer themselves, and the parameters derived are applicable in many other problems, as demonstrated by the following typical examples:

(i) QMO models for the C_{2v} isomers, *cis*-1,2- or 1,1-dihalogenoethylenes, also predict an internal standard at approximately the same level, fully supported by nearly constant PE ionization energies[104] for the 'internal standard':



IE_4^{Cl}	12.64 eV	12.47 eV	12.48 eV
IE_4^{Br}	11.57 eV	11.53 eV	11.60 eV

(9)

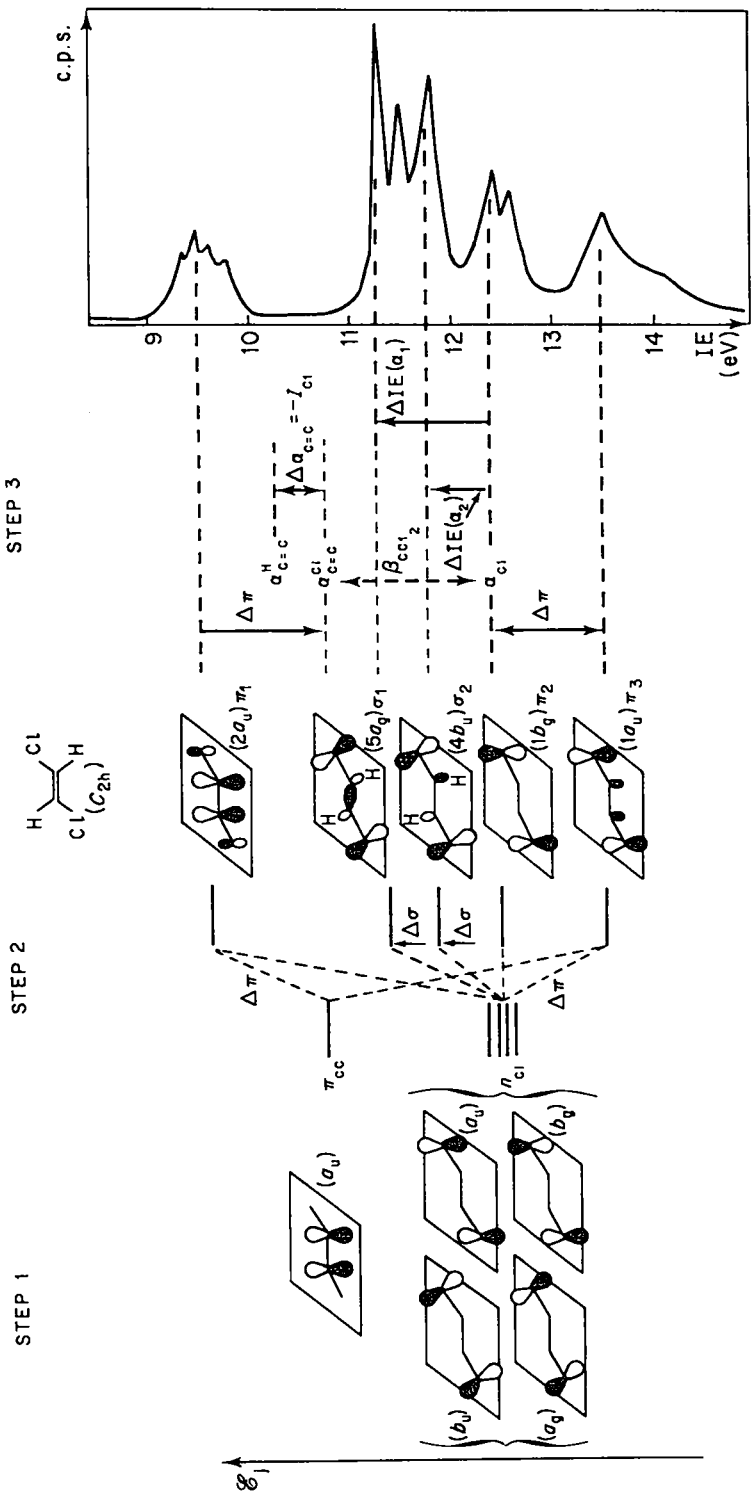


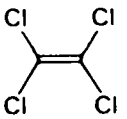
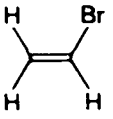
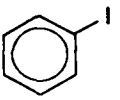
FIGURE 13. Parametrization of the π QMO scheme for *trans*-dichloroethylene by PE spectroscopic comparison.

(ii) The parameters derived, e.g.[104]

X	α_X	$\Delta\pi$	$\alpha_{C=C}$	$\Delta\alpha_{C=C}$	$\beta_{\pi X}$
Cl	−12.64 eV	1.15 eV	−10.85 eV	−0.44 eV	−1.8 eV
Br	−11.57 eV	1.33 eV	−10.88 eV	−0.37 eV	−1.6 eV
I	−10.3 eV	1.4 eV	−10.5 eV	0.0 eV	−1.5 eV

(10)

allow one to calculate π ionization energies for related molecules[6,104]:

(11)

IE			
calc.	9.39/14.64 eV	9.92/12.35 eV	8.77/9.24 eV
exp.	9.35/14.6 eV	9.87/12.30 eV	8 67/9.38 eV

(iii) Analogously, QMO parameters can be obtained for other substituents, e.g. $-NR_2$, $-OR$ or $-SR$[106], and the parametrization procedure can be applied to other problems as well, e.g. to hyperconjugation in compounds H_2CX_2[56,107].

The QMO models for halogen-substituted ethylenes, and especially their parametrization with ionization energies, create a network covering so many experimental details that, particularly in cases of disputed PE spectroscopic assignment[108–111], they often contribute the most convincing argument[104].

A linear correlation between Coulomb integrals α_X and free halogen atom X ionization potentials $IE_1(X)$[112]:

$$\alpha_X = -(K + IE(X)) \qquad \begin{array}{l} IE_1(I) = 10.45\ eV \\ IE_1(Br) = 11.84\ eV \\ IE_1(Cl) = 13.01\ eV \\ IE_1(F) = 17.42\ eV \end{array} \qquad (12)$$

has been found for the following series of compounds HX[98], X—X[69,89], H_3C—X[56], HC≡C—X[113], or R_3Si—C≡C—X[114], and proved to be quite useful in assignment of PE spectra.

In general, as indicated by the few examples presented, QMO models are easy to handle, correlatable to experimental data and comparable with one another by simple perturbation arguments. They thus cross-link numerous otherwise solitary facts, facilitate understanding, and stimulate chemical intuition. With respect to PE spectroscopy, the QMO approach allows the chemist also to incorporate σ ionizations in simple models, e.g. references 6, 56, 113 – as long as the molecules under consideration exhibit some (local) symmetry.

IV. SMALL PROTOTYPE HALOGEN COMPOUNDS

This section on mostly diatomic species, the hydrogen halides HX (Section IV.A) and the halogens XX (Section IV.B), and up to six atomic rare gas fluorides (Section IV.C) intends to bridge the gap between the introduction to PE spectroscopic information (Section II) and the assignment of PE spectra by radical cation state comparison (Section III), and, on the other hand, the more detailed discussion of the individual classes of organic halides. To begin with small molecules obviously has many

advantages. Thus the PE spectra of the linear diatomics HX and XX display in a transparent way many features of halogen substituents, which become obscured to some extent in polyatomic molecules. For an introduction into the point groups $C_{\infty v}$ and $D_{\infty h}$, reference 39 and, especially, reference 115 are recommended.

A. Hydrogen Halides

With the hydrogen halides being the most simple halogen-containing compounds, it is not surprising that their PE spectra have been studied repeatedly[98,116–120] and often with extreme quality. As an example the PE spectrum of HCl is presented (Figure 14(b)), which has been recorded with a molecular beam apparatus[118] allowing for high accuracy in the determination of spectroscopic constants (Table 1).

The nearly atomic nature of the radical cation ground state, assigned to predominant halogen lone pair character, is best demonstrated by the linear

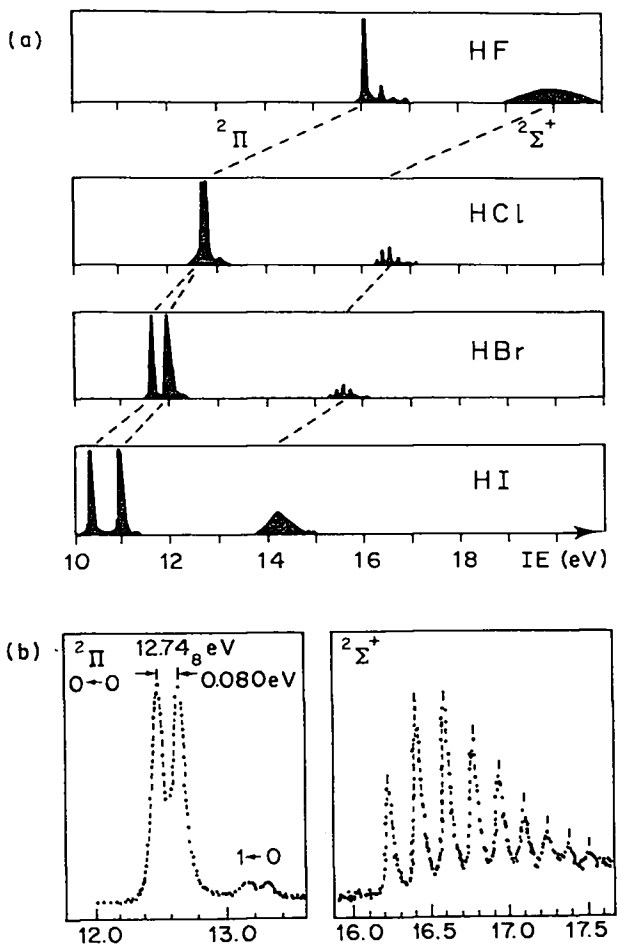


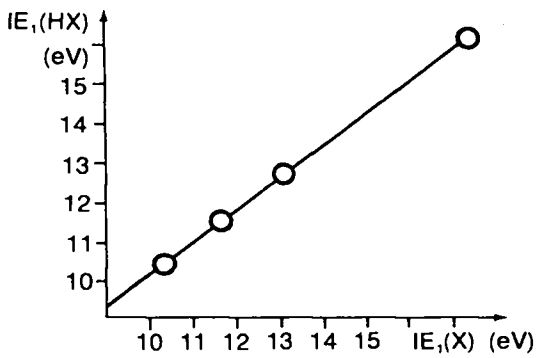
FIGURE 14. (a) Helium(I) PE spectra of the hydrogen halides[98] and (b) high resolution record of the HCl bands at 12.8 and 16.5 eV[118].

TABLE 1. Vertical ionization energies $IE_{1,3}$ (eV), observed vibrational states [$v'_{observed}$], spin–orbit splitting $\Delta IE_{1,2}$ (eV) and dissociation energy $D_0(HX) + IE(X)$ (eV) of the hydrogen halides

HX	$IE_1(^2E_{3/2})$	[$v'_{observed}$]	$\Delta IE_{1,2}$	$IE_3(^2\Sigma^+)$	[$v'_{observed}$]	$D_0(HX) + IE(X)$
HF[11]	16.05_4	[0, 1, 2]	0.030	19.11_8	[0, 1, 2, 3]	19.46[a]
HCl[118]	12.74	[0, 1]	0.08	16.25_4	[0–10]	17.44
HBr[98]	11.67	[0, (1)]	0.33	15.27	Predissociation for $v' \geq 4$	15.59
HI[98]	10.38	[0, (1)]	0.67	13.85–15.0		13.51

[a] $D_0(HF) + IE(H)$.

correlation resulting if first ionization potentials of the hydrogen halides are plotted against those of the halogen atoms[40]:



(13)

Some of the hydrogen halide PE data (Table 1) have been discussed already in preceding introductory chapters. Thus, the vibrational fine structure of HBr^+ (Figures 1 and 2) as well as its spin–orbit splitting (Section II.D) served as illustrative examples for the respective type of PE spectroscopic information on radical cation states. The comparison of each of the equivalent HX^+ states – $^2\Pi(E_{3/2})$, $^2\Pi(E_{1/2})$, $^2\Sigma^+(E_{1/2})$ and $^2\Sigma^+(E_{1/2})$, respectively – has been used to demonstrate the effect of decreasing effective nuclear charge with increasing atomic number of the elements along a group of the periodic table (Figure 11(b) and 'equation' 13). The following and more detailed interpretation of the observed HX^+ vibrational fine structures (Table 1 and Figures 1 and 13(b)), therefore, will only round off the PE spectroscopic comparison of the hydrogen halide radical cation states.

The vibrational fine structure of the $^2\Pi$ band varies considerably for the HX series of molecules (Figure 14(a) and (b)). For HF, the vibrationally excited states $v' = 1$ and $v' = 2$ are easily detected[119] (Table 1). For HCl, only $v' = 1$ can be observed with some confidence[118], and hardly any vibrational activity is connected with the HBr and HI $^2\Pi$ ionizations. This reflects, of course, the increase of bond lengths $\Delta r_e = r_{HX^+} - r_X$ upon ionization being largest for HF, where $\Delta r_e = 8.4$ pm[122]. This lengthening of the bond can be attributed to an avoided crossing of 2Π potential curves, which would lead to $H(^2S) + F^+(^3P)$ and to $H^+ + F(^2P)$[98]. The *ab initio* calculations on the $^2\Pi$ state of HF^+ support this view[123,124].

The vibrational fine structure of the $^2\Sigma^+$ bands also varies regularly within the HX series; its extent is intimately connected with the energies of the dissociation products of HF^+ ($^2\Sigma^+$) (c.f. Table 1). For HF^+, only a shallow, highly anharmonic potential is observed[119]. For HCl, the long progression of 11 members fits in well with a large

dissociation energy of HCl^+ ($^2\Sigma^+$)[118]. For HBr, predissociation for $v' \geq 4$ results in a considerable broadening of the corresponding PE peaks (Figures 1 and 2) whereas HI^+ ($^2\Sigma^+$) is simply dissociative, and, therefore, no vibrational fine structure is observed at all in the third ionization band of HI^+ (Figure 14). On the other hand, even rotational fine structure could be resolved in the PE spectra of HF and DF[125].

To end this section on the PE spectra of hydrogen halides and to demonstrate the capabilities of sophisticated computational methods when applied to small molecules, some spectroscopic constants[126], the equilibrium internuclear distance r_e, the equilibrium rotational constant B_e and the vibrational constant ω_0, are compared with calculated values for the HF^+ ($^2\Pi$) state[88]:

	r_e	B_e	ω_0	
exp.	100.1 pm	17.57 cm^{-1}	3090.4 cm^{-1}	(14)
calc.	100.2 pm	17.54 cm^{-1}	3116.4 cm^{-1}	

Most calculated values are within the limits of experimental error.

B. Halogens and Interhalogens

The diatomic, 14 valence electron halogens still belong to the simpler group VIIB derivatives. Their PE spectra (Figures 6 and 15) display sharp, prominent bands.

The halogen PE spectra correspond well to the 'textbook' QMO scheme for homonuclear diatomics (Figure 6). The lone pair ionizations give rise to sharp, prominent bands, which can be found in all halogen-containing systems. The interaction of halogen lone pairs is substantial, as is demonstrated by the 2–3 eV splitting of the π_g and π_u levels of the halogen molecules. The inner, s-type σ-orbitals are well outside the He(I) range. The assignment of the low energy region of the iodine PE spectrum – $^2\Pi_g(E_{3/2g})$, $^2\Pi_g(E_{1/2g})$, $^2\Pi_u(E_{3/2u})$, $^2\Pi_u(E_{1/2u})$, $^2\Sigma_g(E_{1/2g})$, respectively – has already been discussed in the context of higher order spin–orbit splitting (Section II.D).

The $^2\Pi$ bands of the halogen molecules, as well as those of the hydrogen halides and of the diatomic interhalogens, are split by spin–orbit interaction. In line with a first-order approach, the observed splittings are roughly 2/3 of the atomic splitting[40]; in heteronuclear cases weighted by LCAO coefficients[65]. For $Cl_2^+(^2\Pi_g)$, the spin–orbit splitting happens to coincide with the vibrational spacing[89], a similar situation occurs for FCl^+ [127]. The different splittings of the $^2\Pi_g$ and $^2\Pi_u$ states of iodine have been attributed to higher order effects, i.e. a mixing of π-type and σ-type orbitals[68,71] (see Section II.D).

Additional comments on the PE spectra of the halogen molecules and related phenomena are as follows. For F_2 Koopmans' theorem 'breaks down' (see Figure 9). The rather low dissociation energy of F_2 has been discussed based on PE spectra data[128]. PE spectra of donor–acceptor complexes between Br_2 and alkylamines have been studied[129]. In the case of the I_2 molecule, the adiabatic ionization potential is hidden by 'hot bands'[3,4] and, therefore, could only be determined using 'variable temperature' PE spectroscopy[49] (see Figure 15(b)). In general, the complication due to 'hot bands' explains some of the difficulties encountered in determining adiabatic ionization potentials by photoionization techniques[130]. The PE spectrum of I_2 has been used to assign the UV spectrum of I_2^+[131]; see also reference 71. It should also be mentioned that the molecules X_2, as well as HX, have been used as test molecules for studies of varying photoionization cross-sections depending on excitation energy[132–134].

The diatomic interhalogens ClF, BrF, ICl and IBr display PE spectra[70,127,135], which can easily be related to those of their parent molecules. Spin–orbit splittings of the $^2\Pi$

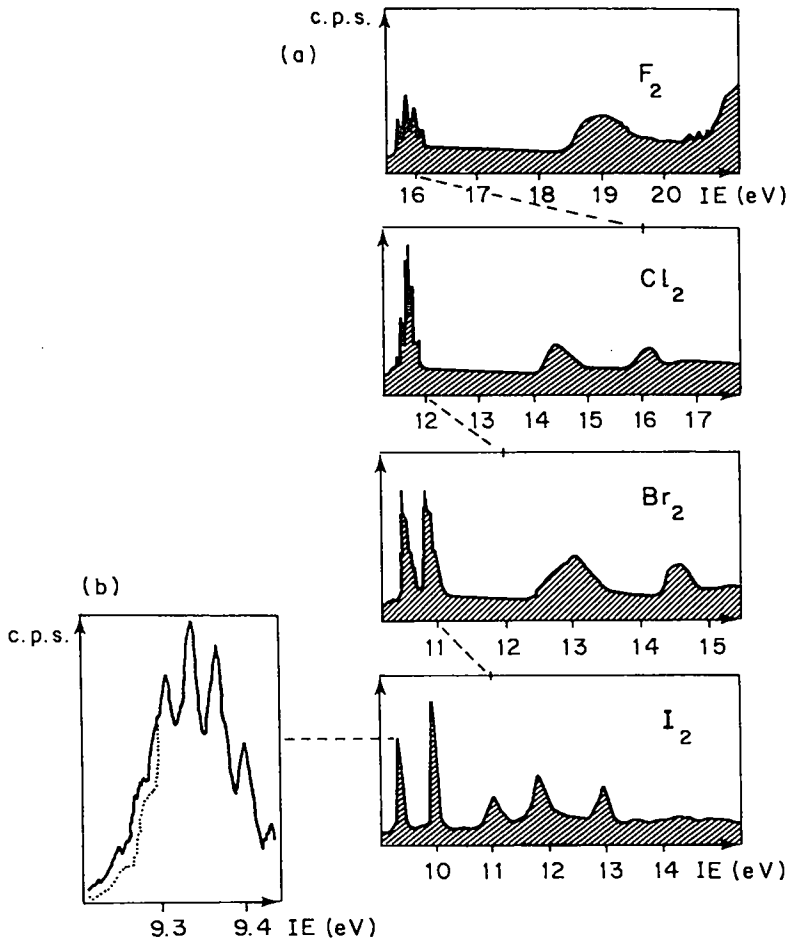


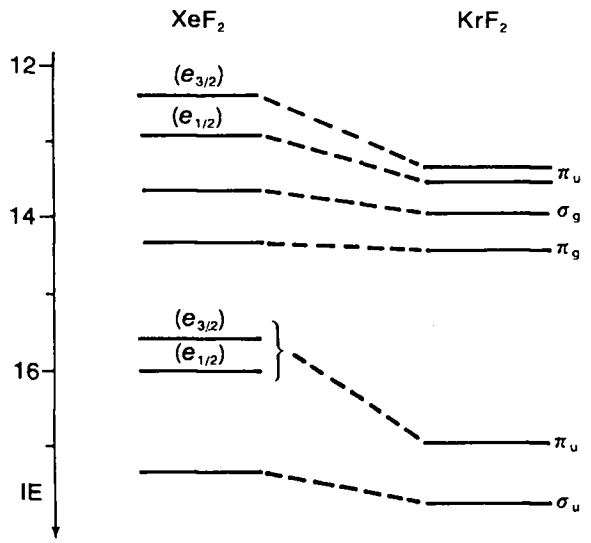
FIGURE 15. (a) Helium(I) PE spectra in different energy regions of the halogens[69], aligned (----) for comparison. The assignment of the iodine PE spectrum is given in Figure 6. (b) The first PE band of I_2, assigned to the $^2\Pi_{3/2g}$ state, at 300 K (——) and at 260 K (·····)[49].

states agree well with the character of the corresponding orbitals. The T-shaped molecules ClF_3 and BrF_3, as well as BrF_5 and IF_5, have also been investigated PE spectroscopically[135–137]. The first intense band at 12.88 eV of ClF_3 (12.38 eV in BrF_3) refers to the two (a_1) and (b_2) lone pair combinations on the central atoms, which, according to minimal basis set *ab initio* calculations, contain significant X—F bonding contributions[135]. The a_2 ionization energy, representative for fluorine lone pairs, is assigned to bands at 15.36 eV (ClF_3)/15.05 eV (BrF_3). Being one of the lowest n_F ionization energies observed so far, its value reflects a substantial electron transfer from the central atom to the fluorines[135]. The second band of IF_5 ($1a_2$) shows a larger ionization energy than the corresponding one of BrF_5, which can be traced to decreased lone pair–lone pair interactions due to larger bond distances in the bromine compound[136].

C. Noble Gas Fluorides

The highly corrosive, yet fascinating rare gas fluorides XeF_2[61,138,139,141], KrF_2[140,141], XeF_4[137,138], XeF_6[138] and XeF_4O[137,142] have been investigated partly by helium(I) and by helium(II) radiation. The assignments are based mainly on SCF calculations[143] applying Koopmans' theorem (see Section II.E). Judging from the regression, $IE_n \approx -0.92\,\varepsilon_j^{SCF}$, the conclusion is drawn that MO models can account for the observed ionization energies, and thus for the bonding in these compounds.

As an informative example, the helium(I) PE spectrum of the linear XeF_2 (Figure 4) will be chosen, the assignment of which has already been discussed with respect to the symmetry-dependent first order spin–orbit coupling (Section II.D): only the $^2\Pi_u$ states contain larger contributions from the central Xe atom and, therefore, exhibit strong splitting into $E_{3/2}$ and $E_{1/2}$ radical cation states[61] ('equation' 15). The $M^{\cdot+}$ state sequence corresponds to the valence orbital occupancy $(2\pi_u)^4$, $(3\sigma_g)^2$, $(1\pi_g)^4$, $(1\pi_u)^4$, $(3\sigma_u)^2$, . . . , and has also been deduced for the closely related krypton difluoride[140,141]. The largest differences in ionization energies observed between XeF_2 and KrF_2 ('equation' 15) concern the $^2\pi_u$ states, for which the largest contribution from the central atom has already been deduced from spin–orbit coupling arguments, and which, therefore, should be most sensitive to the increase in effective nuclear charge from Xe to Kr:



(15)

Although this interpretation incorporates the essential PE spectroscopic data, doubts concerning overlooked 'shake-up' transitions, i.e. processes with simultaneous two-electron excitations, have been published[141]. Attention has also been directed towards the deviations in the calculated SCF eigenvalues, which via Koopmans' theorem yield ionization energies which are too small, i.e. the opposite of the generally observed phenomenon, and which have been attributed to strong correlation effects (see Figure 8).

Analogously, only minor changes are observed PE-spectroscopically, when oxygen is added to XeF_4 to form XeF_4O – except for the additional oxygen lone pair ionizations[142]. This finding is interpreted – although disputed[137] – in terms of a small back-donation $p_O \rightarrow d_{Xe}$, favouring the polar structure $F_4Xe^+—O^-$ [142].

Altogether the halogens, the interhalogens and especially the rare gas halides represent extremely electron-rich molecules. In organic chemistry, only heteroatom centres from groups VB to VIIB will raise the number of electrons in neutral compounds above the four electron per centre level.

V. HALOGENATED HYDROCARBONS AND OTHER SATURATED GROUP IVB HALIDES

Main group elements are often classified into those considered to be electron-deficient (groups IA to IIIB), electron-rich (groups VB and above) and into those with four valence electrons, i.e. the right number to form neutral closed-shell compounds containing, for instance, four single covalent bonds. With few structural exceptions like alkyl anions or silylenes, lone pairs are only introduced via hetero atoms like the group VIIB halogens.

In view of the variety of carbon skeletons and the multitude of their halogen derivatives, these will be covered according to their carbon coordination number 4 as saturated group IVB halides (this section) or according to the carbon centre coordination numbers 3 or 2 as halogen-substituted π systems (Section VI). Sections on halomethanes, on open-chain or cyclic π systems, or on carbonyl halides not only will facilitate the survey, but will also present some of the highlights.

In addition to the literature quoted in the following text, there are general references to the PE spectra of organic halides[2,3–6,8] and an accumulation of PE data[24]. A recent review deals with compounds containing the 'pseudohalogen' cyano substituent[35].

A. Halomethanes

Halomethanes $H_{4-n}CX_n$ have repeatedly attracted the interest of PE spectroscopists: besides investigation of almost the whole series[2,51], special aspects like the lone pair n_X interactions[56], spin–orbit coupling[62] or comparison with corresponding silicon halides[144] are reported. To facilitate access to the rather scattered literature, Table 2 summarizes quotations for the individual halomethane molecules.

Since the details of controversial arguments are beyond the scope of this chapter, only a summary of PE spectroscopic characteristics and the most probable of differing assignments will be given. As an example for halomethane PE band patterns, those of the chloro derivatives[51] are visualized in Figure 16, because in contrast to X = F the lone pairs n_{Cl} are lower in ionization energy (Figure 11), and compared to bromine and iodine spin–orbit coupling is negligibly small (Section II.D).

TABLE 2. References to PE studies of individual halomethanes $H_{4-n}CX_n$

X	CX_4	HCX_3	H_2CX_2	H_3CX
F	2, 51, 57, 132, 146–151, 153–155, 157, 159–161	2, 51, 132, 148, 151, 162	2, 51, 132, 148, 150, 151, 162	2, 51, 132, 148, 150, 151, 162
Cl	2, 51, 56, 57, 144, 147, 151, 156, 159, 165	2, 51, 56, 144, 151, 156, 165	2, 51, 56, 144, 151, 156, 164, 165	2, 51, 56, 58, 144, 150–152, 156, 158, 163, 164
Br	2, 51, 56, 57, 62, 165	2, 51, 56, 62	2, 51, 56, 62	2, 51, 56, 58, 62, 150, 151
I		2, 62	2, 51, 62, 79, 164	2, 51, 58, 62, 150, 151

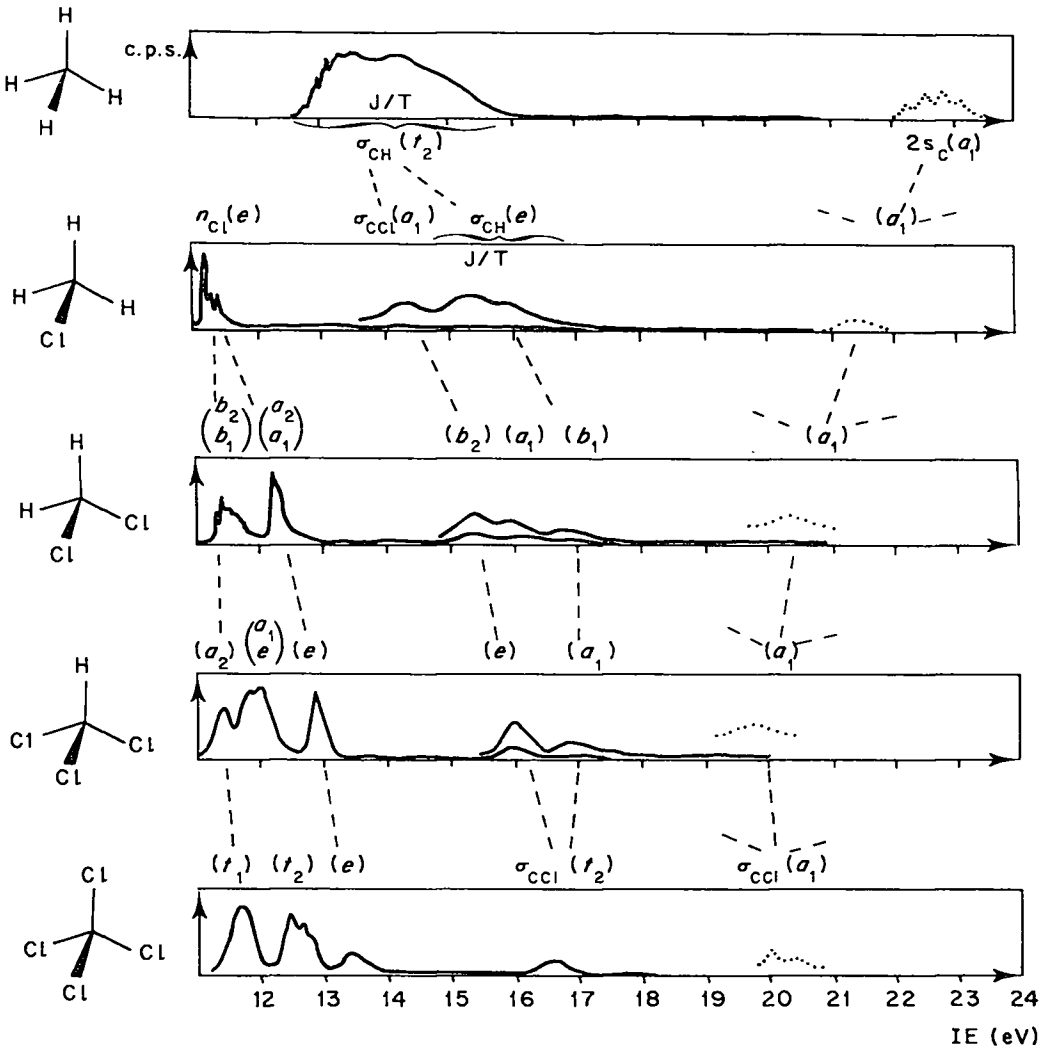


FIGURE 16. PE bond patterns[15] of the chloromethane series $H_{4-n}CCl_n$ with assignment.

Although no direct comparison is possible for molecules differing in number of valence electrons as well as in symmetry, obviously in the PE spectra of compounds $H_{4-n}CCl_n$ the regions can be distinguished corresponding to n_{Cl}, to σ_{CCl}/σ_{CH} and to $2s_C/3s_{Cl}$ ionizations. This order of increasing energy is also found for X = Br, I, whereas for X = F the n_F ionizations are in between σ_{CH} and σ_{CF}. Most of the s-type ionizations have to be measured using the He(II) excitation of 40.78 eV[51,148,21]. The following characteristics may be summarized from a comparison of derivatives $H_{4-n}CX_n$ with substituent X varying from F to I.

1. *Methyl halides, H_3CX*

An assignment of the simple PE spectroscopic splitting pattern of methyl halides (see Figure 16) is easily derived from the methane PE spectrum by adding an *e*-type

lone pair ionization, which corresponds to the first band for H_3CCl, H_3CBr and H_3CI. Its shift relative to the HX ionizations (Figure 10) can be rationalized by hyperconjugative interaction between the two *e*-type orbitals n_{Cl} and σ_{CH_3}[56,164], for which the following PE spectroscopic parameters have been derived[164]:

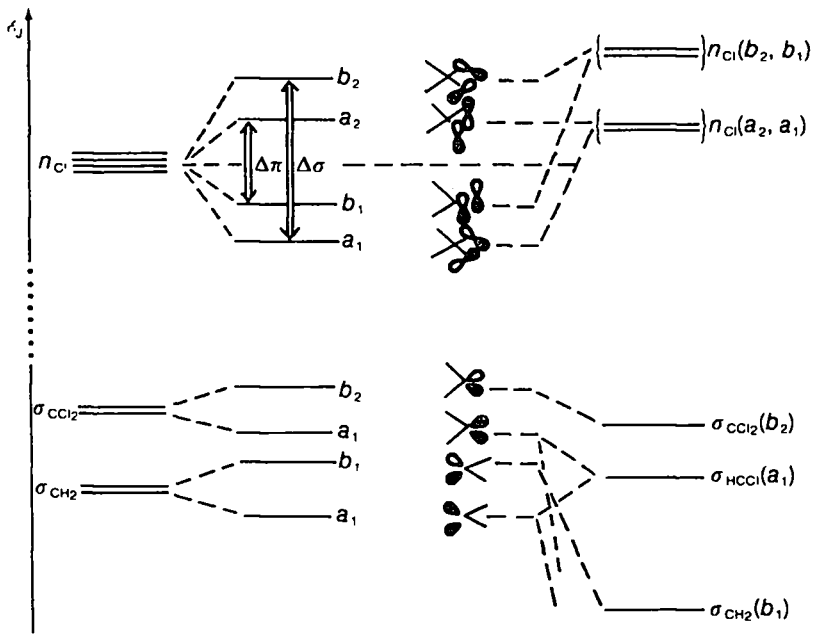
X	α_X	α_{CH_3}	$\beta_{CH_3/X}$
Cl	−12.1 eV	−14.5 eV	−1.6 eV
Br	−11.3 eV	−14.5 eV	−1.5 eV

(16)

For H_3CCl, a PNO–CEPA calculation with an almost saturated basis including polarization functions has been performed[163]. For H_3CBr and H_3Cl, the spin–orbit coupling effect amounts to 0.32 eV and to 0.62 eV, respectively[51], in reasonable agreement with the atomic coupling constants[40,60].

2. *Dihalomethanes, H_2CX_2*

Although no degeneracies are possible for molecules of C_{2v} symmetry, the PE spectra of dihalomethanes (see Figure 16) display several overlapping bands. For the assignment of the H_2CCl_2 ionization pattern, the following QMO scheme can be parametrized using vertical ionization energies[164]:



For methylene chloride, the most probable radical cation state sequence corresponds to QMO order[51] $n_{Cl}(b_2, b_1) < n_{Cl}(a_2, a_1) < \sigma_{CCl}(b_2) < \sigma_{CH}(a_1) < \sigma_{CH}(b_1)$ . . . , which is displayed in Figure 16. The PE spectroscopic parametrization yields splits $\Delta\sigma_{Cl} \sim 1.3$ eV and $\Delta\pi_{Cl} \sim 0.5$ eV, respectively[56,164], and for the hyperconjugation between the b_1 type orbitals n_{Cl} and σ_{CH_2} a resonance integral $\beta_{CH_2/Cl} \sim -1.6$ eV results[164]. For H_2CF_2 [147], the assignment $\sigma_{CH}(2b_1) < \sigma_{CH}(4a_1)$

$< n_F(3b_2) < n_F(1a_2) < \sigma_{CF}(2b_2)$ ... (reference 147 uses a different coordinate system) is complicated by the relatively high fluorine lone pair ionization energy (Figure 10), whereas all others show first the lone pair n_X ionizations. For methylene bromide and especially for methylene iodide, H_2CBr_2 and H_2CI_2, spin–orbit coupling interactions dominate[62] and, therefore, spinor group representations (see Section II.D) should be used to characterize the radical cation states.

3. *Haloforms, HCX_3*

Some ambiguity still remains concerning the position of the lowest $^2A_1$ radical cation state: some prefer it below[156], and some above[51,56] the $^2A_2$ state in $CHCl_3^+$. Assignment is facilitated in the bromoform PE spectrum due to spin–orbit splitting of the *e*-type bands; however, in this case there is disagreement concerning the assignment of the multiplet components. Regarding the large splitting for CBr_4^+: $\Delta(1t_1) = 0.33$ eV and $\Delta(3t_2) = 0.61$ eV[57], the assignment IE($3e$) → 14 eV and IE($4e$) → 16 eV[56] seems less probable[62]. Finally, the lone pair ionizations of iodoform HCI_3 are fully determined by spin–orbit coupling, the most probable assignment being $e_{1/2} < e_{3/2} < e_{1/2} < e_{1/2} < e_{3/2} < e_{1/2}$...[62]. Compared to the many open questions concerning the lone pair ionizations, the assignment of the next higher M^+ states to σ bonding orbitals seems more definite[51,57,148].

4. *Tetrahalomethanes, CX_4*

Under T_d symmetry, the n_X lone pair orbitals transform according to t_1, e and t_2, this sequence being the one determined by pure n_X/n_X overlap. Within the MO model, the t_2 lone pair orbital will be further destabilized by antibonding admixture of the C—X bonding t_2 orbitals. The generally accepted radical cation state sequence (Figure 17) is supported by the results of *ab initio* calculations[148], by chemical comparison within the

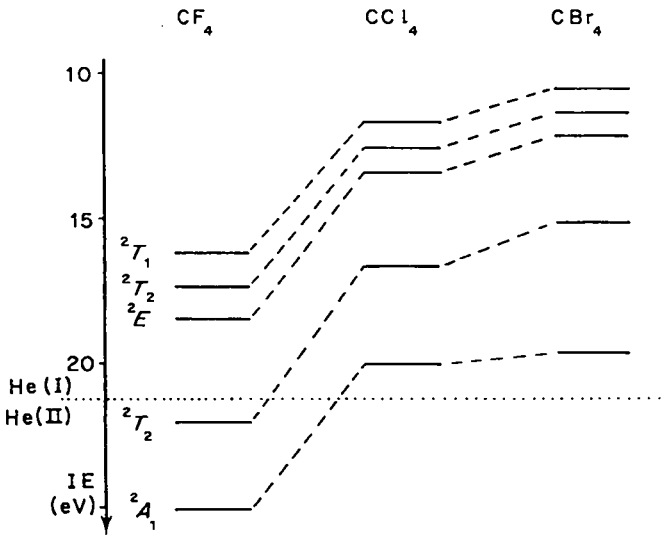


FIGURE 17. Comparison of the PE spectroscopic radical cation state sequence for CF_4, CCl_4 and CBr_4[165].

series $H_{4-n}CX_n$[51] or, for example, with F_3NO[146], by X-ray emission data of CF_4[161], by intensity arguments from X-ray excited PE spectra[154] or by spin–orbit splitting of the $^2T_1$ and $^2T_2$ states[56,57,62].

In this connection it should be mentioned that calculations[57,62] attribute the large CBr_2 spin–orbit interaction – by analogy to BBr_3 and BI_3 for example[62] – to the admixture of σ bonding orbitals. Concerning *ab initio* SCF calculations in the interpretation of the fluoromethane PE spectra[148], the widespread approximation to Koopmans' theorem (equation 6), $IE_n \sim -0.92\ \varepsilon_j^{SCF}$, has been applied. Nevertheless, as this implies corrections of more than 1 eV, the significance of calculated small orbital energy differences – e.g. the 3 eV for $1t_1/4t_2$ in CF_4 – has to be questioned in general.

5. *Further PE spectroscopic investigations on halomethanes*

Numerous other results have been obtained from PE spectroscopic investigations of halomethanes. For instance, analysis of the PE band fine structure corresponding to the ^2E states of H_3CX^+ cations[58] shows that for H_3CI^+ spin–orbit interaction dominates, whereas the complex intensity patterns for X = Cl, Br are due to vibronic interaction[55], with the C—H stretching vibration $\nu_5(e)$ as Jahn–Teller active mode. The fate of the resulting cations $H_{4-n}CCl_n^+$ and CBr_4^+ has been studied[166,167], and halogen loss found to be the preponderant fragmentation process in contrast to results for $H_{4-n}CF_n$[148,168]. Angular distribution measurements for halomethanes[150,151] not only allow one to distinguish overlapping bands in the PE spectra, but yield a high angular parameter β for the non-bonding orbitals in derivatives with X = Cl, Br, I due to the atomic contributions. The more complex behaviour found for X = F is explained by the large mixing of n_F and σ_{CF} orbitals.

The PE spectra of mixed halomethanes, i.e. containing several different halogen substituents, have also been interpreted[169–171].

B. Higher Alkyl Halides

The sharp PE bands arising from lone pair ionizations of halogen substituents X = Cl, Br, I (Figure 5) have been used repeatedly as a probe into the effects of alkyl groups[100,172,173]. For example, a simple relationship[172] proposes that the difference in lone pair ionization energies of an alkyl halide RX and of H_3CX

$$IE(RX) - IE(H_3CX) = \mu_R\chi_X, \tag{19}$$

can be correlated with the product of two parameters, one for R and one for X. The interpretation, however, that equation (19) exclusively represents the inductive effects of the alkyl group R, is an oversimplified one.

The constancy of spin–orbit splitting in lone pair PE bands of several alkyl bromides – independent of widely varying ionization energies – has been observed[17] and subsequently explained by simultaneous hyperconjugation[64], as already discussed (see Figure 5). If hyperconjugative interaction becomes dominant, as, for instance, with the Walsh orbitals of the cyclopropyl ring, one broad and one sharp PE band result (Figure 5; cyclopropyl bromide). Prospective analytical applications, i.e. identification of halogen-substituted hydrocarbons by their sharp lone pair PE bands, have also been explored[11,19,25,186,187]. The needle-like ionization patterns, especially of small halogen compounds (Section IV), are indeed well suited for real-time gas analysis in flow systems: they facilitate the determination of low temperature thermal decomposition channels, the detection of short-lived intermediates or the optimization of heterogeneously catalysed reactions[11] (Section X).

Numerous other saturated organic halogen compounds have been investigated PE spectroscopically. The studies include, for instance, the groups of the haloethanes,

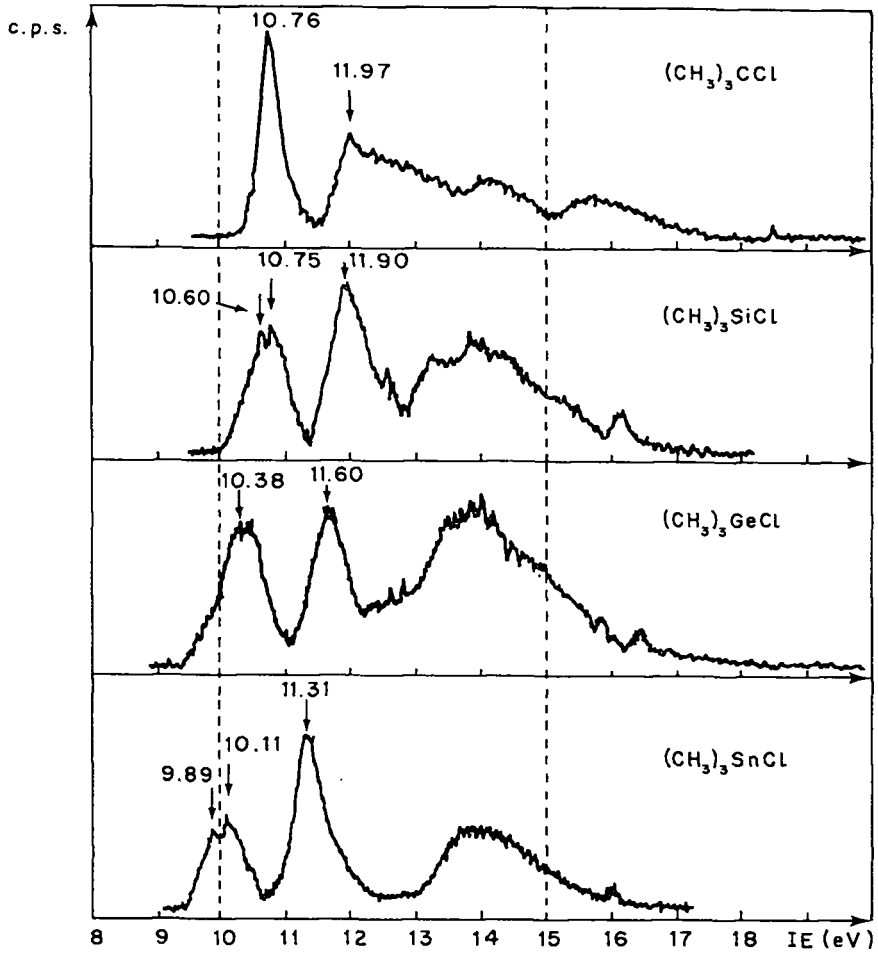


FIGURE 18. Helium(I) PE spectra of the homologous compounds $(H_3C)_3$ ECl of the group IVB elements. E = carbon, silicon, germanium and tin[184].

$X_nH_{3-n}C{-}CH_{3-m}Y_m$[174–183], the iodoalkanes, R—I[65,184], and some larger alkyl halides, $C_nH_{2n+1}X$[100,184] (Figure 18).

Other work on compounds with halogen-substituted alkyl group involves acetone[188] or acetone imines[189].

Repeatedly, perfluoro compounds have been investigated (see also Section VI on carbon π systems). The studies include, for instance, hexafluoro Dewar benzene[190] and hexafluoroethane, for which photoion/photoelectron coincidence measurements have been performed[191]. In general, F_3C substitution has been used quite often to simplify the low energy region of PE spectra, since F_3C groups give rise to PE bands only above 15 eV; see, for example, references 77, 192–196.

C. Halogen Derivatives of Silicon, Germanium and Tin

The PE spectra of the series of group IVB trimethyl chlorides $(H_3C)_3ECl$ with E = C, Si, Ge, Sn (Figure 18) do not differ significantly: all four of them display

two low energy bands, which shift less than 1 eV between C and Sn due to the decreasing effective nuclear charge, and one big ionization hump behind 13 and 17 eV due to numerous overlapping δ_{CH} and δ_{CECl} ionizations[184].

Slightly larger differences are displayed on comparison of the 'parent' hydrogen derivatives H_3ECl or other smaller sized molecules like the penta-atomic tetrafluorides (Figure 19 and Table 3).

It was PE spectroscopic observations like the ionization maximum at silicon for ^2E radical cation states of the chlorides H_3ECl (Figure 19), which suggested some $n_X \rightarrow 3d_{Si}$ back-bonding. Consequently, the attempt to prove or disprove 3d orbital participation undoubtedly became one of the stimuli for the extensive PE spectroscopic studies of silicon, germanium and tin halides (Table 3); it was hoped – in vain[163,197] – that PE spectroscopy, like many other techniques in their time, would be able to furnish a definite decision. The present state of affairs may be summarized as follows: most accurate PNO–CEPA calculations employing an almost saturated basis set both for H_3CCl and H_3SiCl have demonstrated[163], that the inclusion of d-type polarization functions at all centres, and especially for chlorine, does improve slightly the resulting total wave function. By definition, however, no simple orbital approach – as has been discussed extensively with respect to the validity of Koopmans' theorem in Section II.E – can correctly incorporate effects like electronic reorganization or correlation to reproduce the experimental radical cation state data.

In order to illustrate the problems encountered on that route, two cases – that of SiF_4 and that of H_3SiCl (Figure 19 and Table 3) – will be discussed in some detail. Concerning silicon tetrafluoride, the orbital sequence agreed upon[57,147,155] after some dispute[111,149,201] is the same as for the carbon analogue, i.e. $1t_1 < 3t_2 < 1e$ . . . (see

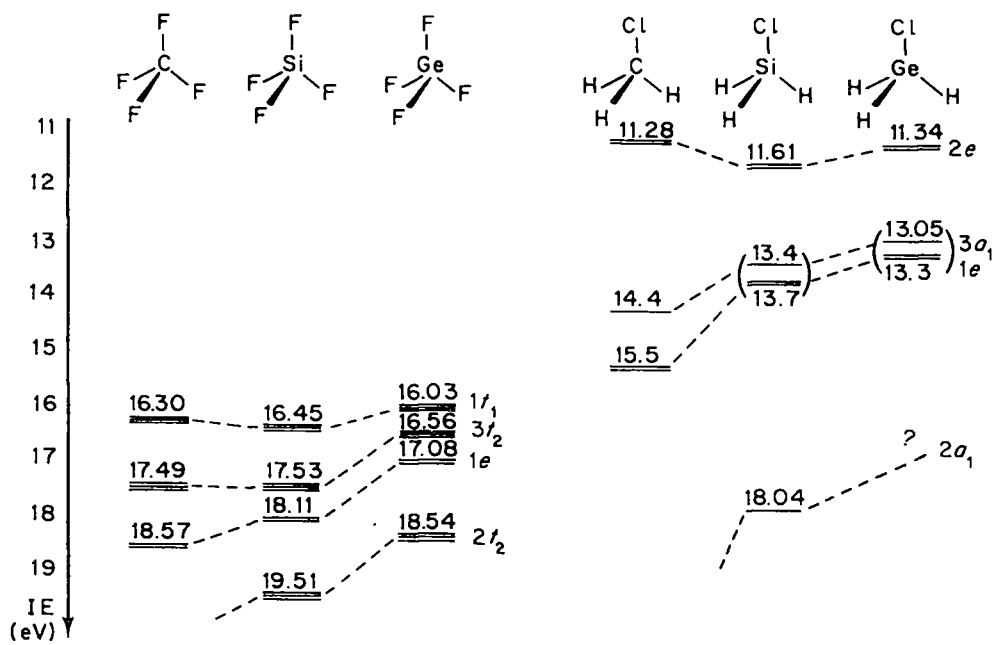


FIGURE 19. Comparison of the radical cation state sequences for certain group IVB tetrafluorides EF_4[147] and monochlorides H_3ECl[152,199] (E = C, Si, Ge, Sn).

TABLE 3. References to PE studies of individual silicon, germanium and tin halogen derivatives $H_{4-n}EX_n$

X	n	$H_{4-n}SiX_n$	$H_{4-n}GeX_n$	$H_{4-n}SnX_n$	Miscellaneous
F	4	11, 57, 143, 147, 149, 155, 159, 160, 201	111, 143, 147, 159, 160, 198		
	3	200			F_3SiX[200] (X = Cl, Br, CH_3, SiF_3)
	2	200, 201	199		
	1	155, 199, 201	152, 199		
Cl	4	57, 144, 147, 201	57, 147	57, 147	
	3	144, 201			$Cl_3Si—SiCl_3$[200]
	2	144, 199, 201	199		$(H_3C)_{4-n}SiCl_n$[184,204]
	1	144, 152, 199, 201	152, 199		$R_{4-n}SiCl_n$(R = $N(CH_3)_2$,OCH_3)[202]
Br	4	57	57	57	
	2	199, 201	199		
	1	152, 199, 201	152, 199		
I	4		203	203	
	2	199	199		
	1	152, 199	152, 199		

Figure 17). However, the following consequences are expected, if silicon is introduced as central atom:

(i) The increase in bond length should diminish 'through space' interaction[105] between the n_F lone pairs, and therefore reduce the split t_1/e as well as increase the t_1 ionization.

(ii) Due to its smaller effective nuclear charge relative to carbon, the central silicon atom should release electron density onto the F ligands, lowering the corresponding ionization energies.

(iii) Assumed back-donation $\overset{\frown}{F—Si}$ should generally raise all those ionization energies which are affected by reduced F atom charge, and especially the two assigned to t_2 and to e orbitals, in which Si π orbitals participate, thereby enlarging the split t_1/e.

(iv) Also hyperconjugation, i.e. mixing of the symmetry-equivalent $3t_2$ and $2t_2$ orbitals, has to be taken into account: according to second-order perturbation (Section V.D), it should contribute the more the smaller $\Delta\delta$ and the larger $\beta_{\pi X}$, i.e. the shorter the bond.

Considering all the above and partly counteracting effects, the PE spectroscopic data (Figure 19) are less conclusive than has been hoped. For CF_4/SiF_4, the split $1t_1/1e$ decreases from 2.27 to 1.66 eV, and if one takes the mean of the $1t_1/1e$ ionizations as a measure of n_F lone pair ionization energy, it is lowered by 0.1 eV (Figure 19). In GeF_4, with all ionization shifted to lower energies, these effects are carried on. Any conclusion concerning the individual interactions listed above, which cannot be separated, has to rely on calculation or estimation. Thus, on the basis of CNDO calculations, a much larger reduction of the split t_1/e has been expected for smaller 'through space' interaction alone[147], and the amount of charge transfer is not easy to establish.

From the H_3SiCl PE spectrum (Figure 19), another possible 'proof' of $3d_{Si}$ orbital participation has been anticipated. Similar counteracting effects should be operative in observable PE band shifts: for the n_{Cl} lone pair ionization energy, a decrease due to d orbital participation would be expected. Enhanced negative charge on the chlorine substituents would also lower the ionization energy. However, for H_3SiCl, hyperconjugation with SiH bonds will introduce antibonding contributions, whereas d orbitals should strengthen back-bonding. Therefore, a cation stretching frequency ν^+_{SiCl} reduced relative to the neutral molecule would 'prove' $3d_{Si}$ orbital mixing – but the observed frequency change $\nu^+_{SiCl} \sim 500\ cm^{-1}$ relative to $\nu_{SiCl} = 545\ cm^{-1}$ [201] is just above the experimental uncertainty (see Section II.A).

Also, all other attempts to detect some PE spectroscopic evidence for d orbital participation proved to be just as futile, an 'experimental' result, which may be rationalized as follows: although d orbitals provide an attractive rationale for higher row group IVA elements, separate 'measurement' of their contribution is impossible. Within the interplay of effects within bonding models, partly opposing each other, their magnitudes can only be estimated from calculations. In this respect, it has been repeatedly claimed that d orbitals are superfluous and can be discarded[30,57,163,197]. In the calculation itself, d orbital participation becomes more and more diffuse in an extended basis set[163], and is only well defined within a minimal basis, making up for some of the deficiencies of the latter. CNDO/2 has been found to overemphasize d orbital participation[197].

Conclusions similar to those obtained from the comparison CF_4/SiF_4 or from H_3SiCl (Figure 19) have been drawn from PE spectroscopic investigations of other silicon, germanium and tin halides (Table 3). Other compounds studied which contain Si—Hal bonds are $[(H_3C)_2N]_{4-n}SiCl_n$ with $n = 2, 3$, and $(H_3CO)_{4-n}SiCl_n$ with $n \sim 1, 2, 3$[202], $(H_3C)_nSiX_{4-n}$[184,204], and the 1,3,5,7-tetrahalo-1,3,5,7-tetrasilaadamantanes $(H_2C)_6(SiX)_4$ with X = F, Cl[205]. In the last case, replacement of SiH bonds in the

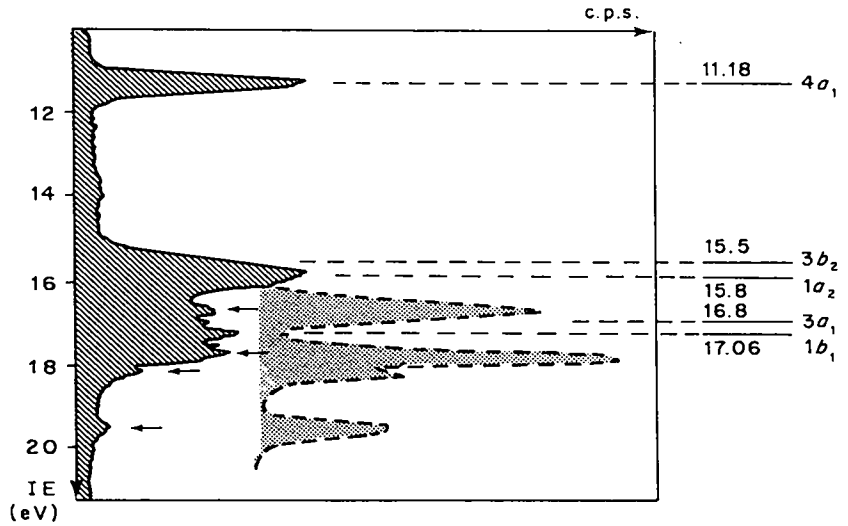


FIGURE 20. PE spectrum of SiF_2[207] (black area) including assignment and compared to that of the reaction component SiF_4 (hatched area) (cf. Figure 19).

parent system by SiF again clarifies the low energy ionization region of the PE spectrum.

Concerning group IVB compounds with coordination number 2, the following PE spectroscopic investigations have been carried out.

The unstable species difluorosilylene SiF_2 has been produced by passing SiF_4 over Si at 1150°C[206,207] as well as by reaction of CaF_2 and Si at 1200°C[207]. Its first PE band, at 11.08 eV[206] or at 11.18 eV[207] respectively, in remarkable agreement, corresponds to the silicon lone pair $n_{Si}(4a_1)$ ionization (Figure 20).

No vibrational fine structure is observed for SiF_2 – in contrast to the first PE band of CF_2 at 12.27 eV[208], assigned to the carbon lone pair $n_C(4a_1)$ ionization with some antibonding F . . . F contributions and exhibiting a 22 peak (!) progression of the CF_2 bending mode $\nu^+_{CF_2} = 650\ cm^{-1}$ [208].

Tin(II) chloride and bromide[209], as well as lead(II) chloride, bromide and iodide[210], have been studied by high-temperature PE spectroscopy. The main difficulties in these studies seem to consist of the identification of impurities in the reliably recorded spectra.

VI. HALOGEN-SUBSTITUTED OPEN-CHAIN AND CYCLIC CARBON π SYSTEMS

Carbon π systems form a multiply-bonded and multifaceted class of compounds. Their PE spectra also show many common features, stretching from low energy π ionization bands frequently exhibiting vibrational fine structure to the interpretation which is often based on π perturbation models[3–7]. Nevertheless, a classification into open-chain and into cyclic delocalized π systems seems advisable. To further reduce the multiplicity of the halogen-substituted compounds, the open-chain molecules have been subdivided into the linear haloacetylenes and into the planar haloethylenes or carbonyl derivatives (Sections VII.A, VI.B, and VI.C); the cyclic molecules into benzene derivatives and larger and/or heterocyclic derivatives (Sections VI.D and VI.E).

These compounds have been thoroughly investigated by PE spectroscopy, partly because of their well resolved informative spectra (c.f. Figures 10, 13, 21–23, 25, 27), but also with a more chemically motivated approach. For instance, disubstituted acetylenes[3,5,63] or ethylenes[57,104,104] offer in their PE spectra (Figures 13 and 21) direct scheme for parametrization, i.e. the determination of Hückel substituent parameters. In addition to *trans*-dichloroethylene (Figure 13) this procedure will be exemplified for dihaloacetylenes ('equation' 21), and for some chlorobenzenes (Figure 27). In addition, a more formal introduction into first- and second-order perturbation is sketched out in Section VI.D.

A. Haloacetylenes

The halogen-substituted acetylenes partly are explosive compounds; they give rise to a wealth of separated PE bands (Figures 21 and 22) with fine structures due to cation vibrations, and for X = Br, I due to spin–orbit coupling[63,113,212] (see Section II.D). The spin–orbit splittings can be well accounted for by a first-order perturbation treatment[63,71,113,210], as exemplified in Figure 21 for diiododiacetylene. The LCBO treatment starts from symmetry-adapted combinations $\pi_{\lambda g}$, $p_{\lambda g}$, $p_{\lambda u}$ and $\pi_{\lambda u}$, constructed from iodine lone pairs p_λ^I and acetylene π_λ^{CC} orbitals. Interaction between each *gerade* and *ungerade* orbital yield the doubly degenerate orbitals $\pi_{\lambda g}$ (1 and 3) and $\pi_{\lambda u}$ (2 and 4), respectively. Spin–orbit splitting $\Delta(j)$ according to

$$\Delta(j) = c_{jX}^2 \, \mathcal{J}_X, \tag{20}$$

where c_{jX} is the halogen p_X atomic orbital coefficient and $\mathcal{J}_X$ is the spin–orbit coupling constant for X, is only correctly reproduced if the LCBO model basis is enlarged by antibonding π_λ^* orbitals of the triple bonds[211]. The experimentally observed spin–orbit splittings $I_{1/2} - I_{3/2}$ of the degenerate doublet cation states range in the case of diiododiacetylene from $\Delta(4) = 0.11$ eV to $\Delta(2) = 0.53$ eV (Figure 21), nicely correlating with the values of the p_X coefficients (equation 20) of the individual orbitals (Figure 21). PE spectroscopic data for dihalodiacetylenes[211], as well as for other haloacetylenes[113,114], fit into correlations with free halogen atom ionization potentials $IE_1(X)$ like 'equation' 13.

