The Chemistry of The Carbon-Halogen Bond: Part 1
Edited by Saul Patai

The chemistry of
the carbon–halogen bond

THE CHEMISTRY OF FUNCTIONAL GROUPS

A series of advanced treatises under the general editorship of Professor Saul Patai

The chemistry of alkenes (published in 2 volumes)
The chemistry of the carbonyl group (published in 2 volumes)
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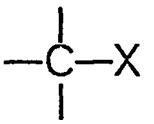
The chemistry of the carbon–halogen bond (published in 2 parts)



The chemistry of **the carbon–halogen bond**

Edited by

SAUL PATAI

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Foreword

The present volume deals with organic compounds in which the functional group is a C—X group, X being fluorine, chlorine, bromine or iodine. The material was again organized according to the general plan of the series 'The Chemistry of Functional Groups', described in the Preface printed in the following pages.

This volume was planned to contain 22 chapters; five of these, on 'Formation of C—X bond', 'Modern synthetic uses of organic halides', 'Syntheses and uses of isotopically labelled halides', 'Fluorocarbons' and 'Optical rotatary dispersion and circular dichroism of organic halides' did not materialize.

Almost all of the originally planned volumes of the series are now either published, in press or in the course of active preparation. Since several volumes were published for which important chapters had not been delivered and, furthermore, since in many of the subjects treated the scientific progress was even faster than expected, it was decided to publish supplementary volumes to the series. These volumes will contain, it is hoped, the 'missing and omitted' chapters from previously published volumes, as well as chapters treating new material and, last but not least, comparative chapters dealing broadly with similarities and differences of related functional groups (e.g. double-bonded groups such as C=C, C=O, C=N— and —N=N—).

Jerusalem, June 1973 SAUL PATAI

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

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

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

This plan entails that the breadth, depth and thought-provoking nature of each chapter will differ with the views and inclinations of the author and the presentation will necessarily be somewhat uneven. Moreover, a serious problem is caused by authors who deliver their manuscript late or not at all. In order to overcome this problem at least to some extent, it was decided to publish certain volumes in several parts, without giving consideration to the originally planned logical order of the chapters. If after the appearance of the originally planned parts of a volume it is found that either owing to non-delivery of chapters, or to new developments in the subject, sufficient material has accumulated for publication of an additional part, 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 (*published in two volumes*)
The Chemistry of the Carbonyl Group (*published in two volumes*)
The Chemistry of the Ether Linkage (*published*)
The Chemistry of the Amino Group (*published*)
The Chemistry of the Nitro and the Nitroso Group (*published in two parts*)
The Chemistry of Carboxylic Acids and Esters (*published*)
The Chemistry of the Carbon–Nitrogen Double Bond (*published*)
The Chemistry of the Cyano Group (*published*)
The Chemistry of Amides (*published*)
The Chemistry of the Hydroxyl Group (*published in two parts*)
The Chemistry of the Azido Group (*published*)
The Chemistry of Acyl Halides (*published*)
The Chemistry of the Carbon–Halogen Bond (*published in two parts*)
The Chemistry of the Quinonoid Compounds (*in press*)
The Chemistry of the Thiol Group (*in press*)
The Chemistry of the Carbon–Carbon Triple Bond
The Chemistry of Amidines and Imidates (*in preparation*)
The Chemistry of the Hydrazo, Azo and Azoxy Groups (*in press*)
The Chemistry of the SO, $-SO_2$, $-SO_2H$ and $-SO_3H$ Groups
The Chemistry of the $-OCN$, $-NCO$, $-SCN$ and $-NCS$ Groups
The Chemistry of the $-PO_3H_2$ and Related Groups

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 1

General and theoretical aspects of the carbon–halogen bond

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I. GENERAL INTRODUCTION

A. Recent Advances in the Study of Molecular Properties

1. The calculation of electronic properties

Previous theoretical chapters of the Functional Group Series summarize basic aspects of the quantum mechanical calculation of molecular electronic structure. The LCAO–MO scheme and different degrees of semi-empirical approximations are, for instance, mentioned in references 1–3. *Ab initio* calculations are dealt with in detail in reference 4.

Advances in technology and increased accessibility of large-scale electronic computers have greatly spurred the development of *ab initio* calculations[5]. There the general aim still is an improved understanding of small molecules, containing but a few second-row atoms. Increased emphasis is laid on the computation of excited and ionic molecular states and of potential curves. The problem of taking into account electron correlation and of finding rapidly converging configuration interaction schemes is very much in the centre of attention. Computations on larger molecules, or on small molecules containing heavier atoms, such as sulphur, phosphorus or chlorine, while not prohibitive, nevertheless become extremely expensive in computer time if a reasonably large orbital basis is used.

One must be careful to use the right method to answer a given question. If numerically accurate predictions are to be obtained, the problem must be tackled on the *ab initio* level where all intermediate quantities are calculated exactly. This in itself is no guarantee of success, however. A result may depend heavily on the orbital basis chosen and on the steps following an initial SCF calculation. But exact numerical agreement between experiment and a computed quantity obtained by semi-empirical means will, by nature, always have a somewhat fortuitous aspect. On the other hand, semi-empirical procedures, possibly even the simplest ones such as the Hückel or extended Hückel[6, 7] methods, may all the more clearly reveal how certain molecular quantities depend on such properties as overall or local symmetry. This has, for