For chloracetylenes – and within a zeroth approximation also for the bromo derivatives – spin–orbit coupling may be neglected relative to the considerably larger π interaction with the halogen lone pairs. As already pointed out in the introductory remarks, the PE spectra of these acetylene derivatives can then be used to parametrize a π-type QMO scheme in close analogy to the procedure demonstrated for *trans*-dichloroethylene in Section III.D (c.f. Figure 13). The π QMO scheme ('equation' 21) is constructed in a self-explanatory way from the three basis orbitals of π symmetry.

Starting from the symmetry-adapted combinations of halogen lone pair orbitals π_g and π_u, only the latter can interact with the acetylene π_u orbital, resulting – within the limits of the LCBO model – in a symmetrical split $\Delta\pi$. Correlation with the PE spectroscopic ionization energies yield the Coulomb integrals α_X, the internal $1\pi_g$ standard, and α_π' for the dihaloacetylenes. Comparison with α_π for acetylene itself, i.e. its first ionization energy $IE_1 = 11.40$ eV[2], allows one to obtain the inductive parameter $\Delta\alpha$. Finally, the resonance integral β_{π/X_2} can be calculated from a Hückel determinant of order 2. The HMO parameters for dihaloacetylenes[63] and *trans*-dihaloethylenes (see equation 9)[104] are given in 'equation' (22), all values being in electron-volts.

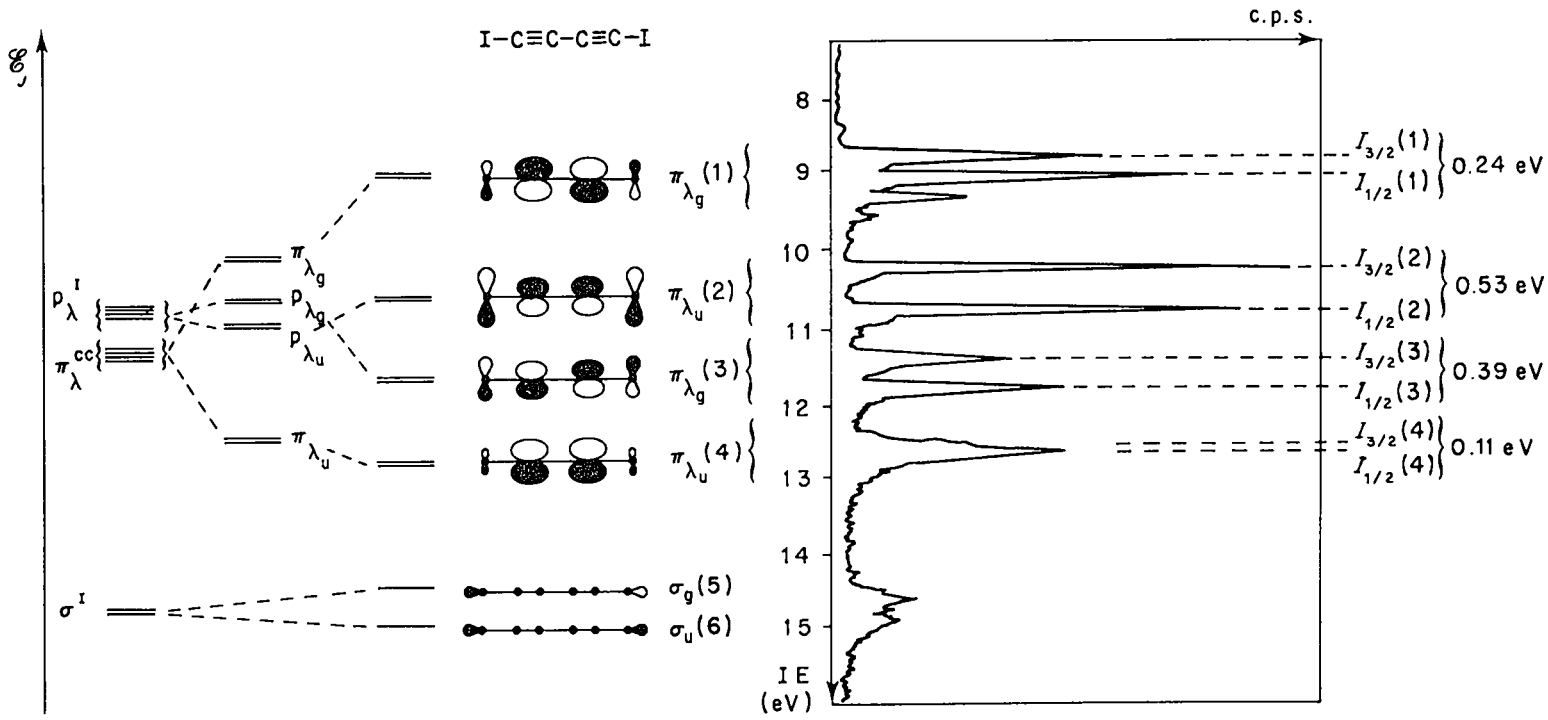


FIGURE 21. PE spectrum of diiododiacetylene from 8 to 15 eV and its assignment based on an LCBO model.

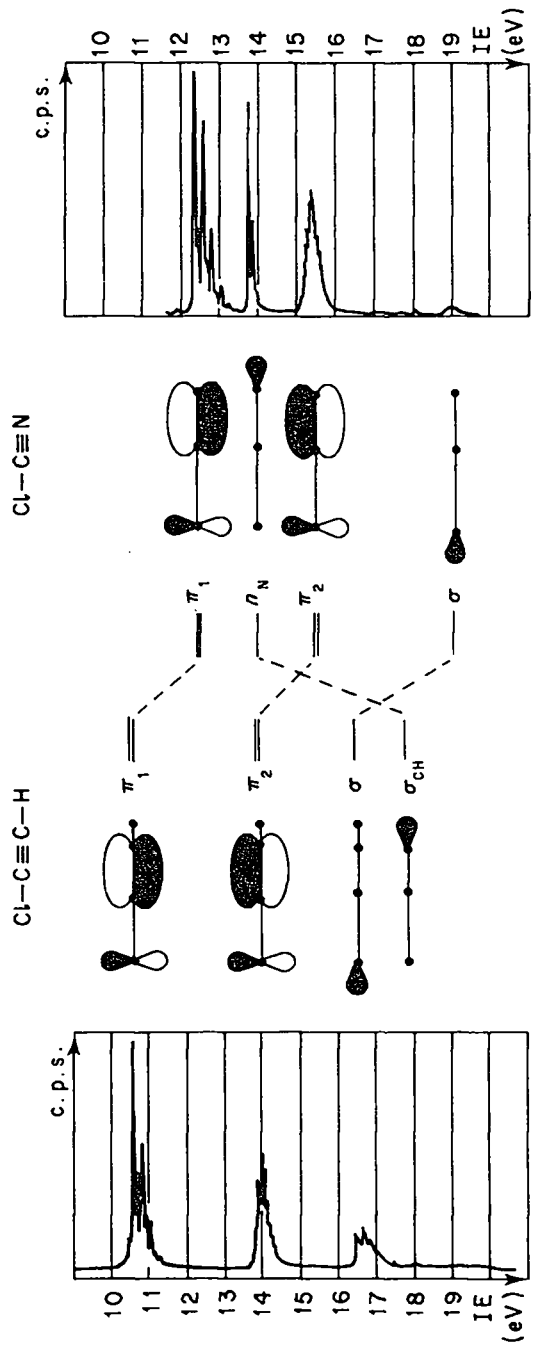
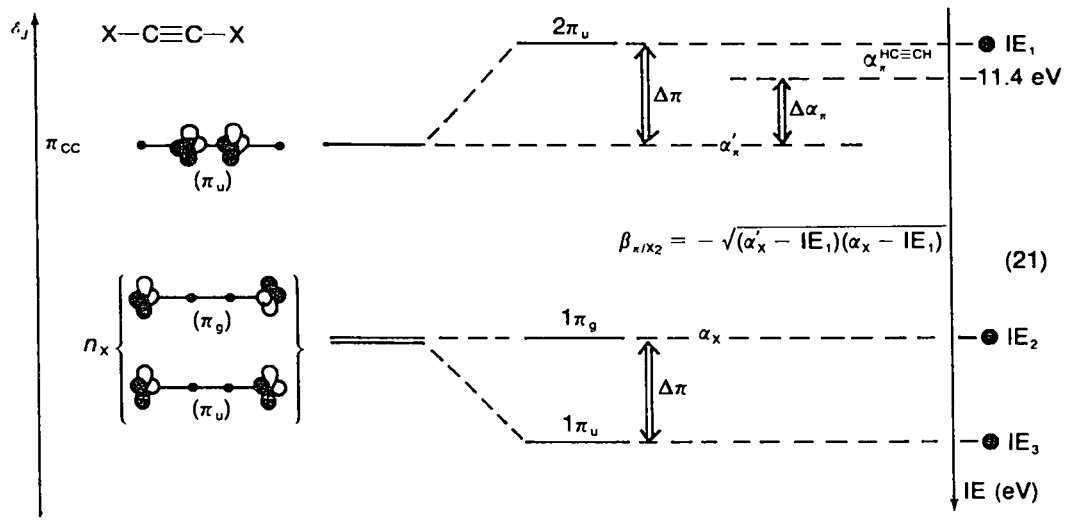


FIGURE 22. PE spectra of isoelectronic Cl—C≡CH[113] and Cl—C≡N[212] with QMO assignment.



	X—C≡C—X			H, X / X, H C=C		
X	α_X	$\Delta\alpha_\pi$[a]	$\beta_{\pi/X}$[a]	α_X	$\Delta\alpha_\pi$[a]	$\beta_{\pi/X}$
Cl	−13.4	+0.26	−1.9	−12.6	−0.44	−1.8
Br	−12.3	+0.50	−1.7	−11.6	−0.37	−1.6
I	−10.9	+0.80	−1.5	−10.3[b]	0[b]	−1.5[b]

(22)

[a] Definitions[63] are: $\Delta\alpha_\pi = 2\delta A_X$; $\beta_{\pi/X} = \sqrt{2}\, B_X$.
[b] Approximate values due to spin–orbit coupling[7].

Although the ethylene parameters ('equation' 10) depend somewhat on the actual assignment discussed below, from both parameter collections ('equation' 22) some generalizations can be drawn:

(i) Iodine substituents are most electron donating and least electron attracting with respect to the π systems —C≡C— and —HC=CH—, respectively. In this context, again the linear correlation between Coulomb integrals α_X and halogen atom ionization potentials $IE_1(X)$ (equation 12) should be emphasized (c.f. reference 211 and references quoted therein).

(ii) Judging from both the $\Delta\alpha_\pi$ and α_X values, the —C≡C— unit withdraws electrons from halogen substituents X = Cl, Br, I, whereas the —HC=CH— moiety and especially methyl groups[211] appear to be electron donating.

(iii) The resonance integrals $\beta_{\pi/X}$ seem to be transferable for orbitals irrespective of the hybridization of the carbon atom. No large differences are observed for halogen substituents X = Cl, Br, I; the different α_X values represent the main factor influencing the splitting pattern.

Following this more 'chemical summary' on substituent perturbation, the PE spectroscopic features of another closely related class of halogen-substituted π systems have to be discussed: the cyanogen halides X—C≡N are isoelectronic with monohaloacetylenes X—C≡CH, i.e. by moving the CH proton into the N nucleus,

the compounds become identical and, therefore, their PE spectra (Figure 22) closely resemble each other.

PE spectroscopic comparison (Figure 22) shows that ionization energies π_1, π_2 and σ are increased due to the higher effective nuclear charge of nitrogen, whereas the σ_{CH} orbital becomes the n_N lone pair – corresponding to the needle-like PE band about 4 eV lower. Geometry changes upon ionization have been discussed for the cyanogen halides[43], and their PE spectra reviewed[35] together with those of other cyanogen derivatives like chloroacetonitriles $H_{3-n}Cl_nC-C\equiv N$[213].

Further PE spectroscopic studies on haloacetylenes concern the vibrational fine structure observed for the monohaloacetylenes[113]: it has been analysed[43,44] using the Franck–Condon scheme and a crude diagonal force field leading to estimates for the radical cations interatomic distances, which are semiquantitatively in agreement with EHMO overlap populations. The extensive PE spectroscopic studies of the interesting halogen-substituted acetylenes have been extended to trimethylsilylhaloacetylenes $R_3Si-C\equiv C-X$[144] and to methylhalodiacetylenes $H_3C-C\equiv C-C\equiv C-X$[211].

B. Haloethylenes

Like the haloacetylenes (Section V.A), these simple derivatives of another prototype π system also give rise to PE spectra which exhibit numerous separated and partly fine structured bands (see 'equation' 13 or 'equation' 23). The PE spectroscopic information can be rationalized by simple MO models as discussed for *trans*-dichloroethylene in Section III.D) and yields MO parameters ('equation' 10 or 'equation' 22) applicable also to chemically related systems ('equation' 11). The following PE spectroscopic survey has been arranged according to the different halogen substituents X.

1. Fluoroethylenes

Their PE spectra are dominated by the vibrationally fine structured π ionization band between 10 and 11 eV[2,95,109], whereas σ ionization energies usually exceed 14 eV (see Figure 23) due to the 'perfluoro effect'[95] exemplified in this review by $F_2C=CH-CH=CF_2$ (Figure 9), F_2CO (Figure 25), F_2CS (Figure 26) or $F_2C=CFCl$ (Figure 23). Besides the fluoroethylenes $FHC=CH_2$[2,109,214,215], $F_2C=CH_2$[2,109], $FHC=CHF$[95], $F_2C=CHF$[95] and $F_2C=CF_2$[95,109], numerous other fluorohaloethylenes such as $F_2C=CCl_2$ and $F_2C=CFBr$[104] have been investigated PE spectroscopically. The Rydberg assignments in the UV spectra of fluoro- and chloroethylenes have also been based on PE ionization energies[24].

2. Chloroethylenes

Their PE spectra and the accompanying radical cation state assignment form a puzzle story, which can be followed by reading the references of the well documented literature[216,109,67,37,104,179,214,108,110] in the order given here. It is to be hoped that the latest assignment[110] is finally agreed upon. With reliable calculations for these compounds missing, the assignment was mainly improved by experimental progress: carefully recorded PE spectra[37,109], X-ray emission spectra of the molecular cations[108] detailed discussion of vibrational fine structures[104] and use of different photon sources[37,108]. The chloroethylene PE spectra (Figures 10 and 23) can also be subdivided into several typical regions.

The first chloroethylene PE band between 9.35 eV ('equation' 11) and 10.15 eV (Figure 23) represents the π_{CC} ionization, while the totally bonding π orbital with

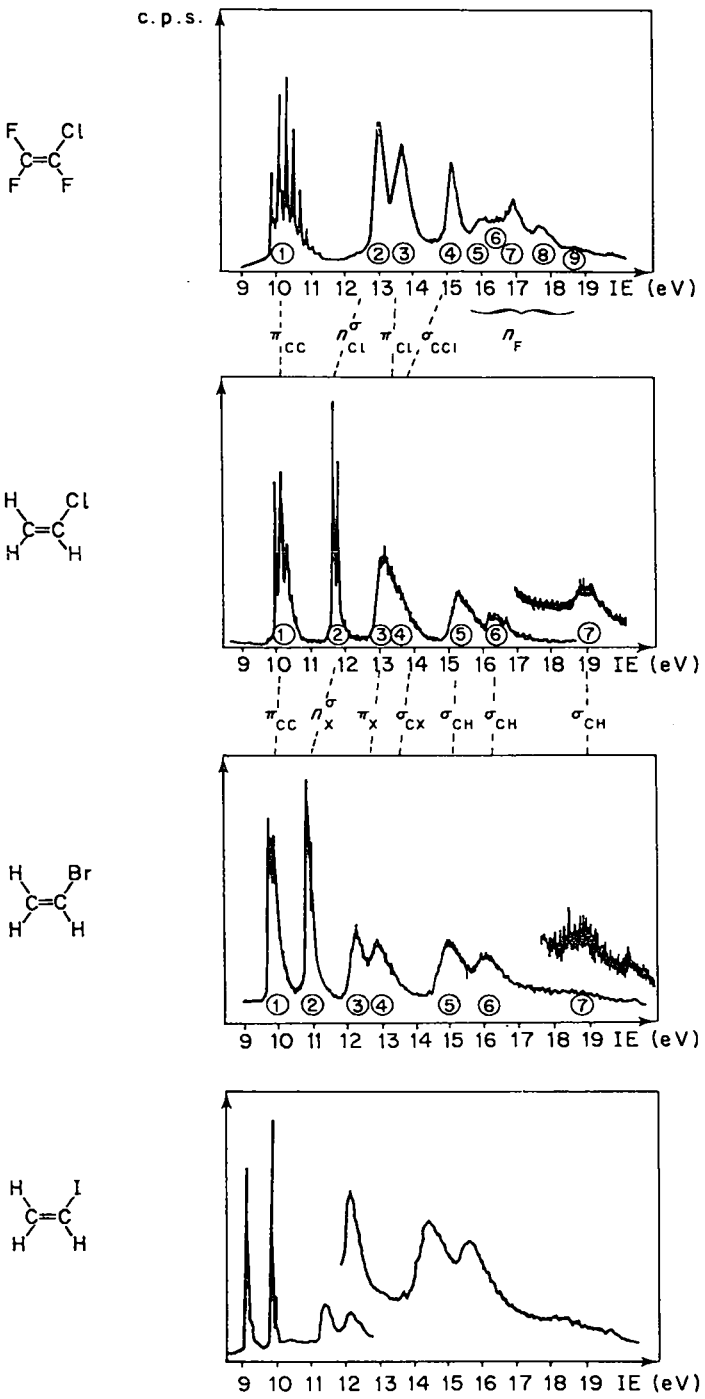


FIGURE 23. PE spectra of vinyl halides $H_2C{=}CHX$, with X = Cl, Br, I, and of trifluorochloroethylene[79,104].

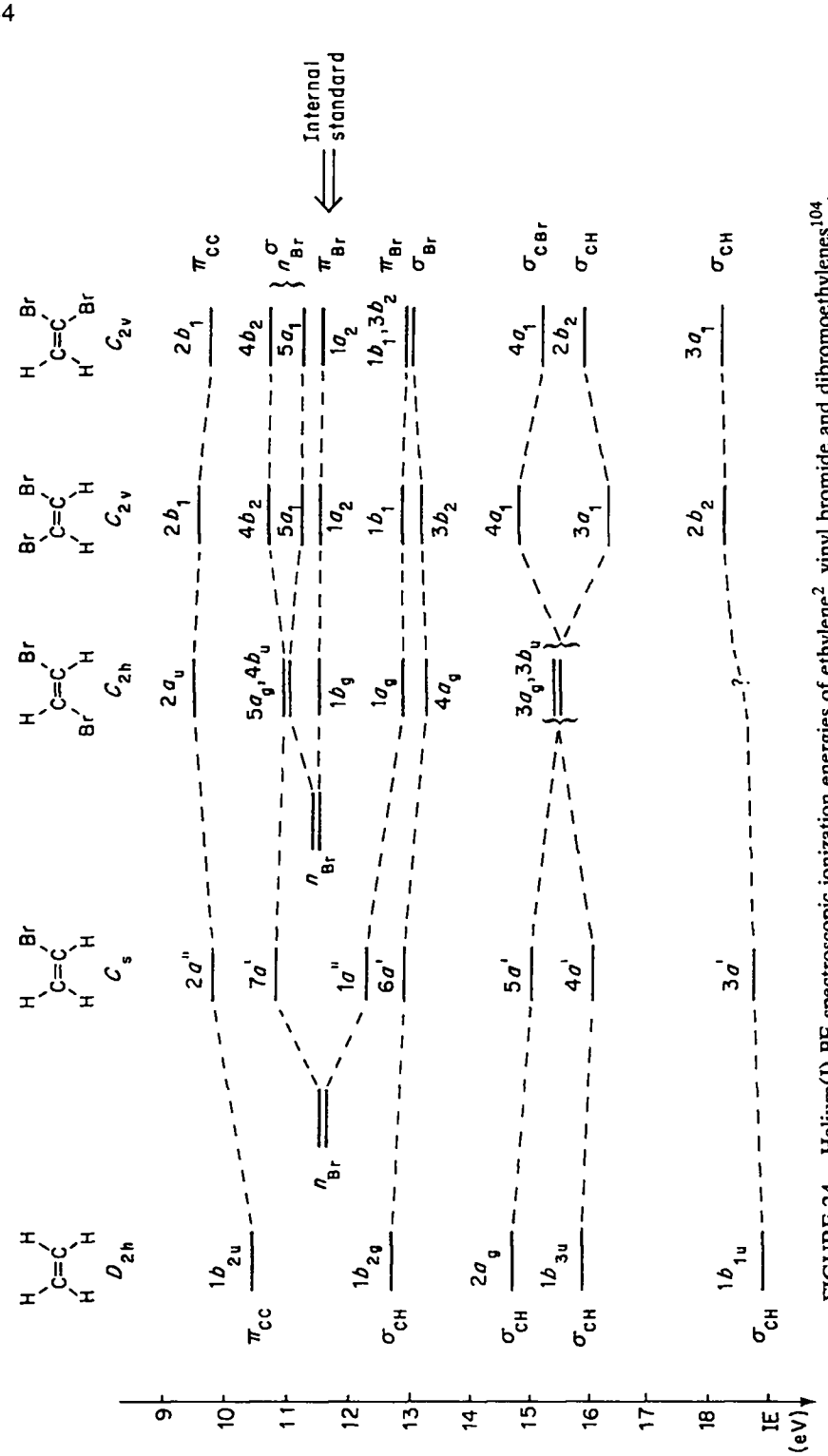


FIGURE 24. Helium(I) PE spectroscopic ionization energies of ethylene[2], vinyl bromide and dibromoethylenes[104].

predominant chlorine distribution is assigned around 14 eV[104]. The corresponding PE band overlaps in some cases with that of the lowest σ_{CCl} ionization. Between π_{CC} and σ_{CCl}, i.e. 11 and 13 eV, the rather non-bonding chlorine lone pairs give rise to mostly sharp and intense bands. The above reasoning is supported by perfluorination[104], which expectedly leaves the π ionization unaffected, and by the detailed analysis of vibrational fine structures[104] as well as by chemical comparison along the series with either different substituents X (see Figure 23) or different substitution patterns analogous to those shown in Figure 24[104].

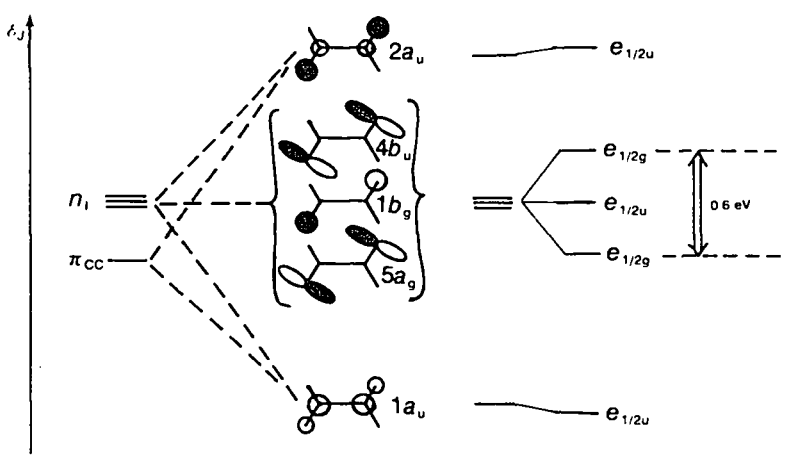
3. Bromoethylenes

The PE spectra of bromo-substituted ethylenes[67,104,212,217–219] closely resemble those of their chloro analogues (Figure 23). The ionization energies along the series ethylene → vinyl bromide → dibromoethylenes are correlated in Figure 24.

The correlation diagram (Figure 24) reveals, for example, how the bromine lone pairs n_{Br} are located between π_{CC} and σ_{CH}; that their π_{Br} combinations (C_{2h}, $1b_g$; C_{2v}, $1a_2$) according to 'equation' (9) form a reliable internal standard, or even allow one to rationalize detailes like the 1.5 eV distance between the ionization assigned to the two symmetry-equivalent orbitals $4a_1$ and $3a_1$ of *cis*-dibromoethylene. The second PE band of *trans*-dibromoethylene cannot consist of two *gerade* lone pair combinations[217], because of spin–orbit coupling[79,104], and its first and second peaks belong to two different cation states[219].

4. Iodoethylenes

Their PE spectra (see Figure 23) are of interest with respect to spin–orbit interactions[65,67,79,212] (see Section II.D). These dominate especially in the lone pair and π ionization regions of iodoethylenes[79]. For instance, in the *trans* isomer, spin–orbit coupling mixes strongly the nearly degenerate iodine lone pairs $5a_g$ and $1b_g$ – in spinor group notation both belong to $e_{1/2g}$ – while the *ungerade* orbitals are only slightly perturbed due to their large energy difference ('equation' 23).



(23)

The distance of the two strongly spin–orbit coupled lone pairs $e_{1/2g}$ should amount approximately to 0.6 eV, the iodine atomic coupling constant $\mathcal{J}_I$ (Section II.D), and the PE spectrum has been assigned accordingly starting with $IE_4 - IE_2 = 0.59$ eV[79].

In vinyl iodide π conjugation is even dominated by spin–orbit coupling: the first two sharp bands are 0.7 eV apart[79], whereas in $F_2C{=}CFI$ the first PE band becomes broadened and the second one moves 1.1 eV away. In the *cis* isomer, the π_{CC} and n_I orbitals all belong to the same C_{2v} symmetry species $e_{1/2}$, and due to almost complete mixing hardly any correlation with the C_{2v} starting orbitals seems possible. In contrast, for the σ orbitals spin–orbit interactions can be neglected in a reasonable approximation, and the orbitals can consequently be labelled within the C_{2v} point group[79]. Altogether, spin–orbit coupling must be accounted for in a correct assignment of iodoethylene PE spectra.

5. *Halogen-substituted C_3 and C_4 olefins*

From the PE spectra of halogen-substituted larger olefins, the allyl halides $H_2C{=}CH{-}CH_2X$[66,212,220], recorded under the presumption of *gauche* conformation[220], have been selected as examples of C_3 and C_4 compounds. Their spectra have been interpreted using two different models: shifts and splittings of the first three PE bands on substituent variation from X = F to X = I are explained either by 'π/C—X bond hyperconjugation', without, however, explicitly accounting for the allyl iodide spin–orbit coupling[220] or by π/n_X 'through space interaction'[64,66] (see Figure 5).

Other halomethyl-substituted ethylenes which have been investigated PE spectroscopically comprise compounds such as $(F_3C)ClC{=}CCl(CF_3)$ and $F_2C{=}CF{-}CF_3$[104]. Fluorobutadiene PE spectra are displayed in Figure 10 as an example of assignment by chemical comparison: the non-planarity of $F_2C{=}CF{-}CF{=}CF_2$ is revealed by the reduced π split relative to 1,1,4,4-tetrafluorobutadiene, $F_2C{=}CH{-}CH{=}CF_2$[93]. Finally, the PE spectrum of tetrafluoroallene, $F_2C{=}C{=}CF_2$, has also been recorded[221].

C. Carbonyl and Thiocarbonyl Halides

Carbonyl difluoride is one of the most impressive examples of the 'perfluoro effect'[26,95,96], which has been discussed in Section III.A as one of the means to assign PE spectra by chemical comparison (Figure 10). A correlation diagram for H_2CO[2], $HFCO$[222] and F_2CO[95] ionization energies (Figure 25) illustrates their relationship.

Figure 25 reveals a 2.6 eV stabilization of the oxygen lone pair n_O, while the π_{CO} ionization remains essentially constant as expected from counteracting σ acceptor and π donor properties of fluorine substituents[95]. An approximation of the Koopmans' defect (Section II.E) by second order contributions within the CNDO parametrization[7,87] – nearly constant for the n_O lone pair (H_2CO, 1.2 eV → F_2CO, 1.5 eV), but increasing for π_{CO} (H_2CO, 0.2 eV → F_2CO, 0.8 eV)[222] – suggests that relaxation and correlation also contribute to the perfluoro effect.

Thiocarbonyl difluoride, F_2CS, furnishes another example of the perfluoro effect: PE spectroscopic comparison of H_2CS[223] and F_2CS[45,53,224] shows an 1.31 eV increase of the n_S ionization energy relative to only 0.18 eV for π_{CS}. The PE spectra of the iso(valence)electronic series F_2CS, $FClCS$[53] and Cl_2CS[45,53,225] are displayed in Figure 26 together with the assignment[53] based on analysis of the numerous vibrational fine structures (Section II.B), the chemical comparison and the results of CNDO calculations.

In all X_2CS PE spectra of Figure 26 the first two bands correspond to electron removal from the orbitals $n_S(4b_2)$ and $\pi_{CS}(2b_1)$; the predominantly fluorine and chlorine lone pair ionizations occur between 15 and 18 eV and between 11.5 and 13 eV, respectively. Ambiguities still unsettled concern the assignment of bands ③/④ $(5a_1/3b_2)$[225] and ⑥/⑦ $(4a_1/1b_1)$[45] of Cl_2CS, and the number of bands in the

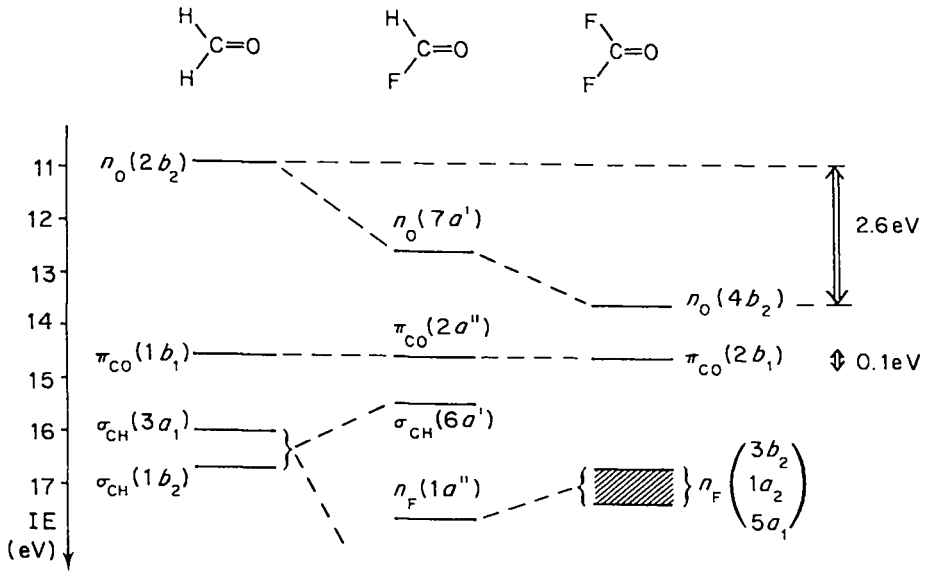
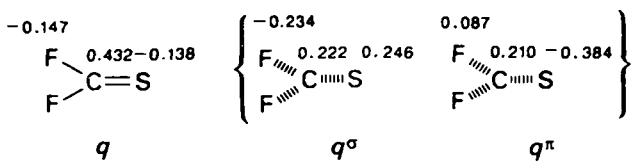


FIGURE 25. Correlation diagram IE_1 to IE_4 of the series H_2CO[2], HFCO[222] and F_2CO[95].

16–17.5 eV region of F_2CS[45,53,224], because the high reactivity of the compound hampers recording of the PE spectrum. An attempt to calculate X_2CS^+ cation geometries from Franck–Condon factors[45] leads, however, to several indistinguishable possibilities. The astonishing observation that the second PE band of F_2CS exhibits a cation stretching frequency $\nu_{CS}^+ = 1400\ cm^{-1}$, unreduced relative to the one of the ground state $\nu_{CS} = 1368\ cm^{-1}$ [53], was taken as a hint of an almost non-bonding character of the $\pi_{CS}(2b_1)$ orbital. The calculated CNDO total, σ and π charges[53],



(24)

offer as an explanation the considerable polarizibility of sulphur[226], and especially the dependence of its σ donor and π acceptor properties on fluorine substituent perturbation. Other thiocarbonyl halides investigated PE spectroscopically are the trifluoromethyl derivatives $F_3CS—C(S)—X$ with X = F, Cl, SCF_3 [192].

The PE spectra of phosgene, Cl_2CO[225,227,228], and of carbonyl dibromide, Br_2CO[228], are less straightforward to assign because of nearly identical n_O and n_{Cl} ionization energies: strong orbital mixing and consequent difficulties in the symmetry assignment result. Nevertheless, the first Cl_2CO ionization clearly originates from $n_O(4b_2)$ – see Figures 25 and 26 – and according to their vibrational fine structure it would suggest that the fifth and sixth bands belong to orbitals $1a_2$ and $1b_1$, respectively. In the Br_2CO PE spectrum, the five structureless bands between 11 and 13 eV have been related to orbitals $4b_2$, $2b_1$, $5a_1$, $3b_2$ and $1a_2$ without definite ordering[228]. In this context, reference is given also to work on acyl halides $H_3C—C(O)—X$[179,229–231].

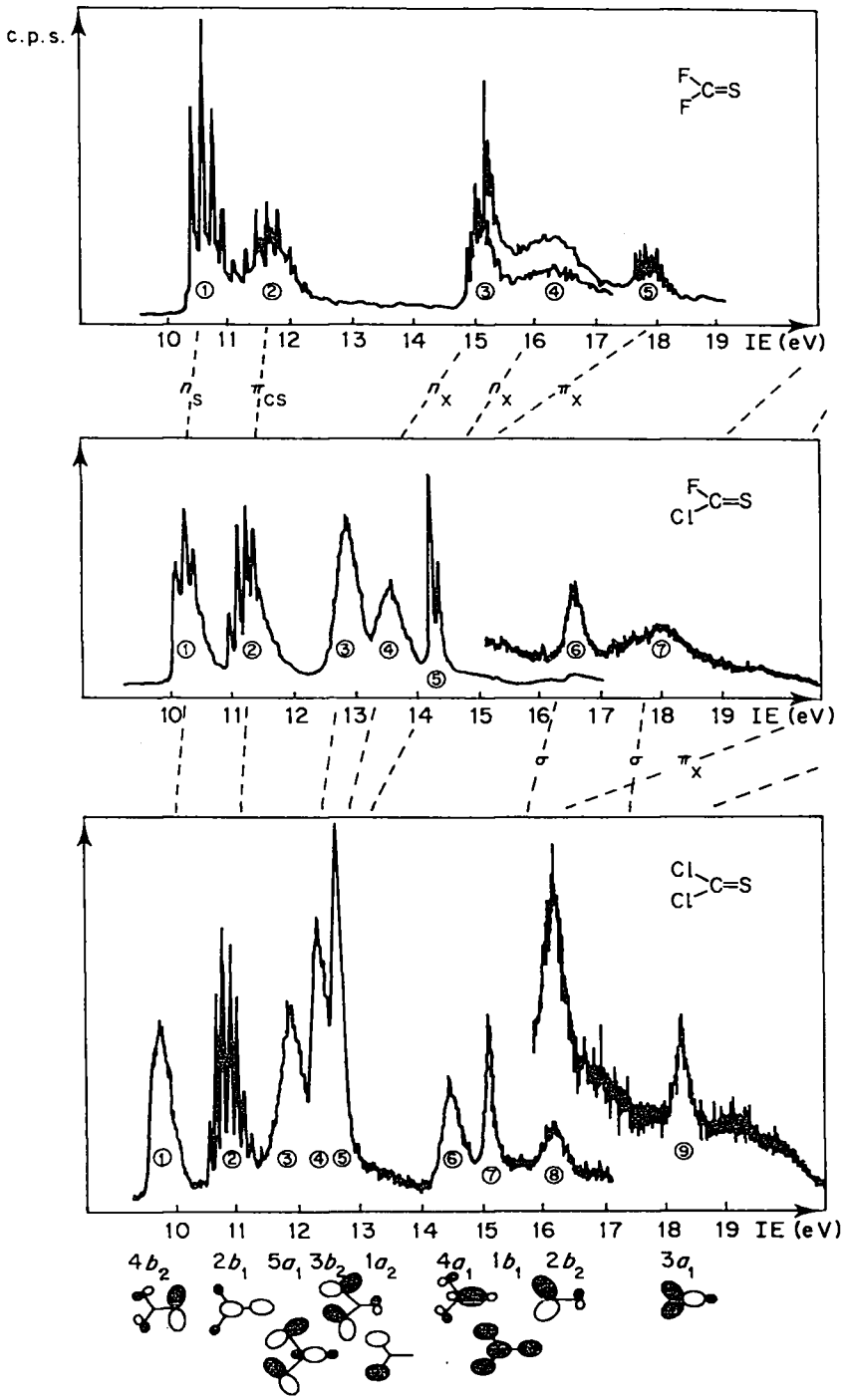


FIGURE 26. PE spectra of thiocarbonyl halides X_2CS, with X = F, Cl, and CNDO orbital diagrams for Cl_2CS.

D. Halogenated Benzenes

The numerous PE spectroscopic investigations of halogen-substituted benzenes (Table 4) have been stimulated only partly by interest in the compounds themselves, and more often in order to support one of the various assignments of the benzene PE spectrum, e.g. references 2, 231, 232, 234, as well as to study substituent perturbations of this 'aromatic' parent system, e.g. references 2, 96, 235–240.

To begin with fluorine substitution, it was recognized rather early[233,250] that π ionizations are not – or are only slightly – affected, whereas σ ionizations appear considerably increased: this 'perfluoro effect' – repeatedly referred to already (see Figures 10, 23, 25 and 26), generalized[95,96] and analysed by *ab initio* SCF calculations[252], is also convincingly demonstrated in the PE spectra of fluorobenzenes (Table 4). The shifts and splittings of the first PE band of benzene at 9.25 eV and assigned to the degenerate $\pi(1e_{1g})$ orbital, which are induced by monofluoro and difluoro substitution (c.f. Figure 27; patterns for chloro derivatives), have been interpreted as being due to an inductive perturbation[238]. The first two ionization energies are almost numerically reproduced by equation (25):

$$IE_{1,2} = 9.25\ \text{eV} - \sum_{\mu} c_{j\mu}^2 \delta\alpha_{\mu}^{F} - n_F \cdot \Delta IE_{\sigma}, \tag{25}$$

where $c_{j\mu}$ is the benzene orbital coefficient, $\delta\alpha_{\mu}^{F} = -1.1$ eV (π perturbation), n_F is the number of fluorine substituents, and $\Delta IE_{\sigma} = -0.1$ eV (σ perturbation).

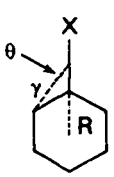
The success of the purely F inductive model can be traced back to no significant conjugative contribution, i.e. the additional second-order perturbation term in equation (26), will be negligibly small due to the large energy difference between benzene

$$\delta\varepsilon_j = c_{j\mu}^2 \left(\delta\alpha_{\mu}^{F} + \frac{\beta_{\pi F}^2}{(\varepsilon_B^{\pi} - \varepsilon_F^{\pi})} \right), \tag{26}$$

and fluorine π orbitals $IE_F^{\pi} - IE_B^{\pi} \sim 7$ eV (see Section III.A). For the third fluorobenzene ionization potential around 12 eV and corresponding to the $\pi(1a_{2u})$ orbital, the prediction (equation 25) deviates to some extent[238]. Anyhow, as long as the denominator in equation (26) remains approximately constant, first-order (inductive) and second-order (conjugative) contributions cannot be separated. This also applies to chlorobenzenes, whose PE spectroscopic splitting patterns (Figure 27) are straightforwardly rationalized by perturbation arguments (equation 26), including the usual π_s/π_{as} orbital sequence switch between *para*- and *ortho*- and *meta*-substitution, and the restored degeneracy in the 1,3,5-trichloro derivative[240].

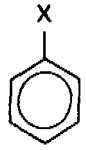
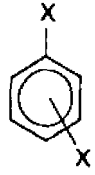
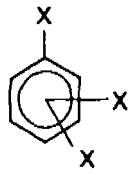
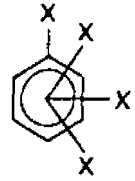
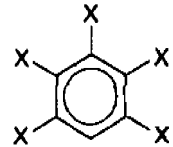
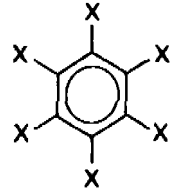
The inductive effect has been analysed more closely by subdividing it into a short-range interaction and a long range interaction[231,240]. The short-range term is the one familiar from π perturbation theory and operative only at the atom bonded to the substituent; the long-range inductive term (LRI) is evaluated by a point dipole approximation (equation 27),

$$LRI = \sum_{i \neq j} \left(\frac{e}{\varepsilon} \right) \frac{\vec{\mu}_X \cdot \vec{r}_i}{|\vec{r}_i|^3} c_i^2, \tag{27}$$



where j are the substituted atoms, $\vec{\mu}_X$ is the C_j—X bond dipole moment, $\vec{r}_i$ is a vector joining the C_j—X bond centre to carbon i, and ε is the effective dielectric constant for electrons.

TABLE 4. References to PE studies of individual halobenzenes

X						
F	2, 231, 232, 234, 236–238, 240, 242, 247, 248	2, 231, 234, 236, 238, 240	231, 234, 236, 240, 243, 249	234, 240	2, 234	2, 14, 96, 234, 236 240, 245, 249, 250
Cl	2, 14, 235, 239–241, 244, 246, 248	2, 235, 239, 240, 241, 251	239, 240	238, 240	238, 240	240
Br	2, 240, 241, 244, 248	2, 240	240			
I	2, 241, 248	240				

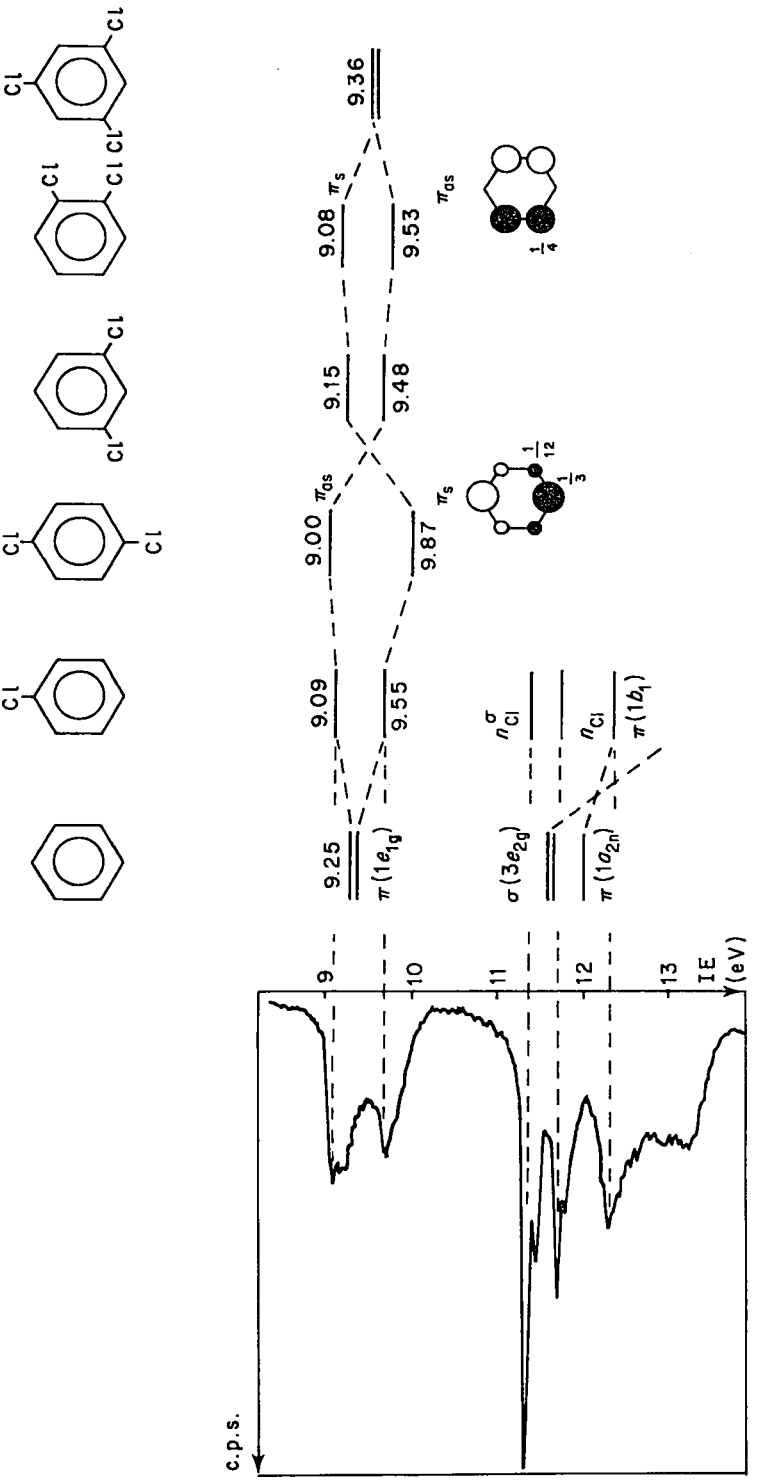


FIGURE 27. PE spectrum of $C_6H_5Cl^2$ and splitting patterns $IE_{1,2}$ for some chlorobenzenes[240].

Introducing the parameter M_X (equation 28),

$$M_X = \left(\frac{e}{\varepsilon}\right)\frac{\mu_X}{R^2}, \tag{28}$$

where R is the bond length in benzene, with $r_i = p_i R$ and the angle θ as defined in equation (27), one obtains equation (29) for a polyhalobenzene:

$$\mathrm{LRI} = \sum_j \sum_{i \neq j} \left(\frac{e\mu_X c_i^2}{\varepsilon}\right)\frac{\cos\theta_i}{p_i^2 R^2} = \sum_j \sum_{i \neq j}\left(\frac{c_i^2 \cos\theta_i}{p_i^2}\right) M_X \tag{29}$$

The total shift, including second-order contributions (equation 26) is then given by equation (30):

$$\Delta E = \sum_{i=j} c_i^2 \gamma_X + \sum_j \sum_{i \neq j}\left(\frac{c_i^2 \cos\theta_i}{p_i^2}\right) M_X, \quad \text{with} \quad \gamma_X = \delta\alpha_X + \frac{\beta_{\pi X}^2}{(E_\pi - E_X)} \tag{30}$$

The condition $(E_\pi - E_X) > c_i^2 \beta_{\pi X}^2$ excludes application to iodine substituents because of their low ionization energy (Figure 10), and also has to be taken into account in correlations with the higher benzene π ionization[240]. For *ortho*-substitution, additional interactions have to be considered[240]. From correlations with numerous experimental values[240,253,254], M_X was found not to vary significantly (−1.10 eV to −1.0 eV), while the γ_X values increase from F(0.62 eV) to Cl (0.78 eV) to Br (1.02 eV), indicating the increased mesomeric contributions to γ_X with decreasing IE_X[240]. Altogether, satisfactory agreement between predicted and observed ionization potentials is achieved. The successful treatment – although the derived parameters are somewhat uncertain due to ill-defined ionization energies and neglect of correlation and relaxation effects – also offers an interesting alternative for describing inductive effects of other polar groups like $-CF_3$, and has been extended, for example, to 9,10-dihaloantracenes[253] and to fluoro-substituted π systems[254]. It has to be mentioned, however, that a 'field and charge transfer' model for substituent effects in halobenzenes is equally well suited to interpret the PE spectroscopic data. Finally, although the origin of these relationships is still not fully understood, the ionization potentials of a variety of halobenzenes have been correlated with Hammett σ constants[255,256].

E. Survey of other PE Spectroscopically Investigated Cyclic Carbon π Systems with Halogen Substituents

Numerous other halogen-substituted, isoconjugate or heteroatom-containing cyclic π systems have been investigated by PE spectroscopy[2–6,35]:

(1) *Isoconjugate systems*: benzene derivatives with different halogen substituents[2,257], halogenated biphenyls[258], octafluoronaphthalene[96], 9,10-dihaloanthracenes[253].

(2) *Haloalkyl derivatives*: benzyl halides[220], trifluoromethyl benzenes[2].

(3) *Azaaromatic compounds*: fluoropyridines[96,259,260], chloropyridines[239], fluorinated diazines[261,262], fluoro-substituted monoaza-[263] and diazanaphthalenes[264,265], cyanuric trifluoride[96].

(4) *Other heterocycles*: bromothiophenes[266], halogen-substituted thiazoles[267], fluoroborazines[97].

Among others, the above investigations have helped to assign PE spectra of parent molecules by, for example, the perfluoro shifts, to establish correlations with other molecular properties like charge transfer excitations[241], and to detect Rydberg series in the (vacuum) UV spectra[24].

VII. HALOGEN DERIVATIVES OF NITROGEN, PHOSPHORUS AND THE OTHER GROUP VB ELEMENTS

The next two sections deal with halogen derivatives of group VB and group VIB elements which constitute a central part of electron-rich, non-metallic main group molecules. Contrary to group IVB compounds, with their variety due to organic chemistry, i.e. the ability of carbon to form different skeletons, many of the compounds to be discussed subsequently are characterized by a 'central heteroatom' (cf. Figures 11, 12, 18 and 19). Thus, typical compounds of group VB are the binary halides, EX_3 and EX_5, as well as in the multiply bonded species $Y{=}EX_3$. In addition, nitrogen in particular can be part of π systems (see Section V.E), giving rise to molecules like X—N=N—X, X—N=O or $X—NO_2$ which contain azo, nitroso or nitro groups, respectively.

The following section on group VB halogen compounds has been subdivided according to increasing complexity of their PE spectra: continuing from the organic π systems (Section V), halogen-substituted π systems will be discussed first (Section VII.B), followed by halides EX_3 and EX_5 (Section VII.C) and finally the multiply bonded species $Y{=}EX_3$ (Section VII.D). Beforehand, some introductory remarks will concern the overall approach and the selection of the PE spectra presented: due to their higher symmetry, and due to the usually small perturbation on alkyl substitution, it is of considerable advantage to discuss first the PE spectra of 'inorganic prototype molecules' (Section VII.A).

A. PE Spectroscopic Comparison of Inorganic Prototype Halides and their Alkyl Derivatives

In many of the group VB and VIB halogen compounds, which might be considered 'inorganic prototype halides', one or several halogen ligands can be exchanged with alkyl or aryl groups. In general, this kind of substitution does not change the PE spectrum completely, but rather only modify it in a predictable way. For example, chlorine ligands and methyl groups both contain seven valence electrons and, therefore, the number of ionizations remains constant for these 'iso(valence)-electronic' molecules. However, on making the substitution $Cl \rightarrow H_3C$, the characteristic chlorine lone pair bands at about 12–13 eV (see, for example, Figures 16 or 23) will vanish and broad σ_{CH_2} ionization peaks will appear shifted about 1–2 eV to higher energies. At the same time, the often high structural symmetry of the inorganic protype halides, which considerably helps in the PE spectroscopic assignment, will be reduced considerably. Therefore it is of advantage first to assign the prototype PE spectrum based on symmetry representations and then interpret the PE ionization pattern of a related alkyl derivative in close analogy comparing 'equivalent radical cation states of chemically related molecules using perturbation arguments'[2–7]. Applying this approach, the PE spectra of the more characteristic prototype halides of group VB and group VIB elements will be presented wherever this is of advantage.

To provide a typical and already somewhat complicated example, the PE spectra of *S,S*-difluorosulphimines, $F_2S{=}N—X$, with nitrogen substituents X = CH_3, CF_3 and Cl have been chosen[268] (Figure 28).

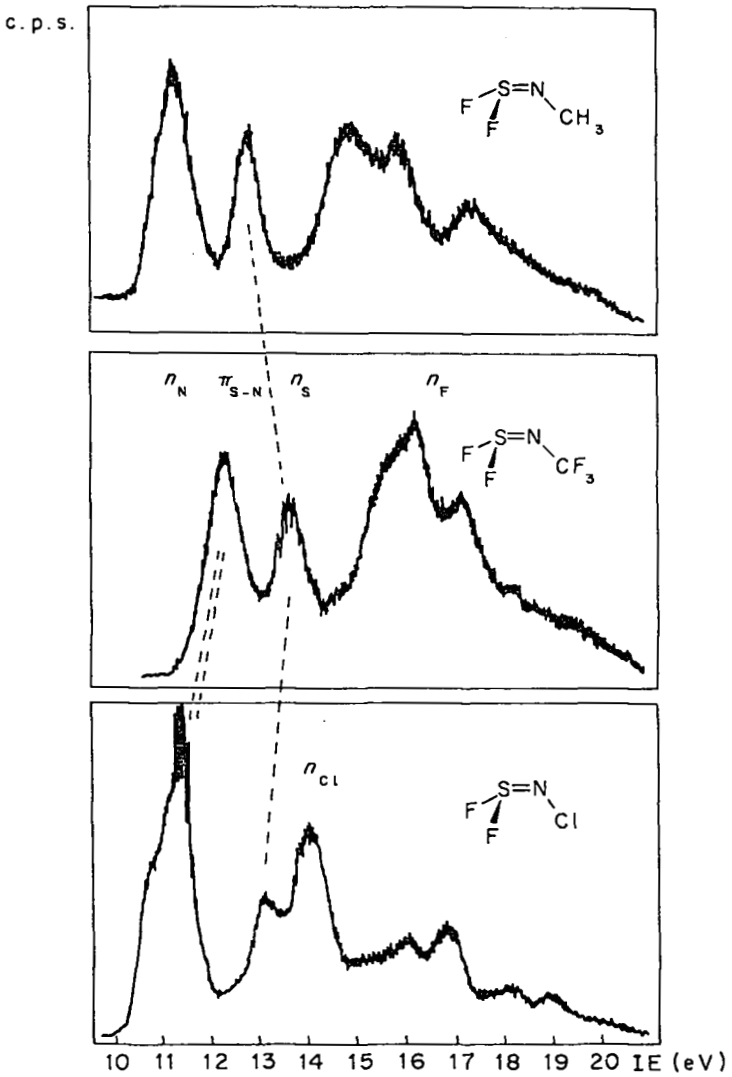


FIGURE 28. Helium(I) PE spectra of *N*-methyl-, *N*-trifluoromethyl- and *N*-chloro-*S*,*S*-difluorosulphimine[268].

As one might already expect from the rather similar ionization patterns (Figure 28), the sequence of the first three radical cation states of the differently substituting *S*,*S*-difluorosulphimines remains the same. According to semi-empirical calculations[268] the ionizations of the nitrogen lone pair n_N and the S=N π system $\pi_{S=N}$, hidden under the first band, are followed by one of the sulphur lone pairs, n_s. The electron-withdrawing effect of the F_3C— group makes this assignment very obvious: the first two ionizations, originating from the adjacent nitrogen-containing parts of the molecules, are shifted by $\Delta IE_{1 \text{ or } 2} \sim 1.2$ eV, whereas the more distant sulphur lone pair is less strongly affected, as demonstrated by the smaller shift $\Delta IE_3 \sim 0.9$ eV.

Expectedly, the exchange $H_3C \rightarrow Cl$ shows a much smaller effect: the inductive stabilization due to the higher effective nuclear charge of chlorine is counteracted by the stronger π-type interaction with the chlorine lone pairs[268]. Summarizing, the characteristic $F_2S{=}NX$ ionization pattern in the lower energy region survives even on $H_3C \rightarrow F_3C$ substitution. On the other hand, the σ ionization region above 14 eV varies substantially, including the additional lone pair ionizations n_F and n_{Cl} (Figure 28).

In order to generalize the $F_2S{=}N{-}X$ example, one may refer to the extensively discussed PE spectra of the series of phosporus compounds $H_3P{\cdots}F_3P{\cdots}F_3P{=}O$ (Section III.C), or to the numerous published PE spectroscopic comparisons of small prototype molecules[2-7], especially for phosphorus compound[33].

B. Halogen-substituted Nitrogen π Systems

The PE spectra of halogen-substituted nitrogen π systems are represented here by the following prototype molecules: the difluoroamino radical $^{\cdot}NF_2$ generated by thermal dissociation of $F_2N{-}NF_2$[269,270] (Figure 29), the azo derivative difluorodiazine $F{-}N{=}N{-}F$[95] (Figure 29), the planar delocalized phosphonitrilic fluoride, $(NPF_2)_3$[271] (Figure 29), the nitrosyl halides $FN{=}O$ and $ClN{=}O$[272-275] (Figure 30), and the nitryl halides $F{-}NO_2$ and $Cl{-}NO_2$[273] (Figure 30).

The structural details for $^{\cdot}NF_2$ and $F{-}N{=}N{-}F$ given in Figure 29 – on comparison with those for $F_2N{-}NF_2$ exhibiting bond lengths d_{NN} = 153 pm and d_{NF} = 139 pm – provide evidence that both compounds contain nitrogen π systems. Analogously, hexafluorocyclotriphosphazene is planar, with 120° angles and equal PN bond lengths which are shortened by about 12 pm relative to PN single bonds. The PE spectra of these different prototype molecules (Figure 29) and those of the nitrosyl and nitryl halides (Figure 30) are discussed separately.

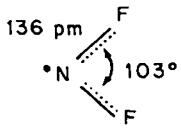
1. *Difluoroamino radical*

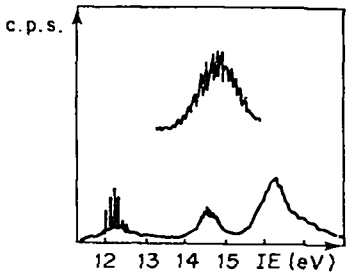
$^{\cdot}NF_2$, generated by heating N_2F_4 in a quartz tube, represents one of the early examples of unstable open-shell species investigated by PE spectroscopy. Koopmans' theorem (Section II.E) does not apply to open shell systems, because removal of an electron leads to either singlet or triplet cationic states. The assignment of the PE spectrum[270] is based on an INDO calculation[269], which suggests as ground state configuration $(3a_1)^2(2b_2)^2(4a_1)^2(1b_1)^2(5a_1)^2(3b_2)^2(1a_2)^2(4b_2)^2(6a_1)^2(2b_1)^1$ with the unpaired electron occupying an antibonding π orbital. The first vertical ionization at 12.10 eV relates to a $^1A_1$ ionic state, reached by removing the unpaired electron. The removal of an electron represented by the $6a_1$ orbital leads to $^3B_1$ and $^1B_1$ ionic states, the energies of which relative to the ground $^1A_1$ ionic state are given by equation (31)

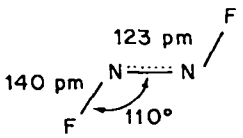
$$^{1,3}\Delta E = \delta_{b_1} - \delta_{a_1} - J_{b_1a_1} + K_{b_1a_1} \pm K_{b_1a_1} \tag{31}$$

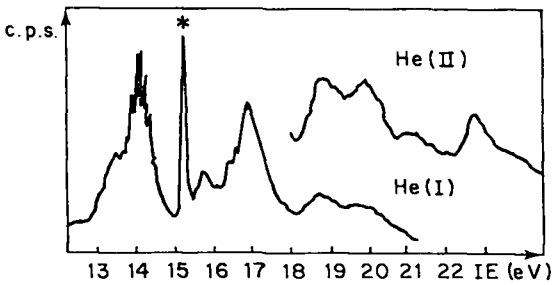
with the plus sign referring to the singlet state and with J and K being Coulomb and exchange integrals, respectively. The INDO calculation[269] estimates ΔE = 2.9 eV for the triplet state and ΔE = 3.9 eV for the singlet state. Accordingly, the PE bands at 14.60 and 16.38 eV are assigned to the $^3B_1$ and $^1B_1$ states, respectively[269,270].

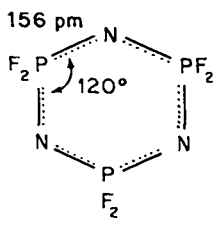
Although the He(I) range covers only ionization 'out of' two occupied molecular orbitals, this example shows clearly the complexity inherent in states with several open shells, and at the same time the tremendous power of simplification embodied in Koopmans' theorem.











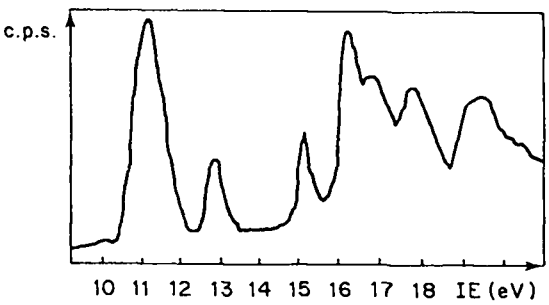


FIGURE 29. Helium(I) PE spectrum of the difluoroamino radical[269,270]; helium(I) and helium(II) PE spectra of difluorodiazine[95]; and helium(I) spectrum of hexafluorocyclotriphosphazene[271]. (The asterisked peak indicates N_2 impurity.)

2. *Difluorodiazine*

The PE spectrum of difluorodiazene[95] (Figure 29) was being studied at a time when the range of applicability of the perfluoro effect (Section III.A) had not been bolstered by extensive experimental evidence. The recorded PE spectrum of *trans*-difluorodiazene[95] may well contain structures due to the *cis* isomer. The assignment from MO calculations, namely $IE(a_g,n_N) < IE(a_u, \pi_{NN})$, is confirmed by the vibrational fine structure displayed in the second band ($\nu_2^+ = 980\ cm^{-1}$) which most probably represents a heavily reduced symmetric N—N stretching mode ($\nu_1 = 1522\ cm^{-1}$). A later investigation of the transient species N_2H_2[274] confirmed the assignment via the perfluoro effect:

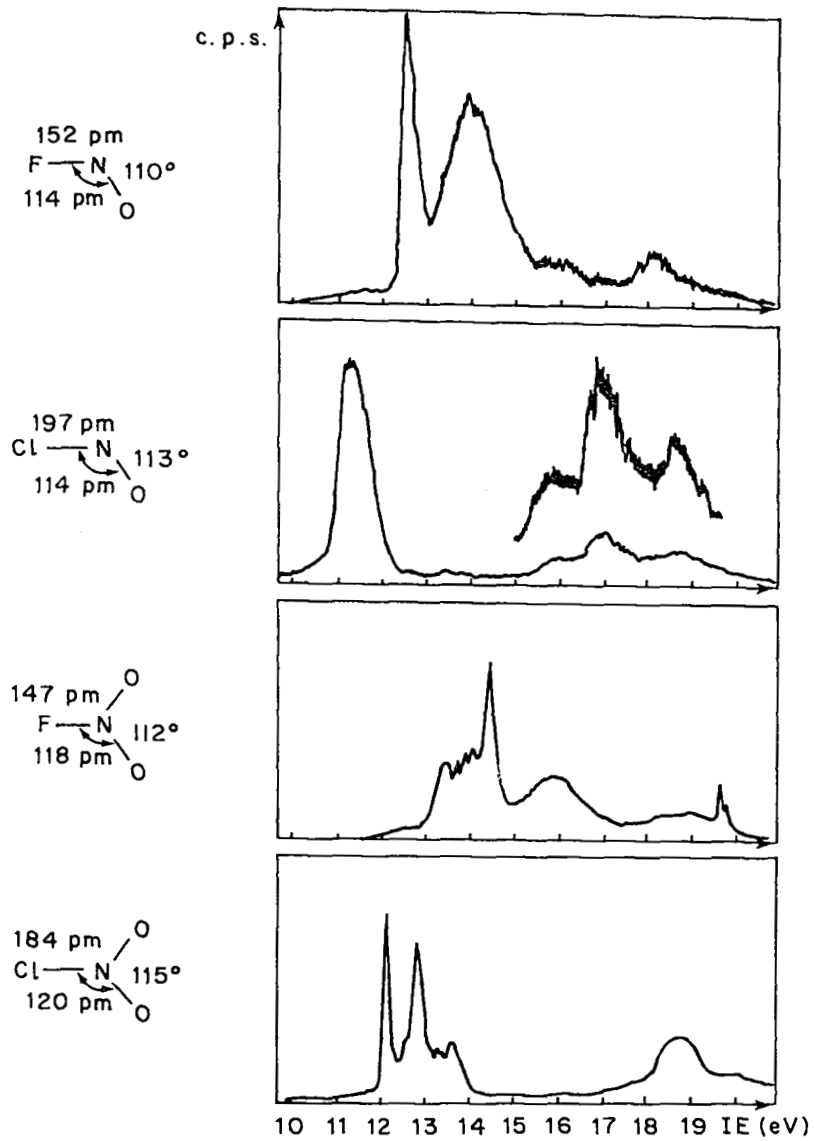


FIGURE 30. Helium(I) PE spectra of nitrosyl fluoride and nitrosyl chloride[272] and of nitryl fluoride and nitryl chloride[273].

$IE_n(M^{\cdot+})$	N_2F_2	N_2H_2	$\lvert\Delta IE_n\rvert$
$IE_1(a_g, n_N)$	13.4 eV	10.02 eV	3.38 eV
$IE_2(a_u, \pi_{NN})$	14.1 eV	14.37 eV	0.27 eV

The in-plane lone pair $M^{\cdot+}$ state is considerably stabilized by fluorine substitution, whereas the π orbital remains relatively unaffected.

3. *Hexafluorocyclotriphosphazene*

Of the phosphonitrilic derivatives of the type $(X_2PN)_n$ known, the PE spectra of the fluorides $(F_2PN)_n$ have been studied for ring sizes $n = 3$–8[271]. The PE spectrum of the planar six-membered ($n = 3$) ring which displays equal PN bond lengths is shown in Figure 29[271]. In the assignment π bonding in-plane ('homomorphic') and π bonding out-of-plane ('heteromorphic') ionizations have been distinguished, whereby the latter involves π orbitals on N and pseudo π orbitals of the PF_2 groups. Simple Hückel-type calculations, exploiting mainly variation of angles within the series $(NPF_2)_n$, $n = 3$–6, allow one to account for the observed PE spectra. The first intense band, at 11.4 eV, corresponds to two pairs of degenerate orbitals, from the homomorphic and heteromorphic systems (e' and e'' in D_{3h}), and the next band, at 13.1 eV, to an accidentally degenerate pair of in-plane and out-of-plane character. Two bands above 16 eV relate to PF-bonding orbitals, the band at 15.4 eV to a single δ_{PN} orbital[269]. Despite satisfactory agreement between calculations and PE spectra, conclusions as to the nature of the bonding are difficult to draw: π_{PN} bonding and nitrogen 'lone pair' orbitals have ionization energies below 14 eV, σ-bonding orbitals all exhibit ionization energies larger than 14 eV. There is definitely an interaction in the in-plane π system, i.e. between the 'nitrogen lone pairs'; yet however, its nature, and the possible extent of these π interactions, remains to be conclusively demonstrated.

4. *Nitrosyl halides*

Nitrosyl halides dissociate at room temperature,

$$2\ XNO \rightleftharpoons X_2 + 2\ NO,$$

with the equilibrium constant increasing from X = F to I. Thus, I—NO remains to be prepared. In addition, the low pressure in the ionization chamber favours dissociation, so that PE spectra of nitrosyl halides are usually contaminated by those of X_2 and of NO, unless these impurities are removed, as in Figure 30[272]. Vibrational fine structure has been observed in several bands of FNO and of ClNO[273,275,276], and the PE spectrum of BrNO has also been recorded[273,275].

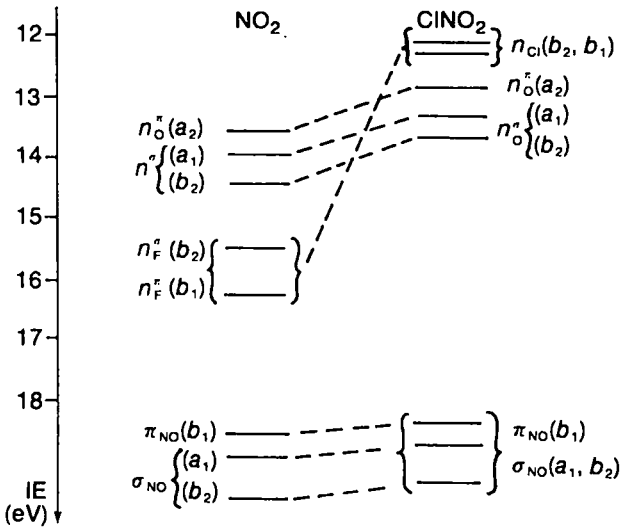
As one might anticipate from the ease of dissociation, the molecular orbitals of the nitrosyl halides closely resemble those of the halogen and nitric oxide moieties. The topmost n_N–n_O ($7a'$) orbital is 'the only true *molecular* orbital'[273]. Accordingly, the orbital is assigned to the first band of the FNO spectrum, whereas all other ionizations of the parent parts are expected at much higher ionization energies. The second band at 14.5 eV then corresponds to the ionizations of the fluorine lone pairs (orbitals $6a'$, $2a''$), correlation and relaxation effects being very large for these two ionization processes due to the availability of low-lying unoccupied MOs on the NO moiety[277]. CNDO/2 calculations suggest three ionization events for the PE band structure around 18.5 eV[272] (Figure 30).

The PE spectrum of nitrosyl chloride (Figure 30) displays one broad band between 11 and 12 eV, which according to CNDO/2 calculations[272] should be composed of three overlapping ionizations assigned to n_N–$n_O(7a')$, $n^{\sigma}_{Cl}(6a')$ and $n^{\pi}_{Cl}(2a'')$ orbitals. This prominent, but unresolved structure is repeated in the chlorine K_β spectrum[278], thereby indicating that the three topmost radical cation states of ClNO contain most of the chlorine 3p electron character. The three bands beyond 15 eV are assigned to $M^{\cdot+}$ states represented by orbitals $\pi_{NO}(1a'')$, $\sigma(5a')$ and $\sigma(4a')$, which closely resemble the $^{\cdot}NO$ ionizations in energy; a more detailed comparison becoming difficult due to singlet/triplet splitting for the latter[273].

5. *Nitryl halides*

Comparing the structural parameters of nitrosyl and nitryl halides (Figure 30) shows a shortening of the XN bonds by 5–13 pm, a lengthening of the NO bonds by 4–6 pm and a slight opening of the XNO angle, which can be rationalized by the charge redistribution on attachment of the second oxygen[54].

Both FNO_2 and $ClNO_2$ are iso(valence)electronic with NO_3^-, HNO_3, or the boron trihalides (Section IX.A). Consequently, the orbital diagram for the $ClNO_2$ (Scheme 32) forms a good starting point for the discussion of the nitryl halide PE spectra (Figure 30). The assignment proposed[273]



(32)

shows a close resemblance between FNO_2 and $ClNO_2$ except for the lone pair n_F and n_{Cl} radical cation states which are shifted according to the lower effective nuclear charge of chlorine to lower ionization energies. The energetic separation into non-bonding and into bonding $M^{\cdot+}$ states is well preserved in $ClNO_2$ – and also in HNO_3[277] – retaining even the 6 eV separation (Figure 30). This keeps in line with similar effective nuclear charges of chlorine and oxygen, whereas fluorine appears most effective in reducing the effective symmetry from D_{3h} to C_{2v}, as indicated by the additional PE band structure due to the fluorine lone pair states around 16 eV (Figure 30 and 'equation' 32).

C. Saturated Group VB Halogen Derivatives

All simple binary halides EX_3 have been studied by PE spectroscopy except for NBr_3 and NI_3, which are unstable. A representative set of spectra is shown in Figure 31 and the first ionization energies are collected in Table 5, which also lists most of the pertinent references. For a summary on PE spectra of phosphorus compounds see reference 33.

The first ionization energies vary in some systematic way, as is obvious from Figure 31 and from Table 5. Expectedly, IE_1 is lowest for SbI_3 and highest for NF_3 with the ionization process involving the lone pair of the central atom. The analysis of finer variations within the set of EX_3 molecules seems to be complicated by several counteracting trends or effects: hybridization theory predicts a pure s lone pair for an angle

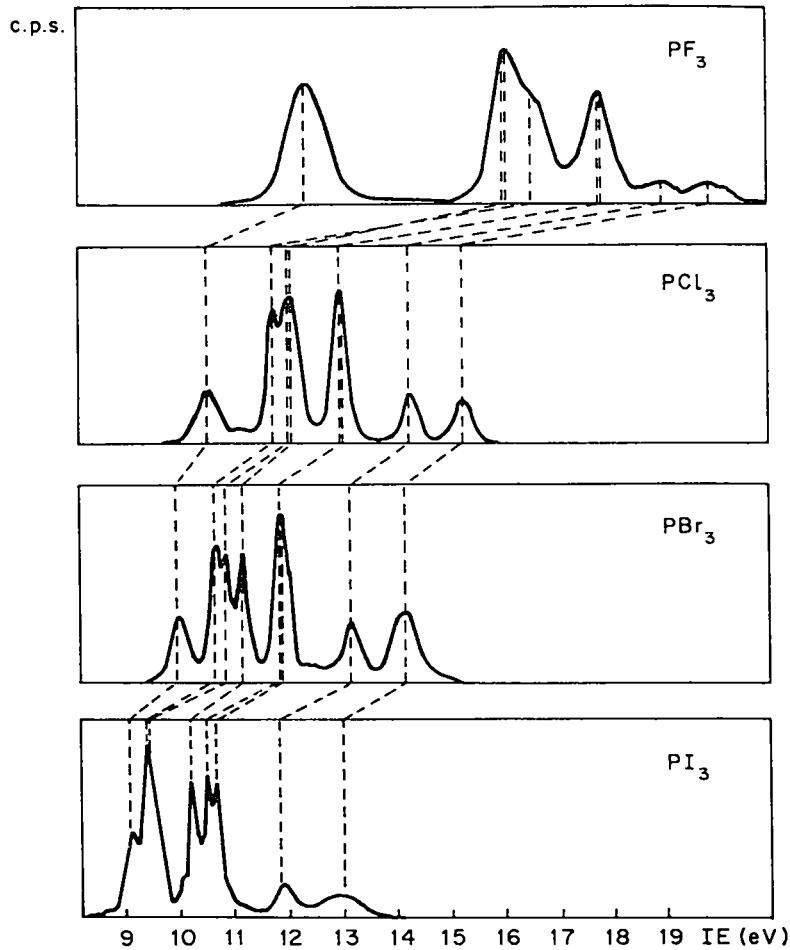


FIGURE 31. PE spectra of phosphorus trihalides[51,72].

TABLE 5. First ionization energies IE_1 (in eV) of group VB halides EX_3

	X			
E	F	Cl	Br	I
N	13.73[51,101]	10.7[51]	—	—
P	12.28[51,101,103,146,282]	10.52[51,72,282]	10.00[51,72]	9.15[72]
As	13.00[51]	10.90[51,284,285]	10.19[284,286]	9.11[284,286]
Sb	12.54[288]	10.70[284,287]	10.07[284,287]	9.05[284,287]

$X\hat{E}X = 90°$ and an sp^3 hybrid for a tetrahedral angle. However, since both the p_z orbital on the central atom E (taking the z-direction as C_3 axis) and the s orbitals transform according to the a_1 representation of C_{3v}, the only reason to exclude, *a priori*, a mixing of s and p orbitals for a 90° arrangement is the large difference in s- and p-type ionization energies of atoms[40]. Whether this mixing is described as hybrid-

ization or by a through bond interaction between the lone pair n_E and the bond orbitals σ_{EX} is a matter of choice, although this ambiguity might create some confusion. In the PE spectra of group VB trihalides, the first ionization energies spread 0.4 eV for the chlorides, 0.2 eV for the bromides, 0.1 eV for the iodides, but 1.5 eV for the fluorides: this clearly indicates a strong mixing of halogen and central atom lone pairs for the chlorides, bromides and iodides, and a strong dependence on the effective core change Z_{eff} (E) for the fluorides, due to a higher degree of localization.

The higher energy bands in the PE spectra of group VB halides (Figures 12 and 31) are advantageously assigned starting from models of planar compounds EX_3 of D_{3h} symmetry like the boron trihalides (Figure 40). The molecular orbitals deduced to represent the radical cation states of the pyramidal C_{3v} systems can be grouped into different classes[33] (see 'equation' 8) and Figure 12:

Type of orbital	D_{3h}	C_{3v}	C'_{3v}
Lone pair on E, n_E	a''_2	a_1	$e_{1/2}$
Bond orbitals E—X, σ_{EX}	a'_1	a_1	$e_{1/2}$
	e'	e	$e_{1/2}, e_{3/2}$
Lone pairs on X, n_X			
Peripheral	e'	e	$e_{1/2}, e_{3/2}$
	a'_2	a_2	$e_{1/2}$
Perpendicular	e''	e	$e_{1/2}, e_{3/2}$
	a''_2	a_1	$e_{1/2}$
s-type	e'	e	$e_{1/2}, e_{3/2}$
	a'_1	a_1	$e_{1/2}$

(33)

The transformation into the spin-adaptable double-group C'_{3v}[39] (see Section II.D) has also been included in 'equation' (33). The PE spectroscopic assignment – exemplified for PF_3 in Figure 12 – can then be based on the following preconceptions and experiences:

(i) The ionization energy reflects the major orbital composition.

(ii) Thus orbital interaction is strong within the a_1 symmetry, resulting in a large gap between IE_1 (n_E) and the next a_1 ionization. This interaction involves mainly $n_E, n_X(a_1)$, and $\sigma_{EX}(a_1)$. It depends strongly on geometry, but in no straightforward way. As a result, the sequence of IE_1 (Table 5) differs in some instances, like PF_3 or PCl_3, from expectation (i).

(iii) There is also a strong interaction between the non-bonding n_X and EX-bonding orbitals of e-symmetry. This interaction, for given X, depends strongly on the X—X distance. As a result, 'perpendicular' lone pairs $n_X(e'')$ are not necessarily perpendicular to the E—X bond.

(iv) The orbital $n_X(a_2)$ is the only orbital of that symmetry and could be used as internal standard for the elucidation of inductive effects. Yet, the corresponding PE bands are less clearly discernible than one would wish.

(v) For X = Br and I, the splitting pattern in the n_X region is mainly determined by spin–orbit coupling[284,286]. In the double group C'_{3v}, doublet states transform as $E_{1/2}$ and $E_{3/2}$. Consequently, not only a splitting of ^2E states results, but $E_{1/2}$ states represented by $e_{1/2}$ orbitals resulting from e, a_1 and a_2 orbitals mix heavily. The key interaction seems to involve $n_X(e)$ and $\sigma_{EX}(e)$ orbitals.

There is agreement on the general assignment of EX_3 PE spectra: $n_E(a_1)$ followed by $n_X(a_2$ and $e)$, next $\sigma_{EX}(e)$ and again a_1, as given in Figure 12 for PF_3; intercalated by the F lone pair ionizations.

Some discrepancies remain, for instance, concerning the ground state of PF_3^+. It has been argued[103], that this state should be of planar geometry, since no anharmonicity was detected in the first PE band. On the other hand, *ab initio* calculations[289] indicate a strong deviation from planarity. In this context it should be mentioned that 'frequency halving' is not observed for PF_3^+ and also not for planar NH_3^+, but is observed in the case of planar PH_3^+ [33,103]. The structural changes on complex formation, as in $H_3B—PF_3$ [33,102,280] or in, for example, $Ni(PF_3)_4$ [279–281,290,301], can be rationalized by the charge distribution around the phosphorus centre[33].

Some PE spectroscopic studies have been performed on mixed group VB halides like fluorohalophosphanes[291] or trifluoromethylchlorophosphanes[193] (phosphanes are saturated three-coordinated phosphorus compounds). Frequently, trifluoromethyl groups have been used to simplify the low energy region of the PE spectra of phosphanes[194,196]. Furthermore, amino-substituted halophosphanes[292–294], as well as group VB methyl-substituted halogen derivatives[288], have been investigated PE spectroscopically.

Surprisingly little work has been done on the PE spectra of the pentahalides of group VB; however, tentative assignments have been proposed for those of PF_5[283,295] and PCl_5[283,296]. Obviously, a definite assignment is quite difficult: although the structures are of high symmetry, there are 10 lone pairs and five PX bond electron pairs to be considered within the He(I) range, and there is hardly much experience with chemically related molecules for any detailed splitting and interaction diagrams. In addition, for PE spectra with many overlapping bands, i.e. closely packed $M^{\cdot+}$ states, even *ab initio* calculations involving Koopmans' theorem are not of great predictive power either (see Section II.E).

D. Group VB Halogen Derivatives Containing Multiple Heteroatom Bonds

A representative set of PE spectra of group VB halogen derivatives of this type is shown in Figure 32 and includes F_3NO[101], F_3PO[101], Cl_3PO[297] and Cl_3PS[297].

The assignment is based on comparison between the EX_3/EX_3Y pairs, as exemplified in Figure 12 for the trifluoride F_3P and its oxide F_3PO. The main differences are the two additional $M^{\cdot+}$ states of *e*-symmetry at low ionization energy, which involve the double bond, and which can be traced to the conversion of the former lone pair n_E into a σ_{EY} bond accompanied by considerable stabilization of the corresponding radical cation state[33] (Figure 12).

The discussion starts best with Cl_3PO[297] (see also references 72, 283). The first band is assigned to the $5e$ orbital, the fairly broad, symmetrical band envelope being contributed to the bonding character of $5e$. Next comes a series of four sharp peaks which are due to ionizations out of the chlorine lone pairs $1a_2$, $4e$, $5a_1$ and $3e$ with the actual sequence determined by intensity arguments: the *e* bands appear to have twice the integrated intensity of the a_2 one. This assignment is further substantiated by the observed spin–orbit splitting of the *e* states especially in Br_3PO[297] and by calculation, which yield the sequences given in Figure 32. Finally, three σ-bonding orbitals, $4a_1$, $2e$ and $3a_1$, correspond to the last three PE bands. The assignment is similar for Cl_3PS (Figure 32), which displays a larger separation between the $\pi_{PS}(e)$ and the halogen lone pair orbitals.

The assignment is different for F_3NO and F_3PO (Figures 12 and 32)[101,146]: accidental degeneracies prevail in the PE spectrum of the nitrogen compound, and the assignment, therefore, remains tentative due to the 'lack of bands'. Phosphoryl fluoride is different in that ionizations out of the fluorine orbitals occur only at high ionization energies, hence the σ_{PO} bonding state comes second (Figure 12)[33,101]. Concerning the vibrational fine structure in the first PE band of trifluoroamine oxide[298], the cationic frequency $\nu^+ \sim 1010\ cm^{-1}$ only correlates poorly with any of the three a_1

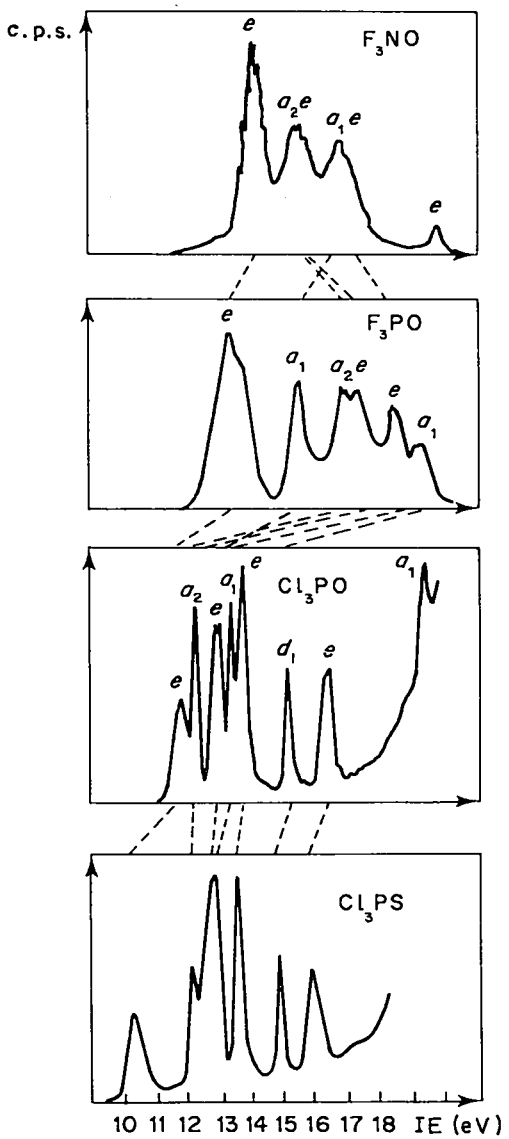


FIGURE 32. Helium(I) PE spectra of nitrogen and phosphorus oxytrifluorides[101] and of phosphorus oxytrichloride and phosphorus thiotrichloride[297].

fundamentals of the molecule $\nu = 1691, 743, 528\ cm^{-1}$. According to an INDO calculation, the corresponding $5e$ orbital contains hardly any N_{2p} contribution. A more general statement[299] would suggest that in highly ionic compounds, as F_3NO presumably is, the removal of an electron from the negative end, namely oxygen, in the formal resonance structure $F_3N^+ O^-$, considerably reduces bonding – in agreement with the observed vibrational fine structure ν^+ in the first PE band of F_3NO.

In the C_{3v} molecules $X_3P{=}Y$, the M^+ state corresponding to the $1a_2$ orbital is of unique symmetry and, therefore, can be used to detect changes in the effective nuclear charge of the halogens. Comparison of the differences of the $1a_2$ ionization energies of pairs of compounds X_3P and $X_3P{=}Y$[101,280,283,297] (see 'equation' 34) demonstrates that

X	Y		
	O	S	BH_3
F	1.2 eV	0.5 eV	1.0 eV
Cl	0.7 eV	0.3 eV	
Br	0.8 eV	0.3 eV	

(34)

'coordination' by oxygen is more effective in removing electron density from the halogen than is 'complexation' by sulphur. The changes with respect to different halogen atoms are surprising. The halogens and oxygen or sulphur compete for electron density. It seems that fluorine is most successful in PF_3, and subsequently can afford a greater loss: adducts like $F_3P{-}BH_3$[33,102,280] or $Ni(PF_3)_3$[279-281,290] can be included in this discussion and obviously support the argument.

Still another analysis is possible with respect to the EX_3/EX_3Y pairs: the E—Y bond strength can be estimated from the stabilization of the lone pair orbital n_E of EX_3 upon complexation, i.e. the differences $IE(5a_1\ PX_3Y) - IE(n_E\ PX_3)$:

EX_3	Y		
	O	S	BH_3
NF_3	3.2 eV		
PF_3	3.4 eV	2.2 eV	1.6 eV
PCl_3	3.0 eV	1.9 eV	
PBr_3	2.4 eV	1.8 eV	

(35)

Although these ionization energy differences are not strictly comparable (for X = F the orbital $5a_1$ is predominantly σ_{EY} bonding and for X = Cl, Br rather of lone pair character) some correlations are obvious: for example, borane coordination proves to be less effective than that of oxygen or sulphur[33].

There is considerable theoretical as well as experimental work available which discuss the donor properties of PF_3. Usually, the quality of calculations is judged from comparison with PE data, and *ab initio* SCF wave functions are subsequently analysed using population analyses or localized SCF orbitals[101,102,280,290,300]. In a cinematographic separation[33], the primary effect seems to consist of a σ-donation of the n lone pair, accompanied by a stabilization of all orbitals of PF_3 and a back-donation of electron density via e orbitals (in C_{3v}). This back-donation is pronounced for Y = O, or S, but hardly discernible for BH_3[33,290]. Although fictitious, all calculations which do use phosphorus 3d orbitals in their basis set, necessarily have to yield a considerable degree of $d_\pi{-}p_\pi$ bonding. The PE spectra of transition metal complexes with PF_3, such as $Ni(PF_3)_4$, which show PE spectra very similar to free PF_3 (Figure 31)[279-281,290,301] will be discussed with the PE spectra of other metal complexes in Section IX.

VIII. HALOGEN DERIVATIVES OF OXYGEN, SULPHUR AND THE OTHER GROUP VIB ELEMENTS

Section VIIIA on 'PE Spectroscopic Comparison of Inorganic Prototype Halides and Their Alkyl Derivatives' has already introduced the approach used in this chapter for

the electron-rich group VIB element halides: the PE spectra of the alkyl derivatives are best discussed starting from those of the inorganic prototype halides which exhibit much higher symmetry and, therefore, are much easier to assign. Subsequently, by predictable perturbations, the alkyl substituents are introduced (see Sections III, V and VI). The procedure has been illustrated, for instance, by comparing the PE spectra of difluorosulphimine derivatives $F_2S{=}NX$ with X = Cl, CH_3 and CF_3[268] (Figure 28). It is once again demonstrated by the pair of iso(valence)electronic sulphur derivatives, Cl—S—Cl and H_3C—S—Cl, the PE spectra of which are presented in Figure 33[224,302,303].

Starting with the PE spectrum of SCl_2[302,303] (Figure 33), the first band at 9.7 eV relates to the sulphur lone pair (b_1 in C_{2v}). The vibrational fine structure observed, $\nu^+ \sim 540\ cm^{-1}$, indicates a slight antibonding contribution from chlorine, since ν^+ is larger than all symmetric ground state fundamentals. The bands between 12 and 13 eV are assigned to three ionization events of symmetry a_1, b_2 and a_2, a specific ordering of which is hard to give: while the b_2 and a_2 orbitals are mostly located on chlorine, the in-plane sulphur lone pair orbital $n^{\sigma}_{S}(a_1)$ carries significant sulphur–chlorine bonding contributions. The next three bands are assigned to $n^{\pi}_{Cl}(b_1)$, $n^{\sigma}_{Cl}(a_1)$ and $\sigma_{SCl}(b_2)$ orbitals, in this order. Finally, the $3s_S$ ionization can be located

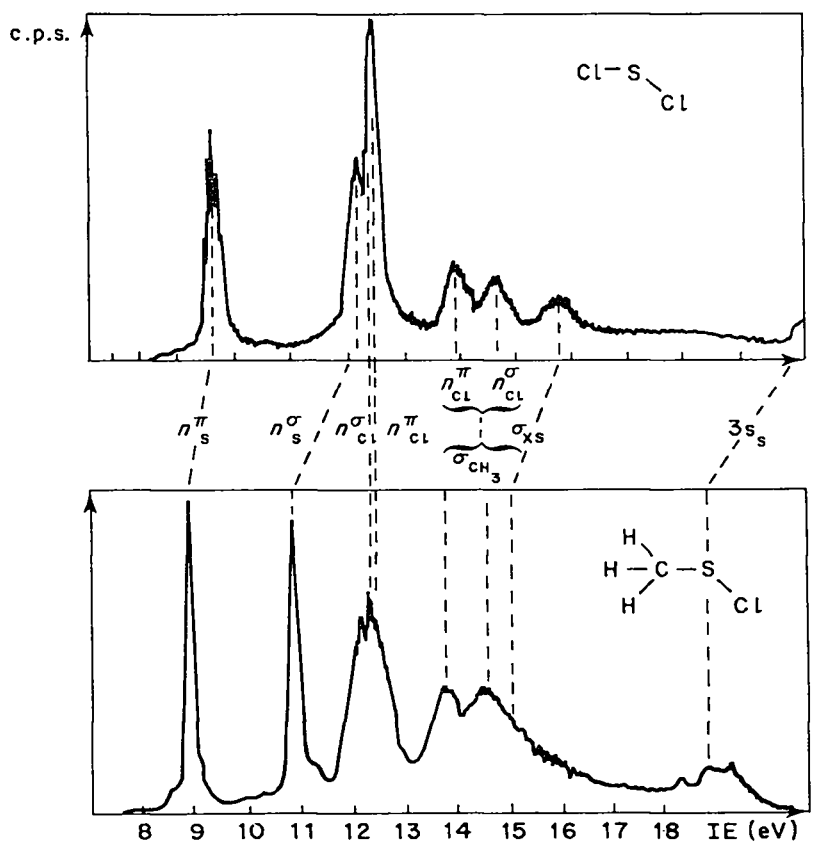


FIGURE 33. Helium(I) PE spectra of sulphur dichloride[302,303] and of methyl sulphur chloride[224].

near 21 eV[302,303]. Switching over to the iso(valence)electronic methyl derivative, this also contains 14 p-type valence electrons and, therefore, according to a useful rule of thumb[6], gives rise to seven ionizations within the helium(I) range. The dominant perturbations are the Cl → C(H) exchange accompanied by a lowering of the effective nuclear charge of one ligand, i.e. by corresponding shifts of $M^{\cdot+}$ states to lower energies, and of a considerable reduction of the skeletal symmetry from C_{2v} to C_1. Although the orbitals lose their symmetry classification, they can still be recognized by their major contributions. Thus, the n_S^{π} lone pair is shifted from 9.7 to 9.1 eV, and down to 8.7 eV in the dimethyl sulphide[241]. Removing one chlorine separates the in-plane sulphur lone pair n_S^{σ} state from the overlapping bands around 12 eV, whereas the chlorine lone pairs n_{Cl}^{π} and n_{Cl}^{σ} approximately remain, now heavily mixed with other contributions. Smaller shifts are observed for the σ ionizations, whereas the $3s_S$ ionization is lowered by about 2 eV, clearly displaying the perturbation due to the reduced Cl—C(H) effective nuclear charge.

Continuing along these lines, the PE spectra of group VIB halides will be presented in the order of oxygen derivatives (Section VIII.A), saturated sulphur halides (Section VIII.B), and halogen-substituted sulphur–nitrogen and sulphur–oxygen π systems (Section VIII.C).

A. Halogen Compounds of Oxygen

The PE spectroscopic studies on the compounds F_2O[95,305], FOH[306,307], Cl_2O[305], ClO_2[270,308] and $FClO_3$[309] are discussed.

Comparison of the PE spectrum of oxygen difluoride[95,305] (Figure 34) with that of water clearly demonstrates again the perfluoro effect (Section III.A): the first ionization potential is hardly affected by the fluorine substitution, expectedly and in line with its π character. However, the $\pi(1b_1)$ orbital in water relates to a non-bonding lone pair orbital, whereas the topmost $\pi(2b_1)$ orbital of F_2O is considerably F—O antibonding. Consequently, the $M^{\cdot+}$ ground state, $X(^2B_1)$, shows a vibrational frequency, $\nu^+ = 1010\ cm^{-1}$, which is larger than the corresponding value, $\nu_1 = 928\ cm^{-1}$, for the ground state of the neutral molecule. The vibrational envelope of the first band, in addition, is more pronounced in F_2O due to the larger topmost orbital relative to the one for H_2O, and also due to the heavier mass of F.

For both HOH and FOF, perturbation calculations have been performed[86]: whereas only small Koopmans' defects result for water, Koopmans' theorem fails badly for the electron-rich fluorine derivative (see Section II.E). Consequently, the oversimplified picture of the perfluoro effect has to be extended by considerable relaxation and correlation contributions[222].

The assignment of the Cl_2O PE spectrum[305] (Figure 34) closely resembles that for F_2O. The first band at 11.02 eV relates to a b_1 orbital, mainly on oxygen, the group of bands at 12.37, 12.65 and 12.79 eV are assigned to three chlorine lone pair orbitals of symmetry b_2, a_1, a_2. Since the a_2 orbital is completely confined to the chlorine atoms, the a_2 ionization is assigned to the sharp peak at 12.79 eV[305].

The photoelectron[306] and the photoionization[307] spectra of FOH have been studied. This molecule has long been thought of as an unstable species, and the rapid deterioration in the ionization chamber of the instrument cannot be excluded[306], because two $M^{\cdot+}$ states predicted within the He(I) range could not be detected. The orbital sequence calculated, a'', a', a', a'', possibly does not reproduce the $M^{\cdot+}$ state sequence A'', A', A'', A' strongly advocated[86], a correlation failure (see Section II.E), for which sometimes the phrase 'breakdown of Koopmans' theorem' is used. The first photofragmention process, $HOF + h\nu \rightarrow O^+ + HF + e^-$, is favoured by the small angle HOF = 97.2°, and the considerable polarity $H^+—O—F^-$ as deduced from NMR studies[304,305].

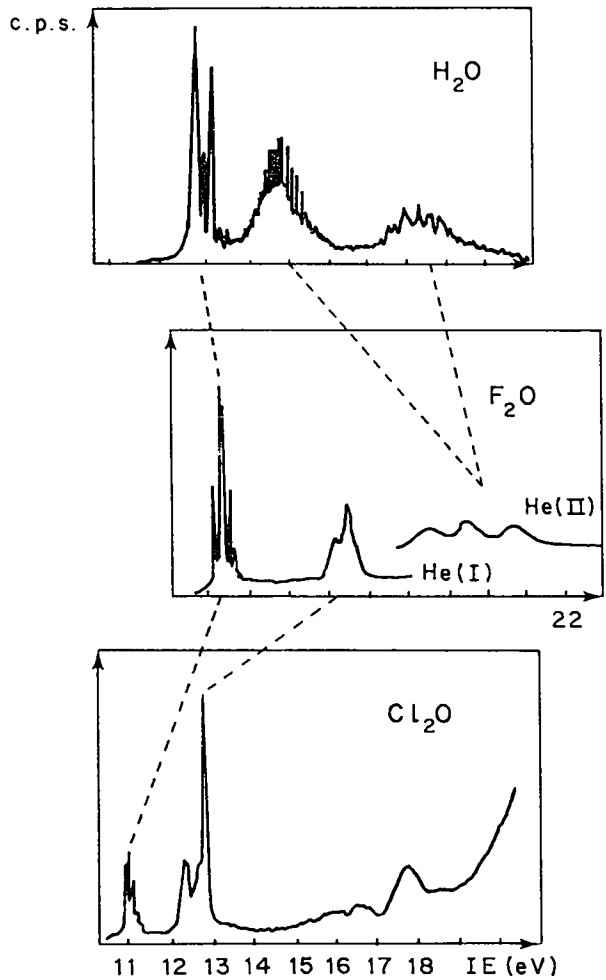


FIGURE 34. Helium(I) PE spectra of water[2], oxygen difluoride[95,305] (together with the lower helium(II) part) and oxygen dichloride[30,270]. The correlation lines are drawn according to major orbital contribution[95].

The PE spectrum of the free radical chlorine dioxide, $^{\cdot}ClO_2$[270,308], has been assigned on the basis of the UV spectrum of the chloryl cation ClO_2^+, which identifies the $^1B_1$ and $^1B_2$ states at 3.76 eV and at 4.59 eV, respectively, above the ground ionic state. The first PE band is ascribed to removal of the unpaired (b_1) electron. The $^3B_1$ and $^3B_2$ states are assigned to the broad structure around 13 eV, which also contains the $^1B_1$ state.

Last but not least in this section, a careful He(I) plus He(II) study of chloryl fluoride, $FClO_3$[309], has to mentioned.

B. Saturated Sulphur Halides XSX, XSSX, SF_4 and SF_6

Of the various saturated sulphur halides containing divalent sulphur, S_nS_2, only the PE spectra of SCl_2 for $n = 1$[302,303] (Figure 33), and FSSF, ClSSCl and BrSSBr for

$n = 2$[303,304,310] (Figure 35) have been studied. In addition to the C_2 isomer F—S—S—F, bonding in the C_s isomer $F_2S{=}S$ has been investigated[304,310].

With few exceptions, the assignment of the XSSX PE spectra (Figure 35) to characteristic molecular orbitals is partly obscured by strong mixing of the latter under C_2 symmetry. Nevertheless, by chemical comparison along the XSSX series including the parent compound HSSH, and accompanied by semi-empirical calculations, the correlations indicated by dotted lines in Figure 35 have been proposed[304]. Starting with FSSF, the double band around 11 eV relates to two sulphur lone pair orbitals of species *a* and *b* in C_2. The splitting of these levels is not only due to direct interaction, which somehow correlates with the dihedral angle, but also to differing admixtures of σ-bonding contributions. The next sharp feature in the PE spectrum of FSSF at 12.94 eV is assigned to the sulphur–sulphur σ-bonding orbital, while bands beyond 15 eV refer to ionizations out of fluorine lone pair orbitals. Replacing fluorine by chlorine and bromine, three changes take place[304]:

(i) Ionizations relating to halogen lone pair orbitals take place at successively lower energies.

(ii) The sulphur–sulphur σ-bonding orbital, which was at a lower IE than fluorine lone pair orbitals in FSSF, is at higher IE than are chlorine and bromine lone pair orbitals in ClSSCl and BrSSBr.

(iii) Spin–orbit coupling becomes important for BrSSBr, such that double group notation should be used in the low energy part of its PE spectrum.

The molecule thiothionyl fluoride, $F_2S{=}S$, displays a PE spectrum only marginally different from its isomeric difluorodisulphane, F—S—S—F[310]. Although this might be a surprise in view of the widely different structures, it is strongly supported by semi-empirical MO calculations[304]. In line with experiments, CNDO/2 predicts two isomers for S_2F_2, the disulphane being the more stable by 0.1 eV, whereas only one stable isomer is predicted – and has been found so far – for S_2Cl_2[304,310], or the parent compound HSSH, itself[7,304].

As regards tetracoordinated sulphur–halogen derivatives, only the PE spectrum of SF_4[311] has been reported (Figure 36). Its assignment is straightforward: the sulphur lone pair ionization leads to the $M^{\cdot+}$ ground state, followed by axial and then by equatorial fluorine lone pair states, and above 17 eV by SF skeleton ionizations.

The PE spectrum of methylene sulphur tetrafluoride can be approached by combining SF_4 with an (excited)[312] CH_2 unit, added to the n_S lone pair to form the $\pi_{C=S}$ bond. Indeed, comparing the structural parameters of the respective SF_4 moieties in both compounds (Figure 36), only small changes accompany the formal addition of a CH_2 unit. Therefore, the assignment starts by assuming an approximately constant n_F ionization pattern with additional σ_{CH_2} ionizations inserted. The most evident difference is the low energy shift of the first ionization on the transformation from an n_S lone pair to a relatively short i.e. electron-rich, $\pi_{C=S}$ bond (Figure 36).

The surprisingly inert molecule SF_6 has led to a series of experimental[2,14,22,51,154,313–315] and theoretical[316] (see the literature review in reference 3–16) investigations: somehow, the molecule has served as testing ground for a variety of semi-empirical and *ab initio* MO calculations, most of which fail to account for the experimental results. The SF_6 PE spectrum (Figure 36: He(I) region) has been tentatively assigned as follows[316]: disregarding fluorine 2s electrons, 18 valence electron ionizations are expected below 30 eV. Due to the high symmetry O_h, seven PE bands are expected, namely t_{1u}, t_{1u}, t_{1g}, e_g, t_{2u}, t_{2g}, a_{1g}. Following roughly the results of the calculations[316], one is forced to assign two ionization events to either 18.5 eV structure or the 17 eV structure. While the former is suggested by band shapes, the latter assignment is strongly favoured by calculations, which account for most of the Koop-

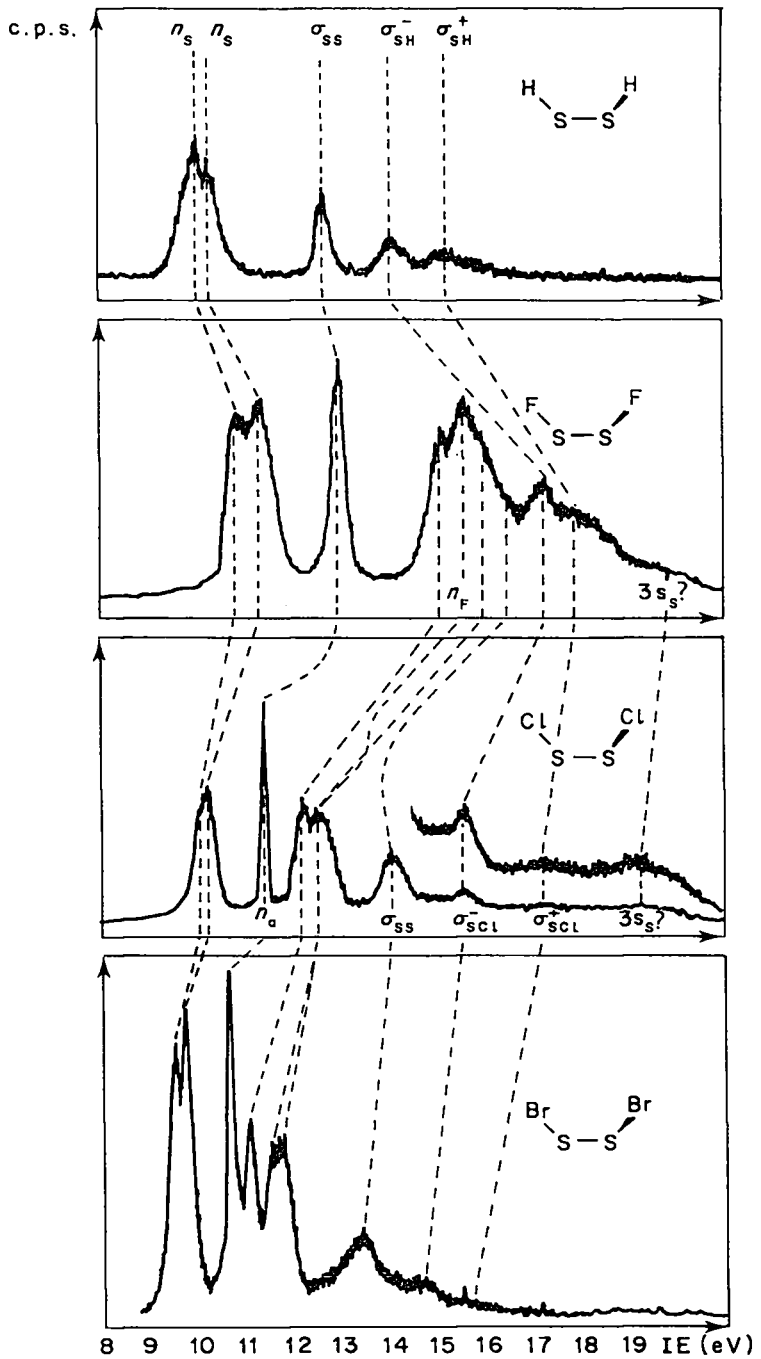


FIGURE 35. Helium(I) PE spectra of difluoro-, dichloro- and dibromodisulphane and assignment starting from HSSH[304].

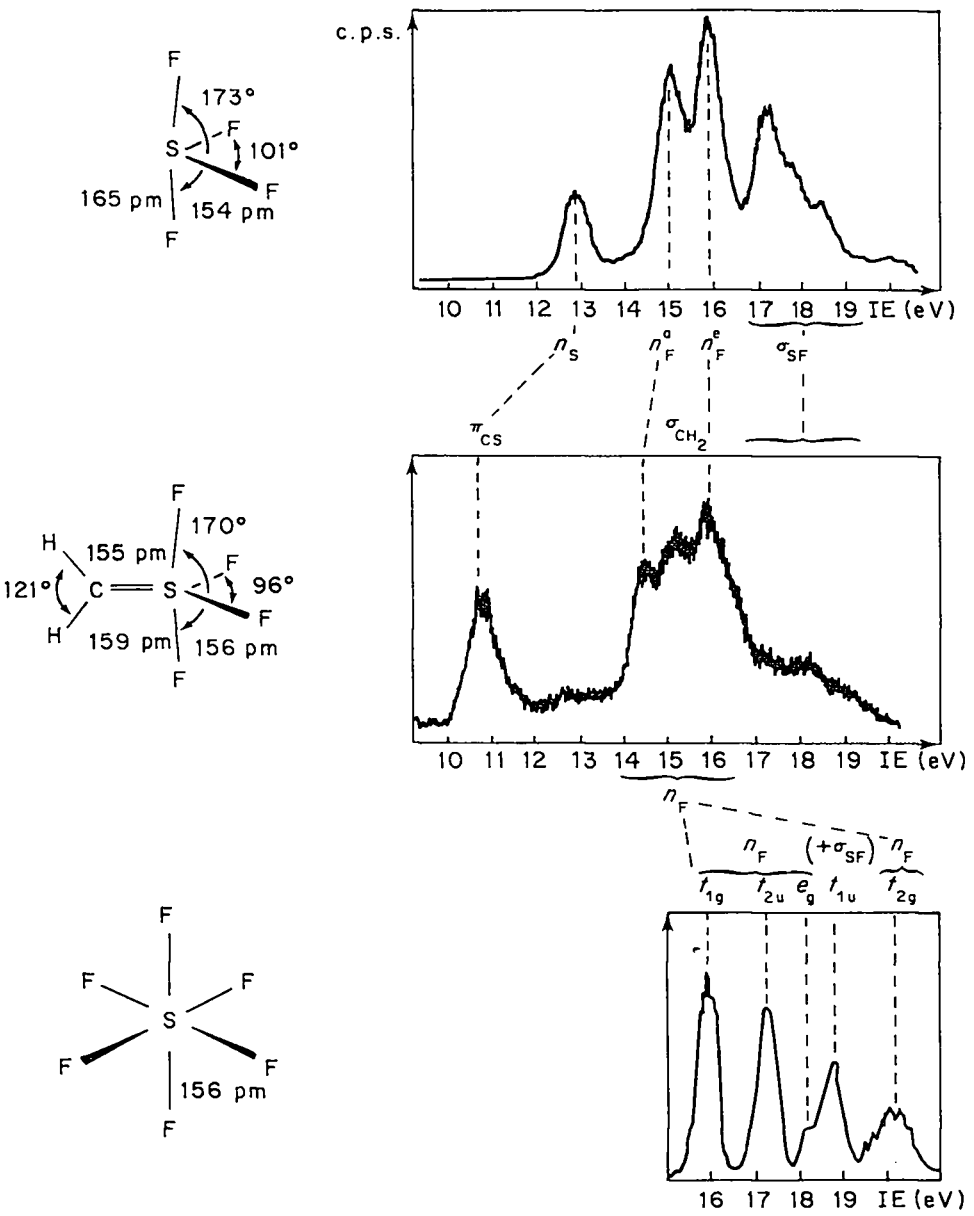


FIGURE 36. Helium(I) PE spectra of sulphur tetrafluoride and of methylene sulphur tetrafluoride[311], and of a sketch of the SF_6 PE spectrum with assignment.

mans' defects. This 'final' assignment is in line with X_α calculations, which account for relaxation effects. Regarding the large correction terms up to 3 eV needed to incorporate relaxation and correlation, it seems of little relevance whether d orbital participation can or cannot be deduced from the SF_6 PE spectrum.

The PE spectrum of SeF_6, TeF_6, and also of MoF_6, WF_6, UF_6 are similar to those of

SF_6[51,315]. Also $ClSF_5$ has been studied[135]; its PE spectrum displays more bands due to reduced symmetry ($O_h \rightarrow C_{4v}$), and the $M^{\cdot+}$ states with large chlorine contributions give rise to prominent peaks[315].

C. Sulphur–Halogen Derivatives Containing Multiple Nitrogen and Oxygen Bonds

The PE spectroscopic discussion of higher valence state sulphur halides in the preceding section will be extended here to include the halogen compounds with S=N bonds like thiazyl trifluoride, $F_3S{\equiv}N$[317], or thiazyl halides, X—S≡N[318–322], as well as those with S=O bonds like thionyl halides, $X_2S{=}O$[323,324], and sulphuryl halides[306,325].

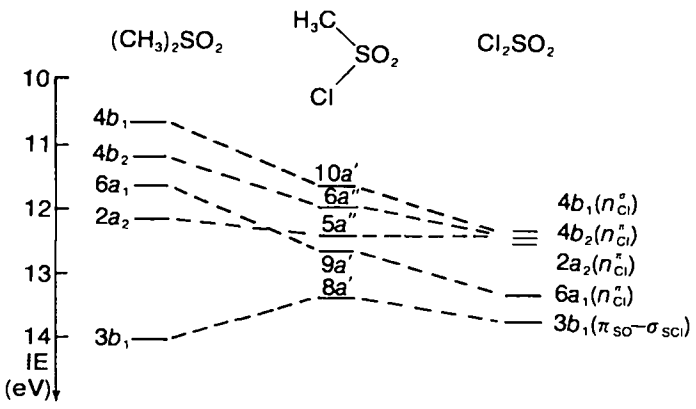
As one of the key compounds in sulphur–nitrogen chemistry, thiazyl fluoride, FSN, has achieved considerable attention from PE spectroscopists[317–322]. The helium(I) PE spectra of FSN, together with those of the related molecules F_3SN and ClSN are shown in Figure 37.

The orbital assignment for the FSN PE spectrum, i.e. $n_S^a(7a')$, $\pi_{SN}(6a')$, $\pi_{SN}(2a'')$, $n_N^a(5a')$, is heavily based on the orbital character and on the analysis of vibrational fine structure in the PE bands[317] (see Figure 37). Thiazyl trifluoride, F_3SN, although exhibiting a structure with rather short SF bonds, can be thought of as an SF_6 derivative in which three fluorines have been replaced by nitrogen. The assignment then is $\pi_{SN}(e) < n_N^a(a) < n_F(e)$ for this C_{3v} molecule, based on correlation with FSN and relative band intensities[317,318] (Figure 37). The PE spectrum of thiazyl chloride, also in Figure 37, has been assigned by comparison with that of the fluorine compound[317] and on the basis of CNDO/2 calculations[320]. The most significant difference to the FSN PE spectrum consists of the coalescence of the second and the third PE band into one peak for ClSN, with the 'π_{SN}' orbitals heavily located on chlorine.

Thionyl and sulphuryl halides have been studied by several PE spectroscopic groups[306,323–325], including also the alkyl derivatives X(R)S=O and $X(R)SO_2$ [323–325]. The representative PE spectra of thionyl halides are shown in Figure 38.

Based on a correlative study involving a variety of molecules R_2SO, the characteristic orbitals of the S=O grouping can be described as sulphur lone pair n_S,$\pi_{S=O}$ and oxygen lone pair n_O. The sequence is also that of the first three bands in the PE spectrum of F_2SO (Figure 38), whereas the spectra of Cl_2SO and Br_2SO contain many additional bands at low ionization energies due to halogen lone pairs, and that a detailed assignment has to rely heavily on calculations[323].

Oxidation to sulphuryl halides X_2SO_2, X = F, Cl, stabilizes the sulphur lone pair by transforming it into an additional π_{SO} orbital and introduces another oxygen lone pair. In



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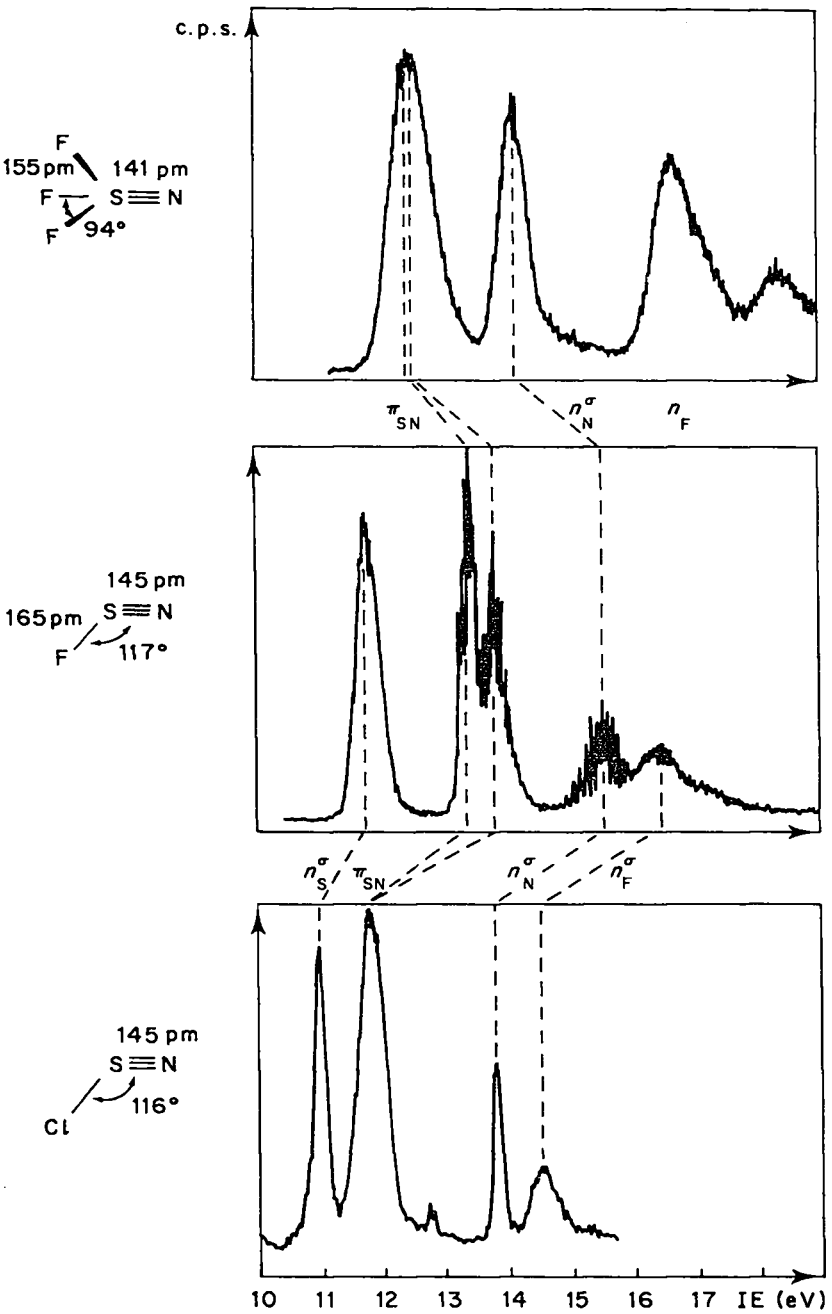


FIGURE 37. Helium(I) PE spectra of thiazyl trifluoride, thiazyl fluoride and thiazyl chloride[317].

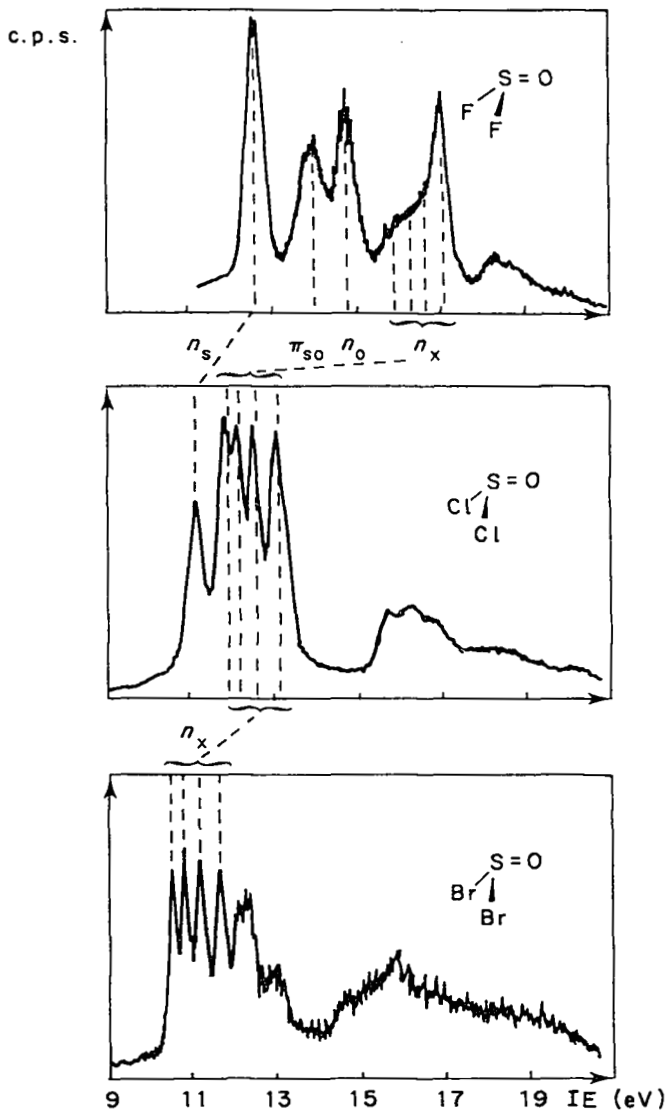


FIGURE 38. PE spectra of thionyl halides X_2SO for X = F, Cl, Br[323].

C_{2v}, no degenerate species are possible, yet the PE spectrum of Cl_2SO displays several overlapping ionization bands. The assignment is based on semi-empirical calculations and, especially, on comparison of equivalent $M^{\cdot+}$ states along series of chemically related compounds, as shown in 'equation' (36)[325].

Once more, substituting the chlorine ligands successively by iso(valence)electronic methyl groups introduces perturbations due to the lowered effective nuclear charge, and due to the reduced symmetry. In the series from sulphuryl dichloride to dimethyl-

sulphone (equation 36), the overlapping ionization bands are spread over a larger energy region, and thus can be assigned separately[325].

In conclusion, reference is given to the PE spectroscopic studies of the radical $FSO_3^{\bullet}$[270] and to the PE spectroscopically optimized (see Section X) thermal decomposition of methyl thionyl chloride[324],

$$H_3C{-}SO{-}Cl \longrightarrow H_2C{=}S{=}O + HCl,$$

which yields the novel short-lived intermediate sulphine, identified by its PE spectrum, i.e. its ionization 'fingerprint'[324].

IX. ELECTRON-DEFICIENT HALIDES AND ORGANOMETALLIC HALOGEN COMPOUNDS

The discussion of the PE spectra of individual organic halogen compounds – and wherever advantageous for the assignment, their usually smaller and highly symmetric

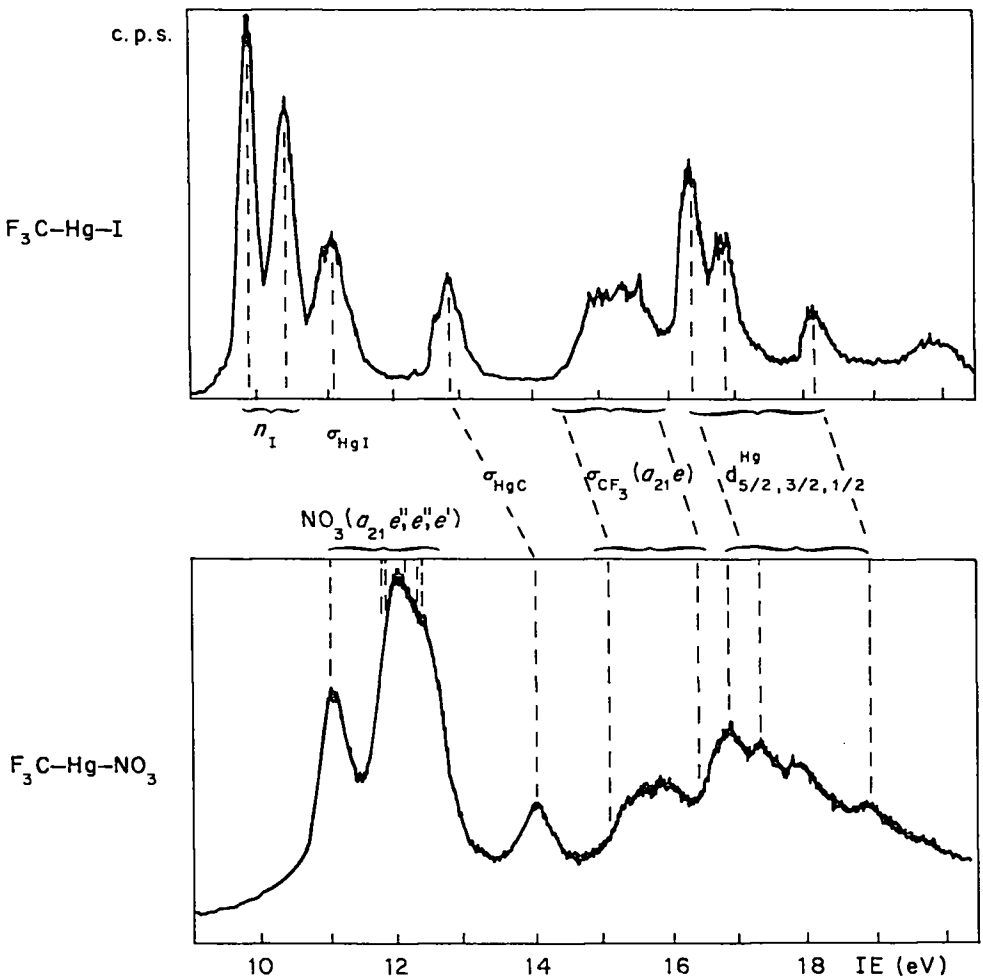


FIGURE 39. Helium(I) PE spectra of $F_3C{-}Hg{-}I$ and of $F_3C{-}Hg{-}NO_3$ with their assignment.

inorganic prototypes (see Section VII.A and introduction to Section VIII) – will end with this chapter. Having already presented the halogen derivatives of most of the main group elements – above all those of carbon (Sections III, V, and VII) – from group IVB to group VIIIB (Sections IV, VII and VIII), the remaining part will be devoted to electron-deficient halides like those of group III elements B to Tl as well as to the organometallic halides, preferentially from the transition elements stretching from group IB to group VIIIA. It is hardly necessary to point out the ever increasing importance of these halogen derivatives, from group IVA polymerization catalysts via low-valent metal complexes to metal clusters.

Just as an introductory example, the helium(I) PE spectra of the volatile trifluoroethyl mercury iodide and nitrate[326] are presented in Figure 39.

The assignment of the $F_3C—Hg—X$ PE spectra (Figure 39) is based on comparison along the series with X = I, N_3, NCO, NO_3 and SCF_3[326] and guided by semi-empirical calculations. Following the low energy, substituent-specific ionizations like the spin-orbit coupled iodine lone pair states or the states of the NO_3 moiety, the ionization patterns at higher energy resemble each other: the $M^{\cdot+}$ states observed are characterized by predominant contributions from the σ_{HgC} bond, the CF_3 group, and finally, the spin–orbit coupled mercury ionic states, $d_{5/2}$, $d_{3/2}$ and $d_{1/2}$, respectively[77,326].

With any completeness in the field of PE spectra of organometallic compounds being outside the scope of this review, only typical examples for each class of compounds will be discussed in the following: electron-deficient boron halides, including the B_4 cluster (Section IX.A); metal halides of group III (Section IX.B), group IIA (Section IX.C) and the transition element groups IVA to VIIIA (Section IX.D) as well as their low-valent complexes (Section IX.E). An outlook on ionic halides (Section IX.F) will bridge the gap to the final Section X, dealing mainly with applications of PE spectroscopy of organic halogen compounds.

A. Boron Halides

The fascinating and electron-deficiency balancing bonding in boron compounds (see, for example, references 6, 23) has attracted the attention of many PE spectroscopists. Special interest has been focused on the four atom/24 valence electron boron trihalides, and although no definitive agreement has yet been reached, the main questions of the BX_3 assignment seem now to be settled[6,32,51,62,78,327–331]. On assigning their PE spectra and characterizing their cation states by idealized molecular orbitals (Figure 40), the strength of π bonding, which can be measured by the ionization energy difference $\Delta\pi = IE(1a_2'') - IE(1e'')$, immediately becomes obvious.

Ab initio SCF calculations on BF_3[330] and on BF_3^+[331] indicate an ordering $1a_2' < 1e'' < 3e'$, whereas semi-empirical methods, e.g. reference 329, tend to put the $1e''$ and $1a_2'$ ionizations at higher ionization energies. Correspondingly, a $3e'$ assignment for the first ionization energy of BF_3 was proposed on the latter basis[329] and seemed to be supported by intensity differences between He(I) and He(II) spectra[51]. However, comparison along the whole BX_3 series[62,328] clearly favours the $1a_2$ assignment ('equation' 37).

The next two ionizations are attributed to the $1e''$ and $3e'$ orbitals based on *ab initio* SCF calculations[330,331], but the reversed sequence $1a_2' < 3e' < 1e''$ is favoured[78] on consideration of vibrational fine structures.

For BBr_3 and BI_3 strong effects of spin–orbit interactions are observed among the low energy PE bands (Figure 40 and 'equation' 37). The splitting pattern can be best rationalized by a mixing of the $3e'$ and $2e'$ orbitals for the E' states and only by a small second-order effect for the E'' state (Section II.D). It should be noted that the terms arising from $3e'$ and $2e'$ orbitals show reversed order: $E_{3/2} < E_{5/2}$ for $3e'$ and $E_{5/2} < E_{3/2}$ for $2e'$. This is due to different interference of the electrostatic and

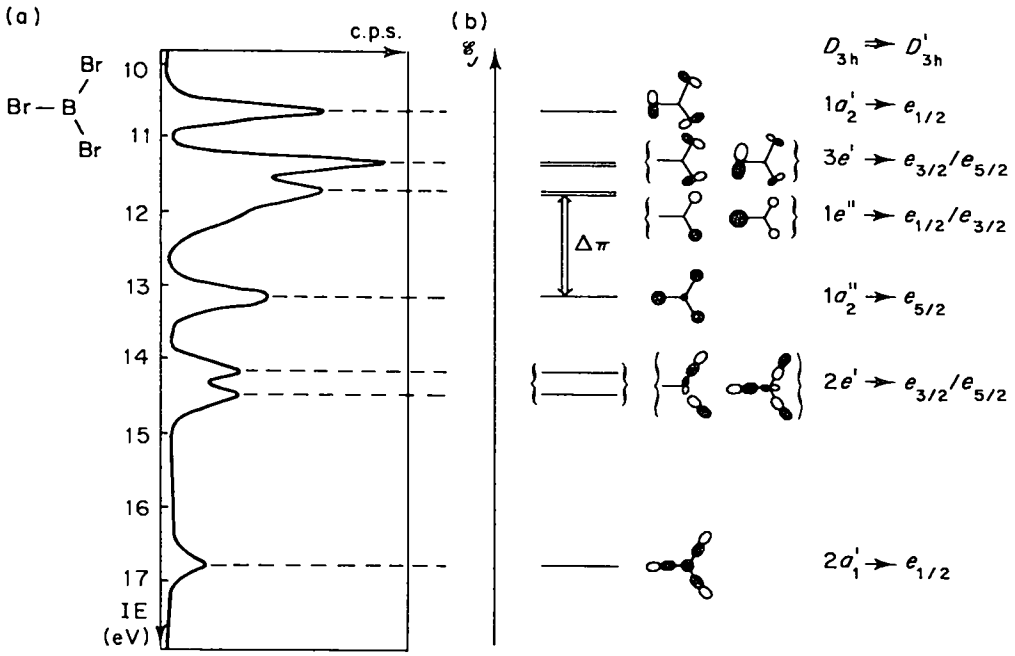
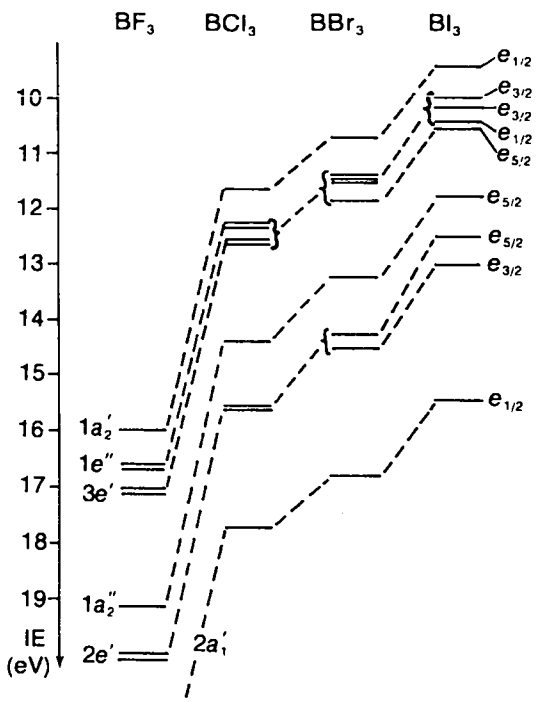


FIGURE 40. (a) Helium(I) PE spectrum of BBr_3. (b) Symmetry-adapted orbitals for boron trihalides in D_{3h} and its double group D'_{3h}.



(37)

relativistic contributions to the interaction matrix elements, leading to a smaller interaction for the $e_{5/2}$ species[62].

The correlation diagram ('equation' 37) for BF_3 to BI_3 shows that, irrespective of the definitive $1e''$ assignment, the split $\Delta\pi = IE(1a_2'') - IE(1e'')$ decreases from BF_3 to BI_3. The π bonding contribution to the total stabilization might be even larger than $\Delta\pi$ by a factor of ~1.5 due to increased electron–electron repulsion[328]. Anyhow, the sequence F > Cl > Br ~ I is just the one needed in the explanation of BX_3 Lewis acidities[6,32,332], neglecting differences in σ bonding as well as steric effects[333].

Other boron halides investigated by PE spectroscopy are B_2F_4[334], B_2Cl_4[334] and B_4Cl_4[335]. The structural backbone of the latter is a B_4 tetrahedron and its PE spectrum (Figure 41) has been assigned[335] using QMO approach (see Section III). The 40 valence electrons can be formally classified within a bond notation by 4 σ_{BCl}, 8n_{Cl} and 4 $3s_{Cl}$, leaving four two electron–three centre σ_{BBB} bonds. The occupied orbitals belong to the T_d representations $\Gamma = 3a_1 + 1e + 1t_1 + 4t_2$, with each σ_{BBB}, σ_{BCl} and $3s_{Cl}$ forming an $a_1 + t_2$ set, and the n_{Cl} splitting into $1e + 1t_1 + t_2$ as in tetrahedral element tetrahalides EX_4 (see Sections V.A and V.C). Inferring from Figure 13 that ionizations are expected around 13 eV for n_{Cl}, around 16 eV for σ_{ECl} and outside the He(I) range for $3s_{Cl}$, the B_4Cl_4 PE spectroscopic pattern (Figure 41) becomes transparent.

The n_{Cl} sequence $t_1 < e < t_2$ – expected for interaction-free lone pairs, but changed relative to the one observed for group IVa tetrachlorides $t_1 < t_2 < e$ – can be explained by an additional t_2 interaction with σ_{BBB}, which compensates the shift due to $\sigma_{BCl}(t_2)$ admixture. To rationalize the considerable separation of the n_{Cl} ionizations $1t_1/1e$, π back-bonding B—Cl into low-lying unoccupied e orbitals of the B_4 skeleton is proposed[335], contributing to the stability of B_4Cl_4.

Other PE spectroscopic investigations of molecules with boron–halogen bonds comprise mixed boron halides[336] alkyl derivatives like $(H_3C)_2B—F$[337,338], Lewis acid/base adducts $F_3B \leftarrow NR_3$[339], halogenated aminoboranes $X_nB(NR_2)_{3-n}$[78,293,333], *B*-trihaloborazines[6,97,340,341] (see also the review on B/N compounds[32]), and halogeno

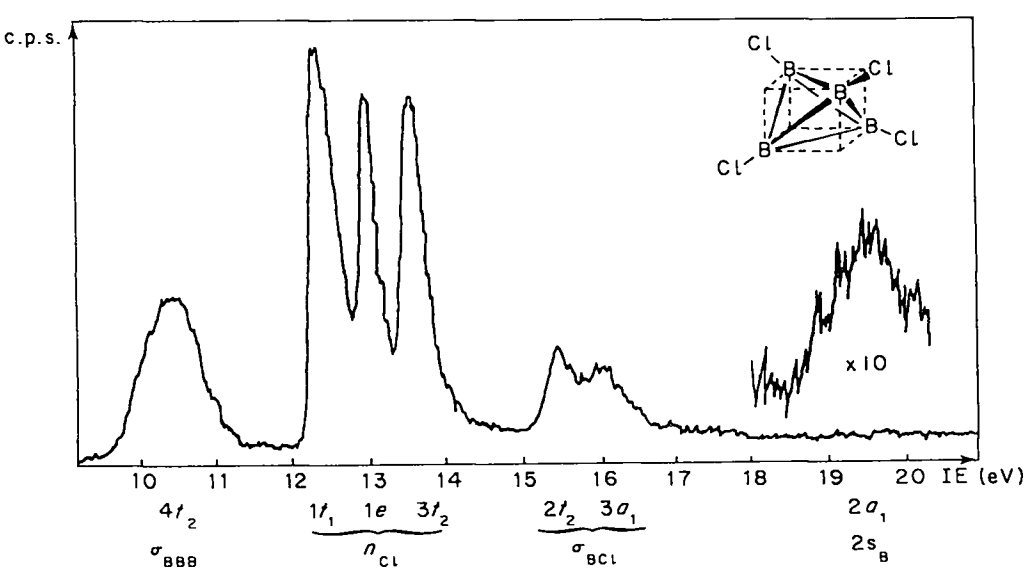


FIGURE 41. He(I) PE spectrum of B_4Cl_4 and its assignment[335].

pentaboranes[342]. The Lewis adducts – see also $H_3B—PF_3$[33,280,300], which displays a PE splitting pattern analogous to OPF_3[33] (Figure 12) – display in their PE spectra the stabilization of the bond-forming amine/phosphine lone pair, which ranges from 3.7 eV in $F_3B{\cdot}NMe_3$ to about 1 eV in $H_3B{\cdot}PF_3$. From comparison within the aminoborane series, it has been deduced[333], that twisting of the dimethylamino groups increases with the halogen substituent radius. BH/BX substitution of borazine or *N*-trimethylborazine leads to shifts of the π_1 ionization, which can be rationalized by first-order perturbation[341], and *B*-trifluoroborazine constitutes another convincing example of the perfluoro effect[96,341], as depicted already in Figure 10. PE ionization energies of some boron–halogen compounds have been used to assign Rydberg states in their (vacuum) UV spectra by fitting the individual excitation energies $h\nu$ into the series formula given by equation (38)[24,337]:

$$\mathrm{IE} - h\nu = R/(n - \delta)^2, \tag{38}$$

where R is the Rydberg constant, n is the main quantum number, and δ is the quantum defect.

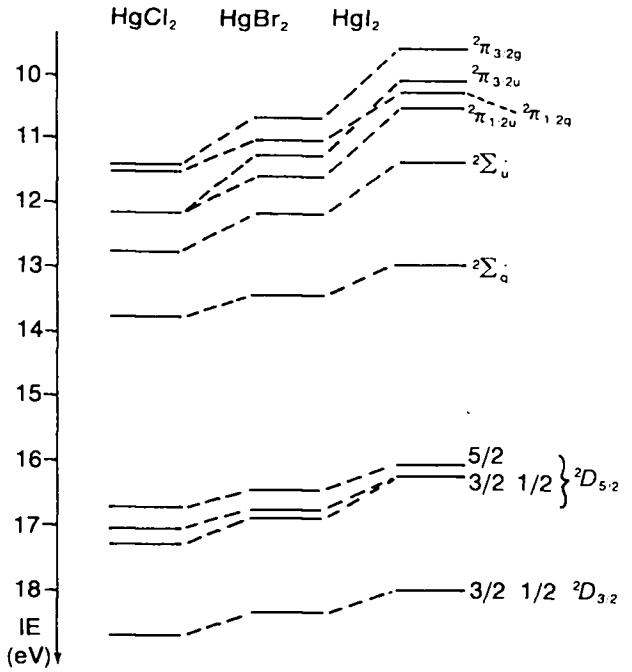
B. Halides of Aluminium and Other Group III Metals

Compared to PE spectroscopic investigations of boron halides, little is known for this class of compounds. A communication[343] deals with the equilibrium $A_2X_6 \rightleftharpoons 2AX_3$ for A = Al, Ga and X = Cl, Br: the spectra of the dimer shows a complex, hard-to-assign multi-ionization pattern, whereas the PE spectra of the monomers – including the indium halides[344] – closely resemble those of the corresponding boron compounds. The first ionization energy of AX_3 obviously does not depend on the central atom A. The splitting of the AX bonding, as well as that of the halogen lone pair ionizations decreases with increasing bond distance, the effect of spin–orbit interaction becoming more and more dominant for the heavier halides. Monomeric and dimeric methyl metal halides $(R_{3-n}EX_n)_{1,2}$ of group III metals have also been studied[343,345].

Considerable effort has been spent in PE spectroscopic studies of monohalides of indium[346] and thallium[299,347–350]. The PE spectrum of the dimeric thallium fluoride, Tl_2F_2, is interpreted assuming a covalent $D_{\infty h}$ structure, the linear conformation critically depending on the metal p-orbital energies as is discussed with respect to the alkali halide dimers[348,349]. The monomeric halides like, for example, TlCl show PE[299,346] and photoionization spectra[347] characteristic of alkali halides (Section IX.F). For TlCl, the first sharp peak at 9.9 eV is assigned to a σ bonded state centred mainly on Tl, while the adjacent broad band with maximum at 10.4 eV relates to the π-type lone pair. A third peak at 13.9 eV is represented by a σ orbital predominantly located at Cl[299,346]. The observed band shapes can be simulated using Franck–Condon factors calculated from potential energy curves for AlCl and $AlCl^+$ [346].

C. Halides of Zinc, Cadmium and Mercury

The PE spectra of $F_3C—Hg—I$ and $F_3C—Hg—NO_3$[326] have been presented in Figure 39 and their assignment discussed as an introductory example to this chapter. Previously, the PE spectra of mercury halides had been assigned in a pioneering publication[76]:



(39)

The radical cation state sequence denoted by $\pi_g < \pi_u < \sigma_g < \sigma_g <$ d shows further splitting of the degenerate levels by spin–orbit coupling ('equation' 39). The spectra and their assignment are spectacular in that the ionization of inner-shell 5d electrons of mercury are observed within the He(I) range. These d ionizations are nearly atomic, and bonding effects only slightly perturb the atomic $^2D_{5/2}$ and $^2D_{3/2}$ levels. The sharpest band is assigned to the $^2\pi_{3/2g}$ level, which experiences only electrostatic effects. Therefore, in the interpretation the point charge potential model familiar from ESCA[22] can be applied[77], by which a chemical shift ΔIE is related to the charges q on the atoms (equation 40):

$$\Delta\mathrm{IE} = Kq_{\mathrm{Hg}} + \sum_{\mathrm{A}\neq\mathrm{Hg}} \frac{q_{\mathrm{A}}}{R_{\mathrm{HgA}}}. \tag{40}$$

The proportionality constant K can be determined from atomic data[40], calculated from SCF perturbation theory[13], or derived from a purely electrostatic model (equation 41),

$$K = (R_{5\mathrm{d}} - R_{6\mathrm{s}})^{-1}, \tag{41}$$

where R represent a mean orbital radius. This last approach leads to considerable charges at the halogen atoms in the halides HgX_2, $q_{\mathrm{I}} = -0.23$, $q_{\mathrm{Br}} = -0.33$, and $q_{\mathrm{Cl}} = -0.42$, respectively. These data, together with those of the zinc and cadmium dihalides, have been related to electronegativity scales, indicating the sequence $\chi_{\mathrm{Hg}} > \chi_{\mathrm{Zn}} \sim \chi_{\mathrm{Cd}}$[351]. Somewhat more pronounced ionicities are derived for mercury dihalides by using K in equation (41) from atomic data[326].

The spin–orbit splitting for the $^2\Pi_g$ state is larger by 0.26 eV than that for the $^2\Pi_u$ state of HgI_2^+ [77]. Good agreement between calculated and experimental splittings is obtained by applying only first-order perturbation theory, and the remaining differences can be attributed to the use of unnormalized orbitals[352].

The PE spectra of the zinc and cadmium halides[351,353–355] are more difficult to obtain due to low vapour pressures. The n_X region is similar to that of the mercury dihalides, while the d-ionizations differ considerably. Bonding effects on the d electrons are comparable to the spin–orbit coupling constants ζ for zinc and mercury, but spin–orbit interaction dominates for mercury 5d ionizations in the dihalides. Furthermore, an electrostatic model predicts as ordering of d-sublevels $\sigma(1/2) < \pi(3/2) < \delta(5/2)$, while a purely covalent interaction would yield the reversed order $\delta(5/2) < \pi(3/2) < \sigma(1/2)$[356]. The latter sequence is found for mercury dihalides (cf. 'equation' (39)), whereas the former situation, i.e. weak crystal field and no covalency, prevails in the zinc dihalides[355]. In this context, vapour phase PE studies of the dihalides of tin[359] and lead[208,359] should be quoted: although no final assignment has been proposed, the ionization energies of the 'inert pairs' have been assigned to weak bands near 16 eV for both SnX_2 and PbX_2[359].

As in preceding sections, the extension of PE spectroscopic studies of the inorganic prototype halides to their organometallic derivatives will conclude the topic discussed. PE spectra of allyl mercuric chloride[357] and of benzyl mercuric chloride[358] have been performed, and the ionization patterns of the *gauche* conformers, present in the gaseous phase, interpreted in terms of $\sigma_{HgC}/\pi_{C=C}$ hyperconjugation. The investigation of the trifluoromethyl mercury compounds $F_3C—Hg—X$ with X = I, N_3, NCO, NO_3 and SCF_3[326] has been reviewed in the introductory remarks to this section (see Figure 39).

D. Transition Metal Halides and Oxyhalides

Examples, to which reference is given to in the following, include titanium tetrahalides[57,203,360,361] which are closely related to the group IVB tetrahalides discussed extensively in Section V (Figures 16, 17, and 19), and VCl_4[360,361] as a d^1 metal compound. The hexafluorides MoF_6, WF_6 and UF_6[51,315] exhibit He(I) PE spectra similar to SF_6 (Figure 36), and also oxyhalides like Cl_2CrO_2[4,203,362] show PE spectroscopic analogies to tetrahedral non-metal molecules like Cl_2SO_2 (Figure 42 and 'equation' 36).

To begin with, the PE spectrum of chromyl chloride, Cl_2CrO_2, is displayed as a representative example in Figure 42.

For CrO_2Cl_2, only six PE bands are observed in the He(I) range (Figure 42) and, therefore, some of the 12 $M^{\cdot+}$ states expected are close in energy. The d orbitals on the chromium are mandatory for the interpretation of the experimental data based on calculations[4,203,363]. As regards, on the other hand, the chlorine lone pair ionizations

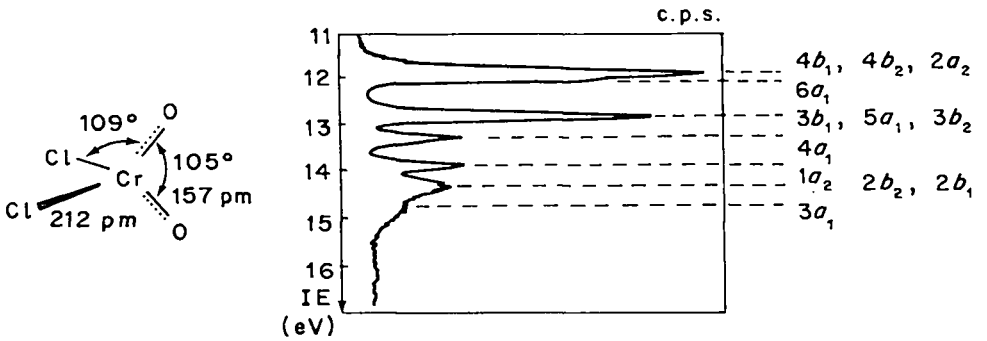


FIGURE 42. PE spectrum of chromyl chloride and its assignment[4,363].

leading to $M^{\cdot+}$ states of symmetries (in orbital notation) $4b_1$, $4b_2$, $2a_2$ or $6a_1$, they closely resemble those of the non-metallic analogue Cl_2SO_2 ('equation' 36). Also in the PE spectra of other oxyhalides like Cl_3VO or Cl_2MoO_2 [203,362] quite a few accidental degeneracies are observed.

The PE spectra of the tetrahedral molecules $TiCl_4$ and $TiBr_4$ [57,203,361,366] rather closely resemble those of the tetrahalides of group IVB elements (Figures 16,17,19). The main difference concerns the $2a_1$ ionization energy which is lowered by 4.6 eV in $TiBr_4$ relative to $GeBr_4$ [57], which reflects among other things, the greater ionicity of these transition metal halides compared to their main group counterparts.

In contrast to this similarity, the nearly tetrahedral vanadium tetrachloride, a d^1 open-shell system, shows a PE spectrum quite different from those of the d^0 tetrachlorides: ionization of the d electron results in a $^1A_1$ cationic ground state at 9.41 eV [361]. The ionizations of the chlorine p-type electrons n_a and σ_{VCL} (see Figures 16 and 17: $t_1 + e + t_2 + t_2 + a_1$) produces a total of 20 cationic states, all accessible by He(I) PE spectroscopy, in contrast to the five $M^{\cdot+}$ states, observed for $TiCl_4$. Singlet and triplet states can be reached from the doublet molecule VCl_4, and doubly open-shell configurations produce different states: $^{3,1}T_1 + {}^{3,1}T_2$ for the t^5e and $^{3,1}A_1 + {}^{3,1}A_2 + {}^{3,1}E$ for the e^3e configurations, respectively [361]. Not all of these states could be resolved experimentally in the recorded PE spectrum of the highly corrosive VCl_4. For the assignable ones, good agreement has been achieved with results from Hartree–Fock–Slater X_α calculations [360], although Koopmans' theorem (Section II.E) applies neither to doublet molecules nor to X_α orbital energies.

The PE spectra of the hexafluorides of molybdenum, tungsten, and uranium are very similar to that of sulphur hexafluoride (Figure 36), shifted to lower ionization energies in the metal compounds [51,315,364].

E. Low Valent Metal Complexes with Halogen Ligands

This section covers the following classes of low valent metal complexes with halogen or halogen-containing ligands:

$MX(CO)_5$	$M(PF_3)_4$	$(F_3C-COCHCO-CF_3)_3M$	$(C_5H_5)_2MX_2$
M = Mn, Re	M = Ni, Pt	$M = Al^{3+}$ to Co^{3+}	M = Ti, Hf, Zr

(42)

as well as some closely related compounds.

The group VIIA pentacarbonyl halides $MnX(CO)_5$ [365–367,369,370] and $ReX(CO)_5$ [368] with X = Cl, Br and I exhibit structures of C_{4v} symmetry. For their PE spectra (Figure 43), one expects two bands to arise from the formal d^6 configuration, namely of b_2 and e symmetry type. In addition, the halogen atom will introduce another e orbital and a metal–halogen σ_{MCl} bonding orbital of species a_1. There is the possibility of mixing of the e(d) and e(X) orbitals, which furthermore can be split by spin–orbit interaction. The PE spectra of the manganese and rhenium pentacarbonyl halides have been studied several times [80,365–369] (Figure 43).

The careful analysis of spin–orbit splittings assigned in the PE spectra [80] indicates that the following sequence of ionization energies is most likely: $e < b_2 < e < a_1$ [368,369]. Accordingly, the topmost orbital is mostly halogen in character for $IRe(CO)_5$, but mostly metal 5d for $ClRe(CO)_5$. The fact that the ligand ionizations occur at lower energy than those of the d electrons has been termed the 'third revolution in ligand field theory' [378], and it is also proposed that the relationship between the ligand field splitting parameter Δ and ionization energies is less direct than Koopmans' theorem might suggest [371]. The PE band close to 10 eV in the rhenium series is assigned to the

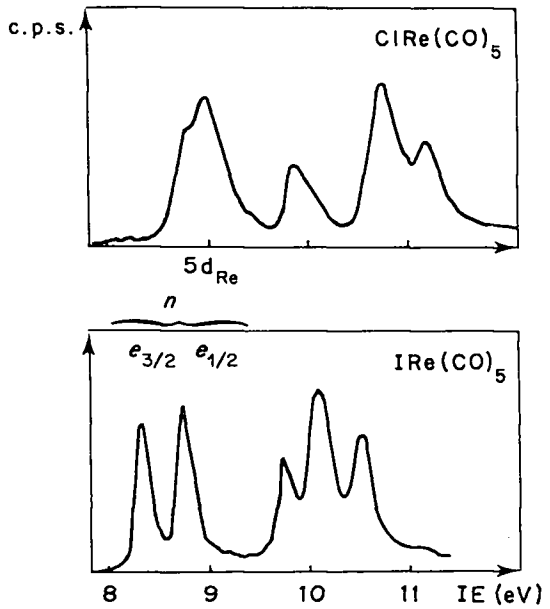


FIGURE 43. He(I) PE spectra of rhenium pentacarbonyl chloride and iodide[80].

b_2 orbital which – by its symmetry – does not contain any halogen contributions. The relatively small spin–orbit splitting of the topmost e-orbital in $ReI(CO)_5$, $\Delta_I = 0.45$ eV, is presumably due to mixing with rhenium d-orbitals ($\xi_{Re} \sim 0.25$ eV)[80]. Furthermore, the PE spectra[369] of dibromo- and diiodotetracarbonyl iron complexes, $FeBr_2(CO)_4$ and $FeI_2(CO)_4$, have been compared to those of the corresponding dihalomethanes H_2CX_2 (Section V.A).

The PE spectra of PF_3 (Figures 12 and 31) and of its phosphorus lone pair adducts (Figures 12 and 32) have already been discussed in Sections III.C and VII.C: on complexation, the lone pairs of the four PF_3 groups are transformed into metal–PF_3 bonds, the orbitals of which – in local T_d symmetry – transform as t_2 and a_1. In the PE spectrum of $Ni(PF_3)_4$ (Figure 44), the $\sigma_{NiP}(t_2)$ components are clearly visible at 13.1 eV, whereas the $^2A_1$ radical cation state is hidden under the fluorine lone pair ionizations beyond 15 eV. As revealed by comparison of the spectra in Figure 43, the n_F ionizations of the PF_3 ligands are not drastically altered upon complexation, indicating only minor changes in the overall as well as the electronic structure of the ligands (cf. Figure 12). The two ionization peaks at 9.55 and 10.58 eV, without counterpart in the PF_3 spectrum, are assigned to d-ionizations of t_2 and e symmetry, based on the approximate 3:4 intensity ratio of the PE bands[279] (Figure 44).

The PE spectroscopic assignment for the analogous complex $Pt(PF_3)_4$ is not agreed upon[279,280]: the two d-electron ionizations are either alloted to the bands at 9.8 eV (t_2) and 12.3 eV (e) according to observed differences in relative intensities[280], or both ($t_2 + e$) to the band structure at 9.8 eV[279]. The relevant discussion concerning ligand field splittings, σ donation and π back-donation and other fictitious model parameters also differs among the different groups of authors[279–281]. Comparison with the PE spectra of $Cr(PF_3)_6$, $Fe(PF_3)_5$ and $HRh(PF_3)_4$[372,373] suggests, however, that the intensity-based[280] assignment is correct. In addition, evidence for an increase in the

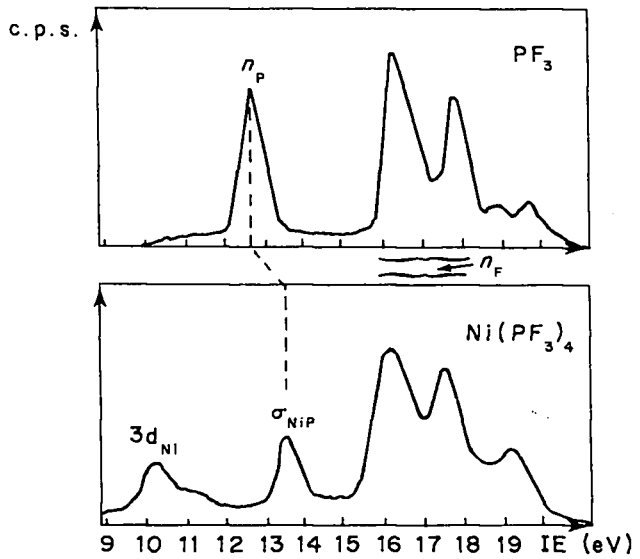


FIGURE 44. PE spectra of tetrakis(trifluorophosphino) complexes of nickel and of PF_3[279].

ligand field splitting and a stabilization of the $MePF_3$ orbital in the sequence Ni ~ Fe < Rh < Pt is discussed[372,373].

Complexes like tris(hexafluoroacetylacetonato)iron(III) are obviously difficult to measure: in the normal-type PE the performance of both the detector and the analyser deteriorates in the course of the experiment[374]. A large series of complexes[374–377] comprising Al^{3+}, Ga^{3+}, Sc^{3+}, Ti^{3+}, V^{3+}, Cr^{3+}, Mo^{3+}, Mn^{3+}, Fe^{3+} and Ru^{3+} as central atoms, suggests again that the first PE band relates to an $M^{\cdot+}$ ground state derived from ligand rather than metal electrons, at least for the heavier transition metal ions Mn^{3+}, Fe^{3+} and Co^{3+} [374,375].

PE spectroscopic studies of $(n\text{-}C_5H_5)_2MCl_2$ complexes of Ti, Zr and Hf[378], as well as of trifluorosilyl-substituted manganese pentacarbonyl[379] are examples for other classes of low valent metal complexes with halogen ligands.

F. Appendix: Ionic Halides

So far, PE spectra of ionic organic halides like tropylium salts or pyridinium hydrochloride have not attracted much attention. In general, ionic halides tend to be volatile only at elevated temperatures, those required range from 400 to 900°C, which are not easily attainable. These high temperatures are accompanied by lack of apparent resolution (hot band activity), low intensity, and often high background signals. Nevertheless, a review on halogen compounds needs at least an appendix on ionic halides, which might one day become an interesting issue in organic chemistry.

Turning to the inorganic prototype approach (see sections VII.A, VIII and IX), the overall knowledge still needs improvement: although ionic halides form the major part of halogen compounds, PE spectroscopic investigations on these have been scarce. Actually, vapours of ionic halides are complex systems, as has already been discussed; for example, for thallium fluoride (Section IX.B), the dimer $(TlF)_2$ is the prevailing species in the gas phase. The alkali halides are known to form polymers in the gas

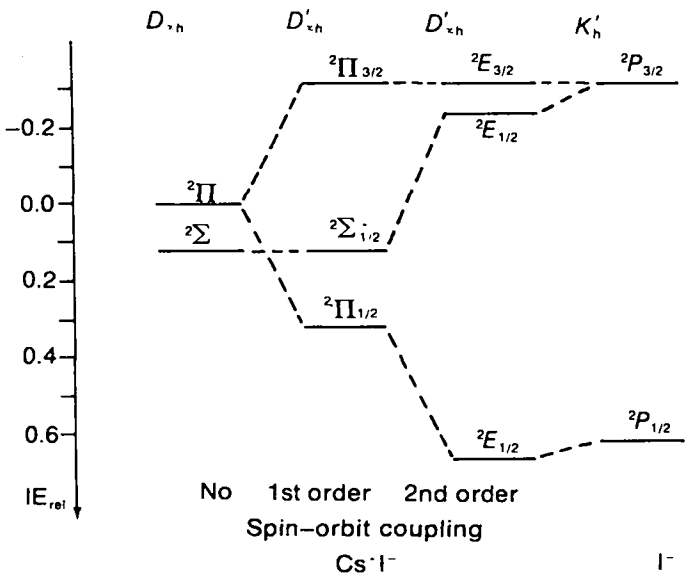
phase. In spite of these formidable experimental difficulties, several groups have succeeded in obtaining reliable PE spectra of ionic halides such as alkali halides MX[380–387] and their dimers $(MX)_2$[382,383], rare earth fluorides MF_3[388] and silver halides[389]. In the following, the discussion will be confined to PE spectroscopic studies of alkali halides (Figure 45).

In the PE spectra of the sodium halide series (Figure 45), the band structure between 10 and 11 eV is attributed to the dimeric species $(NaX)_2$, whereas all other bands belong to the monomers, NaX[382]. Altogether, the PE spectra obtained hint strikingly at the difference between ionic and covalent bonding. For NaCl, for example, the ionization out of the chlorine lone pair,

$$Na^+Cl^- + h\nu \longrightarrow Na^+Cl^{\cdot} + e^-,$$

carries nearly all of the Coulomb attraction energy. Therefore, the halogen p-electrons have to be considered as 'bonding'[299,346], giving rise to broad bands. This is in complete contrast to covalent compounds like acetylene halides $X—(C{\equiv}C)_n—X$, where halogen lone pairs are easily identified by the very sharp nature of the corresponding PE bands (Figures 21 and 22).

Another most interesting feature of the alkali halide PE spectra is spin–orbit coupling, CsCl (Figure 45) showing the largest effect. The interpretation has to consider the following individual contributions:



(43)

Starting from the left, the p-levels of iodine are split by electrostatic interaction into $^2\Pi$ and bonding $^2\Sigma^+$ levels (crystal field effect). Spin–orbit interaction, in first order, splits the degenerate level, and in higher orders both $^2\Sigma^+_{1/2}$ and $^2\Pi_{1/2}$ levels interact to produce the final splitting pattern for the intermediate coupling situation, which for caesium iodide is very close to the atomic case of the I^- ionization energies. It is obvious that the splitting pattern depends critically on the relative magnitudes of the crystal field and the spin–orbit interactions. The crystal field effect is observed only for sodium iodide, whereas it is negligible for the caesium series (Figure 45): in NaI, the double peak at ~7 eV contains the $^2E_{3/2}$ as well as a $^2E_{1/2}$ component, the latter deriving from

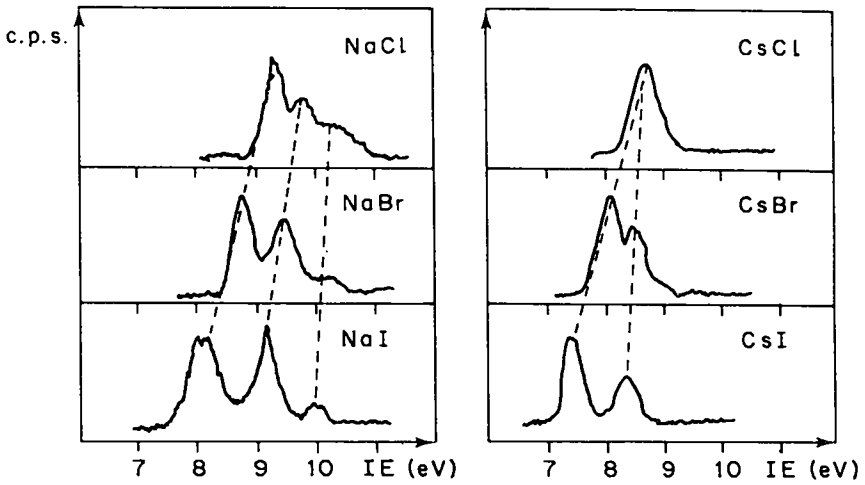


FIGURE 45. PE spectra of sodium and caesium halides[382].

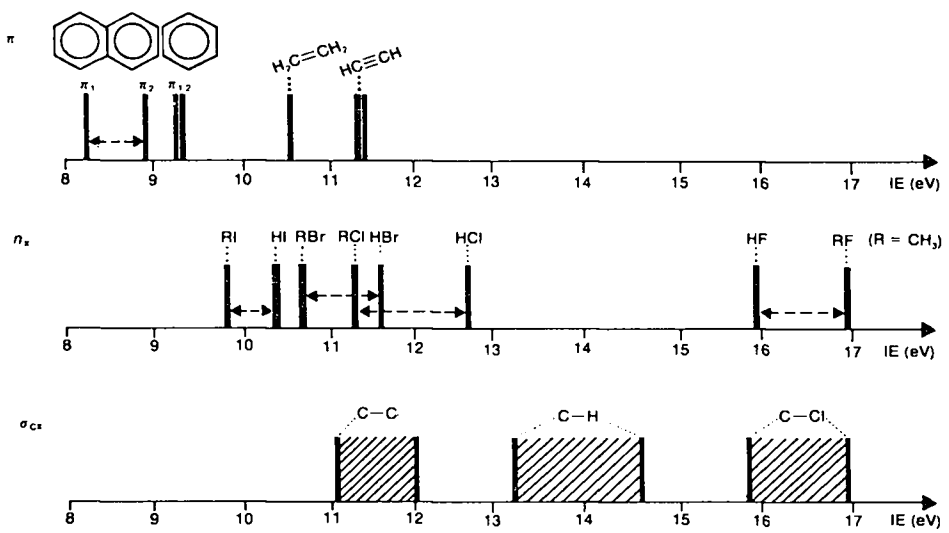
both $^2\Pi_{1/2}$ and $^2\Sigma^+_{1/2}$ states[379–380]. This interpretation has been partly adopted by others[382,383], partly refused[386] and instead crystal field splittings assumed, which by far exceed those indicated by *ab initio* calculations[381,386]. In addition, some bands in the PE spectra of alkali halides[386] have been attributed to the dimers $(MX)_2$[382,386], which strongly supports the original interpretation[379–380]. The alkali halides thus represent extreme examples for higher order spin–orbit interaction effects[68] in halogen compounds (see Section II.D).

X. REAL-TIME GAS ANALYSIS IN FLOW SYSTEMS CONTAINING HALOGEN COMPOUNDS

The introductory remarks (Section I) emphasized the development of PE spectroscopy and noted that much of the early interest in the new method of measurement had been due to the orbital interpretation of the radical cation states. In this regard, the central position of Koopmans' theorem has been stressed (Section II.E), together with the inherent approximations[13] which have to be accepted in correlating ionization energies, and orbital eigenvalues. Furthermore, the total electronic energies which determine the stability of molecules, unfortunately are not the sums of orbital energies. Thus experience from PE spectroscopic studies cannot be transferred directly to interpret other molecular properties, and the molecular dynamics showing up in the vibrational fine structures observed (Section II.B), by definition, are not included in orbital models resting on the Born–Oppenheimer approximation of fixed nuclei. However, because similar matrix elements in the calculations govern 'PE band splittings' and total energies, strong 'orbital interaction' found in PE spectroscopic interpretation will also affect other molecular properties. Altogether, PE spectroscopy is somewhere between 'ideal' and 'useless' for bonding studies depending on the approach from the straightforward comparison of equivalent $M^{\cdot+}$ states of chemically related molecules applying perturbation arguments and the 'number graveyards' produced in order to reproduce everything numerically.

As is evident from this review, several more lessons may be drawn from the assignment of PE spectra. For instance, functional groups like halogen substituents

give rise to PE bands within a certain energy range corresponding to the respective orbital composition:



(44)

(An asterisk indicates the arithmetic mean of the two coupled spin–orbit ionizations, IE_1 and IE_2.) Based on this experience and on the advantageous assignment of PE spectra applying Koopmans' theorem, the symmetry-controlled interaction between characteristic orbitals has formed a major point of this review.

Summing up, a tremendous body of experience has been accumulated over the past 15 years. Among other techniques, PE spectroscopy proves invaluable in teaching molecular orbital theory[5,6,18,390,391] as well as its limitations[7,15,16]. Yet low energy PE spectroscopy is not the only, albeit the most popular, technique to yield information on molecular electronic structure via the study of cationic states. Among the many complementary methods of measurement, the following can be mentioned here: ESCA (i.e. Electron Spectroscopy for Chemical Analysis), which uses X-rays for excitation and furnishes predominantly information on core electrons[3,17,21,22]; photoionization spectroscopy, which scans the exciting wavelength and counts the total number of electrons at a given wavelength[3]; photoion spectroscopy, which is a mass spectroscopic technique, and which yields information on the decay of molecular cations[3]; and X-ray emission spectroscopy, which determines the energy if a core hole is filled by valence electrons and thus leads to energy differences identical with those of PE spectroscopy[3]. Ionization energies are also obtainable from vacuum UV Rydberg spectroscopy[24] (see Section IX.A: equation 38).

Among numerous other facets to be mentioned regarding the 'blossoming' of PE spectroscopy are the design of improved instrumentation[11,393] and novel applications, including, for instance, the absorption of molecules on surfaces[393,394], even liquids[395]. A special application for real-time gas analysis in flow systems[11] is discussed below as the concluding part of this review, and as one of the most promising future aspects for further development of PE spectroscopy.

A. PE Spectroscopic Gas Analysis as a Complementary Method

Many different methods of measurement are available for the analysis of gases in flow-systems, among which gas chromatography (GC), mass spectrometry (MS) and

infrared (IR), as well as far-infrared, have been well established and abundantly applied. With reference to PE spectroscopic gas analysis, as presented here, one must therefore inquire which advantages and disadvantages these methods possess, broadly speaking, and to what extent they complement each other.

Gas chromatography	
Advantages	Well suited for mixtures and their simultaneous separation; simple as far as the instrument is concerned
Disadvantages	No real-time measurement; unknown compounds and especially reactive intermediates can be identified only with difficulty or not at all; no information on structures or states
Mass spectrometry	
Advantages	Even big molecules can be identified by their isotopic patterns; high sensitivity; elaborate measuring techniques with many extensions, such as chemical ionization; large data bank
Disadvantages	Fragmentation patterns of unknown products only predictable under certain conditions; digitalization required for quantitative analysis; no immediate structural information; instrumentation sometimes expensive
Infrared	
Advantages	(To be differentiated for far-IR, IR and Raman spectroscopy, with or without Fourier transform technique.) 'Molecular fingerprint' method with information on structure and state; sensitive; well suited for kinetic investigations
Disadvantages	Selection rules require many small molecules to be IR inactive; interpretation of spectra via normal coordinate analysis difficult; far-IR in particular not well suited for hot gases (emissions!); instrumental expenses sometimes large
Photoelectron spectroscopy	
Advantages	Molecular 'fingerprints' with information on structure and state; favourable interpretation of spectra with MO methods; instrumentally simple; well suited for temperature-dependent investigations
Disadvantages	Not well suited for multicomponent mixtures and large molecules

As can be seen from this greatly simplified comparison, none of these methods for gas analysis is perfect. In practical application combinations such as GC/MS or PES/MS have therefore proven valuable; in many cases GC/PES would also complement each other. As a far-flung speculation one might even dream of a miniaturized PE spectroscopic probe in the reaction zone of a flow tube. Presently, the main achievements in PE spectroscopic gas analysis concern the detection of low temperature reaction channels, including the characterization of short-lived intermediates[3,11,396] (Section X.B), and the optimization of heterogeneously catalysed gas reactions, including the catalyst screening[11,397,398] (Section X.C).

The question whether a given gas reaction in a flow system can be monitored with PE spectroscopy is – if the PE spectra of all components are known – most favourably answered by means of a computer: the basis for this is the linear relationship, verified experimentally many times, between the concentrations of molecules in the gaseous mixture and their (relative) band intensities[11,399,400]. For example, mixtures with known ratios of molecules HCN:NCCN were analysed PE spectroscopically and the agreement with the planimetrically determined band areas verified[400]. In addition, computer programs have been developed in the meantime, which allow PE spectra to be stored permanently, and within minutes to print out the expected PE spectra for gaseous mixtures composed from the constituents in any ratio wanted. This procedure, illustrated here for $H_2SiCl_2/HSiCl_3$ mixtures which are important in the manufacture

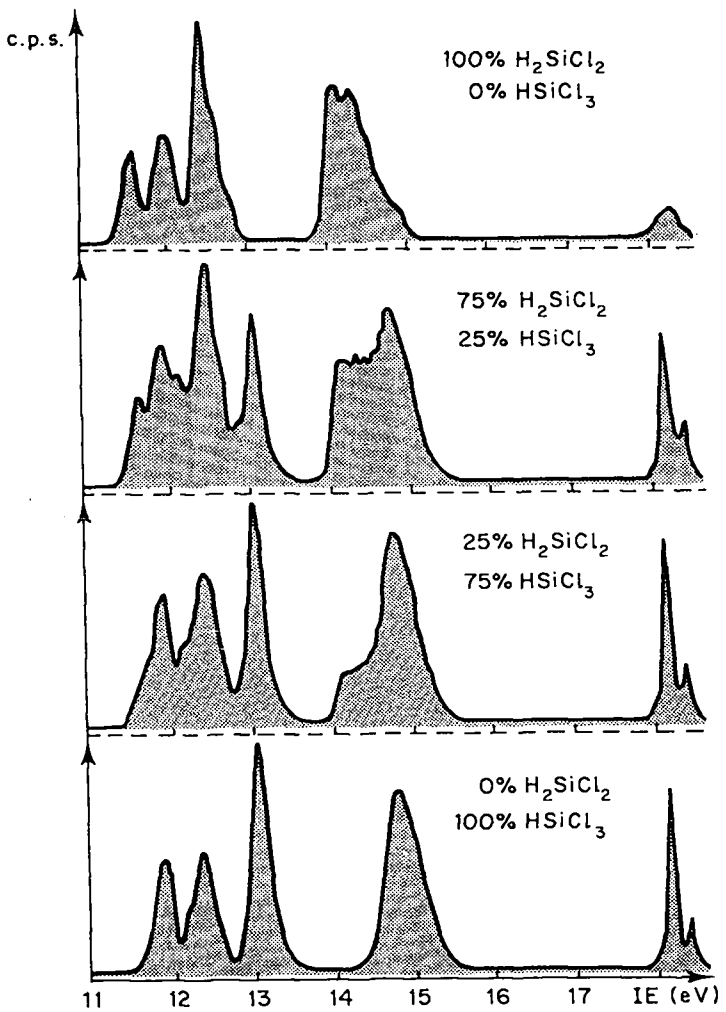


FIGURE 46. Computer-plotted PE spectra of chlorosilane mixtures H_2SiCl_2:$HSiCl_3$ and computer-simulated PE spectra of their mixtures in 75:25 and 25:75 ratios[11].

of pure silicon (Figure 46), is based on the assumption of comparable photo-ionization cross-sections, which is valid at least for chemically related compounds.

Although PE spectroscopic analysis is more complicated for poorly structured band patterns of chemically closely related compounds like the chlorosilanes (Figure 46), it is nonetheless evident that it would be possible to carry out an optimization of reaction conditions with the aim of a maximum H_2SiCl_2 yield, relying on the relative intensities of the bands marked by arrows (Figure 46). It would of course be more favourable if the gas analysis could be performed using a small molecule such as HCl, the PE spectrum of which contains characteristic needle-like peaks (Figures 14 and 1).

Summarizing, gas analysis using ionization patterns does not raise any particular difficulties as even an observer comparatively inexperienced in their interpretation will recognize them more readily than the patterns provided by IR frequencies, mass spectroscopic fragments or NMR coupling. In order to identify known compounds by their band patterns, it is advisable either to look up published PE spectra or to record those of presumed reaction products in advance. For PE spectra of unknown molecules, especially of short-lived intermediates produced for the first time in a gas-phase flow system, the assignment via a comparison of states with chemically related compounds or the quantum mechanical calculation of vertical ionization energies remain as additional possibilities. In addition, the feasibility of PE spectroscopic analyses in gaseous mixtures can be judged by comparison, by projection of the spectra upon one other, or by computer mixing of those of the main components.

B. Thermal Decomposition Channels and the Generation of Short-lived Intermediates

Thermal decompositions do not have to result in tar production: in general, if the temperature of the flow sytem under reduced pressure is carefully raised step-wise, then the point of a specific thermal breakdown of a molecule, i.e. its lowest thermal decomposition channel, becomes visible in small changes of the PE spectroscopic ionization pattern. In addition, short-lived intermediates can be detected in these investigations and identified by their molecular 'fingerprints' especially if the distance between reaction zone and ionization chamber is reduced to a minimum[3,11,396,401,402]. Since 1970, many types of 'reactive intermediates' have been identified and characterized PE spectroscopically: atoms, radicals, radical anions, 'valence-unsaturated' molecules, up to molecules which – like O_3 or $O_2N{-}NO_2$ – react under standard conditions to form thermodynamically more favourable products. (For reviews see references 3, 11, 396.) The lifetimes of these intermediates range from those of vibrationally excited molecules[3,11,396] to those which can be isolated for short times or at low temperatures, like HCP[33] or silabenzene C_5SiH_6[400].

The PE spectroscopic gas analysis as applied to thermal decomposition channels and to the detection of short-lived intermediates will be illustrated here by a single example covering both topics[224]: the gas-phase pyrolysis of methanesulphenyl chloride and the identification of thioformaldehyde, a molecule found in 1971 in interstellar space (see Figure 47).

The preparation of thioformaldehyde, an intermediate which polymerizes only slowly in a low concentration flow system, has been achieved using an apparatus (Figure 47) assembled from parts of a building block set for gas reactions. The methanesulphenyl chloride passes through a heated quartz spiral of 2 m tube length, and decomposes above 750 K and quantitatively at 850 K into a mixture of $H_2C{=}S$ and HCl (Figure 47). The hydrogen chloride split off can be removed by stoichiometric injection of ammonia from a storage vessel via a flow meter and a precision valve (Figure 47), forming an ammonium chloride deposit at the walls of the

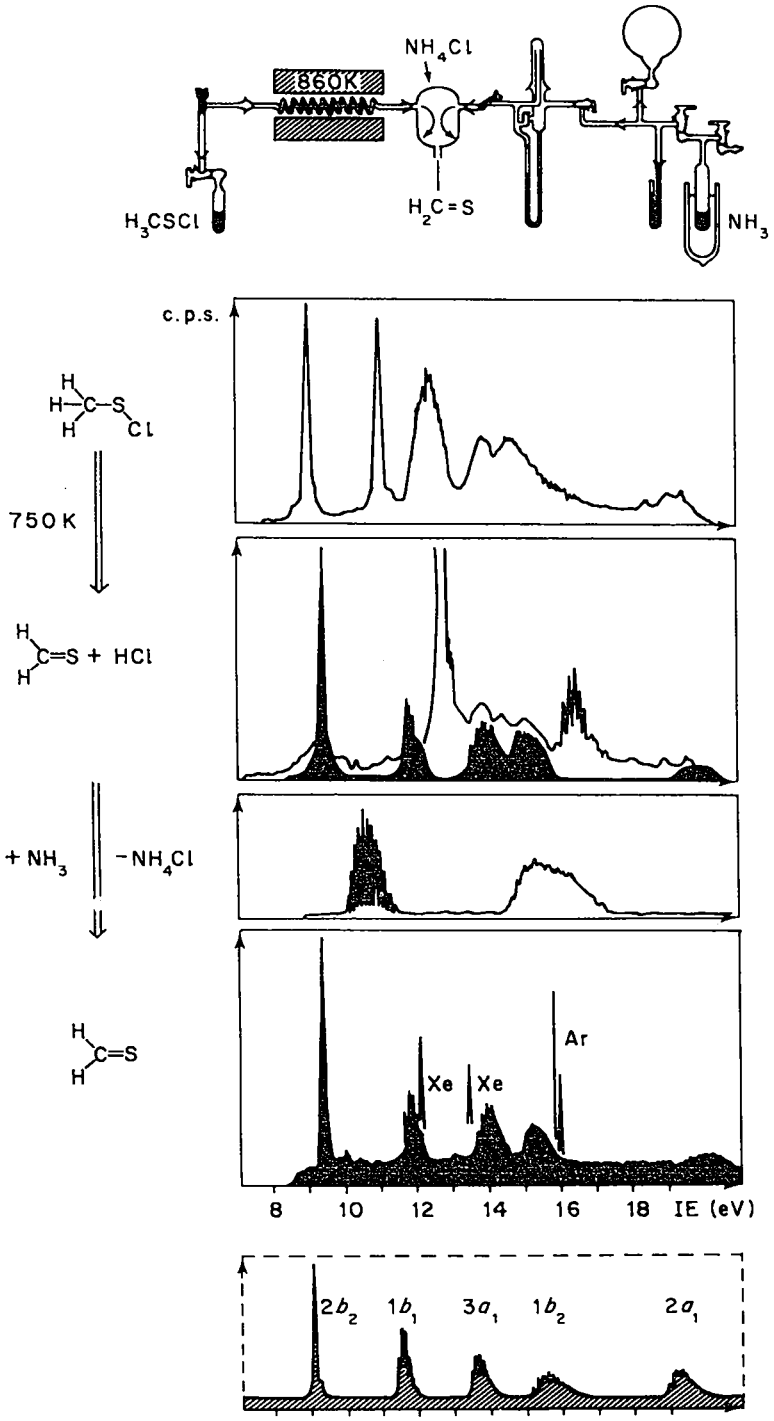


FIGURE 47. PE spectroscopically optimized preparation of thioformaldehyde (blackened) by pyrolysing $H_3C—S—Cl$ at 750 K and removing HCl from the mixture with NH_3, depositing NH_4Cl. The identification is based on a Greens' function calculation of the PE spectrum (computer plot shaded).

reaction chamber. According to the continuously recorded PE spectra, pure monomeric thioformaldehyde remains in the flow system (Figure 47), and is identified and characterized unambiguously by the 'artificial' PE spectrum generated by a computer plot following a Greens' function perturbation calculation. At the same time, the *ab initio* simulated PE spectrum provides ample evidence on the numerical quality of quantum chemical calculations which include most of the correlation energy[224] (see Section II.E).

What kind of general information can be gathered from the intentionally chosen extreme example of the gas-phase preparation of an unknown molecule which cannot be isolated as such? The PE spectra (Figure 47) illustrate how (i) the start of the thermal decomposition can be detected from the changing ionization band pattern, i.e. visually; (ii) the reaction products like HCl can be identified by their published PE spectra (Figures 14 and 47); (iii) the reaction conditions can be optimized by, for example, continuously recording the decreasing intensity of the PE bands of the starting material, H_3CSCl (Figure 47; needles at 9.1 and 11.1 eV), until they vanish; (iv) the correct stoicheiometry of a reaction between gases can be monitored visually – for instance, the injection of the proper amount of NH_3 to deposit HCl completely as NH_4Cl by the vibrationally fine-structured band around 10.48 eV (Figure 47); and (v) unknown reaction products can be detected by their fingerprint-like ionization pattern, the intensity of which has to increase during the optimization of the reaction conditions, and finally also be identified by the PE spectrum either recorded in advance for known products or simulated for small short-lived molecules which cannot be isolated (Figure 47).

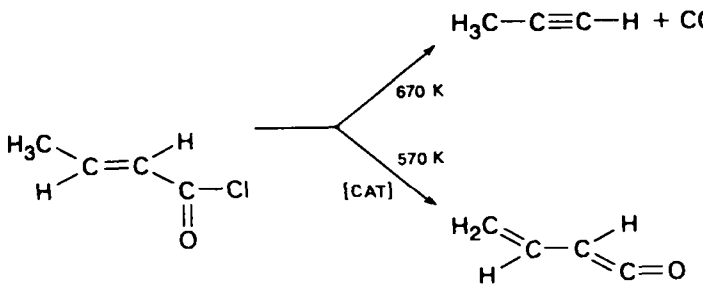
The procedure sketched out can be expanded once the PE band pattern of the product wanted became known: as regards thioformaldehyde, for instance, other precursors have been designed like 1,3-dithietane, the four-membered ring dimer, which on heating yields pure $H_2C{=}S$[403]. The thermal generation method developed has been extended as well to include other thiocarbonyl compounds like thioacetaldehyde[403], thioacetone[403] and thioacrolein[404].

In general, for an optimization of reaction conditions under the PE spectrometer working pressure of 10^{-2} bar one needs approximately 1 mmol of the starting material and about 6–8 h[11]. By connecting the pyrolysis apparatus to the PE spectrometer via a pressure reducing bleeding valve, the thermal decomposition can be carried out under atmospheric pressure as well[11]. The optimized thermolysis conditions allow one afterwards to perform the reaction on a preparative scale, and to isolate the compound; in the case of unstable intermediates like $H_2C{=}S$ such isolation can occur, for example, in an argon matrix at low temperatures.

In the context of this review on the PE spectra of halogen compounds, it should be pointed out in a concluding remark that needle-like ionization bands in particular, i.e. in a great many cases those which are due to the halogen lone pair ionizations, are well suited to the analysis and optimization of gas-phase reactions PE spectroscopically[11].

C. The Optimization of Heterogeneously Catalysed Gas-phase Reactions Using PE Spectroscopy

This last section, dealing with examples of the PE spectroscopic testing of solid state catalysts for gas-phase reactions, should be regarded as an outlook on future developments,[11] since according to the literature only the following three heterogeneous catalyses have so far been worked out using PE spectroscopic gas analysis in flow systems: (i) the reduction of the pyrolysis temperature of crotonic acid chloride using $MgCl_2$ or a rare earth metal chloride mixture on γ-aluminium oxide as a catalyst[405],



(45)

(ii) the cyanation of benzene with cyanogen to form benzonitrile over a partially reduced $CuCl_2$–γ-Al_2O_3 catalyst at 620 K[397]; and (iii) the bromination of trifluoromethane (Figure 48), with the CuF_2 catalyst on charcoal prepared by heating the $CuCl_2$/C contact for 5 h at 800 K in an F_3CH flow[11,398].

$$F_3CH + Br_2 \xrightarrow[[CAT]]{400\ K} F_3CBr + HBr, \qquad (46)$$

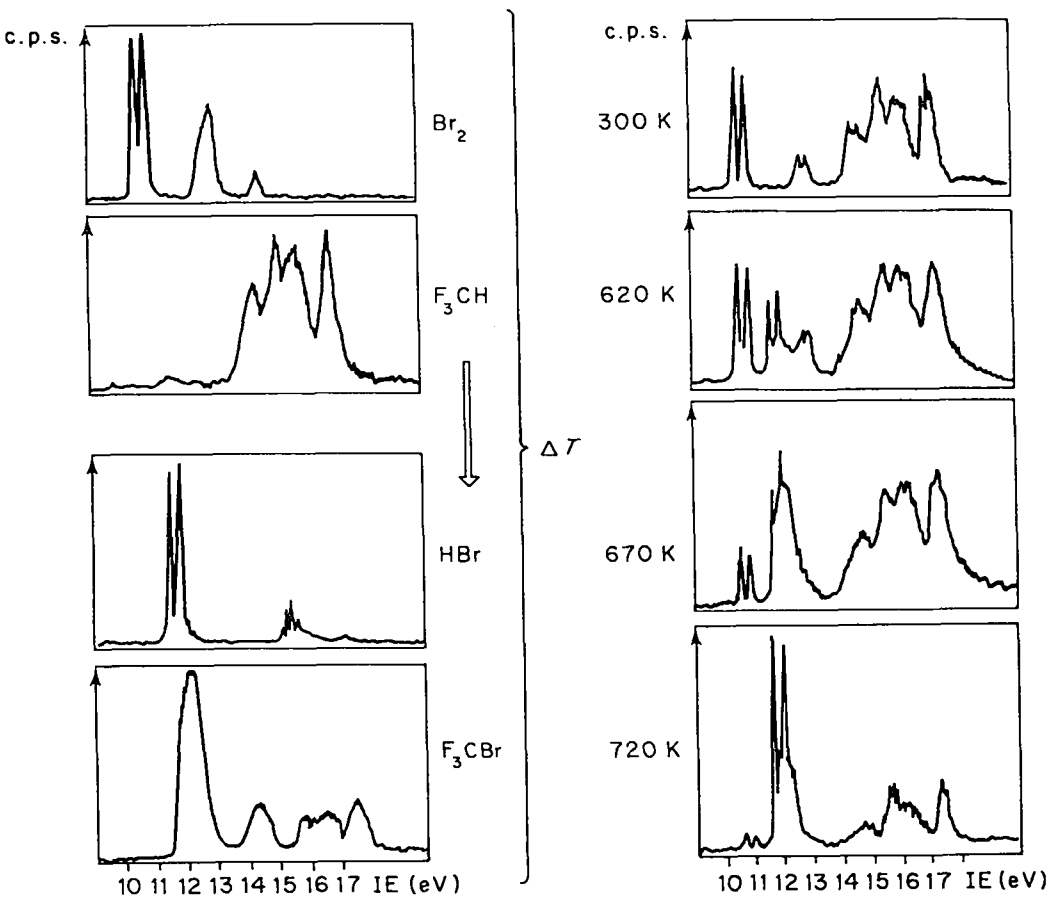


FIGURE 48. PE spectra of the reaction components Br_2, F_3CH, HBr and F_3CBr and of their mixtures at 300, 620, 670 and 720 K.

The gas-phase bromination of trifluoromethane is of technical interest, since the trifluorobromomethane being formed is used as an effective fire-extinguishing agent for the protection of valuable goods. The search for suitable catalysts is worthwhile because of the corrosion problems at higher reaction temperatures.

As becomes obvious from the PE spectra displayed in Figure 48, they are well suited for the gas analysis of the F_3CH bromination: of particular advantage are the needle-like spin–orbit coupled spikes of Br_2 and of HBr. They can be used as 'telltale' probes for the effectiveness of individual catalysts as judged from the temperatures at which the PE bands of Br_2 and HBr are at the same height (Figure 48). An additional advantage of PES analysis is the possibility of recognizing the beginning of fluorination, at high temperatures, of oxidic carriers by F_3CH via the appearing bands of H_2O, CO or CO_2. The accuracy which can be obtained with PE spectroscopy does not exceed 2% even in favourable cases[11,400], so that subsequently a refining optimization on a preparative scale had to be carried out using a conventional catalyst testing apparatus[398]. Nevertheless, there results a considerable saving of time when searching for catalysts: two tests per day and per PE spectrometer can be carried out in the temperature range[11] of interest.

Summarizing, many of the advantages of photoelectron spectroscopic real-time gas analysis and elucidation of reaction conditions in flow systems coincide, if heterogeneously catalysed gas-phase reactions are optimized. As mentioned before (Section X.B), stoichiometry control and variation of temperature as well as of the pressure in most cases are readily accomplished within a day and with only millimolar quantities. Consequently, one catalyst per day and per instrument can be tested over the full range of reaction conditions[11]. Furthermore, the 'real time' gas analysis with a PE spectrometer set up near the catalyst zone responds without delay to the reaction investigated.

It may well be, therefore, that, in the future, and especially with the development of portable and inexpensive PE spectrometers, the application of photoelectron spectroscopy to analyse and to optimize heterogeneous gas-phase reactions will become one of its important facets[11,406].

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CHAPTER **29**

Recent advances in the photochemistry of the carbon–halogen bond

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I. INTRODUCTION

Knowledge of the photochemical behaviour of carbon–halogen compounds has vastly expanded during the past decade. This chapter deals with part of that expansion, namely reactions resulting from ultraviolet or visible irradiation of halocarbon

compounds in solution. The emphasis is on the synthetic and mechanistic aspects of the reactions, and it is hoped that the mechanistic considerations will provide a framework for the many facts reported.

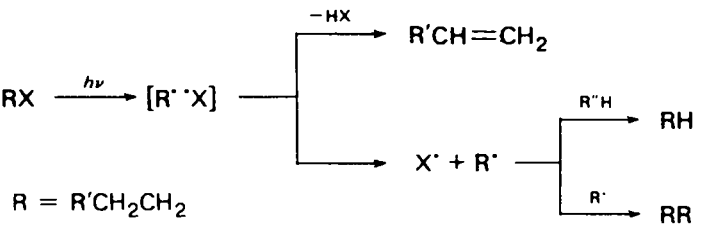
The most notable new aspect is probably the recognition of heterolytic and electron transfer-mediated cleavage processes in the photoreactions of halocarbons, and their delineation from each other and the well known process of direct homolytic cleavage. One can anticipate that future research in this area will centre on examining and exploiting the subtle controls of these reaction pathways.

Earlier reviews have appeared[1,2]. The photochemistry of halocarbons in the gas phase[3] and in the vacuum ultraviolet region[4] have also been reviewed recently.

II. ALIPHATIC, BENZYLIC, HOMOBENZYLIC AND α-KETO HALIDES

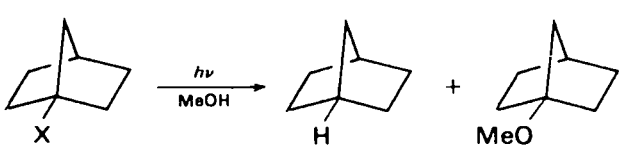
A. Alkyl Halides

Until the early 1970s products of photochemical reactions of alkyl halides in solution were usually attributed to homolytic cleavage of the carbon–halogen bond followed by intra- and intermolecular reactions of the radicals formed[1,2]. An illustrative scheme is shown in equation (1). Since then it has been recognized[5] that



(1)

alkyl iodides and, to a lesser extent, alkyl bromides upon irradiation may undergo not only radical reactions but also ionic reactions such as solvolysis, Wagner–Meerwein rearrangement and 1,3-elimination. The photolytic behaviour of the bridgehead halide **1** in methanol[5] (equation 2) exemplifies that of a number of tertiary alkyl halide

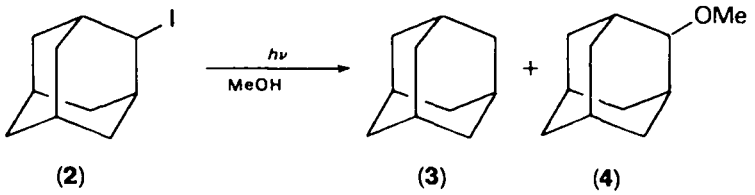


(2)

(1)

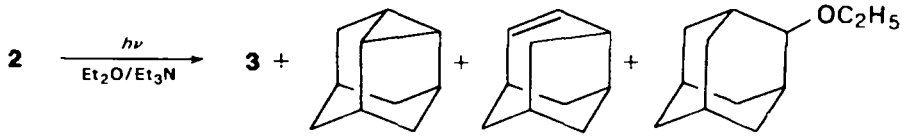
X = I	18%	72%
X = Br	55%	30%

systems for which ionic reactions have been reported[5–7]. Both reduction and nucleophilic substitution products are formed, their yields depending on the nature of the halogen. In secondary alkyl halide systems[5,6,8,9], Wagner–Meerwein shifts and 1,3-elimination may become major processes. 2-Iodoadamantane (**2**) yields the ether **4** as the principal product upon irradiation in methanol[5,6] (equation 3). Under less nucleophilic conditions and in the presence of Et_3N to scavenge the HI formed, **5** and **6** are the major products in addition to the reduction product **3**[8] (equation 4). 2-Bromoadamantane displays analogous behaviour except again that the amount of photoreduction is enhanced compared to that of the iodide[5,6,8]. Some primary alkyl



(2) (3) (4) (3)

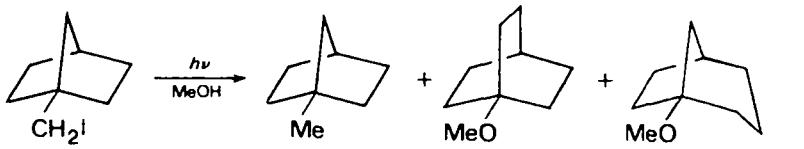
1–5% 95–99%



(5) (6) (4)

18% 55% 8% 4%

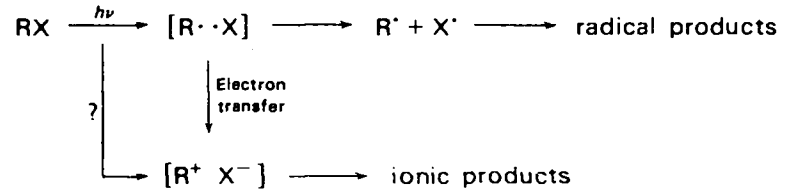
iodides are also reported to afford products of ionic reactions[5,10,11]; an example is shown in equation (5)[5]. The bromide corresponding to **7** yields mainly **8**. For other primary alkyl iodides there is little[9,12] or no[13] evidence that ionic pathways are involved in their photoreactions.



(7) (8) (9) (10) (5)

trace 37% 47%

The ether products presumably arise via nucleophilic trapping of intermediate carbocations. The proportions of the photoproducts of secondary and primary iodides, however, differ from the product proportions obtained in the thermal solvolysis[5,9,11]. In general, more of the thermodynamically less stable isomers are formed in the photoreaction. Thus, for example, in the ground state silver ion-assisted methanolysis of **7**, **9** and **10** are formed in a 10:1 ratio, whereas their ratio in the photoreaction is *ca.* 1:1.3. Such results have been interpreted by the assertion that free ions, having little association with the solvent, must be involved in the photoreaction[5]. Such a free, 'hot' cation will show little selectivity, accounting for the almost statistical ratio of **9** and **10** in the photolysis of **7**. Likewise irradiation of 1-iodooctane in methanol yields predominantly a mixture of 1- (56%), 2- (4%) and 3-octene (2%), which is accompanied by *n*-octane and only a few percent of both 1- and 2-methoxyoctane[5]. Preference for elimination and rearrangements are characteristic of free cations. The ions are proposed[5] to be formed (as ion pairs) via homolytic cleavage of the carbon–halogen bond followed by electron transfer in the initially formed radical pair in competition with its dissociation into free radicals (equation 6). This interpretation is favoured over a mechanism involving direct heterolytic cleavage because of the influences on the reaction of oxygen and the viscosity of the solvent. The observed complete quenching of norbornane formation and partial quenching of methoxynorbornane formation upon irradiation of **1** in oxygen-saturated methanol is explained in terms of trapping of the radical R$^{\cdot}$ by oxygen in competition with electron transfer[5]. However, this



(6)

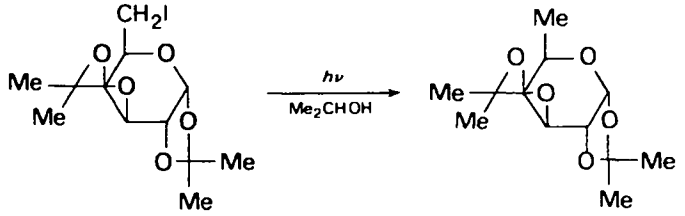
interpretation seems equivocal because it assumes that the radical species trapped by oxygen is also capable of becoming the cation. This amounts to asserting that the free radicals recombine significantly to the ion pair, which is unlikely; or that oxygen may trap R· from the solvent cage, which is also unlikely. The increased proportion of the products of ionic reaction for both alkyl iodides and alkyl bromides in a viscous solvent such as ethylene glycol is thought to be due to an extended life time of the radical pair in that medium, permitting electron transfer to compete more favourably with escape from the solvent cage[5]. Since one would expect the more electronegative bromine to accept an electron more easily than iodine, the lower amount of ionic products for bromides as compared to iodides is surprising. In the framework of the mechanism of equation (6), bromine has been suggested to be less available for electron transfer because it abstracts a hydrogen atom from the solvent cage more readily than does iodine.

Whereas the intermediacy of carbocations in the photolysis of alkyl halides must be inferred from the nature of the products formed, physical evidence for the intermediacy of radicals abounds. ESR[14–18] and IR[19] studies of the products of photolysis of alkyl halides in matrices at low temperature confirm the formation of alkyl radicals. So also does the ESR spin trapping technique in which the short-lived alkyl radicals are converted into relatively long radical species by scavenging them with nitrosoalkanes in solution[20,21]. In a limited number of cases, the formation of halogen atoms has also been observed. The bromine atom has been detected (as a charge transfer complex with the solute) by UV/visible absorption spectroscopy in the matrix photolysis of mono- to tetrabromethane[22]. In the flash photolysis of CHI_3 in mesitylene, both the transient absorptions of CHI_2· and I· (as mesitylene ·I) are detected[23].

Chemical evidence for the intermediacy of alkyl radicals is provided by trapping experiments with O_2 and aromatic compounds. Irradiation of **1** in O_2-saturated methanol and reductive work-up with $NaBH_4$ affords 1-hydroxynorbornane in 47% yield. In toluene as the solvent, a mixture of *o*-, *m*- and *p*-1-tolylnorbornanes is formed in a 51:28:21 ratio, which is close to the ratio obtained in the reaction of toluene with methyl radical (*o*:*m*:*p* = 59:26:15)[5]. Photolysis of CF_3I in fluoro-, chloro- or bromobenzene yields the halobenzotrifluorides in about the same ratio (*o*:*m*:*p* = 48:28:24), as does the thermal reaction at 200°C[24].

Even though methyl radicals are observed by ESR upon the photolysis of methyl iodide in a matrix, the quantum yield of permanent dissociation products is small[25]. In the matrix, the alkyl and I* radicals are held together by cage forces – as shown by luminescence spectroscopy[26,27] – which will lead to recombination of the radicals. In matrices at low temperatures ethyl iodide gives ethene and propyl and isopropyl iodides give propene; the yields of alkenes in these reactions are higher than in the corresponding reactions in solution[25,28]. This can also be attributed to constrictive cage forces.

The photochemical reduction of iodosugar derivatives provides an efficient second step in the conversion of sugars into deoxy sugars[29–31]. Thus, for example, **11**, which is easily prepared from the corresponding hydroxy compound, affords **12** in 95% yield

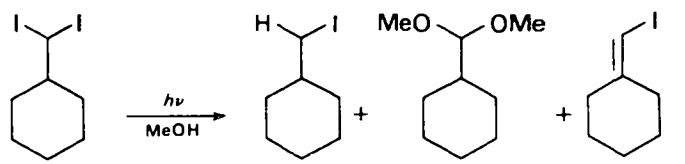


(11) (12) (7)

upon irradiation in isopropyl alcohol[31] (equation 7). The reaction must be carried out in a solvent of good hydrogen atom donating ability, otherwise disproportionation of the radicals to alkene and HI can compete with hydrogen abstraction, making alkene formation a significant reaction pathway. Photolysis of a bridgehead bromide such as bromocubane in the presence of tri-*n*-butyltin hydride gives an excellent yield of the reduced product, whereas dissolved metal reduction does not give satisfactory results[32].

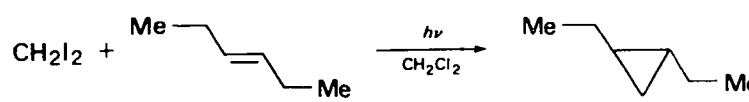
Reductive dehalogenation photoreactions are more efficient with polyhalogenothan with monohalogenoalkyl compounds. As examples, geminal dibromocyclopropanes can be selectively reduced to the monobromides[33] and 1,1,1,3-tetrabromononane yields exclusively 1,1,3-tribromononane[34]. The selectivity is probably due not only to the higher extinction coefficient of the polyhalogeno compound, as suggested by the authors, but also to easier cleavage of the carbon–halogen bond. Progressive substitution of a carbon atom with halogen atoms is known to decrease the bond strength of the carbon–halogen bond: the C—Br bond dissociation energy in CH_3Br, CH_2Br_2, $CHBr_3$ and CBr_4 is 68, 62, 56 and 49 kcal mol^{-1} respectively[35]. For a limited series of multiple bromine-substituted systems a linear inverse correlation between the quantum yield of the reduction and the IR stretching frequency of the carbon–bromine bond is found[36].

Geminal diiodides not only give reduction, but also show ionic type behaviour[37] analogous to that observed for monoiodides, e.g. equation (8)[37]. Carbenoid type



45% (8)

photobehaviour may be also observed. Photolysis of methylene iodide in the presence of olefins affords the corresponding cyclopropane adducts in 80–85% yield[37,38] (equation 9). The reaction is stereospecific. Sterically hindered olefins can also be



(9)

easily cyclopropanated by this method, whereas they react sluggishly in the Simmons–Smith procedure. Photolysis of bromotrichloromethane remains a convenient method of free radical bromination for synthetic[39] and mechanistic[40] purposes. The reaction is highly selective for tertiary hydrogens. A novel displacement of the methoxy group of 1-methoxyadamantane by bromine is effected by irradiation in CCl_3Br[41].

The cleavage of the carbon–halogen bond of alkyl halides can be 'photosensitized' by a variety of compounds, the term 'sensitized' being used in the most general sense to indicate induction of a reaction. Examples of sensitizers discussed below are aliphatic amines, aliphatic ketones, anthracene, phenols and anilines; others described in the literature include 1,3-dimethylthymine[42] and naphthalene[43]. The photodecomposition of alkyl halides in the presence of amines may be of ecological importance since it provides a pathway for the environmental photodegradation of persistent chlorocarbon pesticides which are transparent to sunlight[44,45].

Except for the aliphatic amines, the sensitization presumably occurs via the mechanism depicted in equation (10). For all cases studied, the singlet state of the

$$
\begin{array}{l}
{}^1\mathrm{Sens}^* + \mathrm{RX} \longrightarrow [(\mathrm{Sens}\ldots\mathrm{RX})^*] \\
\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad \mathrm{Sens} + \mathrm{R}^\cdot + \mathrm{X}^\cdot \longrightarrow \text{product} \\
\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad \overset{(a)}{\nearrow} \\
\longleftrightarrow (\mathrm{Sens}^{+\cdot}\ldots\mathrm{RX}^{\cdot -})] \qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad (10) \\
\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad \underset{(b)}{\searrow} \\
\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad \mathrm{Sens}^{+\cdot} + \mathrm{R}^\cdot + \mathrm{X}^- \longrightarrow \text{product}
\end{array}
$$

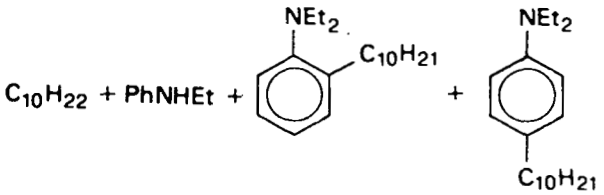
sensitizer is involved in the reaction. Classical energy transfer is, however, not possible since the energies of the sensitizer singlet state are lower than those of most alkyl halides. Interaction of the singlet excited state of the sensitizer is proposed to lead to an exciplex, which either decomposes into the sensitizer, $R^\cdot$ and $X^\cdot$ (a non-classical energy-transfer process, route a) or into the radical cation of the sensitizer and the radical anion of the halide (an electron-transfer process, route b). As is well known from their radiation chemistry[46], electron attachment in carbon–halogen compounds is dissociative, causing alkyl halide radical anions immediately to release X^-. The extent of electron transfer (route b) depends on the electron-donating ability of the sensitizer and the electron affinity of the alkyl halide.

The principal products of the irradiation of aliphatic ketones in the presence of 1,4-dichlorobutane are HCl and 1,3-dichlorobutane, which are the same products obtained upon direct irradiation of 1,4-dichlorobutane[47]. Similarly, the major products of the photolysis of aliphatic ketones in CCl_4 are HCl and C_2Cl_6[48]. The reactions presumably occur via route (a) of equation (10). Interaction of the singlet excited state of the ketones with CCl_4 is evidenced by fluorescence quenching[48,49] and by CIDNP studies[50]. The rate constant of fluorescence quenching of ketones with alkyl halides increases with decreasing ionization potential of the ketone and increasing electron affinity of the halide, indicating that there is significant charge transfer in the quenching interaction[49]. A similar dependence is found for the rate constants of fluorescence quenching for a series of substituted benzenes by the series dichloro-, trichloro- and tetrachloromethane[51].

The efficient quenching of the singlet excited state of anthracene with CCl_4[52,53] leads to formation of product of the sensitizer and halide[53,54]. The primary reaction product is the thermally unstable 9-chloro-10-trichloromethyl-9,10-dihydroanthracene which re-aromatizes by loss of HCl[54]. In line with route (b) (equation 10), this singlet excited state[55] photoaddition is favoured by polar solvents[53]. CIDNP studies show that the initiating radical pair in the reaction is the singlet $\overline{9\text{-Cl-10-anthryl}/CCl_3}^S$[54]). Interestingly enough, excitation of anthracene in unstirred $CHCl_3$ gives fluorescence which varies in time in a periodic or aperiodic oscillating manner[56].

Efficient formation of products via route (b) occurs in the irradiation of the electron-rich *N,N*-dialkylanilines in the presence of alkyl bromides, (e.g. equation

$$n\text{-}C_{10}H_{21}Br + PhNEt_2 \xrightarrow[c\text{-}C_6H_{12}]{h\nu}$$

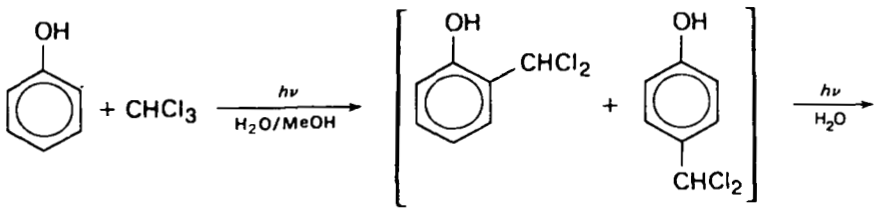


$$C_{10}H_{22} + PhNHEt + \qquad + \qquad (11)$$

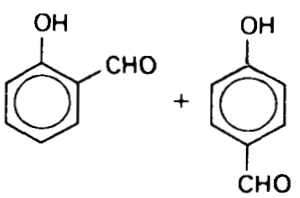
23% 3.6% 48% 31%

11)[44], CH_2Cl_2[57–60], $CHCl_3$[59–61] and CCl_4[59,60,62,63]. The reactions are promoted by polar solvents[64,65]. In accord with an electron transfer mechanism, the observed positions of alkylation of the aromatic amines are *ortho* and *para* – the positions of highest electron spin density in the radical cations of these compounds. In the flash photolysis of diphenylmethylamine[64] and diphenylamine[65] in polar solvents in the presence of CCl_4, the transient absorptions of their radical cations are observed. For triphenylamine in CCl_4, a transient attributed to the solvated radical cation–CCl_4 anion ion pair is observed[64]. For more extensively conjugated aromatic amines such as *N*,*N*′-diphenyl-*p*-phenylenediamine, the photochemical electron transfer is irreversible, the radical cation formed by photolysis in CCl_4 can be observed by conventional spectroscopy at room temperature[66].

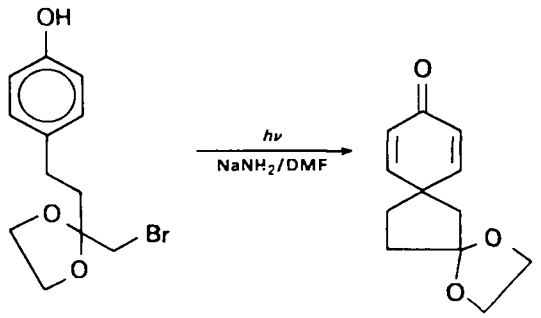
Photochemical Reimer–Tiemann reactions occur when electron-rich aromatic systems such as ferrocene[67] and phenols and anilines[68] are irradiated in the presence of chloroform in an aqueous solution. Thus, for example, phenol affords **15** and **16** in fair yield[68] (equation 12). Intermediates in the reaction are presumably the benzylic dichlorides **13** and **14** formed via route (b) of equation (10), which are photohydrolysed to the corresponding aldehydes (see Section II.C). Upon the irradiation of the same compounds in a mixture of CCl_4 and ethanol, the corresponding ethyl benzoates are formed[67–69] via a similar sequence of reactions.



(13) **(14)**



(15) **(16)** (12)



(13)

(17) (18)

The formation of spiro compound **18** from the phenolate of **17**[70] (equation 13) is an intramolecular version of reactions such as that in equation (11) and probably occurs by the same mechanism.

The photolysis of aliphatic amines and CCl_4 yields amine hydrochlorides, chloroform, hexachloroethane and imines or vinylamines or products thereof[71,72]. The reactions appear to occur via excitation of the ground state charge transfer complex of the amine and the alkyl halide[72], as shown in equation (14). CIDNP studies of reaction (14) show that the formation of the singlet radical pair $\overline{Et_2N\dot{C}HMe/\dot{C}Cl_3}^S$ is the primary step in the reaction[73].

$$Et_3N\cdots CCl_4 \xrightarrow{h\nu} [Et_3N^{+\cdot}\ CCl_4^{-\cdot}] \longrightarrow$$

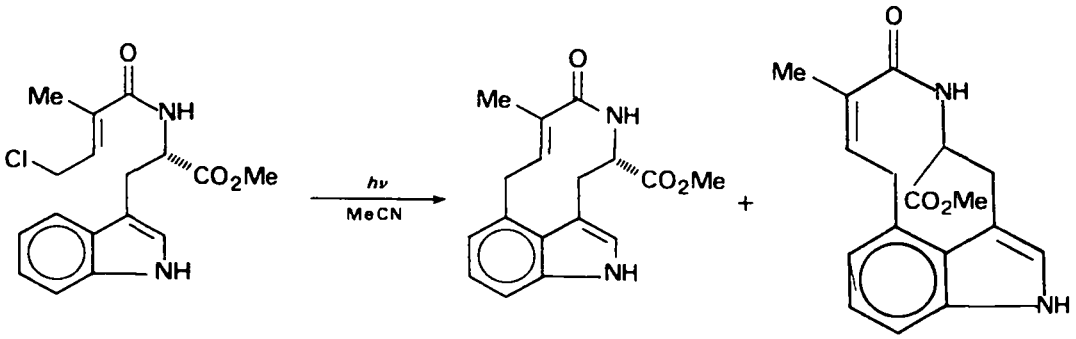
$$Et_3N^{+\cdot} + {}^{\cdot}CCl_3 + Cl^- \longrightarrow \text{products} \quad (14)$$

B. Allylic Halides

The many products, predominantly C_6 compounds, that are formed upon the direct irradiation of liquid allyl chloride[74a] can all be accounted for in terms of homolytic cleavage of the allylic C—Cl bond as the primary process[74]. Spectroscopic evidence for the formation of allyl radicals has been obtained by ESR studies of UV-irradiated allyl chlorides frozen neat at 77 K or in an adamantane matrix[74b]. Similarly ESR and UV/visible spectroscopy show the formation of the pentabromocyclopentadienyl radical from hexabromocyclopentadiene[75].

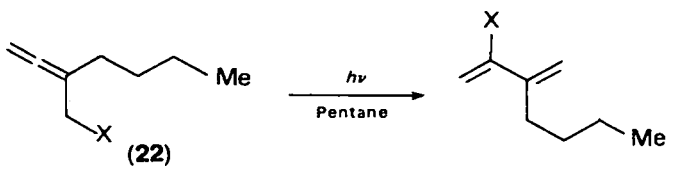
Trapping experiments provide chemical evidence for the intermediacy of allyl radicals. Photolysis of allyl iodide in aromatic solvents yields allylated arenes[76]. The isomer distributions and rate factors indicate that the reaction involves homolytic substitution by a radical having slightly electrophilic character. An intramolecular allylation has also been reported. The chloroallylic amide **19** photocyclizes to the two 10-membered ring lactams **20** and **21**, which have the ergoline skeleton, in 33 and 19% yield, respectively[77] (equation 15).

In appropriately substituted allylic halides an inefficient [1,3] halide shift is observed upon direct irradiation[78–82], e.g. reactions (16)[79] and (17)[78a,80]. Compound **22** (X = Br) rearranges faster than **22** (X = Cl). Irradiation of a mixture of **22** (X = Br) and 3-chloromethylpenta-1,2-diene yields cross-over products demonstrating that the 1,3-shift does not occur intramolecularly but via homolysis and recombination processes[79]. Reaction (17) is catalysed by Cu(II)[80]. The quantitative photoconversion of perfluoro-2,3-dimethylbut-2-ene to perfluoro-2,3-dimethylbut-

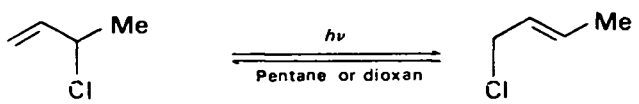


(19) (20) (21)

(15)



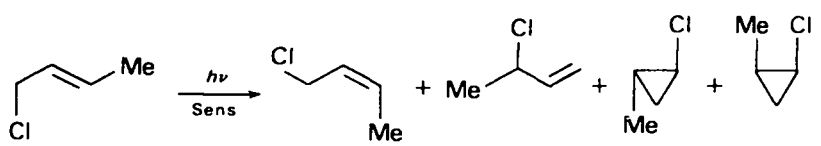
(22) (16)



(17)

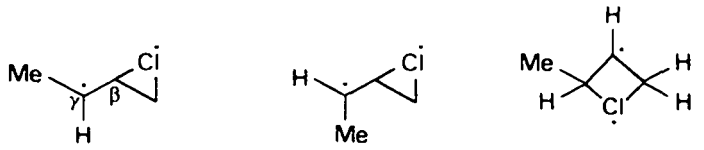
1-ene appears to occur via a photochemically allowed suprafacial [1,3]sigmatropic shift of fluorine[82]. A mechanism involving homolysis and recombination is unlikely in this case because the energy of the C—F bond probably exceeds that of the incident light quanta.

Upon triplet-sensitized irradiation of allylic chlorides and bromides, both 1,3-halide shifts and rearrangement to halocyclopropanes occur in addition to *cis–trans* isomerization. An example is shown in reaction (18)[78]. The formation of



(23) (24) (25) (26) (27) (18)

chlorocyclopropanes is found to be a quite general process[78,81,83] which serves as a useful synthesis of three-membered rings[84]. Notable exceptions are β-chloro- and β-phenyl-substituted allyl chlorides, which undergo only *cis–trans* isomerization and allylic rearrangement[81]. The chlorocyclopropane formation, which is formally a 1,2-shift followed or accompanied by ring closure, similar to the di-π-methane and oxa-di-π-methane rearrangement, is a stereospecific reaction[85,86]. Thus, for example, at low conversions **23** forms mainly **26** and some **27** and **24** forms mainly **27** and some **26**[85]. The reactions are proposed to occur via the chlorine-bridged biradical intermediates **28** and **29**, respectively. Interconversion of **28** and **29** by rotation around the C_β—C_γ bond would account for loss of stereospecificity. Detailed quenching studies of the sensitized reactions of **23**, **24** and **25** show that allylic rearrangement (and *cis–trans* isomerization) occur via a pathway different from that leading to the

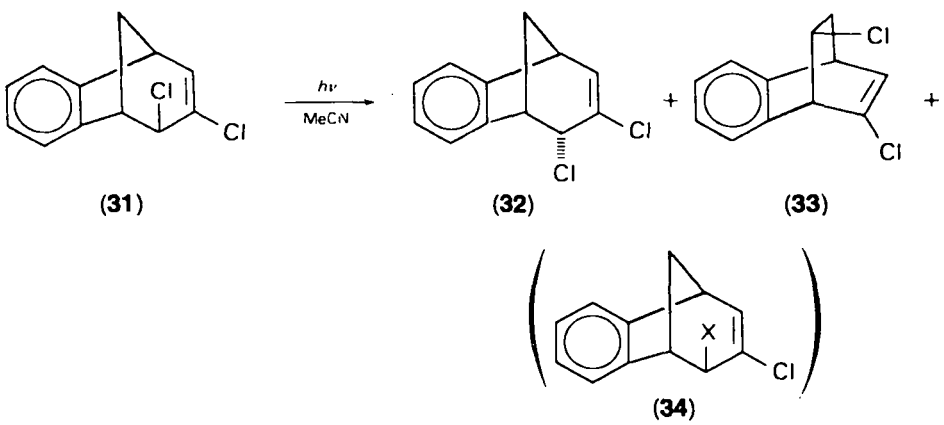


(28) (29) (30)

three-membered rings. Two types of excited state intermediates are proposed; one type, exemplified by **28** and **29**, leads to cyclopropanes, and the other, exemplified by **30**, interconnects the allylic isomers[87].

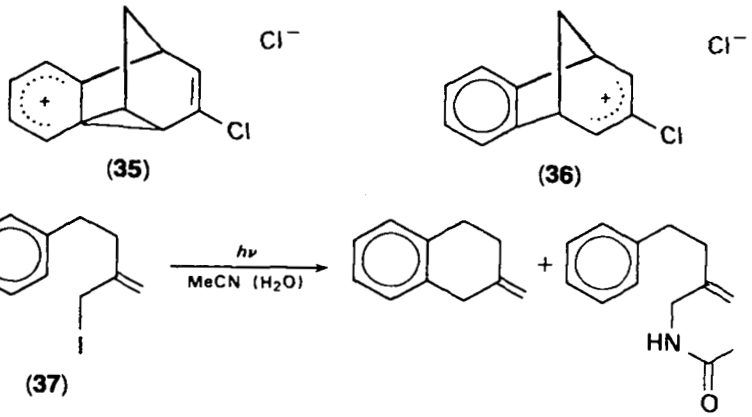
The chemical yield of chlorocyclopropane in a reaction such as (18) is much larger in acetonitrile than in benzene or in cyclohexane. This effect was originally attributed to involvement of an ion-pair intermediate in the cyclization which could be favoured in a polar solvent over competitive generation of other species. However, it is now known that free radicals formed by sensitized homolytic cleavage of the C—Cl bond in acetonitrile recombine rather than give side reaction products[78]. The yields of homolysis products also depend strongly on the concentration of the substrate. β-Methylallyl chloride gives, in addition to 1-chloro-1-methylcyclopropane, dimeric C_8 compounds in yields which increase linearly with the increase in the concentration of the starting material[88] (cf. direct irradiation of allyl chloride).

Cationic intermediates are clearly involved in the singlet excited state reactions of halide systems that are at the same time allylic and homobenzylic[89,90]. An example of such a reaction is the direct irradiation of compound **31** which yields the epimer **32** and the Wagner–Meerwein rearrangement product **33**[90] (equation 19). The reaction occurs more efficiently in polar solvents. Photosolvolysis (yielding **34**, X = $NHCOCH_3$, after addition of water to the irradiated mixture) competes with the photoepimerization and photoisomerization. The products of reaction (19) are



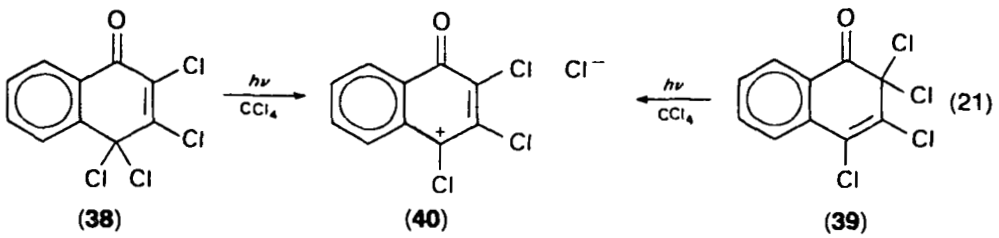
(31) (32) (33) (34) (19)

inconsistent with the intermediacy of radicals; generation of the radical **34** (X = •) by tri-*n*-butyltin hydride reduction of **31** or by photolysis of **31** in cyclohexane affords only unrearranged products. It is proposed that the reaction occurs via the ion pair **35**, which could collapse to **33** and **31** or rearrange to **36**, which in turn could yield **31** and **32** or solvolyse. The thermal solvolysis of **31** gives similar sets of products. As discussed earlier for alkyl halides (Section II.A) the ion pair formation can be envisioned as either direct from the singlet excited state or via homolysis followed by in-cage electron transfer.



(20)

The products of the direct photolysis of **37** (equation 20) are also consistent with a carbocationic intermediate[13]. As in the homobenzylic systems, anchimeric assistance of the phenyl group may play a role in this system. A carbocation is also presumed to form when **38** or **39** is irradiated[91,92] (equation 21). Flash photolysis yields a transient



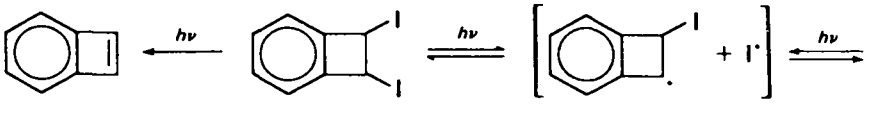
(21)

absorption ascribed to the ion **40**, which is responsible for the well known photochromism of **38** and **39** in solution[91,92] and in the solid state[91,93]. On the basis of time-resolved Raman spectroscopy, however, it has been suggested that the intermediate responsible from the photochromic effect is the radical formed by homolysis of the aliphatic C—Cl bond[94].

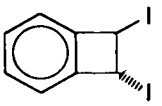
Unlike homobenzylic halides (See Section II.D), homoallylic halides show no enhanced reactivity of the C—X bond. Irradiation of *exo*- and *endo*-5-chloronorbornene and 5,5-dichloronorbornene in the presence of a variety of sensitizers and solvents gives only reduction of the C=C double bond[95].

C. Benzylic Halides

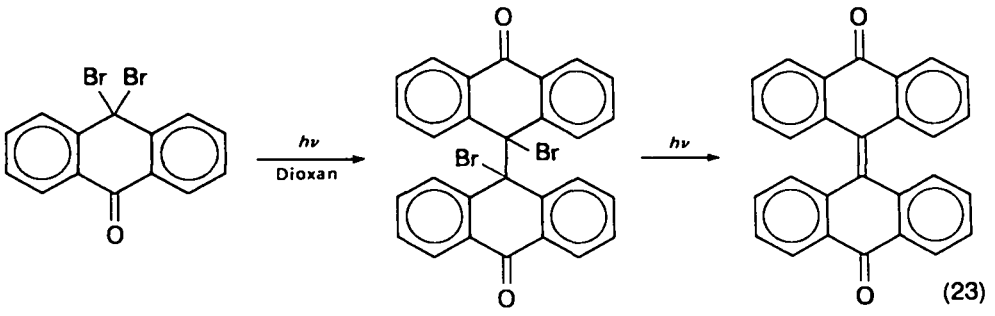
Photolysis of benzylic halides in non-nucleophilic media causes homolytic cleavage of the carbon–halogen bond. The photodetachment of the chlorine atom of benzyl chloride[96] and of a series of methyl-substituted benzyl chlorides[97] in a 3-methylhexane matrix at 77 K has been demonstrated by the observation of the fluorescence emission and excitation spectra of the benzyl radical(s). The ESR signal of what is presumed to be the 2-iodobenzocyclobutyl radical **42** is observed when *cis*- and *trans*-1,2-diiodobenzocyclobutane (**41***c*, **41***t*) are irradiated in argon at 8 K[98] (equation 22). The *cis*-diiodide (**41***c*) yields the *trans*-diiodide and benzocyclobutadiene as the primary products; the *trans* compound (**41***t*) gives only the *cis*-diiodide[98]. The benzylic dihalogeno compound 10,10-dibromoanthrone (**43**) reacts under irradiation to give 10,10′-dibromobianthronyl (**44**) (equation 23); the quantum yield for this



(41c) (42)



(41b) (22)



(43) (44) (23)

process is higher than that for the analogous conversion of monohalogeno 10-bromoanthrone to 10,10′-bianthrone[99]. This is in line with the well known lowering of the C—X bond dissociation energy on attachment of a second halogen to a carbon atom already carrying a halogen (see Section II.A). Benzotrichloride in THF gives a fair yield of $PhCCl_2$–CCl_2Ph and a trace of $PhCCl_2H$[34]. Unlike the corresponding alkyl radical, the more stable $PhCCl_2^{\cdot}$ radical couples more rapidly than it abstracts hydrogen from the solvent.

In nucleophilic solvents, solvolysis products are formed in addition to products derived from homolysis. The photochemical behaviour of benzyl chloride in alcohols and alcohol/water mixtures, which has been extensively studied[100–107] is a case in point. At first, somewhat discrepant reports appeared: benzyl chloride was reported to give no product of photosolvolysis in ethanol[100]; to give only a low yield of solvolysis product in ethanol[101]; to solvolyse very efficiently ($\phi = 1$) in a reaction from the singlet excited state in 1:1 $MeOH/H_2O$[102]; and to give only radical products upon direct irradiation in alcohols and only solvolysis products upon sensitization[103]. However, a consistent picture has now emerged[104–107]. Product distributions are shown in equation (24)[104,106]. Both on direct and sensitized photolysis, products

$$PhCH_2Cl \xrightarrow{MeOH} PhCH_2OMe + (PhCH_2)_2 + PhCH_2CH_2OH + PhMe \qquad (24)$$

hν direct:	26%	23%	37%	trace
hν sens:	45%	2%	15%	trace

derived from heterolysis and homolysis are formed; their yields depend on the multiplicity of the reacting excited state. Increase of the polarity of the solvent increases the proportion of the heterolysis product[105] as does a change of the leaving group from Cl to Br to I[104,106]. The quantum yields of the solvolysis (and to a lesser extent those of the radical product formation) are also dependent on the presence of

substituents in the benzene ring[106,107]. For example, *m*-methoxybenzyl chloride reacts more efficiently by a factor of two in both direct and sensitized photosolvolysis in *tert*-butyl alcohol than does the *p*-methoxy isomer[107]. However, for the large series of substituted benzyl chlorides studied, no simple correlation between quantum yields and substituent constants was found[107].

The products are presumably formed by radical combination reactions of the benzyl radical and by nucleophilic reaction of the benzyl cation with the solvent (equations 25–29).

$$PhCH_2X^* \longrightarrow PhCH_2^{\cdot} + X^{\cdot} \text{ and } PhCH_2^+ + X^- \quad (25)$$

$$X^{\cdot} + CH_3OH \longrightarrow {}^{\cdot}CH_2OH + HX \quad (26)$$

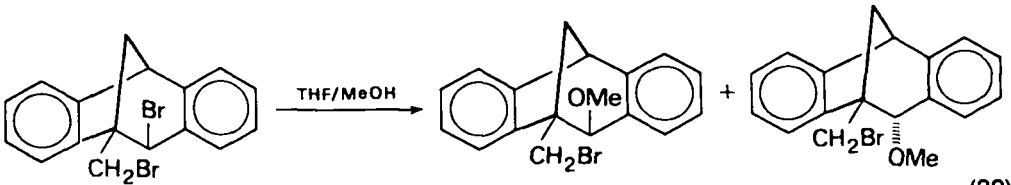
$$2\ PhCH_2^{\cdot} \longrightarrow PhCH_2CH_2Ph \quad (27)$$

$$PhCH_2^{\cdot} + {}^{\cdot}CH_2OH \longrightarrow PhCH_2CH_2OH \quad (28)$$

$$PhCH_2^+ + CH_3OH \longrightarrow PhCH_2OCH_3 + H^+ \quad (29)$$

Hydrogen abstraction by the benzyl radical from methanol is apparently slower than the radical combination reactions (27) and (28); only traces of toluene are formed.

The involvement in the photolysis process of benzyl cations or ion-pairs thereof, identical with or closely similar to those formed in the thermal heterolysis, is indicated by the similarity of the photochemical and thermal nucleophilic capture ratios for benzyl chloride in mixed alcohols[103] and in MeOH/H_2O mixtures[104]. Thus the sensitized solvolysis in methanol/isopropyl alcohol mixtures shows $k_{MeOH}/k_{i\text{-}PrOH}$ = 2.5; for the silver-promoted thermal reaction, the ratio is 2.4[103]. The comparable *exo*/*endo* product ratios of the bridged *exo* benzyl bromide **45** in photochemical and thermal methanolysis (equation 30) also point to similar intermediates in the

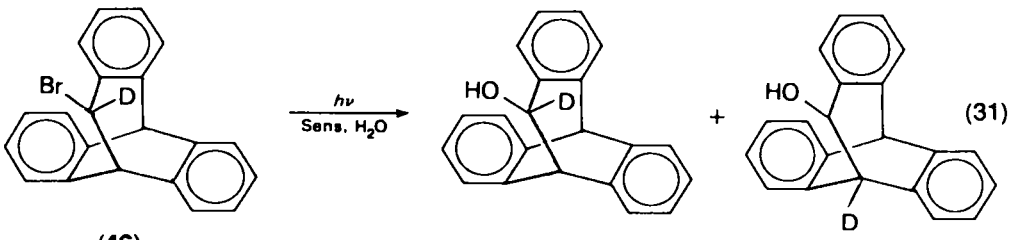


(45) $h\nu$ (at 20°C) 9 : 1

Δ (at 60°C) 7 : 1 (30)

two reactions[108]. The *endo* epimer of **45** gives a different product ratio, which is also comparable for the photochemical and thermal reaction. The available evidence suggests that compound **45** and its epimer, for reasons unclear, solvolyse from the singlet excited state. The intermediacy of a carbocation is evident in the triplet-sensitized photolysis of bromohomotriptycene **46**[109] (equation 31). As noted by deuterium labelling, **46** yields completely scrambled products (and partially scrambled starting material) as does the cationic intermediate generated thermally. The analogous radical intermediate resists rearrangement.

The formation of a cation (**40**) has been observed in the flash photolysis of the allyl benzyl dichloride system **38**[91,92] in CCl_4 (see Section II.B).



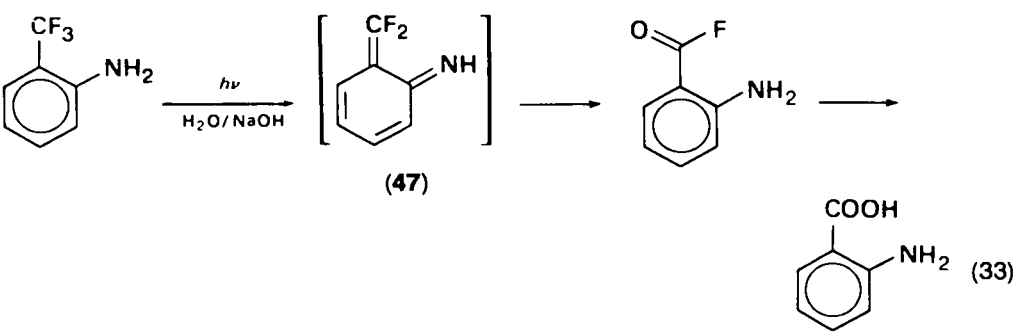
(46) (31)

The benzyl cation moiety (in an ion pair) can be formed, as discussed earlier for alkyl halides, by electron transfer in the radical pair obtained by homolytic bond cleavage of the excited state. It is also possible that the ion pair and the radical pair are formed simultaneously. The influence of the polarity of the solvent is in accord with both possibilities. More elaborate schemes have been proposed[104,106] involving for example the interconversion of loose S and T radical pairs followed by electron transfer in the singlet pair to give a solvent-separated ion pair. Facile spin inversion of the triplet radical $^3(PhCH_2Cl)$ and decay to the ion pair by a spin–orbit coupling mechanism has been suggested as an explanation for the preponderance of ionic products from triplet benzyl chloride[110].

Attachment of a second or third halogen to the benzylic carbon also promotes the heterolysis reaction. Benzal chloride photosolvolyses to benzaldehyde more efficiently than benzyl chloride is converted to benzyl alcohol[101]. Benzotrichloride in alcohols forms alkyl benzoates in fair yield, via the sequence of equation (32) which involves

(32)

the formation of ethyl chloride and benzoyl chloride[101]. Benzotrifluoride is inert[101]. However, introduction of strongly electron-donating substituents such as O^-— and NH_2— in the aromatic ring, especially in the *meta* position, renders the trifluoromethyl group susceptible to photohydrolysis[111]. The corresponding carboxylic acids are formed. Flash photolysis of *o*-trifluoromethylaniline indicates the intermediacy of a quinoid compound **47** and of a benzoyl fluoride (equation 33). The reaction occurs by heterolytic C—F bond cleavage from the singlet excited state[111]. For a series of isomeric trifluoromethyl naphthols[112], a linear correlation between the excited state charge density at the carbon atom carrying the trifluoromethyl group and the photochemical reactivity is found[111].



(47) (33)

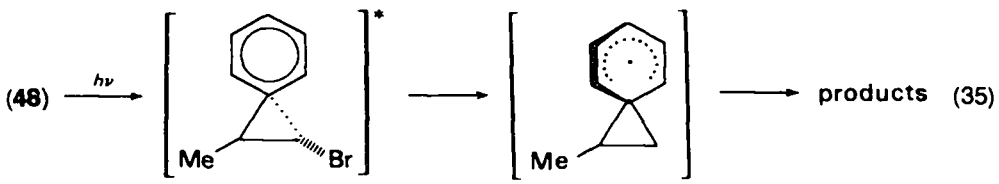
D. Homobenzylic Halides

An aryl group at the β-carbon atom of an alkyl halide exerts an important influence on the photochemistry of the carbon–halogen bond. Upon irradiation of 1-bromo-2-phenylpropane (**48**) with light of wavelength 254 nm in hexane in the presence of CCl_4[113] (equation 34) or in hexane[114], products of phenyl migration are

$$\underset{\textbf{(48)}}{PhCHMeCH_2Br} \xrightarrow[CCl_4/hexane]{h\nu\ (254nm)} PhCHMeCH_2Cl + PhCH_2CHMeCl \quad 54 : 46 \qquad (34)$$

$$\textbf{(48)} \xrightarrow[CCl_4/hexane]{h\nu\ (313\ nm)} PhCHMeCH_2Cl$$

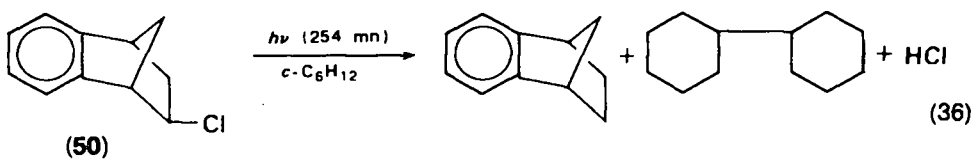
formed. With 313 nm light no[113] or almost no[114] rearrangement occurs. The rearrangement at $\lambda_{exc} = 254$ nm presumably results from an intramolecular energy transfer from the phenyl group to the C—Br bond via a phenyl bridged transition state such as **49** (equation 35). At $\lambda_{exc} = 313$ nm only the absorption band due to a



(49)

transition of the C—Br chromophore is excited. The homobenzylic trichloride DDT (2,2-bis(4-chlorophenyl)-1,1,1-trichloroethane) also shows wavelength-dependent photobehaviour. At $\lambda_{exc} = 310$ nm, DDT only gives reductive dechlorination, yielding DDD (2,2-bis(4-chlorophenyl)-1,1-dichloroethane) and HCl[44]. At $\lambda_{exc} = 254$ nm under otherwise comparable conditions, many additional products are formed[115].

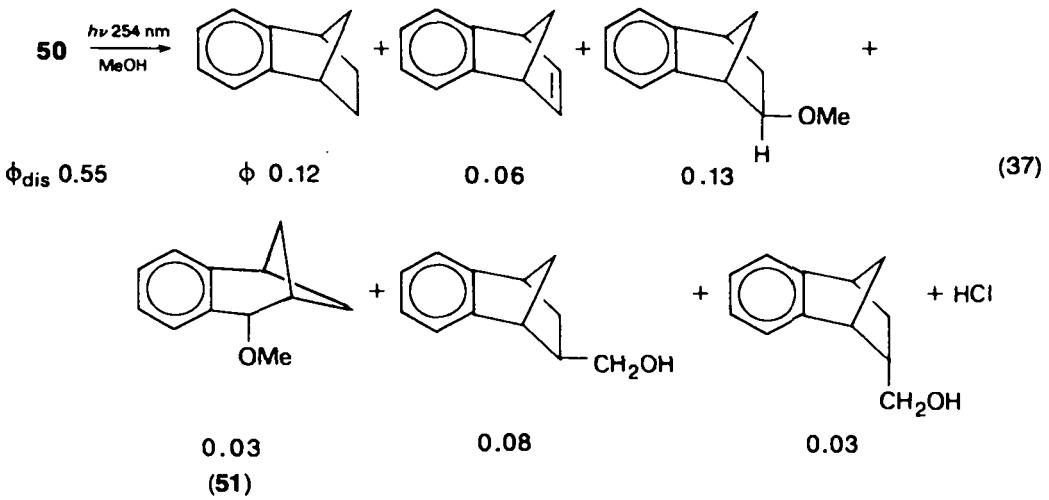
The influence of the aryl group is subject to stereoelectronic requirements[116,117]. Upon photolysis in cyclohexane at 254 nm, where the C—Cl bond is virtually transparent, both the *exo* chloride **50** and its *endo* isomer undergo reductive dechlorination (equation 36). The efficiency of the reaction of the *exo* compound,



(50)

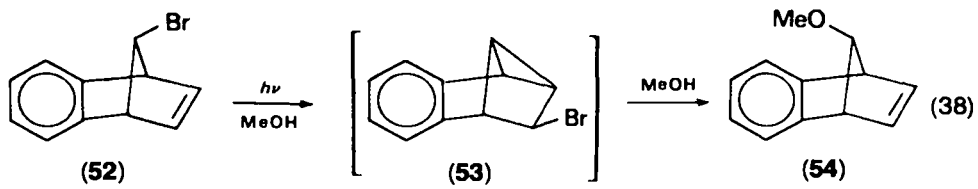
$\Phi_{dis} = 0.25$ Φ 0.10 0.04 0.18

however, is 20-fold more than that of the *endo* compound (ϕ_{dis} *endo*-**50** = 0.013)[116]. The same phenomenon is observed in methanol as the solvent (ϕ_{dis} *exo*/*endo* = 0.55/0.019). In this case products typical of ionic reactions become admixed with products typical of free radical reactions (equation 37)[116]. The cations presumably involved in the formation of the ionic type products are not the same as those involved in the thermal solvolyses. Compounds such as **51** are not formed in the thermal solvolysis of 2-substituted benzonorbornenyl derivatives. The *anti* arrangement of the chromophoric aryl group and the C—Cl bond apparently required for high photoreactivity can be ascribed to the ease of forming a species analogous to **49** via energy or electron transfer.



(37)

The photosolvolysis of **52** also does not lead to the products expected on the basis of its thermal behaviour[118]. Both **52** and its *syn* isomer give the *syn* solvolysis product **54** (equation 38). The rationale for the behaviour of this system does not, however,



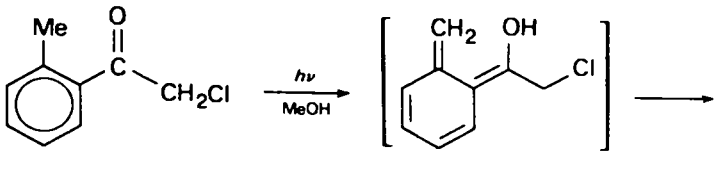
(38)

involve a hot carbocation. The reaction occurs via the di-π-methane product **53**, which thermally solvolyses to **54**. Compound **53** can be observed in irradiations at low temperature.

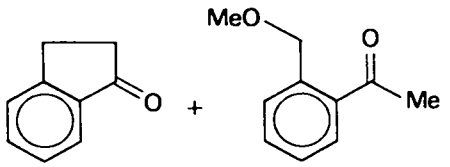
The photochemical decomposition of DDT can be sensitized by aromatic amines[44]. From the products formed, it can be inferred that the reaction occurs according to the electron transfer mechanism of route (b) of equation (10). Introduction of methoxy groups in the chlorophenyl moieties of DDT produces a bathochromic shift and makes intramolecular sensitization via electron transfer feasible[119].

E. α-Haloketones

Photolysis of α-haloketones in solution generally yields products resulting from cleavage of the carbon–halogen bond and not those characteristic of ordinary ketones. Reductive dehalogenation and elimination of HX are the commonly reported reactions for the relatively few simple α-haloketones studied[120–122]. Thus, for example, β-halo-α-tetralones yield both α-tetralone and α-naphthol on irradiation in methanol; the efficiency of formation of both products increases in the order Cl < Br < I[121]. In cases in which the C—F bond can be reduced, ketone photochemistry is competitive. 2-Fluorocyclohexanone in methanol yields both cyclohexanone and methyl 6-fluorohexanoate[122]; the latter product arises via Norrish type I cleavage of the ketone. In the chloro compound **55** photoenolization competes with C—Cl bond cleavage but it does not with C—Br bond cleavage in the corresponding bromo compound. The presumed intermediate photoenol **56** or its *E* isomer cyclizes to



(55) (56)



(57)

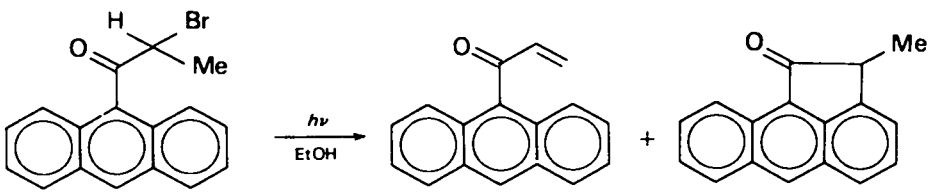
39% 57%

(39)

indanone or reacts with methanol to yield **57** (equation 39). The bromo compound only affords *o*-methylacetophenone[123].

The reductive dehalogenation products such as α-tetralone above probably arise via homolytic cleavage and hydrogen abstraction from the solvent, whereas the elimination products such as α-naphthol above probably arise by disproportionation of the keto alkyl radical. Physical evidence has been obtained for the formation of $RCOCH_2^{\bullet}$ radicals[124,125] and halogen atoms[126,127] upon the irradiation of α-haloketones. ESR studies show that the benzoyl methyl radical is produced in the photolysis of α-iodoacetophenone[124]. In the flash photolysis of chloro- and bromoacetone in water, the transient absorptions of $Cl^{\bullet}$ or $Br^{\bullet}$ (as a charge transfer complex with water) are observed[127]. Both the chlorine atom and the 1-formyl-1-methylethyl radical are trapped by cyclohexene when α-chloroisobutyraldehyde is irradiated in cyclohexene as a solvent[128].

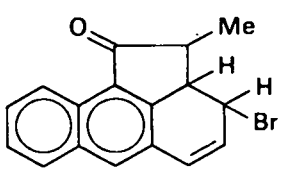
In α-haloketo compounds such as **58**, intramolecular alkylation occurs in addition to elimination and reduction[129–132]. The ratio of the products **59** and **60** (equation 40) is



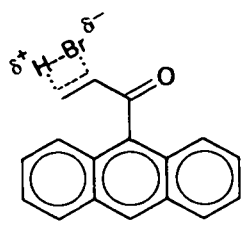
(58) (59) (60)

42% 41%

(40)



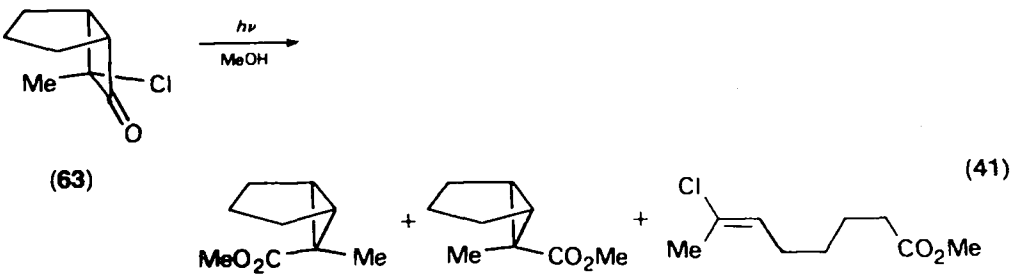
(61)



(62)

strongly temperature dependent[130,131]. In photolysis at room temperature, the ratio is ~1, but at 77 K only **59** is formed. The effect is ascribed to prohibition of rotational motion of the propionyl group necessary for the formation of **60** when the solvent is rigid, as at low temperature. By UV absorption spectroscopy two intermediates have been observed in this reaction: one[129,130], at dry ice temperatures, leads thermally or photochemically to **60** and is presumably **61**, the other[132], at 77 K, leads to **59** on heating and is postulated to be **62**. Intermediates like **62** have also been observed in the photochemical dehydrohalogenation of alkyl halides in matrices.[25]

Unlike other bichromophoric alkyl halide systems, α-haloketones show no great propensity for the formation of products of ionic type reactions. For none of the above systems irradiated in alcohol or even in water[120] is substitution of halogen by solvent observed. Only in special cases do ionic type photoreactions prevail. In a reaction analogous to the Favorskii rearrangement, irradiation of the α-chlorocyclobutanone **63** in methanol affords the cyclopropyl esters **64** and **65** in addition to the ring-opened product **66** (equation 41)[133]. The reaction is modestly stereoselective. The *endo*-chloro

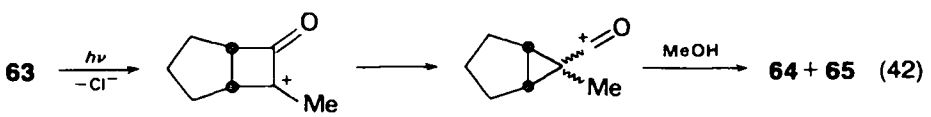


(63) (41)

(64) (65) (66)

ϕ 0.43 0.28 0.09

isomer of **63** gives smaller amounts of **64** and **65** and predominantly the stereoisomer of **66** by an α cleavage. The photo-Favorskii reaction presumably occurs via photoionization followed by, or occurring with, ring contraction involving the ions **67** and **68** (equation 42). In view of the stronger interaction of axial relative to equatorial

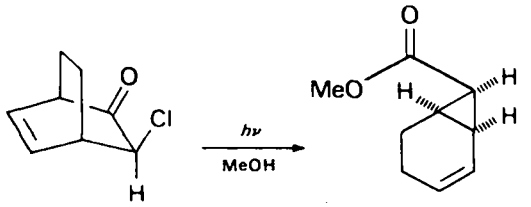


(42)

(67) (68)

α-chlorine with ketones, the axial carbon–chlorine bond will probably be more easily ionized. Since **63** has a preferred conformation with the chlorine axial this would explain why **63** forms **64** and **65** more efficiently than **66** whereas the *endo*-chloro isomer forms **66** more efficiently.

Stereochemical control of a different kind is apparent in the photolysis of systems such as **69**[126,134]. Whereas **69** affords the norcarene **70** in 55% yield (equation 43), the *endo* isomer of **69** yields no **70** (or its epimer) whatsoever[126]. *Anti* arrangement of the alkene group and the C—Cl group in this homoallylic compound appears to be required for efficient reaction and is reminiscent of the situation in homobenzylic halide systems (see Section II.D).



(69) (70) (43)

The photolysis of α,α,α-trichloroacetophenone in methanol also yields products typical of ionic reactions. In addition to α,α-dichloroacetophenone, methyl benzoate and methyl benzoylformate are formed, resulting from nucleophilic attack on the carbonyl carbon and the α-carbon, respectively[135].

F. α-Halocarboxylic Acid Derivatives

1. Reduction and solvolysis reactions

Photolyses of α-haloesters yield products of C—X bond cleavage and the usual photochemical reactions of unsubstituted esters[136] are almost completely suppressed. The products obtained in non-polar hydrogen-donating solvents[137–140] (e.g. equation 44)[138], arise from homolytic cleavage of the C—X bond and subsequent hydrogen

$$ClCH_2CO_2Et \xrightarrow[c\text{-}C_6H_{12}]{h\nu} HCl + EtOAc + c\text{-}C_6H_{11}Cl + c\text{-}C_6H_{11}CH_2CO_2Et \quad (44)$$

$$\phi \quad 0.7 \qquad 0.4 \qquad 0.14 \qquad 0.2$$

abstraction from the solvent molecule by the primary radicals and from recombinations of the various radicals present. It was shown by deuterium labelling that in the case of the poor hydrogen-donating solvent, benzene, the ester itself can act as hydrogen donor[140]. The intermediate radical $^{\cdot}CH_2CO_2Et$ can be trapped by I_2. This was shown by irradiating ethyl chloroacetate in cyclohexane in the presence of I_2; the reaction gave ethyl iodoacetate at the expense of the organic products of reaction (44)[137–139]. ESR observations of the photolyses of ICH_2COOH and ICH_2CONH_2 in an Ar matrix at 4 K also indicate homolysis[141]. Even reduction of a C—F bond is reported: in a 2,3,3-trifluoropropanoate ester, the α-fluorine is replaced by hydrogen upon irradiation in THF[142]. Photochemical C—F bond cleavage, however, is probably not involved; the reducing agent is suggested to be $H^{\cdot}$ produced by photolysis of the solvent.

In α, α-dichloroesters, C—Cl bond cleavage is even more efficient than in the monochloro compounds, approaching a quantum yield of unity[143]. In α,α,α-trichloroesters[144] and -amides[145], cleavage of the bond between the trichloromethyl group and the carboxyl carbon competes with C—Cl cleavage. For benzylic α-chloroesters, reductive dechlorination is only a minor reaction since the benzylic radical abstracts hydrogen from the solvent at a low rate compared with the rate of the competing reactions (see equation 45)[146].

$$PhCHClCO_2Et \xrightarrow[c\text{-}C_6H_{12}]{h\nu}$$

$$HCl + PhCH(C_6H_{11})CO_2Et + (PhCHCO_2Et)_2 + C_6H_{11}Cl + PhCH_2CO_2Et \quad (45)$$

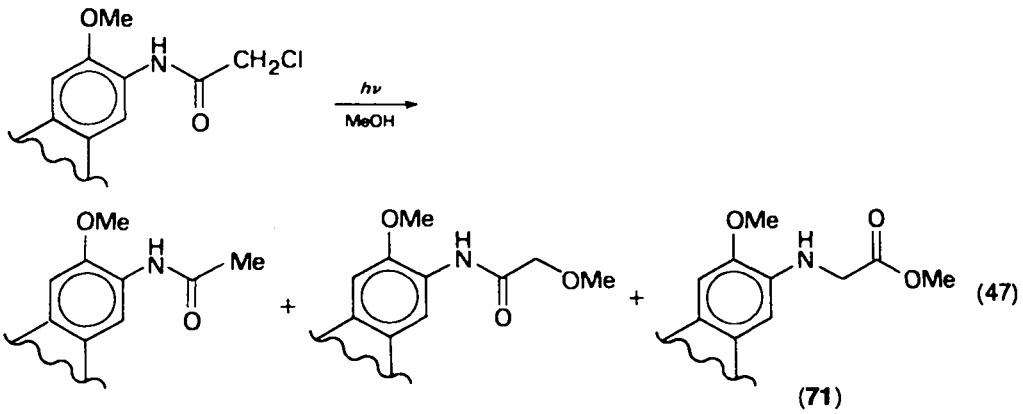
$$\phi \quad 0.5 \qquad 0.26 \qquad 0.08 \qquad 0.04 \qquad 0.04$$

The C—Cl bond cleavage is limited to the case in which the chlorine is at the α-carbon of the ester. β- and γ-monochloro esters show only photoreactions typical of esters[147].

In polar solvents, both reduction and solvolysis products are formed, as reported for chloroacetic acid (equation 46)[148,149], dichloroacetic acid[150], and the chloroacetyl

$$\underset{\phi\ 0.34}{ClCH_2COOH} \xrightarrow[H_2O]{h\nu} \underset{0.19}{Cl^-} + \underset{0.12}{HOCH_2COOH} + CO_2 + \underset{0.08}{CH_3COOH} \qquad (46)$$

derivatives of anilines[151–153] and benzyl amines[153,154]. The novel rearrangement product **71** observed in reaction (47)[152] suggests the intermediacy of an α-lactam in the ionic solvolysis process.



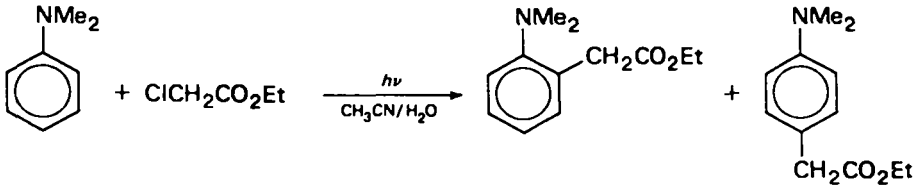
(47)

(71)

2. *Intermolecular alkylation reactions*

Irradiation of ethyl chloroacetate in a solvent such as benzene[155] or toluene[156] gives ethyl phenylacetate or ethyl tolylacetate (*o*:*m*:*p* = 6:11:1) in low yield. Diethyl succinate is formed as a by-product. These inefficient photoalkylation reactions are catalysed by Lewis acids MX_n, but in that case no diethyl succinate is found. This indicates that, unlike in the uncatalysed reaction, the free radical $^{\cdot}CH_2CO_2Et$ is not involved. The reactive species may be a charge transfer exciplex such as $[MX_n^{\delta-}\text{---}Cl\overset{\delta+}{C}H_2CO_2Et]^*$ formed via energy transfer from the excited aromatic compound. The isomer distribution of the ethyl tolylacetates (*o*:*m*:*p* = 1.7:2.4:1) formed in the presence of $AlCl_3$ is not in accord, however, with simple electrophilic attack on ground state toluene. One may be dealing with an electrophilic attack on an excited aromatic, a type of reaction displaying its own set of orientation rules[157].

Photochemical Friedel–Crafts reactions of α-haloesters and -amides occur efficiently with electron-rich aromatic compounds such as phenol and anisole[158], *N*,*N*-dimethylaniline (DMA)[159] and indole[160] in aqueous solution. An example is shown in equation (48). Aromatic compounds without electron-donating groups are not alkylated under these conditions. The reaction is strongly suppressed in organic solvents. The reactions very probably occur via electron transfer from the singlet-excited aromatic compound to the electron-poor chloroacetyl moiety, the process being followed by cleavage of the C—Cl bond and combination of the radical with the aromatic radical cation (equation 49). Interaction between the singlet-excited aromatic compound and the chloroacetyl group is clear from the efficient quenching of



(48)

$$^1DMA^* + ClCH_2CO_2Et \longrightarrow [exciplex] \longrightarrow$$

$$[DMA^{+\cdot} + {}^{\cdot}CH_2CO_2Et + Cl^-] \longrightarrow \text{products} \quad (49)$$

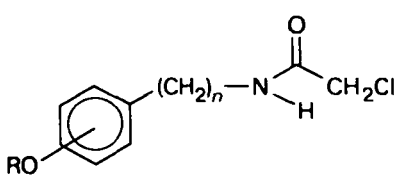
the fluorescence of the former by the latter[161–164]. The quenching efficiency more or less parallels the reduction potential of the quencher[162] and the oxidation potential of the quenchee[163]. By flash photolysis the radical cations of 2,6- and 2,4-dimethoxynaphthalene resulting from quenching by chloroacetonitrile have been observed[163]. The almost exclusive *ortho/para* substitution found in the alkylation of *N,N*-dimethylaniline and phenol is in accord with the positions of calculated highest odd electron density in the radical cation of DMA and the phenoxy radical. Of the seven isomeric indole acetates formed upon irradiation of indole and methyl chloroacetate, the 4-isomer predominates; the 4-position shows the highest calculated spin density in the radical cation[160]. Electrophilic and radical substitution in indole occur almost exclusively in the pyrrole moiety.

Photoalkylation of aromatic amino acids with chloroacetamide has been studied as a means of photochemically modifying proteins. In agreement with the mechanistic conclusions noted above only the electron-rich tryptophan and tyrosine residues are reactive in this process[164].

3. *Intramolecular alkylation reactions*

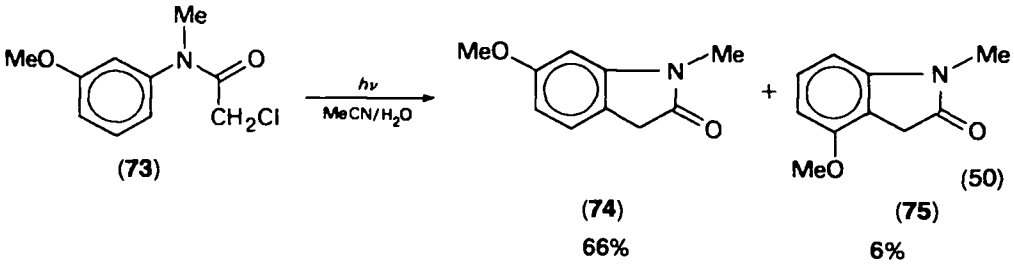
Photolysis of chloroacetyl derivatives of amines appropriately substituted with electron-rich arenes in aqueous solution affords intramolecular alkylation. The many new examples of this reaction, in addition to those already known in 1971[1] demonstrate the considerable potential of this reaction for the synthesis of novel heterocyclic compounds.

Most studies have focused on hydroxy- and methoxy-substituted systems such as **72**. Depending on the length of the alkyl chain and the position of the OR group, a variety of products are formed. Compounds **72** (n = 0, R = CH_3)[153] and related systems[151,152]



(72)

do not photocyclize. Instead, reduction and solvolysis of the side chain occur (see above). The unreactivity in ring closure is attributable to the *trans* form of the amide group which prevents close approach of the chloromethyl group to the aromatic ring. Introduction of an alkyl group on the amide nitrogen increases the stability of the *cis* form, and permits the reaction. Thus **73** gives efficient closure to the oxindoles **74** and

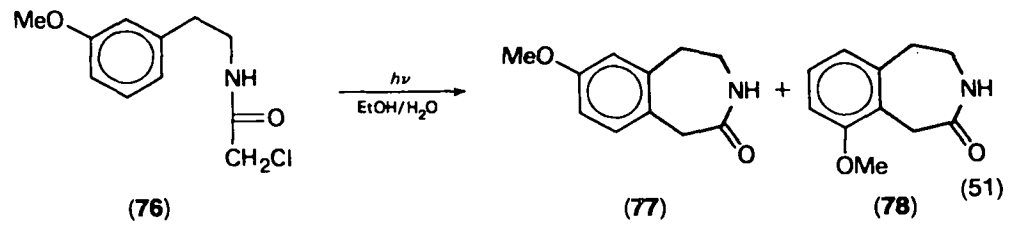


(73) (74) (75)

66% 6%

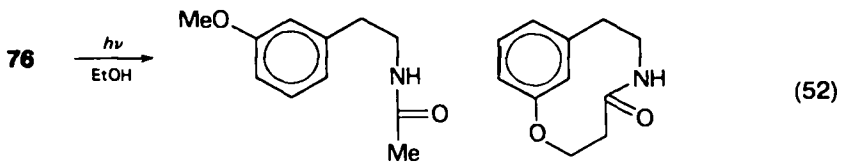
75 (equation 50)[153]. A similar situation pertains for the homologues 72 (n = 1). Closure to isoquinolinones for the unalkylated amides occurs only with the highly activated *meta*-hydroxy-substituted compound[154]. The *N*-alkylated systems cyclize readily[153].

No such restrictions are apparent for the next higher homologues 72 (n = 2). Compound 76 gives the benzazepinones 77 and 78 in 27 and 30% yield, respectively, in



(76) (77) (78)

aqueous ethanol[165]; in ethanol itself, benzazepinone formation is suppressed, being supplanted by formation of the reduction product 79 and the 10-membered ring lactam 80 (equation 52)[165]. The closure of systems related to 76 has been utilized as a



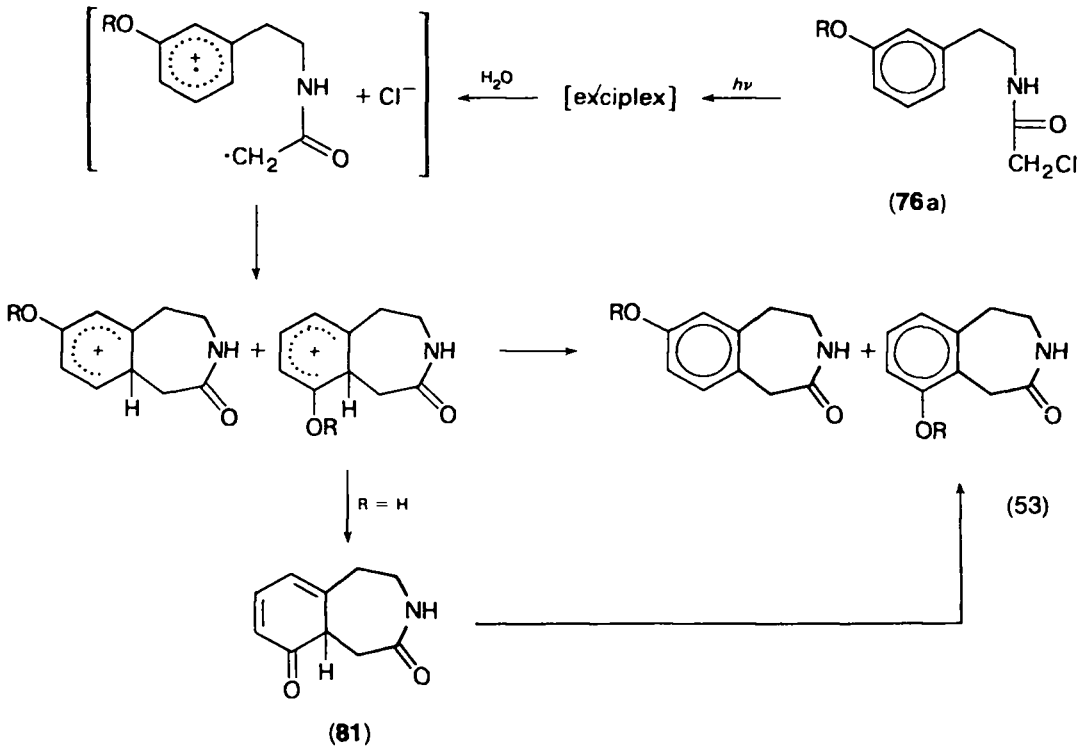
(79) (80)

key step in the synthesis of complex heterocycles[166–168]. Representative reactions such as (51) have been studied in detail[169–171], and presumably occur via the mechanism depicted in equation (53). Intramolecular electron transfer in an exciplex from the singlet excited state of the aromatic chromophore and the chloroacetyl moiety leads to cleavage of the C—Cl bond. The resulting alkyl radical couples with the aromatic radical cation. Supportive evidence for this mechanism is provided by the following data:

(1) The fluorescence of 72 (n = 1–5) is significantly less than that of the corresponding *N*-acetyl compounds, indicating that intramolecular singlet quenching occurs in the former[153].

(2) The yields[169] and quantum yields[171] of 77 and 78 are increased by an increase in the polarity of the solvent.

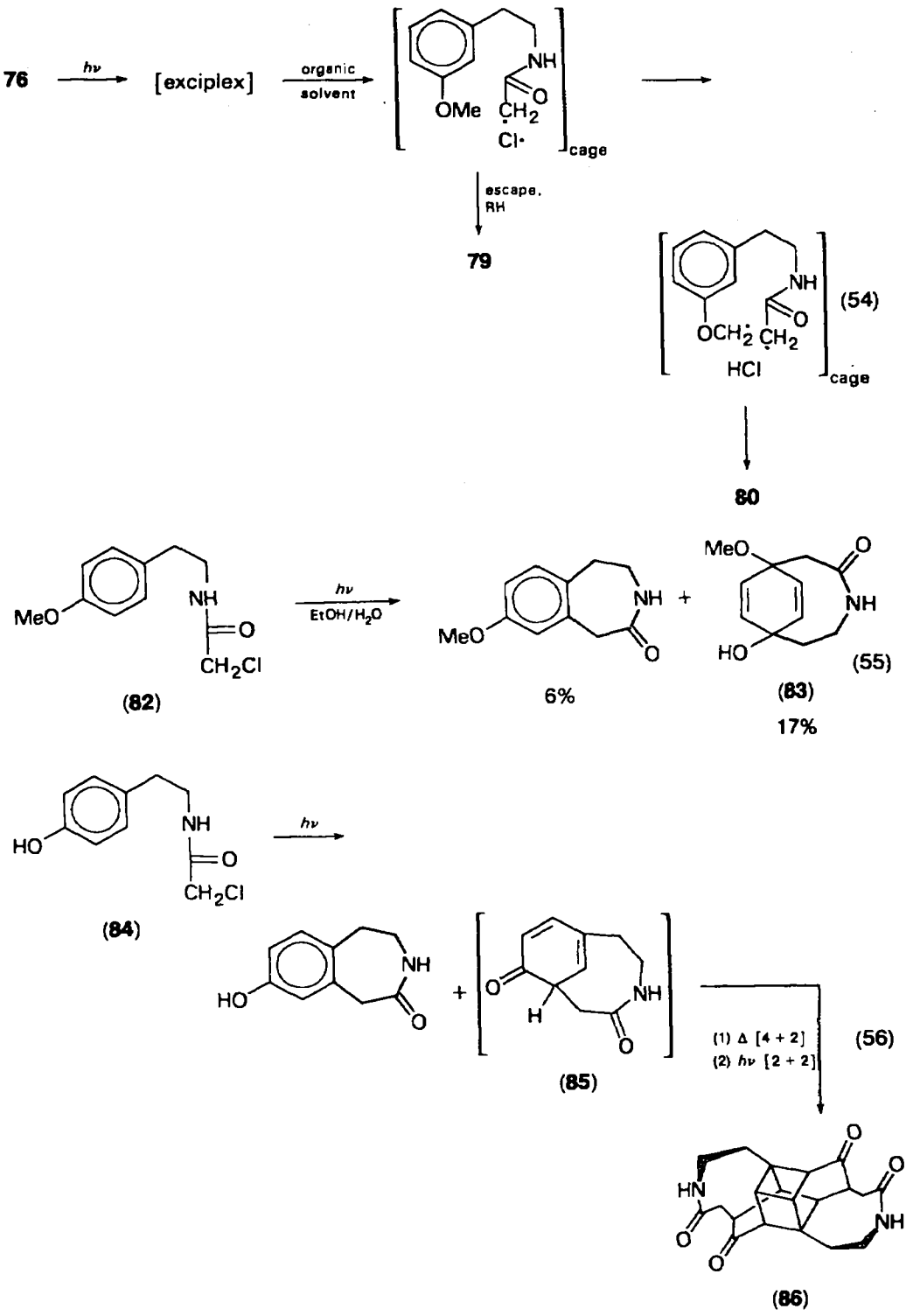
(3) The reactivities of the positions of the aromatic ring correspond with the calculated odd electron densities in the intermediate radical cation (or phenoxy radical in the case of a hydroxy substituent)[169,176].

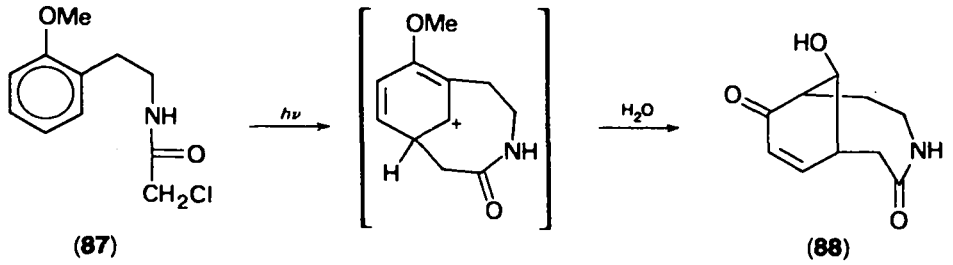


(4) For **76a** (R = H) the transient absorption of the intermediate cyclohexadienone **81** has been observed by flash photolysis; in agreement with the assignment of the transient, the presence of base increases its rate of decay[170].

Greater reactivity is generally observed for hydroxy-substituted compounds relative to the methoxy-substituted analogues. This difference may result from the greater efficiency of electron ejection from phenols or from higher reactivity of the resulting phenoxy radical in the coupling process. In non-polar media it appears that intramolecular energy transfer rather than electron transfer occurs, resulting in homolytic cleavage of the C—Cl bond (equation 54). Probably because of the proximity of the methoxy group to the C—Cl bond in the exciplex, the Cl atom may abstract a hydrogen atom from this group. The formation of **80** is favoured by viscous media indicating that the process occurs in a cage[171].

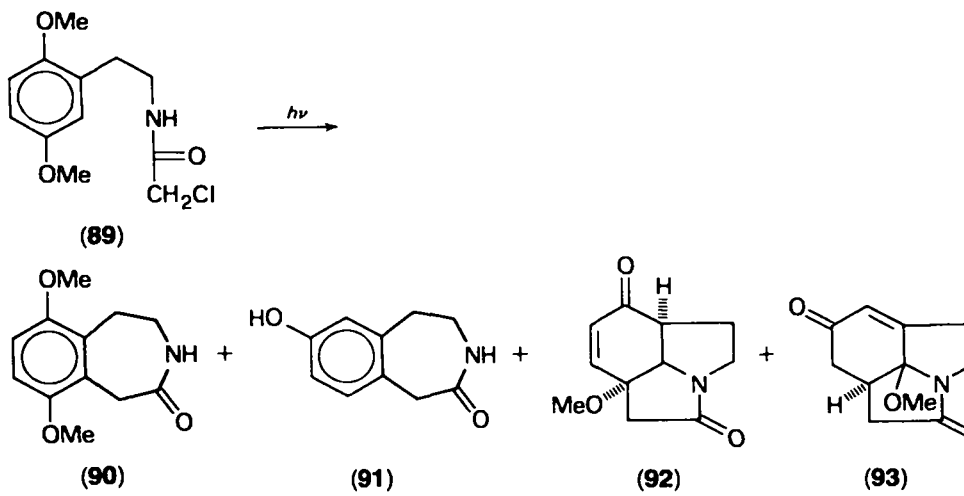
Compounds **72** (n = 2) which, unlike **76**, have the OR group at positions *ortho* or *para* to the side chain are not suitable for azepinone formation. In those cases different products are formed resulting from attack on the position *ortho*, *para*, or *ipso* to the alkoxy group, i.e. the positions with the highest odd-electron density in the radical cation. The *p*-methoxyphenylethylamine derivative **82** yields mainly **83**, which results from *ipso* attack on the radical cation and capture of the resulting cation by water (equation 55)[172]. Likewise **84** yields mainly the photochemically unstable dimeric cage product **86** which derives from the 2,4-cyclohexadienone **85** via a thermal [4 + 2] dimerization followed by a photochemical [2 + 2] cycloaddition (equation 56)[173]. Intermediate **85** has been observed by flash photolysis and trapped as a Diels–Alder adduct by the photolysis of **84** in the presence of *N*-ethylmaleimide[174]. The *o*-methoxyphenylethylamine derivative **87** yields **88** via *para* attack (equation 57).[175].


76
hν
[exciplex]
organic solvent
OMe
NH
O
CH2
Cl·
cage
escape, RH
79
OCH2 CH2
HCl
(54)
80
MeO
(82)
EtOH/H2O
6%
HO
(83)
17%
(84)
(85)
(1) Δ [4 + 2]
(2) hν [2 + 2]
(56)
HN
(86)



(87) (88) (57)

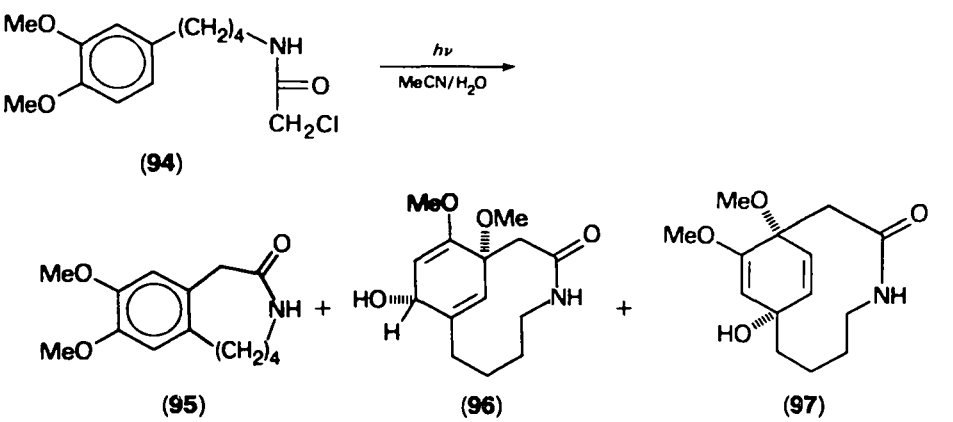
The 2,5-dimethoxyphenylethylamine derivative **89** yields products of attack at C-6 (**90**), C-2 (**91**), C-5 (**92**) and C-3 (**93**) (equation 58)[176].



(89) (58)

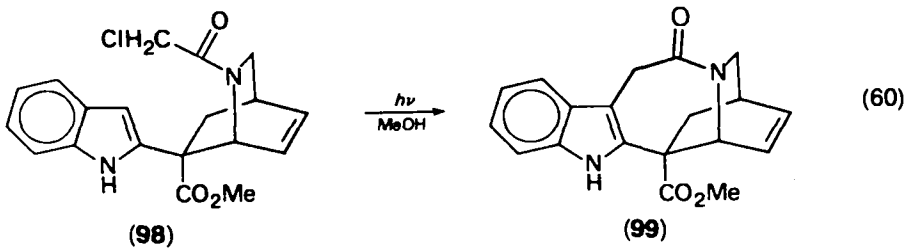
(90) (91) (92) (93)

Extension of the methylene chain in **72** to $n = 3$[173,177,178], $n = 4$[178,179] and $n = 5$[179] relaxes the geometrical limitations for attack *ipso* to the alkoxy group apparent in **76**. Thus, for example, the ω-phenylbutylamine derivative **94** yields both the benzazoninone **95** and the products **96** and **97** resulting from *ipso* attack (equation 59)[179]. The proportion of the latter products increases with the length of the methylene chain.

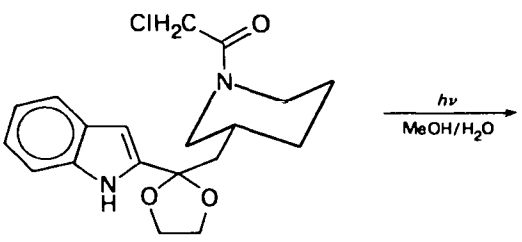


(94) (95) (96) (97) (59)

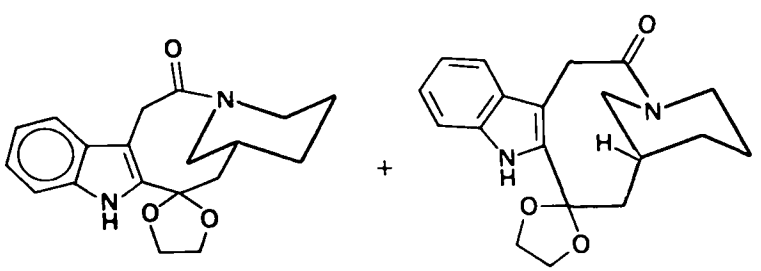
A limited number of compounds analogous to **76** and **82**, in which an *N,N*-dimethylamino group is the electron donor, has been studied[180,181]. Their behaviour parallels that of the methoxy- and hydroxy-substituted systems. A series more extensively investigated consists of *N*-chloroacetyl derivatives of 2-indolyl-substituted alkylamines with two[182–184], three[185], four[182,185–188] or five[185] carbon atoms between the amino group and the indole. In all cases the alkylation occurs at the 3-position of the indole, permitting the synthesis of polycyclic indole derivatives, including alkaloid skeletons, with medium-sized rings fused to the *b*-side of the indole ring. Thus, for example, compound **98** gives the catharanthine derivative **99** in 45% yield (equation 60)[184], and **100** affords the stereoisomers **101** and **102**, containing the quebrachamine skeleton, in 50% yield (equation 61)[186,187]. The principal product, **101**, in the latter



(98) (99) (60)



(100)



(101) (102) (61)

reaction is less stable than **102**. Its stereochemistry corresponds to the preferred conformation of **100**, suggesting that the ground state conformation controls the product stereochemistry.

The *N*-chloroacetyl derivatives of seven isomeric indolylethylamines yield azepinoindoles and azocinoindoles in fair yield through photocyclization at the *ortho* and *peri* positions[188].

III. VINYL AND ACYL HALIDES

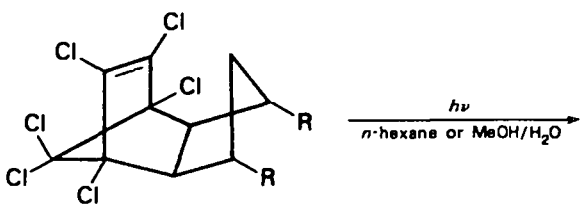
A. Vinyl Halides

Photolysis of vinylic halides causes cleavage of the carbon–halogen bond as well as reactions characteristic of alkenes. The incidence of the various products depends upon the halogen and the multiplicity of the reacting excited state. Cleavage of the C–X bond may be homolytic or heterolytic, resulting in subsquent reactions of radical or ionic character.

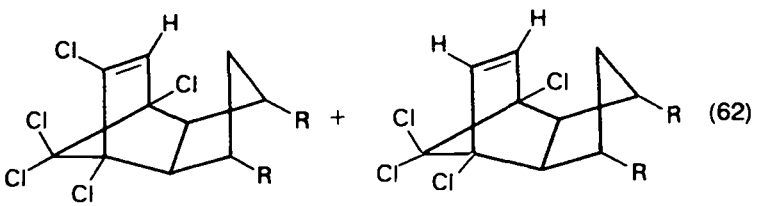
Irradiation of simple vinyl chlorides, bromides and iodides in non-nucleophilic hydrogen-donating solvents affords mainly reductive dehalogenation products. The products presumably are formed via homolytic cleavage of the carbon–halogen bond and subsequent hydrogen abstraction. Vinyl radicals are powerful hydrogen-abstracting species; as an example abstraction of hydrogen from an sp^3 carbon atom by such a species is 10–15 kcal mol^{-1} exothermic.

Simple vinyl chlorides in nucleophilic hydrogen-donating solvents undergo reduction and no photosolvolysis, whereas the bromides yield some photosolvolysis products. For vinyl iodides under these conditions photosolvolysis is the major process (see below). Irradiation of vinyl chlorides and bromides in CD_3OD has been used to synthesize the corresponding specifically deuterated alkenes in high yield[189].

Photochemical reductive dechlorination of the vinyl chloride chromophore has ecological importance[190–193] since it is a major abiotic transformation of persistent polychlorinated cyclodiene insecticides such as aldrin and dieldrin. In many cases the dechlorination accomplishes detoxification. The photochemical reactions of **103** (R = CO_2Me), the methyl ester of the main metabolite of aldrin (**103**, R = —CH=CH—), exemplify the photochemical behaviour of this class of compounds. (For a more complete review, the reader is directed to reference 193.) Direct irradiation of **103** in *n*-hexane or $MeOH/H_2O$ gives replacement of one or two vinylic chlorines by hydrogen in consecutive steps (equation 62)[194]. For all cases



(103)

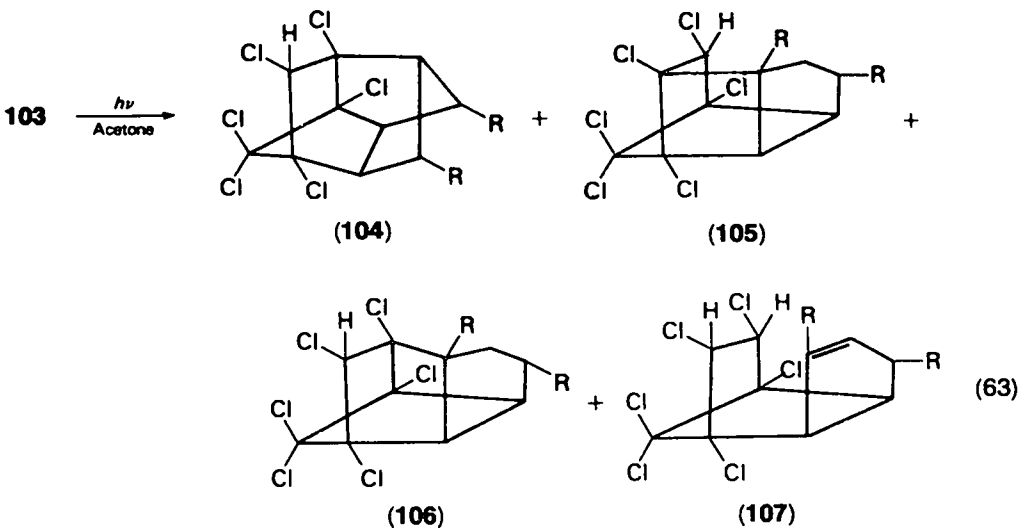


(62)

studied, the dechlorination of the monodechlorinated products occurs with about the same, but low, efficiency ($\phi = 10^{-4}$–10^{-3} in *n*-hexane), as that of the starting cyclodiene insecticide[195]. The reactions are about as efficient in $MeOH/H_2O$ as in *n*-hexane[196]. In $MeOH/H_2O$ in the presence of KOH, however, photodegradations of aldrin and dieldrin are accelerated and different products are formed[196]. That the reductive dehalogenation is strictly intermolecular has been shown by the use of

deuterated solvents[189,194,197]. The half-filled σ orbital of the vinyl radical intermediate from, for example, **103** is approximately orthogonal to the σ bond of the methylene hydrogens; this renders internal hydrogen abstraction impossible since it apparently requires a linear arrangement of the reaction centres[197].

In the sensitized irradiation of **103** (R = CO_2Me), isomerizations occur to the half-cage compounds, **104**, **105** and **106**, and the double hydrogen transfer product **107** (equation 63)[194,198]. At −70°C **107** is the sole product; **104**, **105** and **106**, which are

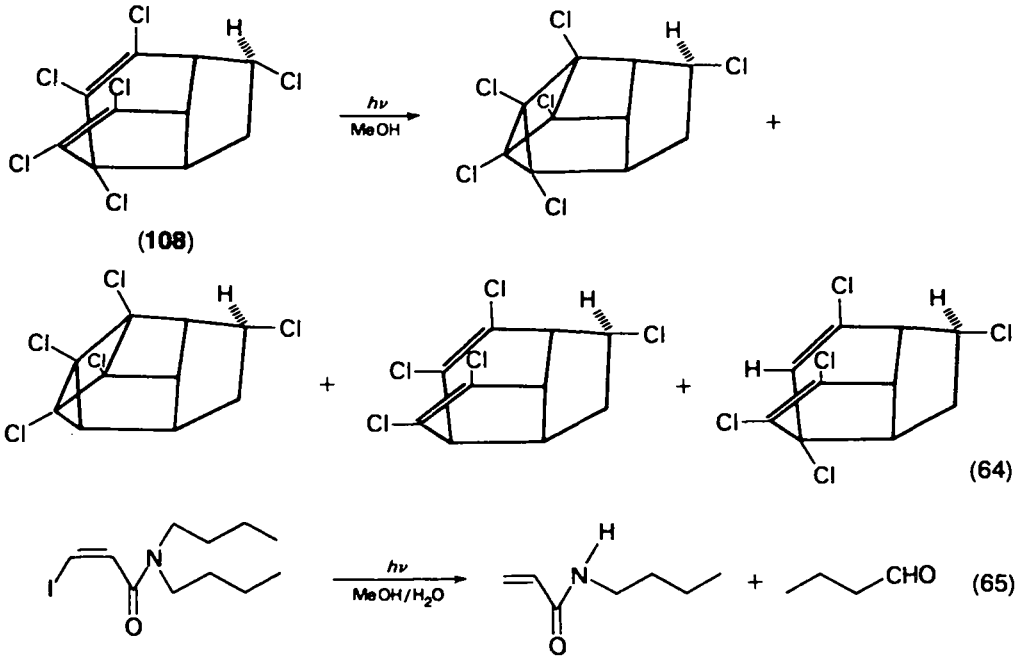


(63)

formed only above −30°C, can be produced by photosensitization from either **103** or **107**[198]. The double hydrogen transfer is reversible: sensitized photolysis of **107** also reforms some **103**. These reactions do not detoxify the insecticides since the photoisomers are usually more toxic than the corresponding parent compound. By use of deuterated solvents[194,199] and deuterated substrates[200,201], the isomerizations have been shown to be strictly intramolecular. They presumably occur via abstraction of an adjacent hydrogen by the triplet alkene chromophore. The p orbital of the excited alkene moiety may align colinearly with the methylene hydrogen[197] resulting in hydrogen atom transfer and subsequent carbon–carbon bond formation leading to **104**, **105** and **106**, or subsequent transfer of a second hydrogen leading to **107**. The C—C bond formation apparently has a higher free energy of activation than the transfer of a second hydrogen. The occurrence of intramolecular double hydrogen transfer in the present class of compounds[194,198,199,202], is not limited to systems such as **103** (R = CO_2Me) in which formation of a conjugated double bond may provide driving force; indeed (R = H) affords **107** (R = H) in good yield[199].

Other photoreactions observed in the cyclodiene insecticides are reductive dechlorination of allylic chlorines and [2 + 2] cycloadditions. Only in special cases[203,204] is the allylic bridgehead chlorine replaced by hydrogen upon irradiation. [2 + 2] cycloadditions occur usually upon sensitized irradiation in systems with a suitable second carbon–carbon double bond and lead to cage compounds[204,205]. α-Chlordene (**108**) shows both of these modes of reaction (equation 64)[204].

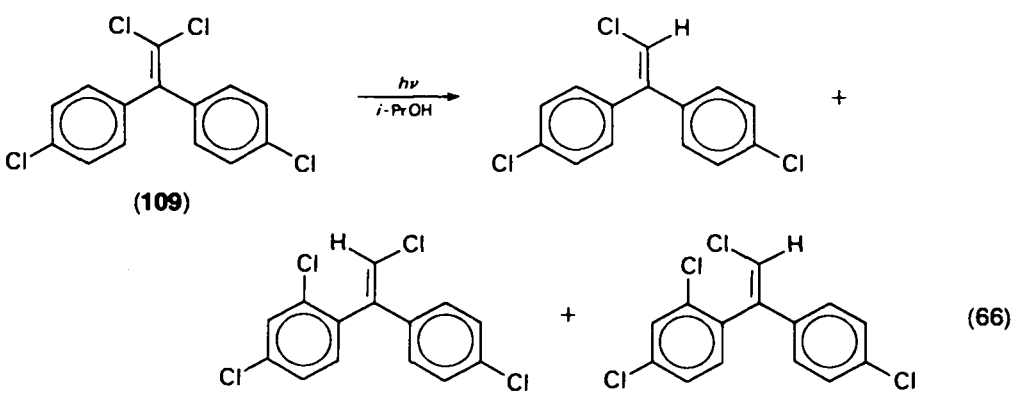
Intramolecular hydrogen abstraction by a vinyl radical presumably occurs in the photolysis of *N*,*N*-dialkyl-β-iodoacrylamides which afford dealkylated acrylamides (equation 65)[206]. The hydrogen atoms on the carbon atom α to the amide nitrogen atom are easily abstracted. The resulting α-amido radical must proceed to a labile



intermediate such as an enamide or an *N*-(α′-iodo)alkyl amide which is subsequently hydrolysed. The process provides a new method of selectively degrading secondary amines.

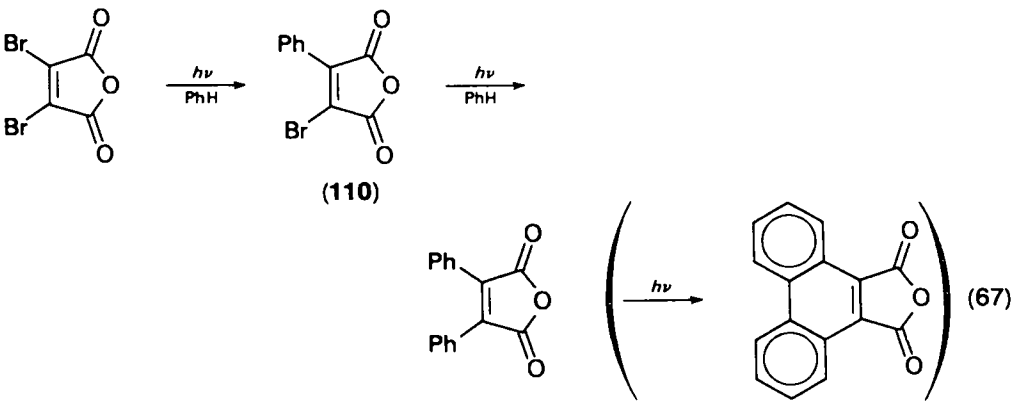
Intermolecular double hydrogen transfer has also been observed. Irradiation of *trans*-α,β-dibromostilbene in cyclohexane in the presence of an hydrogen acceptor such as I_2 or O_2 gives *meso*-1,2-dibromo-1,2-diphenylethane in 48% yield[207].

α,α-Dichloro-[208,209] and α,α-dibromoalkenes[210] can be selectively photoreduced to the corresponding monohalo compounds. In DDE (**109**), a major residue of DDT in the biosphere, photoisomerization occurs[208,209] in a yield comparable to the photoreduction yield, even in a good hydrogen-donating solvent such as isopropyl alcohol (equation 66). Formation of the isomerization products may involve a sequence of homolytic cleavage of the vinyl carbon–chlorine bond, capture of the chlorine atom by one of the aromatic rings, and intramolecular hydrogen transfer in



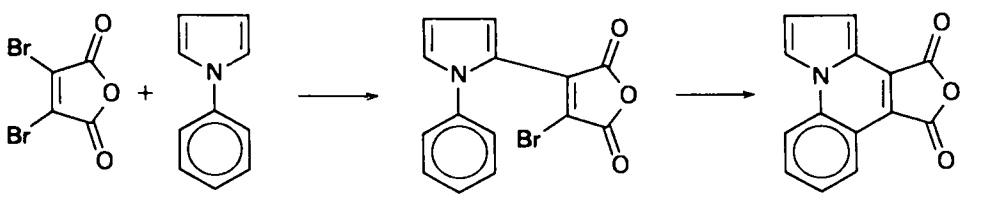
the intermediate diradical. Photolysis of **109**[211] and related α,α-dichloroalkenes[212] in the presence of O_2 leads to highly unstable dioxetanes, which can be observed by flash photolysis. The dioxetanes decompose into $COCl_2$ and the corresponding benzophenones; the overall process accounts for the well known formation of the latter product in the photolysis of DDT[44,115].

Photolysis of dihalogenomaleic anhydride and dihalogenomaleimide in the presence of aromatic compounds yields vinylated arenes. The dibromo compounds have been used most often, and examples of intermolecular vinylation therewith include reaction with benzene and substituted benzenes[213,214], naphthalene and anthracene[214], *N*-phenylpyrrole[215,216], thiophene and furan[217], indole[218], benzo[*b*]thiophene[219], and 1,3-dimethyluracil[220]. As an example irradiation of a benzene solution of dibromomaleic anhydride results in successive substitution of the bromine atoms by phenyl groups (equation 67)[213]. The vinylation occurs much more efficiently with an



(67)

electron-rich aromatic compound such as *N*-phenylpyrrole (equation 68)[215]. The quantum yield of formation of **110** in CCl_4 is 0.10, whereas that of **111** in CCl_4 is 0.67[219]. Reactions such as (68) are proposed to occur via a moderately polar exciplex

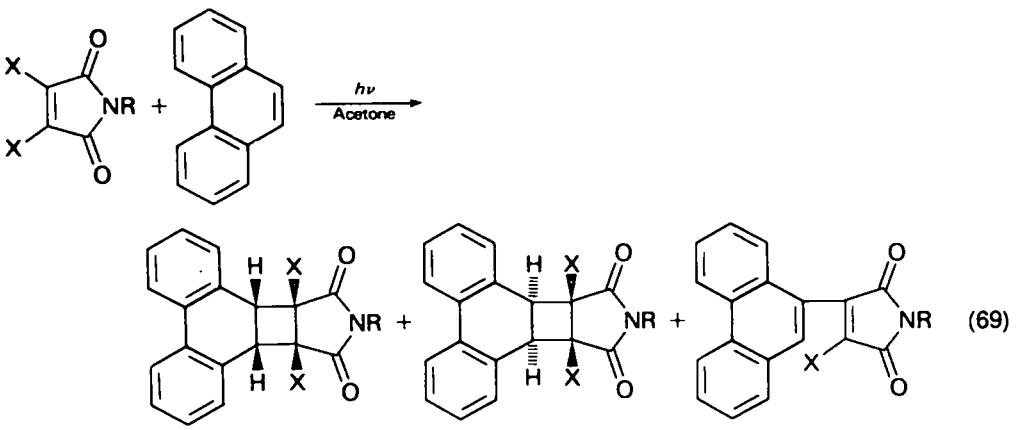


(68)

formed from the triplet of the maleic anhydride and a ground state arene. The observed solvent effects are suggestive of an exciplex mechanism. The quantum yield of **111** decreases on going to more polar solvents[215]. A somewhat different trend is found in the reaction of dibromomaleimide with indole; in this case, the quantum yield increases on going from cyclohexane to ether as the solvent but it decreases again when highly polar solvents are used[218]. The latter solvent effect is attributed to enhancement of radiationless transitions of the excited CT complexes leading to quenching by the polar solvent. The requirement of the reaction for a moderately strong CT interaction in the exciplex is also clear from substrate modification studies. Unlike dibromomaleimide, the more electrophilic dibromomaleic anhydride does not

give a photoproduct with indole. However, upon replacement of one of the bromine atoms in dibromomaleic anhydride by the electron-rich thienyl group, reaction does occur[218]. The positions of substitution (2- in naphthalene, 9- in anthracene, 2- in pyrrole, thiophene, furan and indole, and 3- in benzo[*b*]thiophene and pyridine) are probably determinated by interactions in the exciplex rather than interactions attending coupling of an aromatic radical cation with a carbon radical. The latter appears to apply in the photoreaction of indole with methyl chloroacetamide, which gives mainly substitution at the 4-position (see Section II.F.2).

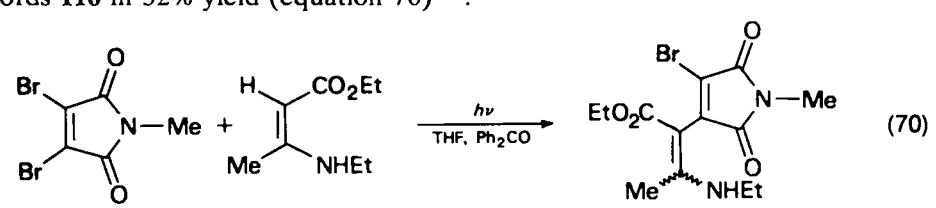
Some of the above reactions are accompanied by[214,219] or dominated by[220] cyclobutane adduct formation, which is the mode of reaction for the non-halogenated maleic acid derivatives. In general, cycloaddition is the major or exclusive process for dichloro systems and an unimportant process for the diiodo compounds. This increasing preference for substitution in the order Cl < Br < I has been systematically investigated for the dihalomaleimides and, for example, phenanthrene (equation 69). For X = Cl only **112**, and **113** are formed; for X = Br, **112**, **113** and **114** are formed, for X = I only **114** is formed[214].



(112) **(113)** **(114)**

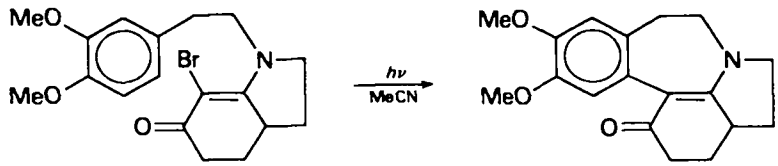
Dichlorovinylene carbonate is reported to yield only cycloadducts upon irradiation in the presence of a variety of aromatic compounds including electron-rich ones[221]. With benzene, a very inefficient substitution also occurs[222].

Electron-rich alkenes such as enamino esters or ketones may also be photovinylated. Thus, irradiation of *N*-methyl dibromomaleimide in the presence of **115** affords **116** in 32% yield (equation 70)[223].



(115) **(116)**

In suitably aryl-substituted vinyl halides intramolecular vinylation may occur. A diversity of examples of this reaction has been reported[215,216,224,225]. The second step of reaction (68) is a case in point; it shows a solvent dependence similar to that for the

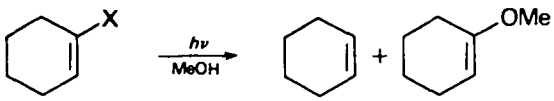


(117) (118) (71)

intermolecular vinylation[215]. Intramolecular vinylation has been used as a key step in the synthesis of nitrogen heterocycles[226,227]. Thus, for instance, the tetracyclic azepine **118** is formed in 38% yield upon photolysis of **117** (equation 71). Compound **118** can also be synthesized by intramolecular photoarylation (see equation 127).

The photoreaction of 3,5-dibromo-2,6-dimethylhepta-2,5-dien-4-one to 2-bromo-5-isopropylidene-3-methylcyclopent-2-enone, which occurs in very low yield, is formally an intramolecular vinylation of an alkane[228].

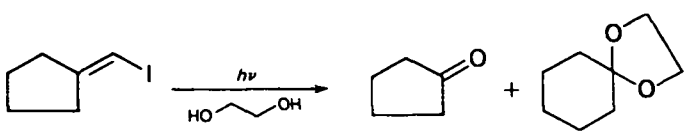
Photolysis of vinyl halides may give ionic reactions such as solvolysis and Wagner–Meerwein rearrangement admixed with radical reactions. Thus, upon irradiation of 1-iodo- or 1-bromocyclohexene in methanol, nucleophilic substitution occurs in addition to reduction (equation 72)[229]. The ratio of the products depends on



(72)

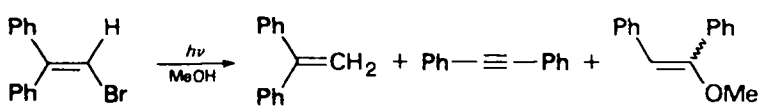
X = I	19–27%	65%
X = Br	62%	26%

the halogen; the bromo compound yields less substitution product than does the iodo compound. The same trend has been found for the corresponding alkyl halides (see Section II.A). In the case of the vinyl iodide **119** a ring-expanded solvolysis product is formed (equation 73)[239].



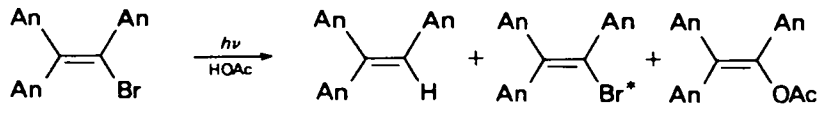
(119) 50% 30% (73)

Photosolvolysis and photo-Wagner–Meerwein shifts are also important processes for aryl-substituted vinyl bromides in nucleophilic media[226,230–232]. Thus, for example, upon irradiation of **120** in methanol *cis*- and *trans*-α-methoxystilbene and tolan are formed (equation 74)[230]; systems such as **121**, in the presence of azide ions in



(120) (74)

	32%	22%	18%
+Cu(OAc)$_2$	23%	38%	33%

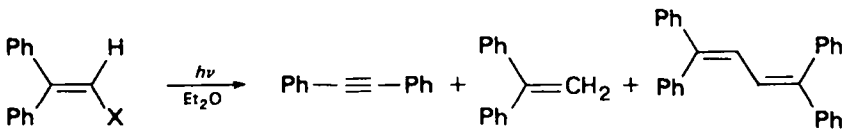


(75)

(121)

87×10^{-3} M NaOAc	$\phi = 0.001$	0.20	0.01
71×10^{-3} M Et_4NBr^*			

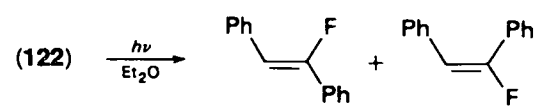
acetonitrile[231] or acetate and (labelled) bromide ions in acetic acid (equation 75)[232], afford the corresponding vinyl azides (or products thereof), acetates and bromides in high yield. For a series of 1,1-diaryl-2-bromoethenes in benzene[233] and for the 1,1-diphenyl-2-halogenoethenes (**122**, X = Cl, Br, I) in cyclohexane or ether[234,235], tolan formation is the major process in addition to reduction (equation 76). No trend of increasing amounts of tolan in going from X = Cl to Br to I is observed. For **122** (X = F) no reduction or tolan formation occurs; instead a mixture of *cis*- and *trans*-α-fluorostilbene is obtained (equation 77)[235,236]. Tolan is also the main product in the irradiation of α-chloro- and α-bromostilbene in cyclohexane or ether; α-fluorostilbene only displays *cis–trans* isomerization[237].



(76)

(122)

X = I	19%	51%	6%
X = Br	23%	34%	10%
X = Cl	25%	28%	10%



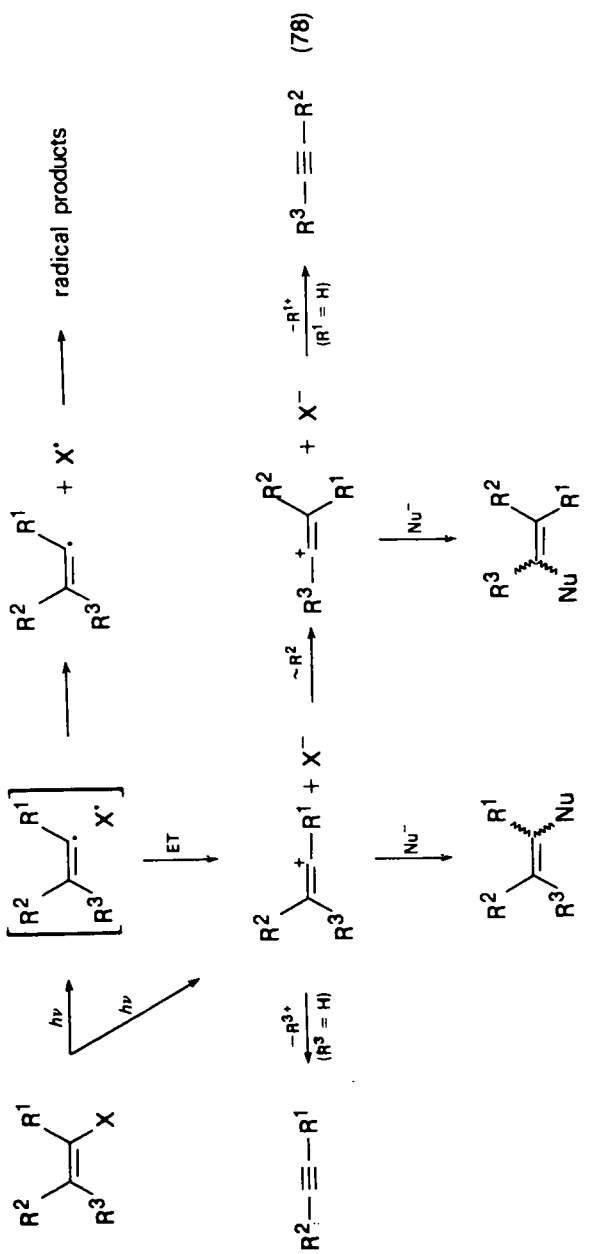
(77)

X = F

The solvolysis products are presumably formed via trapping of an intermediate (rearranged) carbocation by the solvent or the added nucleophile. The tolans are suggested to form by loss of a proton from an intermediate (rearranged) cation[234,235]. The ions may be produced via homolytic bond cleavage of the carbon–halogen bond and subsequent electron transfer in the resulting radical pair in competition with its dissociation into free radicals, or via direct heterolysis of the carbon–halogen bond (equation 78). No experiments have yet been described to distinguish these possibilities.

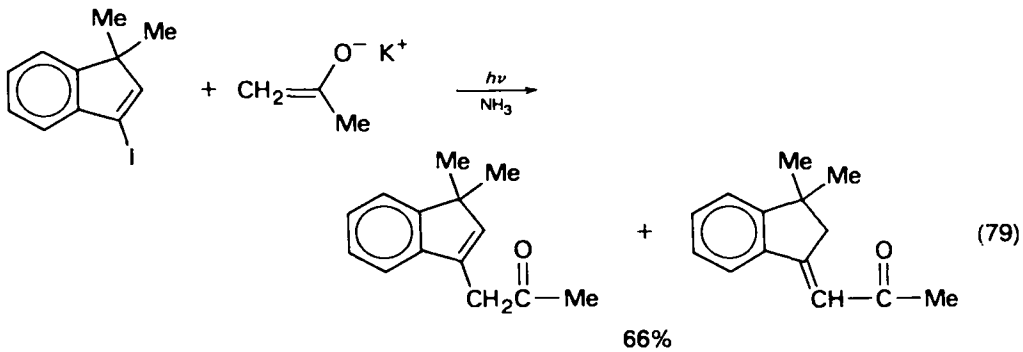
Addition of Cu(II) salts enhances the amount of tolan and the 1,2-diphenyl-1-methoxyethenes at the expense of the reduction product in the irradiation of **120** in methanol (equation 74)[230]. Presumably the vinyl radical which escapes from the solvent cage can be oxidized to the vinyl cation by electron transfer to the Cu(II) ion.

In the reaction of systems such as **121** clear chemical evidence for the involvement of ions identical to or very similar to those involved in thermal solvolysis is provided by nucleophilic capture ratio studies[232]. Thus the photochemical reaction of **121** (equation


radical products
ET
hν
hν
Nu⁻
Nu⁻
(78)

75) shows a selectivity towards bromide and acetate ions ($\alpha_{h\nu}$) of 25.5 at 25°C. Correcting for the temperature dependence of the selectivity, the factor would be 22 at 120°C. The thermal reaction of **121** at 120°C shows a selectivity $\alpha_{\Delta} = 22$[238]. Physical evidence for the intermediacy of ions comes from flash photolytic studies[239–241]. In the flash photolysis of systems such as **121**, an ionic transient is observed by electrical conductivity measurements[239,241]; a transient presumed to be the carbocation is observed by electronic absorption spectroscopy[240,241].

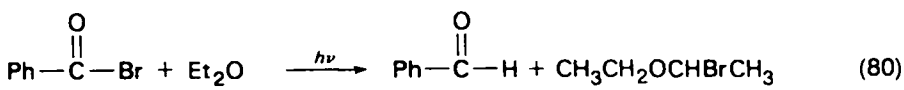
Several vinyl halides undergo nucleophilic substitution upon irradiation in the presence of acetone enolate ion or thiophenoxide ion in liquid ammonia[242] (equation 79). Reactions of this type are well known in aryl halide photochemistry (see Section IV.C) and the present reaction presumably occurs similarly via the $S_{RN}1$ mechanism.



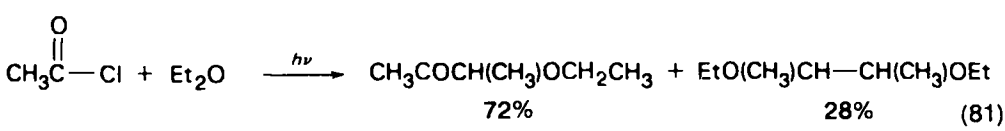
(79)

B. Acyl Halides

Relatively few reports on the photochemistry of acyl halides have appeared since the subject was reviewed in the early 1970s[1,243]. In general, these substances undergo photolytic cleavage of the carbon–halogen bond in solution. Thus, benzoyl bromide[244] and acetyl chloride[245] in the good hydrogen-donating solvent, diethyl ether, efficiently yield products arising from acyl and halide radicals; the quantum yield of formation of benzaldehyde and $CH_3COCH(CH_3)OCH_2CH_3$ is 0.25 and 0.10 respectively. The formation of different main products may be related to the bond strengths of HCl (103 kcal mol^{-1}) and HBr (87 kcal mol^{-1}) relative to that of the acyl hydrogen bond



(80)



(81)

(87 kcal mol^{-1}). In reaction (81) the chlorine atom rapidly abstracts a hydrogen from the ether leaving the carbon radicals to combine. In reaction (80) the hydrogen abstraction by the bromine atom will be much slower, enabling the acyl radical to compete for the hydrogen[243–245]. When hydrogen donors are absent, as in the irradiation of neat **123** (X = Cl, Br, I), decarbonylation to give FSO_2CF_2X occurs[246]. The acid fluorides of perfluoroalkane carboxylic keto acids (**124**), however, undergo selective α-cleavage photochemically at the ketone carbonyl and decarbonylation, resulting in radical coupling products[247]. The carbon–carbon bond of oxalyl chloride is

FSO_2CF_2COX (123)

$(CF_3)_2CFCO(CF_2)_nCOF$ (124)

much weaker than the α-carbon–carbon bond of other acyl chlorides. Accordingly, its photolysis in cyclohexene yields acid chlorides which derive from both C—Cl and C—C bond cleavage. Upon treatment of the irradiated mixture with ethanol both *cis*- and *trans*-ethyl 2-chlorocyclohexane-1-carboxylate and ethyl 1-cyclohexenylglyoxylate are found[248].

Irradiation of a benzene solution of benzoyl chloride and anthracene gives 2- and 9-benzoylanthracene[249]. This photoinduced Friedel–Crafts acylation is proposed to proceed via an exciplex involving charge transfer from a singlet-excited anthracene to a ground state benzoyl chloride. The exciplex is proposed to decay to a zwitterionic σ complex which yields product by elimination of HCl. The positional selectivity may be determined by interactions in the exciplex. A charge transfer interaction between the singlet excited state of anthracene and benzoyl chloride is indicated by fluorescence quenching experiments. For a series of substituted benzoyl chlorides and anthracene the quenching rate constant increases with increasing electron attracting ability of the substituent[249]. Similarly, for a series of substituted naphthalenes and acetyl chloride, the quenching rate constants increase with the electron-donating ability of the quenchee[250]. Intramolecular fluorescence quenching occurs in the acid chloride of 1-naphthylacetic acid. However, in the reaction in benzene only a small amount (4%) of intramolecular acylation product (2-(2*H*)-acenaphthylenone) is formed. The main product (84%) is 1-(chloromethyl)naphthalene which is formed by decarbonylation[251].

Ethyl chloroformate gives both decarbonylation and decarboxylation upon irradiation. The products are CH_3CH_2Cl, CO_2, CO and HCl[252]. Photolysis of cyanogen iodide (ICN) in a matrix yields iodine isocyanide (INC)[253]. In the presence of arenes, photolysis of ICN produces aromatic nitriles in fair yield[254].

IV. AROMATIC HALIDES

A. Reductive Dehalogenation Reactions

Photolysis of aryl halides in solvents containing abstractable hydrogens leads to reductive dehalogenation. This process has recently been intensively studied, in particular for aryl chlorides, not least because some of these compounds are important environmental pollutants. Photochemical dehalogenation is a major pathway in their degradation in nature[191,192,255].

Reductive dehalogenation is a quite general process for ArX (X = Cl, Br, I) in a variety of solvents; it is notably facile when easily abstractable hydrogens are available. Photolysis of a series of PhX in CD_3OD has been used to synthesize the corresponding PhD in high yield[189]. The reduction is sometimes accompanied by biaryl formation (Section IV.B.1); and minor amounts of substitution products are formed in nucleophilic solvents such as alcohols (cf. Section IV.C). No reductive defluorination of ArF is found. The high energy required for C—F bond cleavage prevents this reaction. Instead valence isomerizations to Dewar benzenes occur upon irradiation of polyfluorinated benzenes in alkane solvents[256]. A nucleophilic photosubstitution takes place in alcohols (Section IV.C).

The final step in the formation of ArH from ArX is often the abstraction of a hydrogen atom by the aryl radical resulting from homolysis of the C—X bond (equation 82). Chemical evidence for the formation of such radicals has been obtained by trapping them with radical scavengers such as I_2 (leading to halogen exchange)[257]

$$ArX^* \longrightarrow X^\cdot + Ar^\cdot \xrightarrow{RH} ArH \qquad (82)$$

and $(RS)_2$ (leading to sulphides)[258]. The radical has been observed in the flash photolysis of chlorpromazine[259]. The rate of formation of the radical is a function of X. Cleavage of the aryl–Br bond is so rapid that energy transfer to a second chromophore within the molecule cannot compete with it[260]. The cleavage of the aryl–Cl bond is slower and intramolecular quenching may occur[261].

The radical may not always be formed by direct homolysis of the C—X bond of the molecule in its reacting excited state. In ArCl both the singlet and triplet excited states are in principle available for reaction. In contrast in ArBr and ArI, generally only the triplet state is available because the internal heavy atom effect[262] greatly shortens the singlet life time by enhancing the rate of intersystem crossing $S_1 \rightarrow T_1$. As can be seen from Table 1 there is usually a large energy deficit between the triplet excitation energy and the C—Cl and C—Br bond dissociation energies.

The presence of an electron donor (D) provides an indirect route for C—X bond cleavage. Electron transfer from the donor to the excited aryl halide forms an aryl halide radical anion, which in turn releases the halide ion[270] (equation 83). Examples with alkylamines, hydroxide ion, dienes, and the aryl halide itself as donors have been reported.

$$ArX^* + D \longrightarrow D^{+\cdot} + ArX^{-\cdot} \longrightarrow Ar^\cdot + X^- \qquad (83)$$

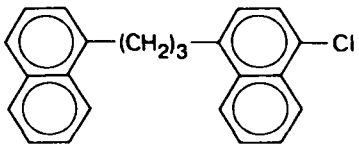
The different courses of the reactions of 1-chloronaphthalene (NpCl) and chlorobenzene in alkane solvents, which have been studied in detail, nicely illustrate the case of aryl halide as a donor. In 1-chloronaphthalene direct reaction from the triplet excited state is not feasible, because the energy of the state is considerably smaller than the C—Cl bond dissociation energy. The reduction[265,271,272] occurs in an inefficient process from the singlet excited state, presumably by way of electron transfer via an excimer (equation 84). The quantum yield of the reaction increases with the concentration of the halide. Self-quenching of the fluorescence of the

$$^1NpCl^* + NpCl \rightleftharpoons [excimer] \longrightarrow NpCl^{+\cdot} + NpCl^{-\cdot} \qquad (84)$$

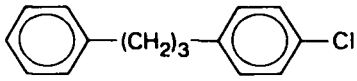
TABLE 1. Bond dissociation energies and singlet (E_S) and triplet (E_T) excited state energies (in kcal mol^{-1}) of some arenes and corresponding aryl halides.

X	Bond dissociation energy of PhX[263]	E_S[264]			E_T[264]		
		PhX	NpX[a]	PhC_6H_4X[b]	PhX	NpX[a]	PhC_6H_4X[b]
H	110	110	90	~96[d]	84	61	66
F	124	107	90, –		84	60, –	–, –
Cl	94[c]	105	90, 89	–, ~95[d]	82	59, 60	72[f], 65[268] (~66)[g]
Br	80	105[266]	89, 89		~80[e]	59, 60	65, ~66[g]
I	64					59, 60	63[269], ~66[g]

[a]NpX = halonaphthalene; values for 1- and 2-isomer respectively.
[b]PhC_6H_4X = halobiphenyl; values for 2- and 4-isomer respectively.
[c]Values ranging from 80 to 95 kcal mol^{-1} are found in the literature; for a discussion see reference 265.
[d]Values estimated from spectra in reference 267a.
[e]Value estimated from spectrum in reference 267b.
[f]Value estimated from spectrum in reference 268.
[g]Value estimated from spectrum in reference 267c.



(125)



(126)

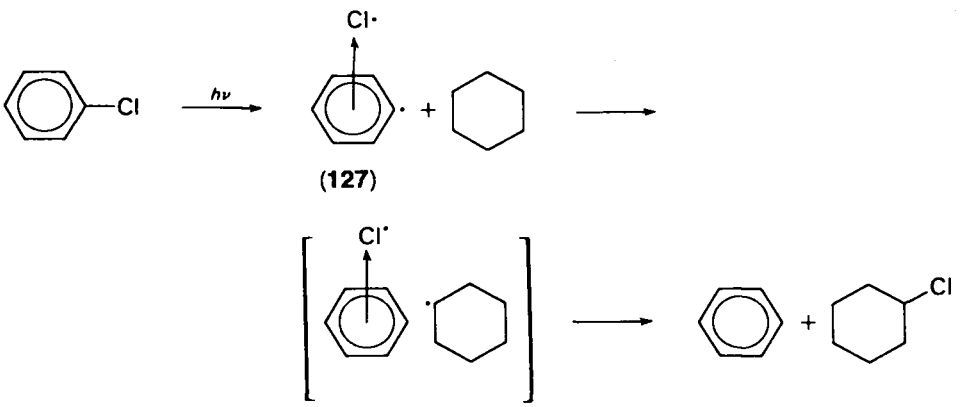
substrate and emission of the excimer are observed[272]. Compounds such as **125** which form an intramolecular excimer are more photolabile than chloronaphthalene itself[265]. The radical cation, $NpCl^{+\cdot}$, will arylate chloronaphthalene or the naphthalene formed in the reaction. The former reaction accounts for the formation of a binaphthyl product containing two chlorine atoms[272].

If, on the other hand, the triplet energy is comparable to the C—Cl bond dissociation energy, as in chlorobenzene (PhCl), the reduction is an efficient process from the triplet excited state[265], initiated by a simple homolysis[265,273] (equation 85).

$$^3PhCl^* \longrightarrow Ph^{\cdot} + Cl^{\cdot} \qquad (85)$$

Excimers are formed but their formation is detrimental to the reaction. The quantum yield of the reaction decreases with increasing concentration of the chlorobenzene and no biphenyls are formed. Compounds such as **126** that form intramolecular excimers are less photolabile than chlorobenzene itself[265,274].

In order to account for the large amount of chlorocyclohexane formed in the photolysis of chlorobenzene in cyclohexane it has been proposed[275] that the reactive species in the hydrogen abstraction is not the free Ph radical but the Ph radical complexed with the Cl atom (π-chlorobenzene, **127**) (equation 86). Subsequent work



(127)

(86)

however, has cast doubt on this proposal, since in other alkane solvents large amounts of chloroalkanes are not formed and *o*-chloropropylbenzene yields no side chain-chlorinated propylbenzenes. The chlorocyclohexane is probably derived from the sensitized addition of HCl to cyclohexene which is formed by disproportionation of the cyclohexyl radical[273].

In the monochlorobiphenyls[276], whose triplet energies are nearer to the C—Cl bond dissociation energy than in the case of chloronaphthalene, the reaction also occurs from the triplet state. Excimers do not appear to participate in the photochemistry. The reduction shows strong positional selectivity: $\phi_{o\text{-Cl}} = 0.39$, $\phi_{m\text{-Cl}} = 0.0011$ and $\phi_{p\text{-Cl}} = 0.0006$ in isooctane. The higher reactivity of the *ortho* compound is due to the higher energy content of its triplet state. *Ortho* substituents sterically destabilize the

planar[268] triplet state. A higher reactivity of the *ortho* compound is also found (though less conspicuously) in the photolysis of the bromobiphenyls in cyclohexane[277]. In this series the reactions occur via the electron transfer mechanism of equation (84), and a steric effect must thus also operate in the radical anion.

High quantum yields of reaction of *ortho* X-substituted compounds are also observed in polychlorinated biphenyls[276,278,279] and terphenyls[280] and in polybrominated biphenyls[277].

In other substituted chlorobenzenes the reduction likewise shows positional selectivity. In the dichlorobenzenes[281] and the chlorophenyl ethyl carbonates[282] the quantum yields vary in the order $o > m > p$; in the chloroanisoles and chloroanilines the order is $m > o > p$[281]. In the dichlorotoluenes, -anilines and -phenols positional selectivities are similar to those for the monochloro compounds[283]. The trichlorobenzenes show different positional selectivities for the singlet and triplet reactions. An illustrative example is 1,2,4-trichlorobenzene which gives mainly 1,4-dichlorobenzene on direct irradiation, but mainly 1,3-dichlorobenzene on sensitization[284,285]. Pentachlorobenzene yields 1,2,3,5-tetrachlorobenzene[286]. Polychlorodibenzo-*p*-dioxins are also selectively photoreduced. The 2-Cl is lost preferentially which means that the most toxic compounds are the most easily photolysed[287].

Inefficient reductive dehalogenation reactions such as those of 1-chloronaphthalene[272], chlorinated[276,288] and brominated[277] biphenyls and chlorinated terphenyls[280] are accelerated by the electron donor Et_3N. Thus, for example, the quantum yield of reduction of 4-chlorobiphenyl in an alkane solvent increases from 0.0006 to 0.083 by the addition of 0.15 M Et_3N[288]. These reactions occur by way of electron transfer via an exciplex intermediate (equation 87). For

$$^1ArX^* + Et_3N \rightleftharpoons [\text{exciplex}] \longrightarrow ArX^{-\cdot} + Et_3N^{+\cdot} \qquad (87)$$

1-chloronaphthalene[272] and the chlorinated biphenyls[276,288] it has been shown that the exciplex is formed from the singlet excited state. Exciplex fluorescence has been observed in a number of cases [272,276]. In accord with the mechanism, increase of the polarity of the medium increases the acceleration[272,288,289]. In systems where large amounts of biaryls are formed, their formation is suppressed upon the addition of amine[272,280]. In these cases reaction (87) competes with reaction (84) and so decreases the amount of $ArX^{+\cdot}$, which is responsible for the biaryl formation. Reductions that are already efficient are little accelerated or not at all by Et_3N. In that case reaction (87) cannot effectively compete with direct homolysis (equation 85) or the intersystem crossing preceding it. In the Et_3N-assisted reduction of the bromobiphenyls, the *ortho*-substituted compounds are the most reactive, just as in the direct photolysis which is assisted by the aryl bromide[277].

The fate of the $ArX^{-\cdot}$ depends on the reaction conditions and on the nature of the Ar group. In alkane solvents reaction (88) will occur. In media where protons are available, reaction (89) can compete with reaction (88) if the radical anions are

$$ArX^{-\cdot} \longrightarrow X^- + Ar^\cdot \xrightarrow{NEt_3 \text{ or } RH} ArH \qquad (88)$$

$$ArX^{-\cdot} + H^+ \longrightarrow [ArXH]^\cdot \longrightarrow ArH + X^\cdot \qquad (89)$$

sufficiently long lived[270]. For some aryl monochloro and monobromo aromatics deuterium incorporation is indeed observed in the reduced aromatic product when the irradiation is carried out in $CH_3CN/D_2O/Et_3N$[289]. The photoreduction of 9,10-dichloro- or 9,10-dibromoanthracene in *n*-heptane in the presence of alkyl or alkyl aryl amines is much more efficient with secondary than with tertiary amines. When R_2ND instead of

R_2NH is used, deuterated 9-X-anthracene is obtained[290]. The reactions quite probably proceed via reactions (87) and (89) with the radical cation of R_2NH as the proton source.

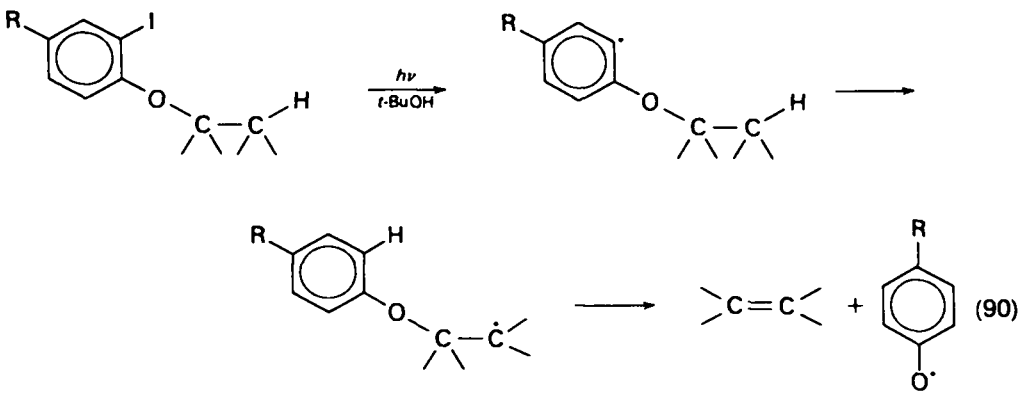
The amine-assisted reductions are sometimes accompanied by small amounts of substitution of X by R_2N—[290,291]. In the dimethylaniline-assisted reaction of halobenzenes, biphenyl formation (see Section IV.B.1) is as important as reduction to benzene[292,293].

Hydroxide ion can also act as an electron donor. The quantum yield of naphthalene formation in the irradiation of 1-chloronaphthalene in $MeOH/H_2O$ increases from 0.004 to 0.04 upon addition of 3 M KOH[291]. The regioselectivity in the dechlorination of polychlorinated biphenyls in alkaline alcoholic solution differs from that in neutral solution[279]. The difference is ascribed to steric and electronic factors in the radical anion formed in the former case versus steric factors in the triplet excited state in the latter.

Reductive dehalogenation of compounds that are not very reactive is also assisted by dienes[271,272,294,295]. This is at first sight surprising since dienes are well known quenchers of excited states, but it results from the diene acting as a donor. The reactions involve the singlet excited state of the aryl halides[272,295]. Fluorescence of an intermediate exciplex has been observed[295b]. With 1-chloronaphthalene and piperylene in methanol, formation of adducts can be rationalized as arising from attack of the solvent on the radical cation of the diene[272]. Also the formation of binaphthyl is again suppressed. For 9,10-dichloroanthracene and 2,5-dimethyl-2,4-hexadiene, it has been proven that the reduction involves protonation of the radical anion of the aromatic compound by the radical cation of the diene or by water if present[295]. The reaction in the presence of perdeuterodiene or D_2O affords 9-chloro-10-deuteroanthracene.

Bromide and iodide ions do not increase the rate of reduction; they decrease it in a series of triplet state reactions[296]. The authors suggest that these ions increase the rate of the $T_1 \rightarrow S_0$ transition by an external heavy atom effect[262].

A few synthetic applications have been reported[189,297]. An intramolecular hydrogen abstraction by an aryl radical formed by photolysis of an aryl halide, followed by loss of a stabilized radical (equation 90) provides a new method for the synthesis of



(90)

alkenes. The reaction must be carried out in a solvent with hydrogen atoms which are available only with difficulty, otherwise intermolecular hydrogen abstraction occurs. The method has been successfully used to introduce carbon-to-carbon unsaturation in a number of carbohydrates[297].

B. Arylation Reactions

1. Intermolecular arylation

Photolysis of aromatic halides in arene solvents produces biaryls. This reaction, already well established for iodo-[298] and bromobenzenes, has turned out to be a general process for chlorobenzenes as well. A variety of substituted chlorobenzenes gives the corresponding biphenyls upon irradiation in benzene[199]. Irradiation of neat mono- to tetrachlorobenzene yields polychlorobiphenyls with one Cl less than in the two molecules of starting material[300]. The arylation, which in some cases is accompanied by reductive dechlorination[261,299], is not successful when the chlorobenzene contains another aromatic moiety with a lower excited state energy than chlorobenzene. Due to intramolecular energy transfer 1-biphenyl-2-*p*-chlorophenylethanes and 1-naphthyl-2-*p*-chlorophenylethanes are photostable[261].

The mechanism of the reaction of halobenzenes PhX (X = Cl, Br, I) with arenes such as the halobenzenes, benzene and anisole is still adequately described by equations (91)–(93).

$$PhX \xrightarrow{h\nu} Ph^{\bullet} + X^{\bullet} \quad (91)$$

$$Ph^{\bullet} + ArH \longrightarrow [Ph{-}ArH]^{\bullet} \quad (92)$$

$$[Ph{-}ArH]^{\bullet} + X^{\bullet} \longrightarrow Ph{-}Ar + HX \quad (93)$$

New data supporting this mechanism are as follows:

(1) The isomer distribution of the biphenyls obtained on irradiation of aryl halides in monosubstituted benzenes is characteristic for radical reactions. Iodobenzene in fluorobenzene gives *o*-, *m*- and *p*-fluorobiphenyl in a 51:38:11 ratio[301]; with chlorobenzene in anisole the ratio is 56:20:24[299], and with neat chlorobenzene (at the lowest reported conversion) the ratio is ~1:1:1[302].

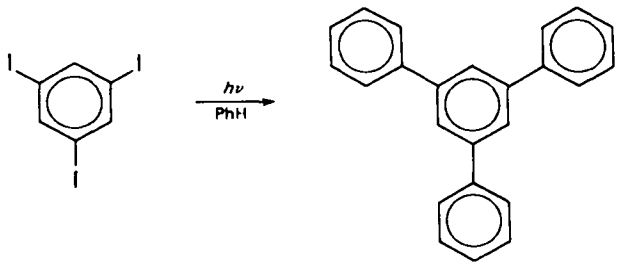
(2) The relative reactivity of attack on anisole and benzene during chlorobenzene photolysis is 2.3[299]. Thermally generated phenyl radicals show an (anisole:benzene) relative reactivity of 2.0.

(3) In di- and polyhalogenobenzenes the heavier of the two different halogens is selectively displaced, i.e. the weaker carbon–halogen bond is cleaved. *p*-Bromochlorobenzene gives 4-chlorobiphenyl[299], and pentachloroiodobenzene gives only 2,3,4,5,6-pentachlorobiphenyl[286,303], in benzene as a solvent.

(3) The presence of a radical scavenger (e.g. 2,2-diphenyl-1-picrylhydrazyl, DPPH) inhibits the biphenyl formation from polychlorobenzenes[300].

(4) The intermediate cyclohexadienyl radicals have been detected by flash photolysis. In the flash photolytic studies of 1,4-dibromobenzene and 4-bromobiphenyl in benzene[304] (equation 94), and 4-iodophenol in benzene[305], transient absorptions of the cyclohexadienyls **128** were observed. The absorptions decay in a second-order reaction. An excess of $Br^{\bullet}$ decreases the life time of the intermediate whereas use of perdeuterobenzene instead of benzene increases the life time[304]. In the latter study the transient absorption of $I^{\bullet}$ (complexed to benzene) was also observed[305].

$$ArBr \xrightarrow{h\nu} Ar^{\bullet} + Br^{\bullet} \xrightarrow{PhH} \underset{\textbf{(128)}}{\overset{H}{\underset{Ar}{\bigcirc}}} \xrightarrow{Br^{\bullet}} Ar{-}Ph \quad (94)$$



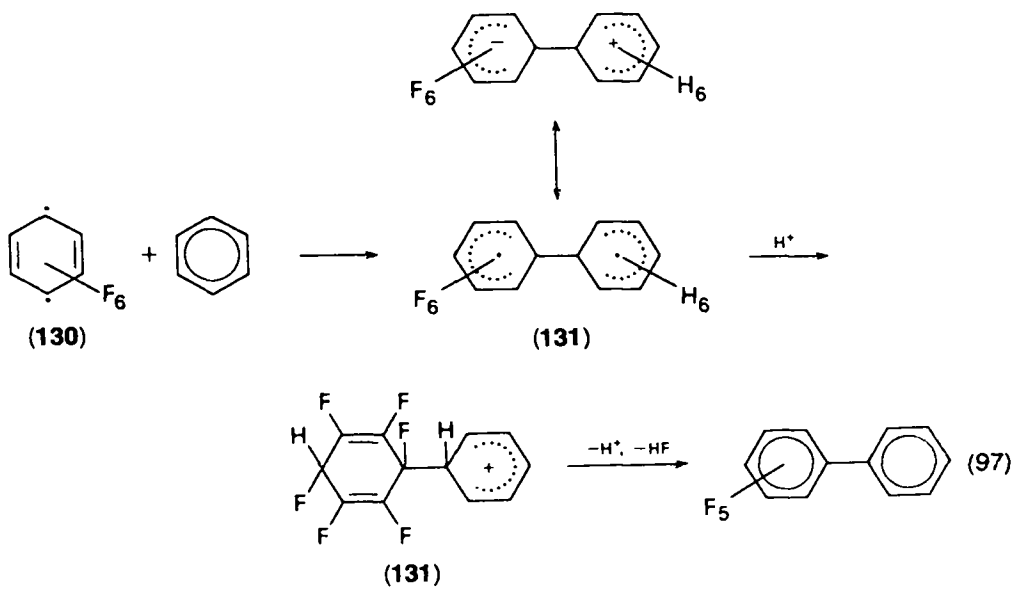
(95)

(129)

Intermolecular arylation is a particularly useful method of aryl–aryl bond formation in the synthesis of polyphenylated compounds. As an example, 1,3,5-triphenylbenzene (**129**) is formed in 79% yield from 1,3,5-triiodobenzene[306] (equation 95). Hexafluorobenzene also reacts photochemically with benzene to produce predominantly 2,3,4,5,6-pentafluorobiphenyl (equation 96)[307]. With toluene, a

$$C_6F_6 + C_6H_6 \xrightarrow[(254\ nm)]{h\nu} C_6F_5{-}C_6H_5 + HF \qquad (96)$$

mixture of *o*-, *m*- and *p*-pentafluorophenyltoluenes is formed in a 1.3:1.05:1.0 ratio. Similar ratios are obtained when $C_6F_5^{\bullet}$ is generated thermally from the corresponding benzoyl peroxide or photochemically from C_6F_5I[308]. However, involvement of the $C_6F_5^{\bullet}$ radical in reaction (96) is quite unlikely. The energy of excitation is considerably lower than the energy required for homolysis of the C—F bond (Table 1). Moreover, the reaction is very sensitive to solvent polarity and the presence of proton donors, unlike the reactions of the halides described above. The authors suggest that the reactive species is triplet C_6F_6 which is essentially the biradical (**130**) which mimics the behaviour of $C_6F_5^{\bullet}$ (equation 97). The resulting polarized diradical, **131**, will be stabilized by a polar medium. A sequence of protonation, deprotonation, and loss of HF are proposed to account for the product.

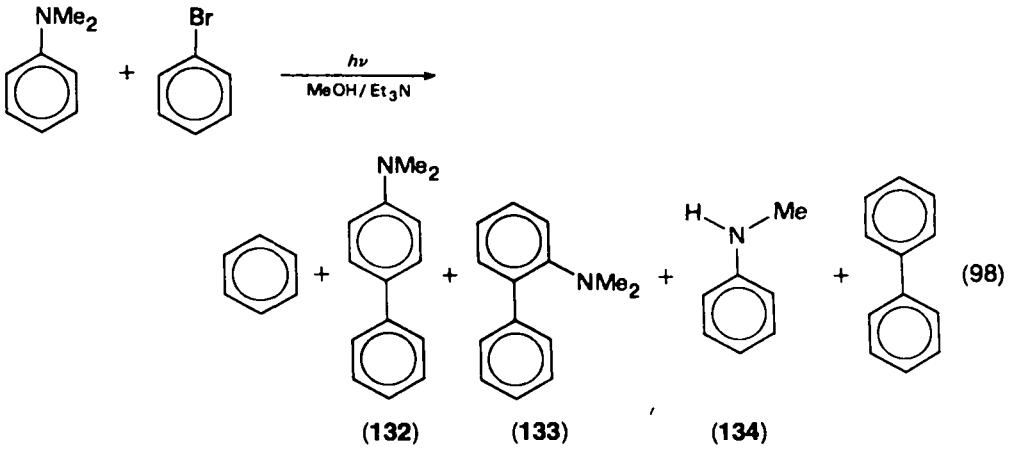


(130) (131)

(97)

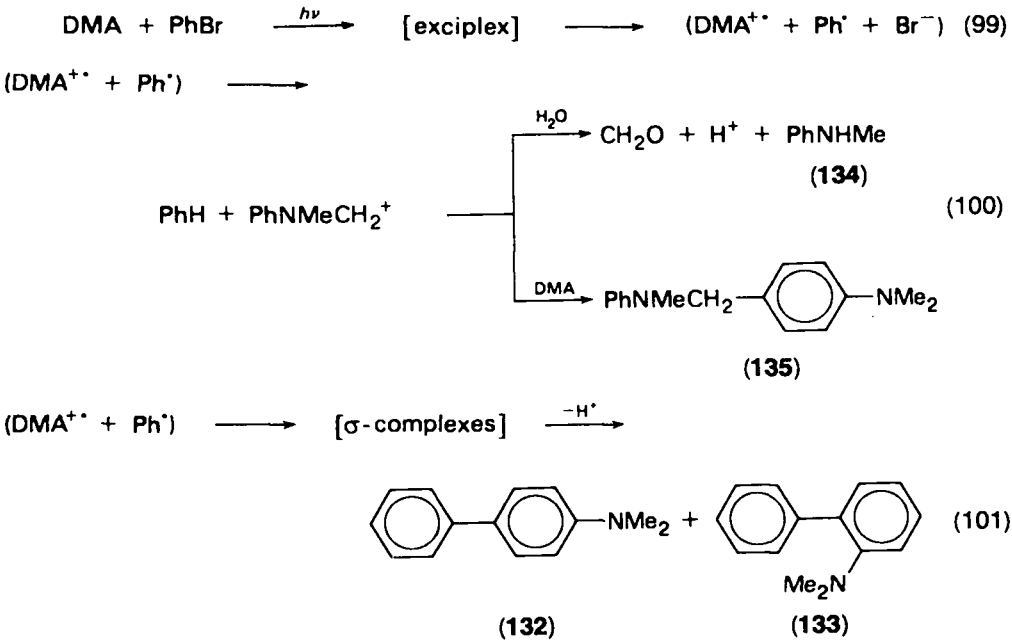
(131)

The scheme of reactions (91)–(93) also does not apply for the irradiation of aryl halides in the presence of very electron-rich arenes such as *N*,*N*-dimethylaniline (DMA) in a solution of methanol/triethylamine (equation 98)[292], or without solvent[293].



(132) **(133)** **(134)**

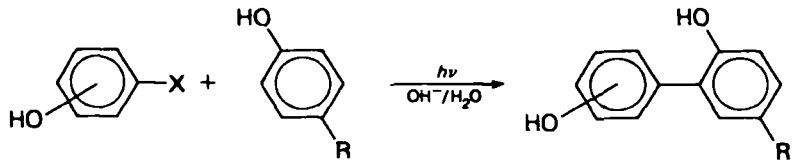
This reaction, in which benzene and the *p*- and *o*-dimethylaminobiphenyls **132**, and **133** are the main products, appears to involve electron transfer from the *N*,*N*-dimethylaniline to bromobenzene, leading to the DMA radical cation and the bromobenzene radical anion. The anion will immediately decompose into phenyl radical and Br^- (equation 99) (see Section IV.A). In a cage the phenyl radical will



abstract hydrogen from the DMA radical cation, leading to benzene and **134** and at very high concentration of DMA also to **135**[293] (equation 100) or react with the radical cation to form **132** and **133**, (equation 101). Alternatively, **134** may be formed

by acid-catalysed decomposition of **135**[293]. A possible major pathway in which the phenyl radical first escapes from the cage and then reacts appears unlikely for two reasons: the benzene formed contains a high percentage of C_6H_5D when *N,N*-di(trideuteromethyl)aniline is used instead of DMA[292] and no *meta* substitution is found. A free phenyl radical would abstract hydrogen mainly from the solvent and react mainly with DMA (giving a *meta* substitution product as well as the *ortho* and *para* derivatives). The electron transfer occurs via an exciplex, the fluorescence emission of which has been observed in a solution of DMA in bromobenzene[292].

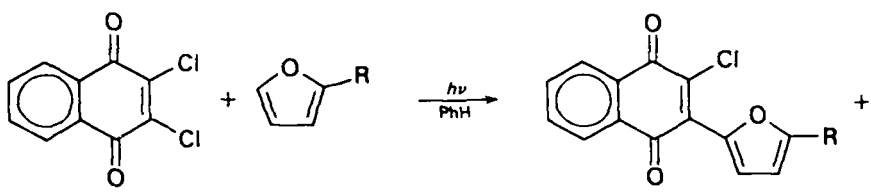
Quite probably the formation of dihydroxybiphenyls upon irradiation of *p*-halophenols in the presence of an excess of *p*-substituted phenols in alkaline solution (equation 102)[309] also occurs via this mechanism. Only substitution *ortho* to the OH



(102)

group is found. The reaction of tetrachlorophthalonitrile with anisole producing the 2'- and 4'-methoxy-2,3,5-trichloro-4,5-dicyanobiphenyls[310] presumably also occurs by way of electron transfer. In this case no concurrent reductive dehalogenation is found, indicating that with a more stable radical anion coupling with the radical cation to form an intermediate analogous to **131**, can compete effectively with decomposition into an aryl radical and Cl^-. Alternatively a direct coupling route from the substrates to the intermediate, without intervention of discrete radical ions, may be operative.

Haloquinones such as **136** react with the electron-rich furan to form the 2-furylnaphthoquinones **137** (equation 103)[311]. The initial formation of a charge

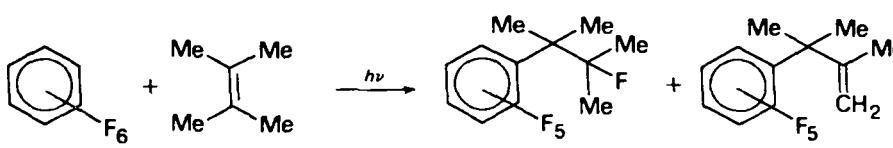


(103)

(136) **(137)**

transfer complex is essential for the reaction. In ^{1}H-CIDNP spectra strong polarized signals are observed suggesting that the charge transfer state decays to **137** via a radical (ion) pair.

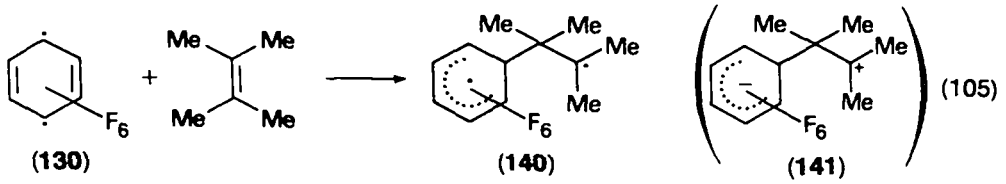
In special cases alkenes are also photoarylated. Irradiation of hexafluorobenzene in the presence of the electron donor alkene 2,3-dimethylbut-2-ene affords both **138** and **139** as primary products of the reaction[312] (equation 104). In contrast to the reaction



(104)

(138) **(139)**

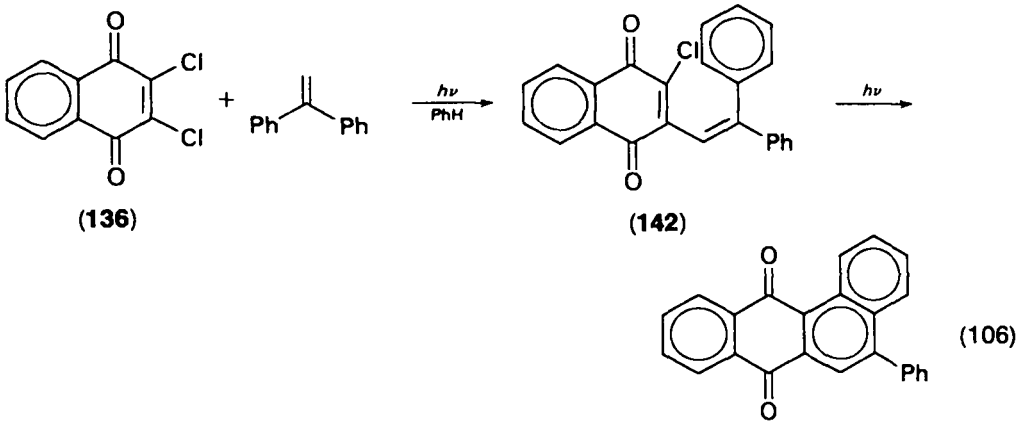
of C_6F_6 with benzene (equation 96), proton donors and a polar medium have hardly any effect. This suggests that a biradical (**140**) rather than a zwitterionic intermediate (**141**) (equation 105) is involved. Reactions of the monohalogenobenzenes with



(130) (140) (141) (105)

cyclopentene also give products derived from insertion into the C—X bond[313]. For example, chlorobenzene yields 60% of a mixture of *cis*- and *trans*-2-chloro-1-phenylcyclopentane. With electron-deficient alkenes such as maleic anhydride and maleimide, C_6F_6 only forms 2:1 photocycloadducts[312]. Fluoro-, chloro- and bromobenzene also give only cycloadducts and no arylation products with these alkenes[314].

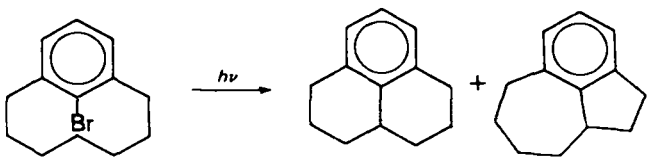
Quinones such as **136** react with 1,1-diphenylethene[315] (equation 106). 1,1-Diphenylethene easily forms radical cations with electron-poor photosensitizers[316], and the reaction pathway appears to involve ions rather than radicals, since with 1,1-dicyclopropylethene as the alkene, an analogue of **142** is



(136) (142) (106)

produced with no opening of the three-membered ring[317]. If a radical at the cyclopropylcarbinyl carbon is formed, opening of the three-membered ring would be expected. A similar reaction is also reported for 1-phenyl-1-(2-thienyl)ethylene[318] and 1-phenyl-1-(2-*N*-methylpyrrol-2-yl)ethylene[319]. As the products (**142**) easily photocyclize (see Section IV.B.2) and actually do so under the reaction conditions, the sequence of equation (106) forms a facile entry to a large series of polycyclic aromatic hydrocarbons[320].

Alkanes may also be arylated. In the direct irradiation of aryl halides in alkane solvents small quantities of alkyl arenes are sometimes formed[275,280]. This formal reverse Friedel–Crafts type reaction is an important process if proximate transannular hydrogens are available. **143** gives **144** and **145** in a 1:1 ratio in 86% yield[321] (equation 107). Intermolecular substitution of a hydrogen atom on a saturated carbon by an aryl group is a major reaction in the direct irradiation of tetrahalophthalonitriles in ethers[322], and in the sensitized irradiation of C_6F_6 in methanol[323] and cyclohexane[324]. In the first reaction, which presumably involves electron transfer, the 4-X-substituent is replaced by an α-alkoxyalkyl group; in the latter reactions a hydroxymethyl and a cyclohexyl radical, respectively, resulting from hydrogen abstraction from the solvent by the sensitizer, attack C_6F_6 yielding $C_6F_5CH_2OH$ in 48% yield and $C_6F_5—C_6H_{11}$ in 61% yield, respectively.

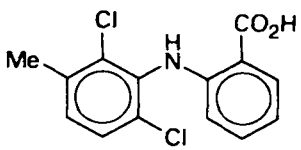


(143) (144) (145) (107)

2. Intramolecular arylation

In suitable aryl halides intramolecular photoarylation[497] may occur. This photochemical cyclodehydrohalogenation is a useful alternative to other methods of aryl–aryl bond formation[325] and has been used extensively in the synthesis of alkaloids. Reactions forming rings from five up to 13 members have been described.

In systems where two aryl groups are connected by a single atom (—CH_2—[326], —NH—[327], —O—[328]), five-membered rings are formed. Thus, for instance, the anthranilic acid derivative **146** yields the carbazoles **147** and **148** in a 1:1 ratio[327] (equation 108). An aryl halide moiety connected through a single atom to a polycyclic aromatic hydrocarbon can give a six- or a five-membered ring on closure[329–331]. The benzoylindole **149** gives only **150** and no **151**[330] (equation 109).



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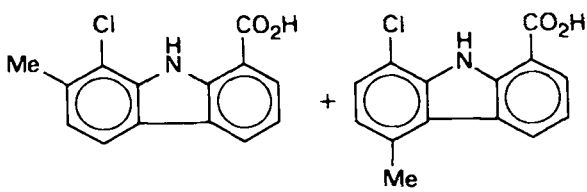
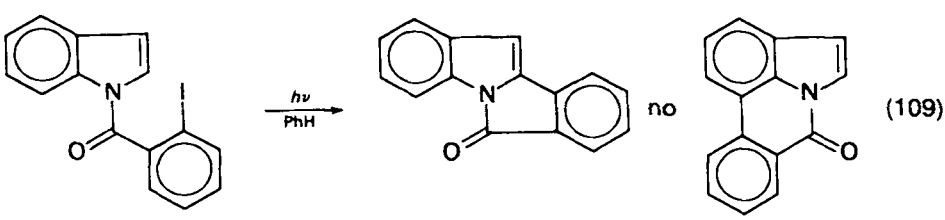
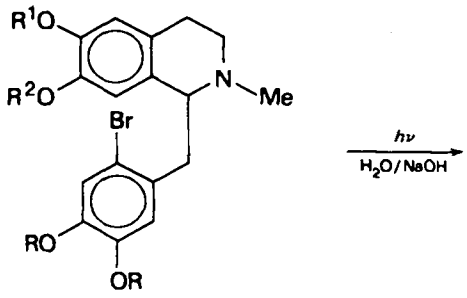


(147) (148) (108)



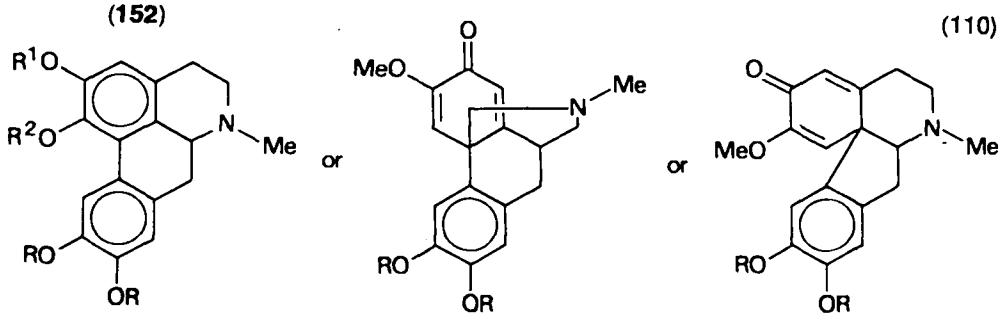
(149) (150) (151) (109)

Ring closure in the 1-(2-X-benzyl)tetrahydroisoquinoline system **152** has been successfully applied as the key step in the synthesis of isoquinoline alkaloids[332]. The presence of OH groups in the isoquinoline ring has a profound influence on the course of the reaction in alkaline solution. This was recognized in the early work[332] and has been confirmed by further examples. Compound **152** ($R^1 = R^2 = Me$) gives the apoporphine **153** ($R^1 = R^2 = Me$). A 7-OH group (**152**, $R^1 = Me$, $R^2 = H$)



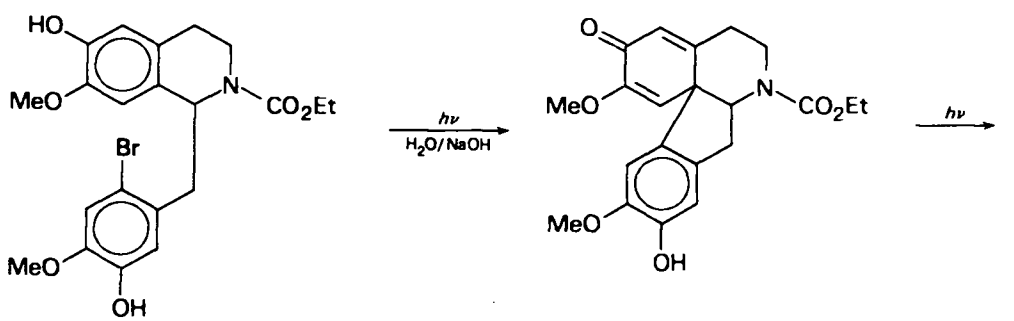
(152)

(110)

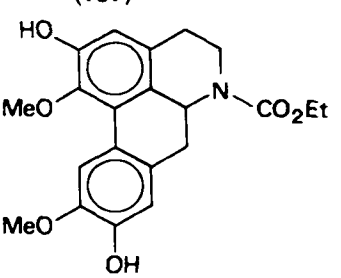


(153) (154) (155)

facilitates[333] the closure to **153** (R^1 = Me, R^2 = H) but now attack *para* to the OH group also occurs, yielding the morphinandienone alkaloid **154**[334]. A 6-OH group in **152** (R^1 = H, R^2 = Me) directs the attack to its *para* position, yielding the dienone



(156) (157)



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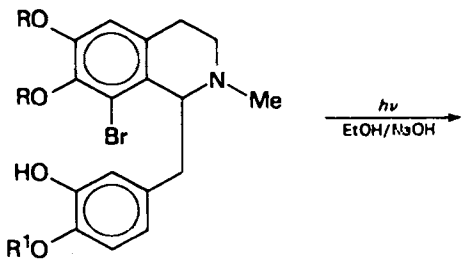

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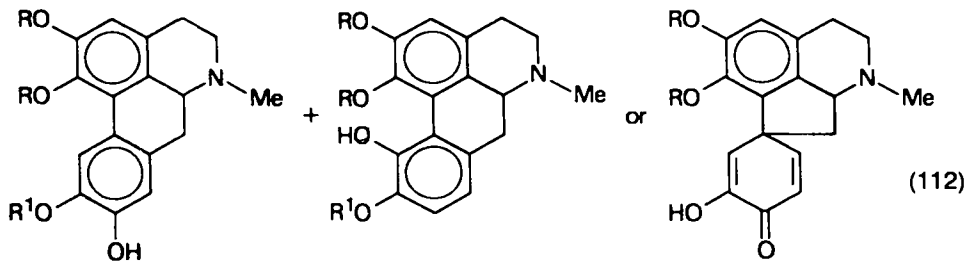


(112)

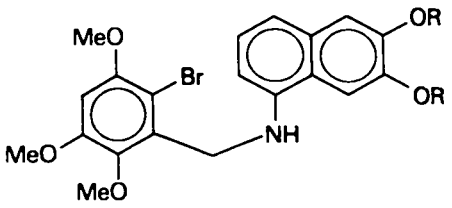
(160) (161) (162)

alkaloid **155**[335]. The formation of the apoporphine boldine (**158**) from **156** is actually a two-step photochemical process via the spirodienone **157**[336]. Parallel phenomena are observed in the 8-bromoisoquinoline systems **159**: **159** (R^1 = Me) yields the aporphines **160** and **161** and **159** (R^1 = H) gives the proaporphine **162**[337]. Reactions (110)–(112) form an intramolecular version of the intermolecular coupling of halogenophenols in alkaline medium yielding dihydrobiphenyls (Section IV.B.1). Although the mechanisms of these reactions have not been investigated, quite probably electron transfer from the phenolic moiety to the aryl halide part is involved. This would explain the activating and *ortho/para*-directing influence of the O^- group. A large influence of the OH group would on this basis not be expected and, indeed, has not been found. For the nor-analogues of compounds **152** and **156**, which are irradiated as their hydrochloride salts according to the method of Kupchan[338], only aporphine skeleton (nor-**153**) formation is reported[339].

The intramolecular counterpart of reaction (**98**), for which an electron transfer mechanism has been established[292,293], has also been studied[340,341]. In line with an electron transfer mechanism, **163** having a naphthylamine moiety of low ionization potential gives a high yield of the phenanthridine **164** (equation 113). Alkoxy substituents in the naphthyl moiety accelerate the reaction[341].

Extension of the connecting chain of compounds such as **152** and **156** by an additional one $-CH_2-$ unit causes the corresponding homologous alkaloids to form by photocyclodehydrohalogenation[342,343]. Systems such as **165**[344] and **166**[345] also photocyclize (equations 114 and 115). Again a strong directing effect of the O^- group is observed. Medium-size ring formation also occurs in more simple systems[346,347]. As an example, irradiation of the hydrochloride salt of **167** (n = 1, 2) produces the dibenzazepine **168**, (n = 1) in 57% yield or the dibenzazocine **168** (n = 2) in 33% yield[347] (equation 116).

Conjugation between the two aromatic moieties along an unsaturated connecting chain (—CH=CH—, —CH=N—, —CONH— or —N=N—[348]) introduces the



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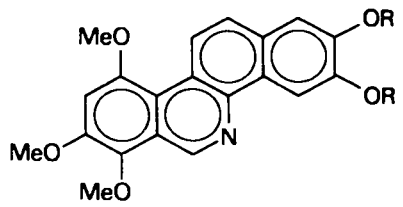
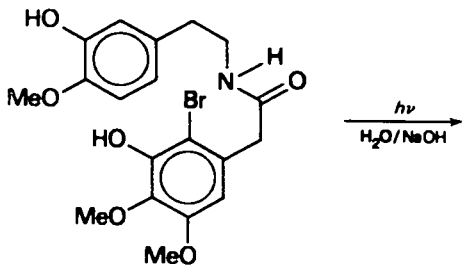
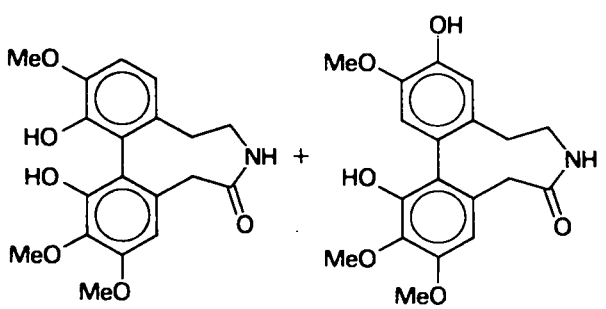


(164) (113)



(165)



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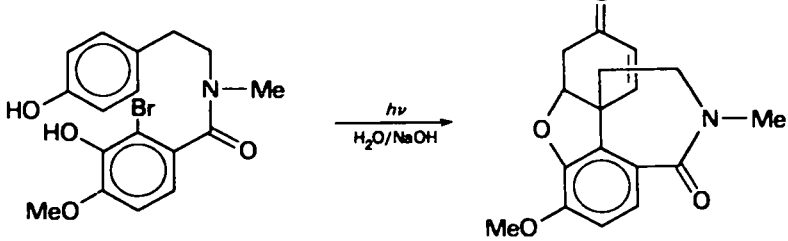
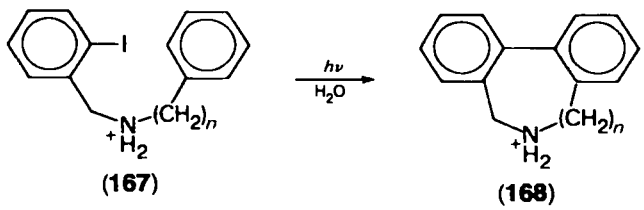
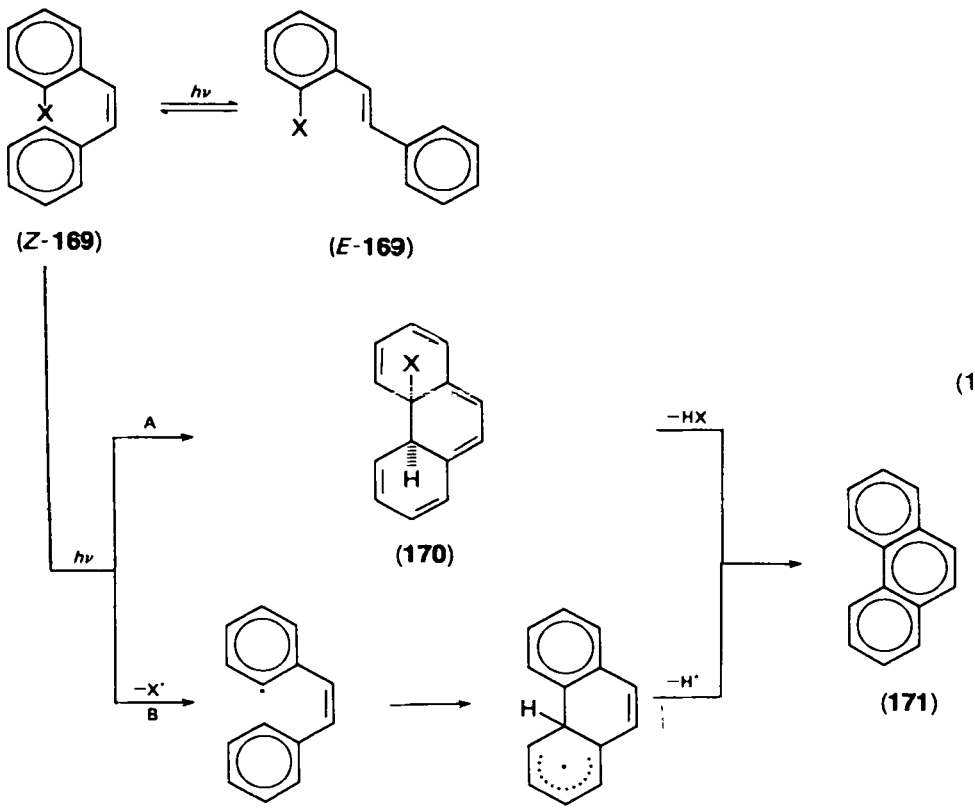


(166) (115)



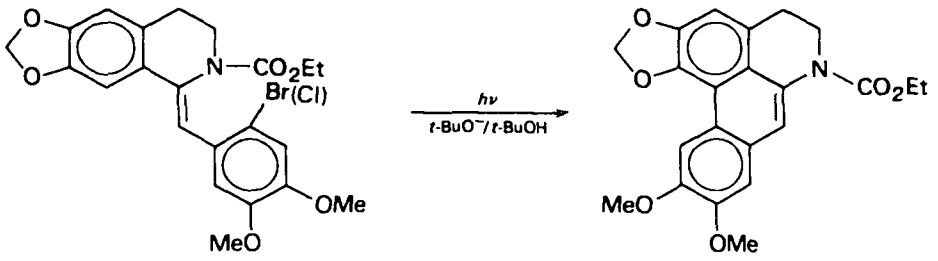
(116)

possibility of alternative mechanisms. Depending on the strength of the C—X bond the stilbene **169** may yield the phenanthrene **171** via electrocyclization to **170** followed by elimination of HX (route A), or via homolytic C—X bond cleavage and subsequent radical substitution (route B) (equation 117).



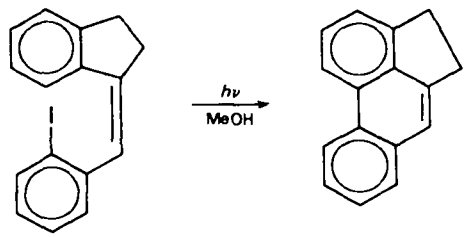
(117)

For X = Br or Cl, the presence of a strong base greatly improves the reaction, suggesting that route A is the important one. A case in point is aporphine **173** which is produced from **172** in much higher yield (72%) in the presence of potassium *tert*-butoxide than in the presence of calcium carbonate (24%)[349] (equation 118). In the former case the *tert*-butoxide causes the presumed *trans* dihydrophenanthrene subunit of the intermediate (analogous to **170**) to undergo a smooth *E*2 elimination. The possibility of a nucleophile-induced homolysis (see Section IV.A) by the *tert*-butoxide, however, is not excluded by the available evidence. The methodology has been successful in the synthesis of a number of aporphines[350], a dioxoaporphine[351] and steganone[352].



(172) (173) (118)

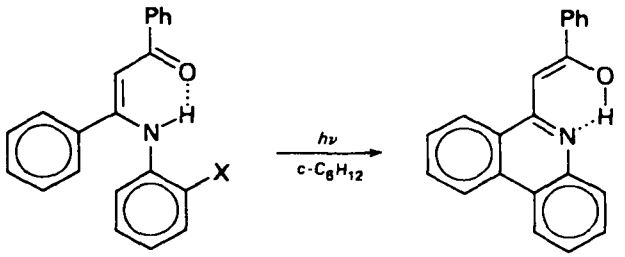
For X = I route B is followed. As the radical substitution process is less restrictive in ring formation than the electrocyclization, it is possible to cyclize systems with X = I that fail to react with X = H[353–355]. For example, compound **174** gives a fair yield of acephenanthrene (equation 119) whereas the parent benzylideneindane does not



(174) (119)

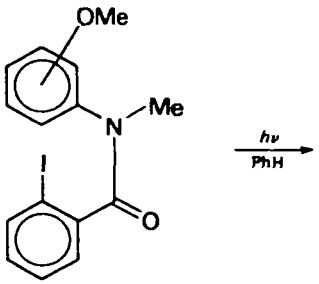
photocyclize[354]. With stilbene-like systems, which can undergo photoelectrocyclization in competition with cyclization via homolytic cleavage of the C—I bond, the iodo group does not direct cyclization selectively to the carbon atom carrying the I; products resulting from arylation at both the 2- and the 6-position are obtained[356].

The ring closure is not successful in systems such as benzylidene anilines in which the *Z* isomer cannot be populated. This difficulty can be overcome by forcing the system into the right geometry by incorporating the —C=N moiety in a ring[357] or by derivatizing it as in **175** with a configuration-holding hydrogen bond (equation 120). In the latter case the derivatizing moiety is easily removed after the photocyclization[358].

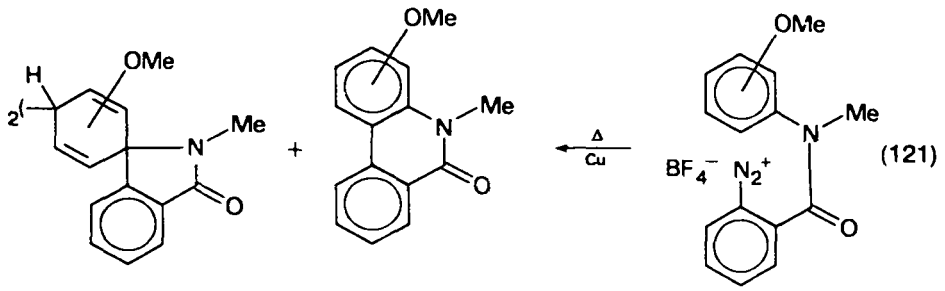


(175) (120)

The mechanistic dichotomy in the behaviour of iodo- versus bromo- or chlorostilbenes is also observed in the ring closure reactions of iodo- and bromobenzamides. The photolysis of **176** yields the same products in a ratio similar to that given by the thermal decomposition of the corresponding diazonium salt **177**[359], a process known to involve a phenyl radical (equation 121). On the other hand, the



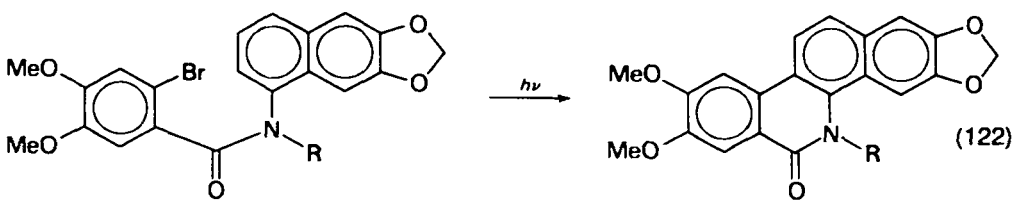
(176)



(177)

(121)

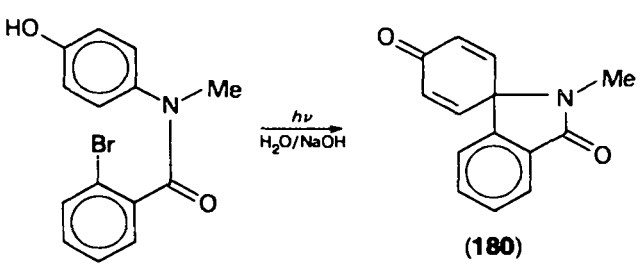
closure of **178** to the phenanthridone **179**[360,361], which is efficient photochemically (equation122), does not occur when the radical is generated electrochemically from



(178) (179)

(122)

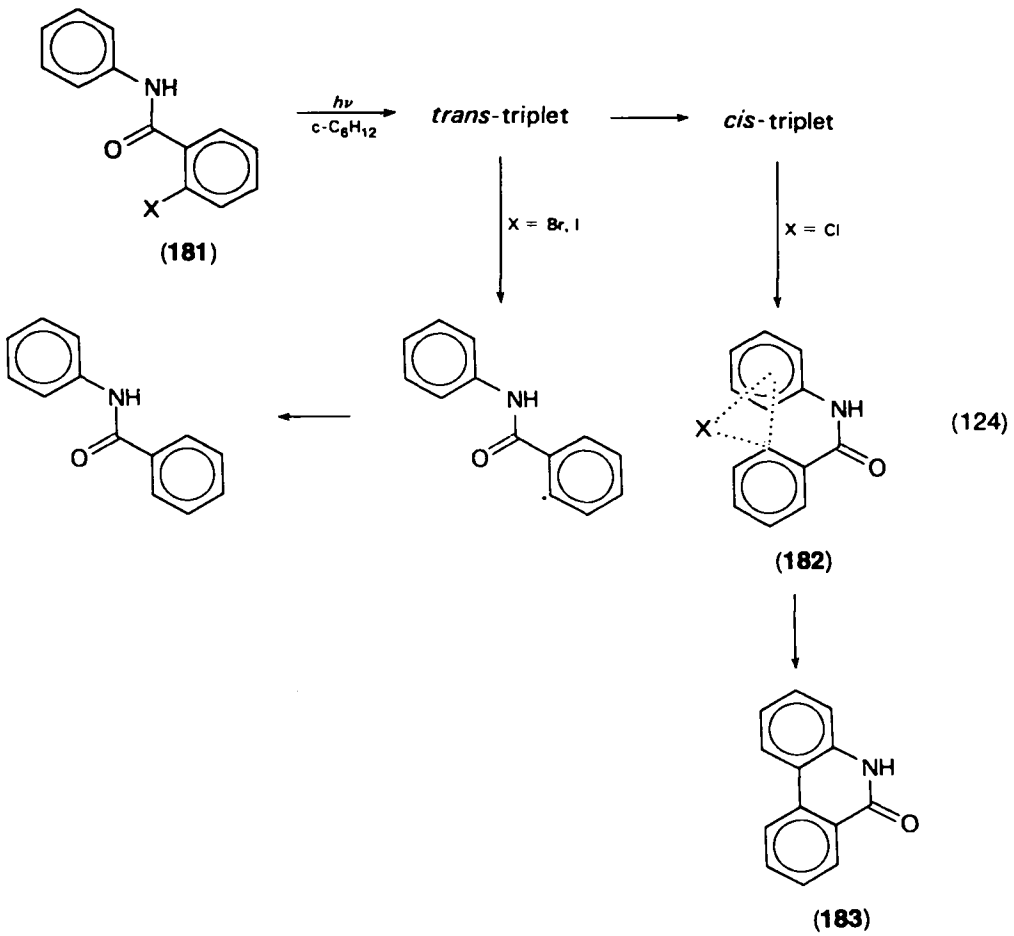
178[361]. This could suggest that route A of equation (117) is followed. The reaction could also, however, be of the electron transfer type, in which case the comparison between the behaviour of the electrochemically generated radical and the photoresults is not necessarily valid. With a 4'-OH group in the benzamide, no 'electrocyclization' product is found; instead attack occurs *para* to the O^- group (equation 123)[362]. The yield of **180** is greatly improved by carrying out the reaction with sodium amide in DMF or HMPA[363].



(180)

(123)

Contrary of the situation in *N*-methylbenzanilides, the *Z* configuration is only populated to a minor extent in benzanilides. The yields of cyclization are therefore often quite low. Polar solvents and the presence of HO and O^- groups increase the yield[364,365]. Compound **181** (X = Br, I) gives only reduction in cyclohexane, and **181** (X = Cl), interestingly enough, gives a high yield of phenanthridone **183** and no reduction whatsoever (equation 124)[366]. The authors propose that, in view of the

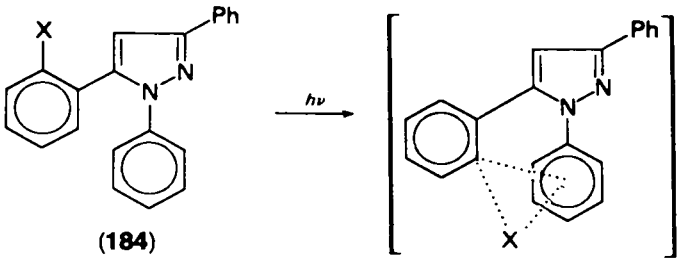


(181) (182) (183) (124)

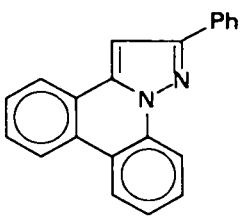
C—Cl bond strength and the energy content of the excited state, C—Cl bond homolysis requires assistance from π complexation of the developing Cl radical. Complexation can only occur in the *cis* configuration leading to exclusive cyclization of the chloride via **182**. For **181** (X = Br, I) unassisted homolysis from the *trans* configuration can occur.

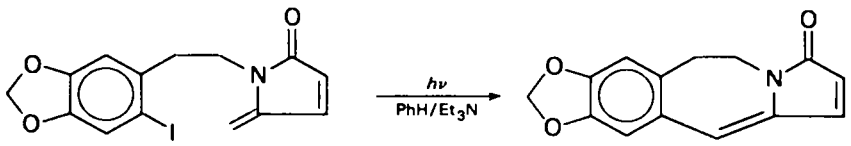
A mechanism of assisted homolysis has also been proposed[367] for the closure of **184** (X = Cl, Br, I) (equation 125)[368]. The chloro compound cyclizes faster than the iodo compound, and no reduction is observed for any of the halides.

Intramolecular arylation of a carbon–carbon double bond has also been used successfully in the synthesis of alkaloids[227,369–374]. In the available examples, the C=C bond is part of an enamine. Thus, for instance, photolysis of the enamide **185** affords a



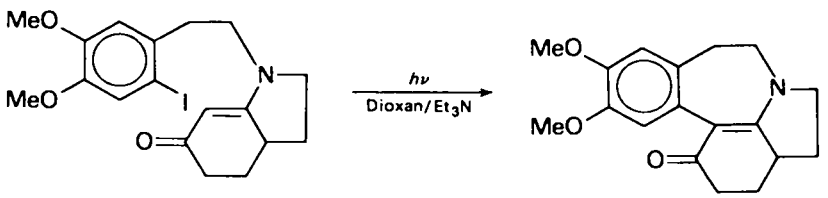
(184) (125)





(185) (186) (126)

46% yield of **186** (equation 126), an advanced synthon for cephalotaxus alkaloids[371]. The enamino ketone **187** gives the tetracyclic azepine **118** in 50% yield (equation 127)[227].



(187) (118) (127)

C. Nucleophilic Aromatic Substitution Reactions

Many of the reductive dehalogenation reactions of aryl chlorides described in Section IV.A are accompanied by the formation of minor amounts of substitution products when photolysis is carried out in nucleophilic solvents. It has been proposed[272,375] that reduction and substitution are not independent processes but are mechanistically linked. In the case of chlorobenzene a pair of radical ions is produced via a triplet excimer (equation 128)[375]. The radical anion will lead to reduction in the usual fashion and the radical cation to substitution via attack of the nucleophilic solvent (equation 129) (see below). Reactions occurring via the mechanism of

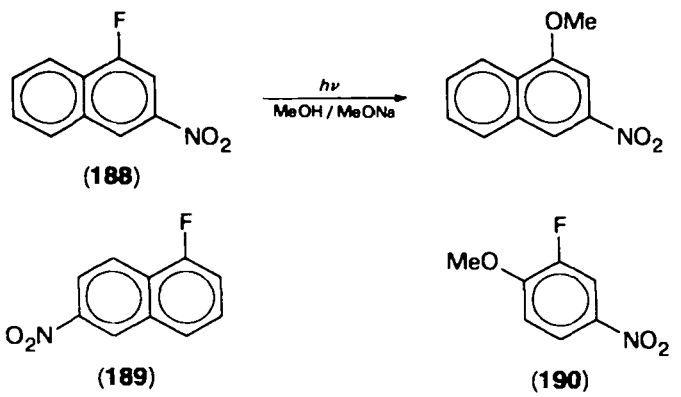
$$ArCl^* + ArCl \rightleftharpoons \text{excimer} \longrightarrow ArCl^{+\cdot} + ArCl^{-\cdot} \quad (128)$$

$$ArCl^{+\cdot} \xrightarrow{ROH} ArOR \quad (129)$$

equations (128) and (129) should show a dependence on the concentration of the aryl halide. This conclusion is supported by the fact that chlorobenzene at 6×10^{-2} M[375] gives photosubstitution in methanol (albeit with low efficiency) but does not do so at 10^{-3}–10^{-4} M[376]. A similar concentration dependence is known for fluorobenzene[376,377] and the fluoronaphthalenes[271,378], for which substitution is the only reaction.

With substrates or reaction conditions more amenable to substitution, much more efficient reactions are obtained. Different characteristic behaviour is observed, depending on the presence of extra substituents on the aryl halide, and the nature of the nucleophile and the solvent. Analogous behaviour is found for other nucleophilic aromatic photosubstitutions[379] in which halogen is not the nucleofugic group; the differences result from the occurrence of different mechanisms[380–382].

In one category, the presence of a nitro group in the aryl halide has an activating and *meta*-directing effect. All of the 12 fluoronitronaphthalenes investigated are more reactive than the fluoronaphthalenes, but only the *meta*-substituted **188** and the extended *meta*-substituted **189** give highly efficient ($\phi \simeq 0.3$) replacement of F upon irradiation in the presence of methoxide ions, hydroxide ions and methylamine[378,383] (e.g. equation 130). Delineation of the rate constants that constitute the quantum

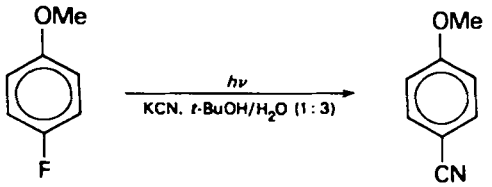


(130)

yields shows that the rates of reaction of the triplet excited states of compounds **188** and **189** with nucleophiles (Nu) are indeed very high[384]; e.g. the rate of reaction of the triplet of **188** with OH^- is 1×10^8 l mol^{-1} s^{-1}. The *meta* activating effect of the nitro group is also manifested in the photolysis of **190** in H_2O or H_2O/OH^-; only substitution of fluorine is observed[385]. These compounds react according to the mechanism described in equation (131), the so-called S_N2 ^{3}Ar*mechanism[381]. The presence of the nitro group is proposed to facilitate the transition from the excited state surface to the σ-complex on the ground state surface by decreasing the energy gap between these surfaces, especially in the *meta* case[382].

$$^3ArX^* + Nu^- \longrightarrow [ArNuX]^- \longrightarrow ArNu + X^- \qquad (131)$$

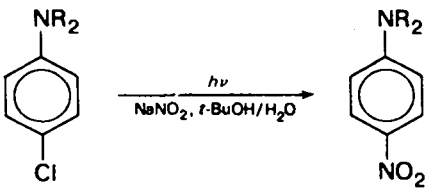
In a second major category, the presence of an electron-donating substituent such as $-OCH_3$, $-O^-$ or $-NH_2$ ($-NR_2$) in the aryl halide has an activating and generally *ortho/para* directing influence on nucleophilic substitution reactions in aqueous organic media. Thus, for example, only 2- and 4-fluoroanisole give efficient substitution of the fluoro group by CN^- in aqueous *tert*-butyl alcohol (equation 132), whereas in the 3-isomer almost exclusive replacement of an *ortho* or *para* ring hydrogen atom by the nucleophile occurs[386]. Likewise, in the reactions of the isomeric



(132)

$\phi_{lim} = 0.5$

monochloroanilines or *N*-alkylated derivatives with NO_2^- in aqueous methanol or *tert*-butyl alcohol (equation 133), the chemical yields and quantum yields of

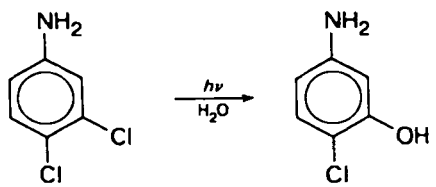


(133)

$\phi_{lim} = 0.33$

substitution vary in the order *para* > *ortho* ≫ *meta*[387–390]. The same order of reactivity has been observed with CN^- [388,391] and SO_3^{2-} [390,392] as the nucleophile. The photosubstitution of chlorine also occurs with $S_2O_3^{2-}$ [393] and SCN^- [388,394]. The authors presume that an electronically excited state of $\pi-\pi^*$ character is necessary for the reaction to occur on the basis that introduction of a nitro group in the haloaniline inhibits the substitution, while introduction of a cyano or a methylsulphonyl group does not[395]. The activating and *ortho/para* directing effect of the amino group has also been observed in halonaphthalenes[396].

In contrast to the behaviour of the monochloroanilines, of the isomeric monochlorophenols in aqueous alkali, the *meta* isomer affords by far the highest yield of dihydroxybenzene[397]. Also in contrast, irradiation of 3,4-dichloroaniline (**191**) in water results in substitution of the chlorine atom *meta* to the amino group (equation 134)[398]. Compound **191** has, however, also been reported to yield 3,4-dicyanoaniline



(134)

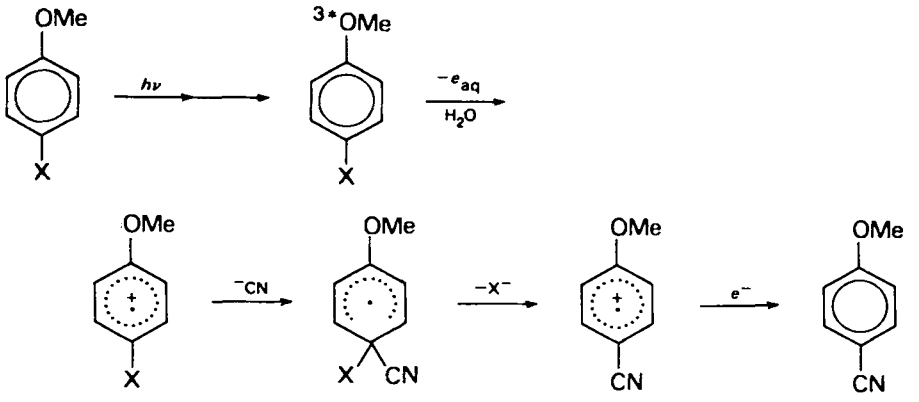
(**191**) $\phi = 0.052$

via 3-chloro-4-cyanoaniline upon irradiation in 0.1 M KCN in 43% aqueous *tert*-butyl alcohol[399]. For a series of dichloroanilines, the order of reactivity in substitution of the chlorine by CN^- in *tert*-butyl alcohol/water is *o* > *p* > *m*[399].

The quantum yields of substitution of the 4-halogenoanilines and of the 4-halogenoanisoles decrease in the order F ~ Cl > Br > I. Reductive dehalogenation becomes dominant with the heavier halogens. In mixed dihalogenoanilines, however, the heavier halogen is substituted first. In addition, only a small amount of monosubstitution product is found compared to the amount of disubstitution product[399]. This situation is reminiscent of the reactions of dihalogenobenzenes

according to the $S_{RN}1$ mechanism (see below) and may indicate that similar reaction steps are involved.

Despite their overt similarities, detailed studies of reactions (132) and (133), indicate that they involve different mechanisms. Reaction (132) has been proposed to proceed via the formation of a radical cation from the triplet excited state of the aromatic compound, a so-called $S_{R+N}1$ $^3Ar^*$-type mechanism (equation 135)[386]. This



(135)

(192)

conclusion stems from the fact that anodic cyanation in which the intermediacy of radical cations is generally accepted of the isomeric fluoroanisoles yields the same products in the same ratio as does the photoreaction. Also the quantum yield of reaction (132) increases strongly with increasing water content of the water/*tert*-butyl alcohol solvent. Moreover, transient absorptions of a solvated electron and a radical cation, whose life time is decreased by addition of cyanide ion, are observed by laser flash photolysis[382,386]. The donor substituent facilitates the reaction by lowering the ionization potential of the aryl halide, and the water-rich medium provides the necessary solvation energy for the electron and the ions formed. The *ortho/para* directing effect of the methoxy group agrees with the calculated charge densities in the radical cations. At high substrate concentrations, the product radical cation, $ArNu^{+\bullet}$ (**192**) may abstract an electron from the starting material (equation 136),

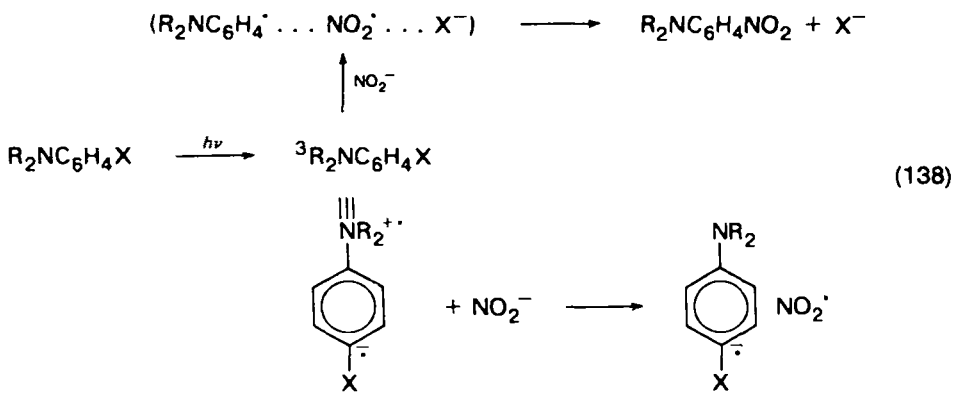
$$ArNu^{+\bullet} + ArX \longrightarrow ArX^{+\bullet} + ArNu \qquad (136)$$

making a chain reaction possible. The quantum yield of the photocyanation of 4-chloroanisole has been found to increase with increasing substrate concentration and at high concentrations to exceed unity[382].

For reaction (133) it is concluded that a radical cation is not significantly involved[400,401]. Irradiation of the isomeric chloroanilines in the presence of electron acceptors causes mainly substitution of a ring hydrogen by a nitro group rather than substitution of halogen as in the direct photoreaction[400]. The authors assume reaction (137) to operate under these conditions. Radical cation formation is observed in the

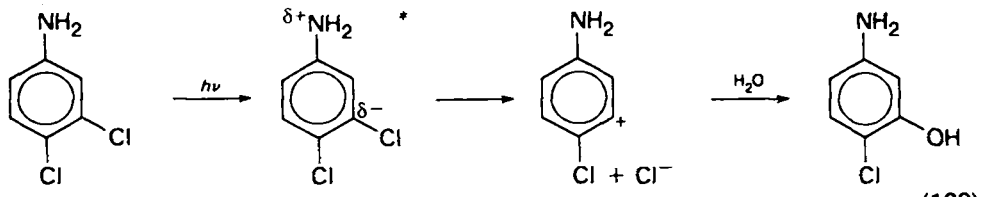
$$ClC_6H_4NR_2 + Ar_2C{=}O \xrightarrow{h\nu} ClC_6H_4NR_2^{+\bullet} + ArC{=}O^{-\bullet} \qquad (137)$$

flash photolysis of the reaction mixture of equation (133) but with a lower quantum yield than that of product formation. The accumulation of the nitro product is faster than the decay of the radical cation in the presence of nitrite ions[401]. The reactive triplet excited state is proposed to act as an electron acceptor and not as a donor (equation 138)[391].



(138)

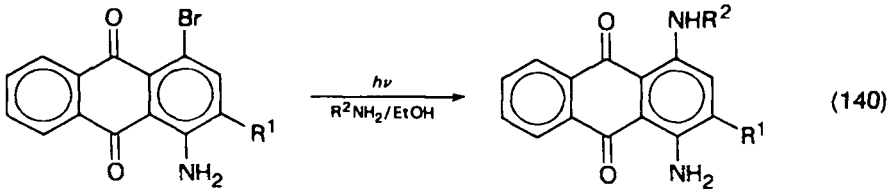
Reaction (134) and others in which a *meta*-directing effect is found are suggested to proceed via an aryl cation intermediate produced from the singlet excited state by heterolytic cleavage of the *meta* C—Cl bond[398] (equation 139). The cleavage is



(191) (139)

induced by the large electron density on the *meta* carbon. The reaction appears to require a high concentration of water in the solvent. The presence of neither hydroxide ions nor cyanide ions affects the rate of photolysis. 3-Chlorophenol in 0.35 M cyanide affords large amounts of resorcinol and only a small amount of 3-cyanophenol[397]. Added nucleophiles apparently cannot compete with the large concentration of the water solvent for the unselective aryl cation.

The activating effect of the amino group is also observed in the substitution reactions of 1-halogenoanthraquinones with ammonia or alkyl amines (equation 140).



(140)

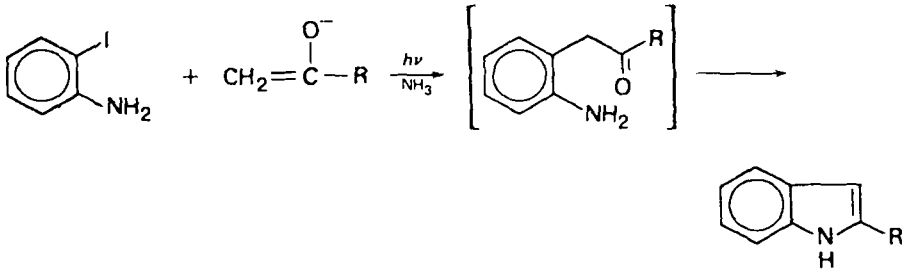
Photoamination only occurs if an NH_2 group occupies either the 2- or the 4-position ($R^1 = H$[402,404], $R^1 = SO_3Na$[405–407]). Oxygen is necessary for these reactions to occur, and it is suggested that the amine attacks an exciplex of the quinone with oxygen[407].

In yet another major category of nucleophilic photosubstitution reactions of aryl halides, activation by another substituent is not required. Thus the substitution of the halogenobenzenes with a nucleophile such as the acetone enolate anion in liquid NH_3 (equation 141) or DMSO occurs in ~65% yield[408]. A variety of substituents is compatible with this type of reaction, but the presence of a 3-nitro or a 4-oxido group is actually deleterious for the reaction[409,410]. Unlike the situation in the two other major

$$PhX + CH_2{=}C(O^-){-}CH_3 \xrightarrow[NH_3]{h\nu} PhCH_2{-}C(=O){-}CH_3 + X^- \qquad (141)$$

types of nucleophilic substitution, the overall relative reactivity of the halobenzenes is PhI > PhBr > PhCl > PhF[408,411]. This order is found to hold for all nucleophiles tested, although the ratios vary somewhat with the nature of the nucleophile[380,412,413]. The quantum yields of the reactions are frequently in the order of 10–50[414]. As the reactions serve to arylate quite a number of enolates, sulphanions and phosphanions whose arylation is difficult to achieve otherwise, the reactions have important synthetic applications. Prior to the review by Norris (Chapter 16 in this volume), two reviews of these reactions had appeared, one focusing on the mechanistic[380] and the other on the synthetic[415] aspects.

Nucleophiles reported recently to have been used successfully include the enolate anions of *N*,*N*-dimethylacetamide[416], and of esters[417]; the $PhSe^-$ [418] and $PhTe^-$ [418,419] anions and the phosphanions $(EtO)_2PO^-$ [420,421], Ph_2P^- [422], $PhP(OBu)O^-$, Ph_2PO^-, $(EtO)_2PS^-$ and $(Me_2N)_2PO^-$ [423]. As found earlier, this type of reaction occurs not only with halobenzenes but also, and in general more efficiently, with polycyclic aromatic halides[416,418,419]. Using an *o*-amino- or an *o*-methoxy-substituted halobenzene as the substrate and a ketone enolate as the nucleophile provides facile syntheses of indoles (e.g. equation 142)[424,425] and benzo[*b*]furans[426] respectively in high yields.



(142)

The reactions have been established[380] to occur via the radical chain mechanism of equations (143)–(146), the so-called $S_{RN}1$ Ar* mechanism. Photons stimulate the

$$ArX + Nu^- \xrightarrow{h\nu} ArX^{-\bullet} + \text{residue} \qquad (143)$$

$$ArX^{-\bullet} \longrightarrow Ar^{\bullet} + X^- \qquad (144)$$

$$Ar^{\bullet} + Nu^- \longrightarrow ArNu^{-\bullet} \qquad (145)$$

$$ArNu^{-\bullet} + ArX \longrightarrow ArNu + ArX^{-\bullet} \qquad (146)$$

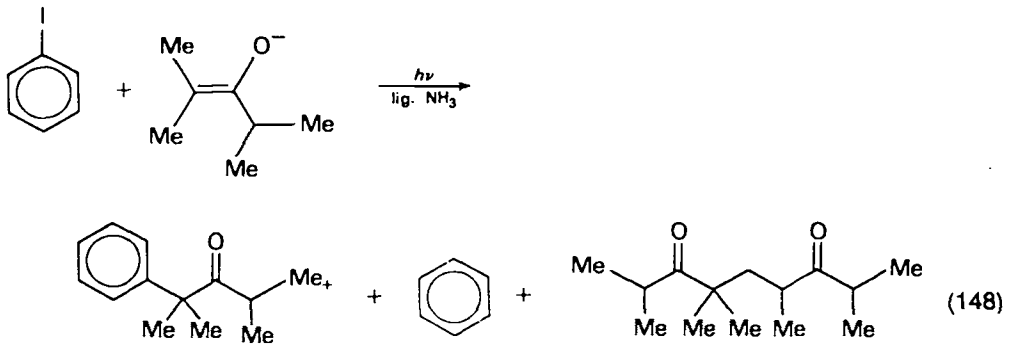
electron transfer from the nucleophile to the substrate forming a radical anion, which decomposes into an aryl radical and an halide anion. The substrate anion radical may also be produced by sodium or potassium metal. The aromatic radical reacts with the nucleophile to give a new radical anion, which transfers its extra electron to the substrate. An alternative radical chain mechanism in which the substrate radical anion undergoes a direct replacement by the nucleophile (equation 147) followed by step (146) (a $S_{RN}2$ Ar* mechanism) can be discarded on the basis that the relative nucleophile reactivities do not depend on the nucleofugic group X[427].

$$ArX^{-\bullet} + Nu^- \longrightarrow ArNu^{-\bullet} + X^- \qquad (147)$$

Provided that the radical chain in the $S_{RN}1$ Ar*-type reaction is long and that step (144) is the only pathway effectively available to $ArX^{-\bullet}$, relative substrate reactivity is determined by step (146). Indeed, the order of reactivity of the halobenzenes[408,411] and that of a series of aryl bromides (for example $NpX > PhC_6H_4X > PhX$)[418,428] parallel the order of ease of reduction of these compounds. The different reactivity ratios of pairs of halogenobenzenes with respect to different nucleophiles can be interpreted by assuming that the rate of step (146) will depend on the nature of Nu in $ArNu^{-\bullet}$.

The occurrence of reactions of Ar$^\bullet$ and $ArNu^{-\bullet}$ which compete with steps (145) and (146) respectively will retard the rate and lead to reduced yields of the substitution product.

The important competing reaction of Ar$^\bullet$ is hydrogen abstraction. Thus, only solvents such as NH_3 and DMSO which do not easily donate hydrogen atoms can be effectively used[409,410,429]. In many other solvents reductive dehalogenation is the major or exclusive process. Moreover, with ketone[430,431] and ester[417] enolates containing β hydrogen atoms as nucleophiles (e.g. in equation 148)[431] the yields of the substitution



(148)

products are decreased by reduction and radical coupling products originating from β-hydrogen abstraction from the enolate. Transfer of the hydrogen atoms from the carbon adjacent to the enolate anion to the aryl radical has been proven by deuterium labelling[417].

The important competing reaction of $ArNu^{-\bullet}$ is fragmentation. Thus, with $^-CH_2CN$[411,432], ^-SR[433] and $PhTe^-$[418] as nucleophiles products are obtained, in addition to the simple substitution products, which derive from expulsion from the intermediate $ArNu^{-\bullet}$ of CN^-, R$^\bullet$, and Ph$^\bullet$ respectively, in competition with step (146). For example, the sluggish reaction (149)[432] yields mainly products derived from step (150). Decyanation does not occur with substrates such as halonaphthalenes,

$$PhBr + {}^-CH_2CN \xrightarrow{h\nu} PhCH_2CN + PhCH_2CH_2Ph + PhCH_3 \quad (149)$$

$$PhCH_2CN^{-\bullet} \longrightarrow PhCH_2^\bullet + CN^- \quad (150)$$

halobiphenyls, and halobenzophenones, the aromatic portions of which can act as electron sinks[410,434,435]. In these cases, stabilization of the radical anions may result from a lowering of the rate of fragmentation, enabling the anions to survive long enough to undergo the bimolecular electron transfer step of equation (146). Alternatively, the charge may have to reside in the cyano moiety in order for the anion

radical to expel CN^-. Fragmentation of a different kind is shown in the reactions of iodobromo- and diiodobenzenes. These compounds afford very little monosubstitution product and much disubstitution product, even at low conversion[413,436,437]. The disubstituted product is not formed from the monosubstituted product[438]. This remarkable result is attributed to the propensity of the primary product radical anion $XArNu^{-\bullet}$ to react by equation (151) rather than by equation (146a). High concentrations of ArX_2 will favour step (146a) at the expense of step (151); the ratio of

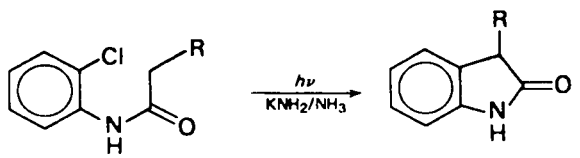
$$XArNu^{-\bullet} \longrightarrow {}^{\bullet}ArNu + X^- \quad (151)$$

$$^{\bullet}ArNu + Nu^- \longrightarrow ArNu_2^{-\bullet} \quad (152)$$

$$XArNu^{-\bullet} + ArX_2 \longrightarrow XArNu + ArX_2^{-\bullet} \quad (146a)$$

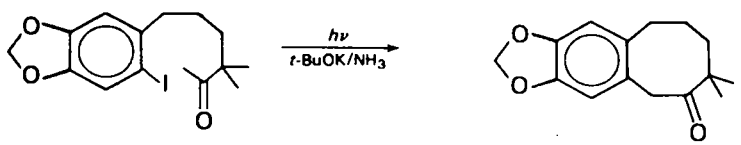
mono- to disubstitution product indeed increases with increasing substrate concentration[439]. With X = Cl or F step (151) will also compete less easily with step (146a). Iodochlorobenzenes give mainly, and iodofluorobenzenes give only monosubstitution[413]. Likewise a *p*-Cl-substituted radical anion fragments faster than does a *m*-Cl-substituted one. *p*-Iodochlorobenzene yields much more disubstitution product than does the *meta* isomer[413].

The intramolecular photo-$S_{RN}1$ aromatic reaction has been applied successfully in the synthesis of five-membered to 10-membered ring systems. Thus, for example, the oxindole **194** is obtained in 57% yield from the dianion of **193** (equation 153)[440] and **196** is formed from the anion of **195** in 73% yield (equation 154)[417,441]. Ring closure to a



(153)

(193) **(194)**



(154)

(195) **(196)**

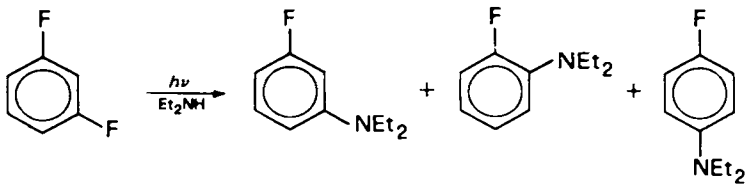
seven-membered ring in 94% yield in a reaction analogous to (154) is a key step in a synthesis of cephalotaxine[442]. Cyclizations of compounds which unlike **195** are not α,α-dialkylated are less successful since then there is a competition with intramolecular transfer of the β-hydrogen atom[417,441].

The photoreduction of aryl halides by $NaBH_4$ in CH_3CN/H_2O[443] presumably also proceeds via a radical chain mechanism with steps (155) and (156) as the propagation cycle. The quantum yield of the reaction of iodobenzene is 7.5. The results of deuterium labelling with 4-chlorobiphenyl as substrate are in accord with this mechanism; with 3-chlorobiphenyl they are not[444]. Irradiation of ArX in the presence of R_3SnD has been used to synthesize specifically deuterated arenes[445].

$$Ar^{\bullet} + BH_4^- \longrightarrow BH_3^{-\bullet} + ArH \quad (155)$$

$$ArX + BH_3^{-\bullet} \longrightarrow Ar^{\bullet} + BH_3 + X^- \quad (156)$$

All of the above nucleophilic substitution reactions in all categories are regiospecific, i.e. the nucleophile becomes attached at the position of the halide group. This is not the case in the reaction of fluorobenzenes with alkylamines[446,447]. Both direct and cine substitution products are formed (equation 157). Deuterium distribution in



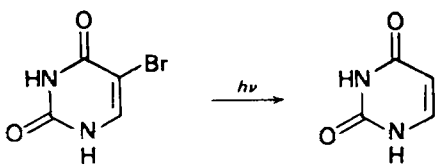
(157)

the products of the reaction with Et_2ND shows that the direct and cine substitution products arise via addition of the amine, followed by elimination of HF or DF[446,447]

V. HETEROAROMATIC HALIDES

The photochemical behaviour of heteroaromatic halides has been studied much less than that of carboaromatic halides. The available examples show that the two classes of compounds often behave similarly upon irradiation, and that there are also intrinsic differences.

Irradiation of heteroaromatic halides in the presence of hydrogen donors affords reductive dehalogenation. Thus, 5-iodo-[448–450] and 5-bromouracil[451–454] (equation 158)[453] give uracil with a quantum yield which depends on the concentration of the



(158)

H_2O/0.1*M* *i*-PrOH	$\phi = 0.0018$
i-PrOH	$\phi = 0.015$ (0.018)[454]
THF	$\phi = 0.028$

hydrogen donor and its hydrogen-donating ability[452,453]. Apart from simple alcohols[450] and inorganic reducing agents[449], deoxy-D-ribose can also act as the hydrogen donor[451–453]. This process involving the deoxyribose residue is thought to lead to the single-strand break observed ($\phi = 0.03$) in the photolysis of DNA in which thymine is replaced by 5-bromouracil[452].

The reductive dehalogenation of heteroaromatic halides displays positional selectivity. For example, the photodebrominations of 2-bromo- and 3-bromopyridine in hexane occur with quantum yields of 0.7 and 0.3, respectively[376]. Photolysis of pentachloropyridine causes the chloro substituent at C(3) to be replaced with high selectivity; 2,3,4,6- and 2,3,5,6-tetrachloropyridine are formed in a ratio of 20:1 upon irradiation in diethyl ether[455]. Likewise, pentabromopyridine yields 2,3,4,6-tetrabromopyridine and 2,4,5-tribromopyridine[286]. The cleavage of the labile C(3)—Cl bond in 4-bromotetrachloropyridine is competitive with that of the C—Br bond; in 4-iodotetrachloropyridine only C—I cleavage is observed[286].

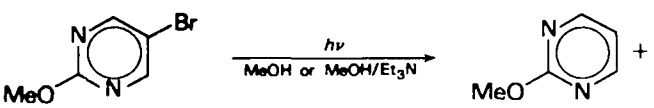
2-Bromothiophene has a larger propensity for photoreduction than does 3-bromothiophene[456]. In accord with this observation, in the photolysis of perbromothiophene the loss of the C(2)—Br is more extensive than that of the C(3)—Br substituent[286]. Reductive defluorination of heteroaromatic compounds in general does not occur. An example is the irradiation of polyfluorinated diazines which results only in valence bond isomerization[256].

The above reductive dehalogenation reactions are all thought to occur via homolytic cleavage of the carbon–halogen bond and subsequent hydrogen abstraction (equation 82). Chemical and physical evidence for the formation of radicals exists. The radicals resulting from the photocleavage of the C—X bond in 5-iodo- and 5-bromouracil have been trapped by O_2 [448–451], with the consequent formation of isodialuric acid. The radical from 5-iodouracil has been trapped by disulphides $(RS)_2$ [457] and that from 5-bromouracil by sulphhydryl compounds (RSH) such as cysteine and glutathione[458], resulting in replacement of the halogen by SR. The latter coupling reactions may play a role in the photochemical cross-linking of bromouracil-containing DNA and proteins[458]. In the irradiation of the individual neat bromopyridine isomers at 77 K, the ESR spectra of the corresponding σ-pyridyl radicals resulting from scission of the C—Br bond are observed[459]. ESR experiments also show that 5-fluoro-, chloro- and bromouracil yield the corresponding π-radical anions upon irradiation at 77 K in aqueous glasses. The Cl- and Br-substituted anions form the 5-uracilyl σ-radical upon heating, with chloride ion being expelled less rapidly than bromide ion. The F-substituted anion radical is stable in the temperature range amenable to the glasses[460]. For 5-bromouracil a transient presumed to be the 5-uracilyl radical has been observed by flash photolysis[461]. The identities of the possibly related transients observed in the flash photolysis of 9-chloroacridine are unclear[462].

The triplet-sensitized photoreduction of 5-bromouracil does not occur via a radical pathway[454]. The high percentage of uracil-5-*d* (UD) formed upon the sensitized irradiation in $(CH_3)_2CHOD$ indicates that a proton rather than a hydrogen atom is transferred. The reaction is proposed to occur via electron transfer from the solvent to the triplet bromouracil (BrU). This yields a radical anion which is apparently sufficiently stable to be protonated rather than to undergo halogen detachment (equation 159).

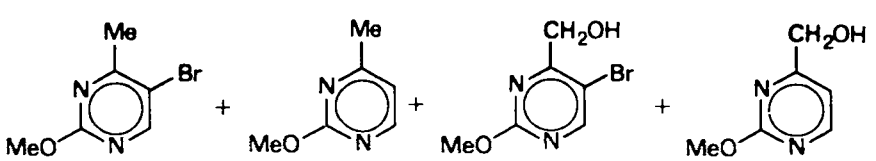
$$^3BrU + i\text{-}PrOD \longrightarrow i\text{-}PrOD^{+\cdot} + BrU^{-\cdot} \xrightarrow{+D^+,\ -HBr} UD \qquad (159)$$

In what is one of the first examples of the phenomenon of electron donor-sensitized photoreduction, the photochemical debromination of 5-bromopyrimidines (equation 160) is accelerated by alkyl amines[463,464]. The quantum yield of the formation of **198**



(197) **(198)**

(160)



from **197** in CH_3CN increases from 0.09 to 0.9 upon addition of 0.4 M Et_3N; in methanol it increases from 0.1 to 4! The reaction in methanol is proposed to occur via the mechanism of equations (161)–(164)[464]. Chain carriers in this free-radical chain

$$^*ArBr + Et_3N \longrightarrow \text{exciplex} \longrightarrow ArBr^{-\bullet} + Et_3N^{+\bullet} \quad (161)$$

$$ArBr^{-\bullet} \longrightarrow Br^- + Ar^\bullet \xrightarrow{CH_3OH} ArH + {}^\bullet CH_2OH \quad (162)$$

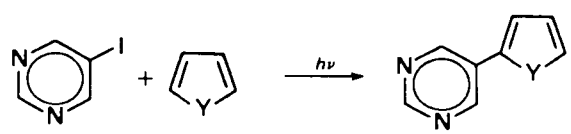
$$^\bullet CH_2OH + Et_3N \longrightarrow {}^\bullet CH_2O^- + Et_3\overset{+}{N}H \quad (163)$$

$$^\bullet CH_2O^- + ArBr \longrightarrow ArBr^{-\bullet} + CH_2O \quad (164)$$

reaction are the $^\bullet CH_2OH$ and $^\bullet CH_2O^-$ radicals[465]; the Et_3N acts both as an electron donor in the initiation step and as a base catalyst in the propagation step. The minor methylated and hydroxymethylated compounds arise via attack of $^\bullet CH_2OH$ on the aromatic ring.

For the photoreduction of bromoquinolines and bromoisoquinolines to occur, the presence of an electron donor such as Et_3N, OH^- or CN^- is required[466], and the primary process is proposed to be electron transfer from the donor to the photoexcited heteroaromatic. In contrast, when the quantum yield of reduction of 5-bromouracil is plotted against the concentration of hydroxide ion, three plateaus appear, the quantum yield increasing with increases in hydroxide ion concentration. This effect is attributed to the greater propensities of the mono- and dianion of 5-bromouracil to undergo photocleavage[453].

Photolysis of heteroaromatic halides in solutions of arenes or heteroarenes is a convenient method for the synthesis of aryl-substituted heteroaromatic compounds. Thus, for example, the irradiation of 3-iodopyridine[467] and 5-iodopyrimidine[468] in the presence of furan, thiophene, or *N*-methylpyrrole (equation 165) affords the



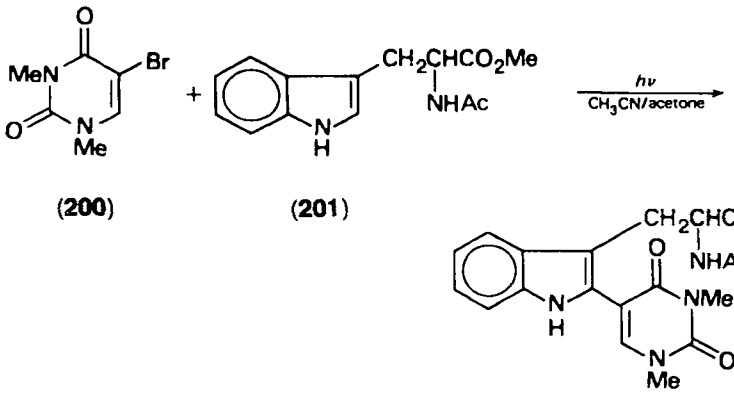
(165)

Y = O, S, NMe (**199**)

3-(2-heteroaryl)pyridines and 5-(2-heteroaryl)pyrimidines, respectively, in 50–70% yield. In the case of thiophene (Y = S), a small amount of the (3-heteroaryl) isomer of **199** is found. The reaction is less successful for pyrrole, where only low yields of **199** (Y = NH) are obtained. Arylation of benzene has also been described: 5-phenylpyrimidine[468] and 5- and 6-phenyl-*N*,*N*′-dimethyluracil[469] are obtained in good yields by the photolysis of the corresponding iodo derivatives in benzene. Similarly chloro- and bromo-*s*-triazines give 5-phenyl-*s*-triazines in fair yield[470].

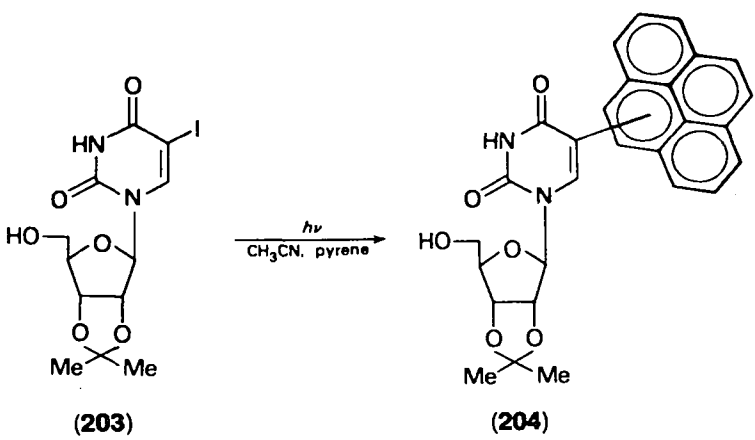
Analogous to the reductive dehalogenation, the arylation reaction is also regioselective. In pentachloropyridine the C(3)—Cl substituent is selectively replaced[286,455], as is the C(6)—I substituent in 5,6-diiodo-*N*,*N*′-dimethyluracil[469].

5-Bromo-*N*,*N*′-dimethyluracil (**200**) photoarylates various indole derivatives, but does so efficiently only in the sensitized reaction[471]. Direct irradiation of **200** and the tryptophan derivative **201** yields 75% *N*,*N*′-dimethyluracil and 15% of **202**; in the acetone-sensitized reaction **202** is the sole product in 67% yield (equation 166). In all indole derivatives studied the arylation occurs at the 2-position of the indole nucleus. The reaction is thought to occur via electron transfer by way of a triplet exciplex yielding the indolyl radical cation and the bromouracil radical anion. Coupling between



the radical ions would be expected to occur at the position of highest charge density in the indolyl radical cation which happens to be the 2-position. Substitution at the 2-position of indole also occurs in the photoreaction with dibromomaleimide (see Section III.A) but not in the photoreaction with methyl chloroacetate (see Section II.F.2) where substitution occurs mainly at the 4-position. For the latter reaction it is proposed that the coupling occurs between the radical cation and the radical resulting from halide loss from the methyl chloroacetate radical anion. This will occur at the position of highest spin density and that happens to be the 4-position. The photocoupling with **200** is specific for tryptophan among the aromatic amino acids, and a similar reaction – or the one with sulphur-containing amino acids[458] – may occur in the photo-cross-linking of bromouracil containing DNA with proteins[471].

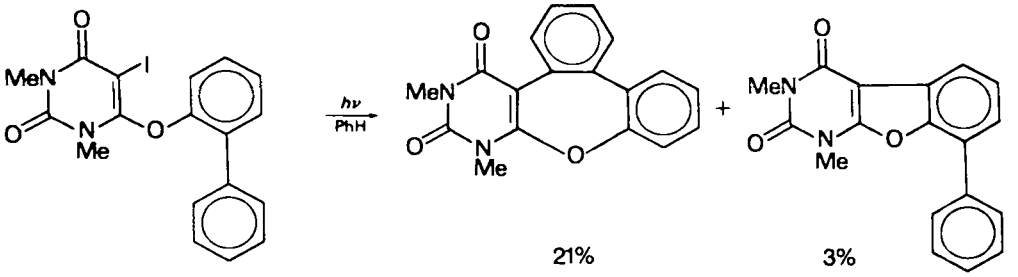
Addition of electron-rich photosensitizers[472] such as 2-methoxynapthalene enables reaction (166) to occur with otherwise unreactive indole derivatives[473]. In this case a sequence of two electron transfer processes is proposed. Irradiation of 5-halouridines in the presence of (hetero)arenes provides a useful method for the direct synthesis of 5-(hetero)arylpyrimidine nucleosides[471,474,475]. Thus, in a reaction analogous to (166), the indolyl group can be introduced at the 5-position of the uridine nucleus in 70% yield[471]. Photolysis of **203** in the presence of pyrene gives **204** in 31% yield[474].



The photolysis of iodothiophenes in benzene is a most useful method for the synthesis of phenylthiophenes[476]. Likewise, 2-iodothiazole[477] and 4- and 5-iodoisothiazole[478] in a solution of a variety of substituted benzenes give a large variety of the corresponding aryl-substituted heterocycles. The relative rates of substitution and the proportions of the isomeric products are in accord with a homolytic aromatic substitution by radicals with electrophilic character[477,478].

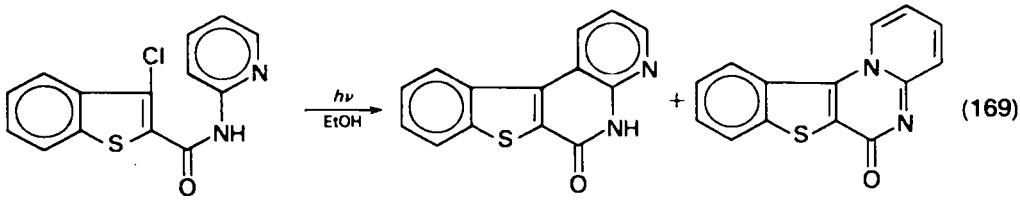
Isolated examples of photoarylation of alkenes and alkanes by a heteroaromatic halide have also been reported. The photoreaction of 3-chlorotetrafluoropyridine with ethene to give 3-(2-chloroethyl)tetrafluoropyridine is formally an insertion of the C=C into the C—Cl bond[479]. Replacement of an alkyl hydrogen by an heteroaryl group has been observed as a side reaction[463]. It is a major reaction in the direct irradiation of tetrachloropyrimidine in ether[286] and in the sensitized irradiation of pentafluoropyridine in methanol[480]. In both cases regiospecific substitution occurs: the former reaction yields 2-alkoxyalkyl- and 5-alkoxyalkyl-substituted trichloropyrimidine, and the latter reaction gives 4-(hydroxymethyl)tetrafluoropyridine.

Examples of photochemical intramolecular heteroarylation have been reported for systems in which the two (hetero)aromatic moieties are connected by $-CH_2-$[326,481], $-O-$[286,482,483,484], $-S-$[286,482,483], $-NH-$[286,482] and $-CONH-$[485]. In general, in the systems connected by a single atom, a five-membered ring is formed. In irradiation of **205** seven-membered ring formation takes precedence over five-membered ring formation (equation 168)[484]. The photocyclodehydrohalogenation is



(205) (168)

not successful when both rings are very electron deficient[326]. The ring closure of the anilide **206** (equation 169) presumably occurs via photoelectrocyclization, followed by

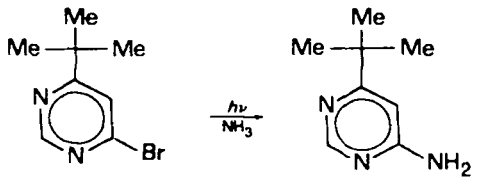


(206) (169)

elimination of HCl rather than by homolytic cleavage of the C—Cl bond and subsequent substitution (cf. equation 117).

Apart from heteroaromatic $S_{RN}1$ reactions, examples of nucleophilic heteroaromatic photosubstitution reactions[496] are quite scarce. The 2-, 3- and 4-bromopyridines in aqueous solution[376,486] or in aqueous NaOH[486] yield 2-pyridone, 3-hydroxypyridine and 4-pyridone, respectively, with quantum yields[486b] of 0.30, 0.14 and 0.2. Since the

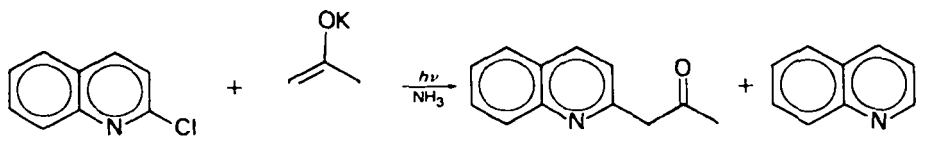
quantum yields are independent of the hydroxide ion concentration the reactions are proposed to occur via heterolytic cleavage of the C—Br bond (cf. equation 139), yielding a heteroaryl cation, whose further reaction occurs with high efficiency which is not affected by the hydroxide ion concentration[486b]. 2-Fluoropyridine is photo-inert under these conditions but it does react in a 1:1 mixture with diethylamine[487]. Unlike the analogous reaction with fluorobenzenes (equation 157), no cine substitution products are formed, indicating that an addition–elimination sequence is not involved. Whereas irradiation of bromobenzene in liquid ammonia gives no reaction, the 4-bromopyrimidine **207** affords **208** in > 95% yield (equation 170)[488]. The reaction



(170)

(207) **(208)**

shows the characteristics of an $S_{RN}1$ reaction. The relative ease of substitution is I > Br > Cl and the radical scavenger di-*tert*-butyl nitroxide greatly suppresses the reaction. The reactions of 2-chloroquinoline[489,490] (equation 171) and the



(171)

90% 4%

halopyridines[491] with a variety of potassium ketone enolates in liquid ammonia upon illumination with 350 nm light are aromatic nucleophilic substitution reactions with carbanionic nucleophiles which occur via the $S_{RN}1$ mechanism depicted in equations (143)–(146) in Section IV.C. The lithioketone enolates react much more sluggishly. The reactivity of a series of haloaromatic compounds towards potassioacetone is 2-chloroquinoline > 2-bromopyridine > bromobenzene[491]. In the 2-halopyridine series the relative reactivity is Br > Cl > F[491]. The trends may be accounted for if the relative substrate reactivity is determined by step (146); the reactivities parallel the ease of reduction of the haloaromatic substrate to the radical anion. The order of reactivity of the isomeric bromopyridines toward potassioacetone in liquid ammonia is 2 > 3 > 4[491], which differs from their order of reactivity towards H_2O in the heterolytic reaction (see above) and can probably be accounted for similarly. 2,6-Dibromo- and 2,6-dichloropyridine react with the potassium enolate of pinacolone to form the disubstituted product without accumulation of a monosubstituted intermediate. This result can be uniquely explained in the framework of the $S_{RN}1$ mechanism by the occurrence of reactions (151), (152) and (146a) as discussed in Section IV.C. The relative rates of reaction (171) in various solvents vary in the order PhH ~ Et_2O ≪ DME < THF < DMF < DMSO[492]. This order of reactivity parallels the increasing order of dielectric constants of these solvents. That THF can be satisfactorily used in this reaction, whereas it can not be used with iodobenzene, probably reflects the low reactivity of quinolyl radicals relative to phenyl radicals in abstraction of hydrogen atoms.

Ketone enolates also undergo photo $S_{RN}1$ substitution with halogenated pyrimidines[493,494], pyridazines[494] and pyrazines[494]. In a process analogous to (142), the reaction of 2-chloro-4-aminopyridine with ketone enolates in liquid ammonia provides a facile synthesis of 4-azaindoles[495].

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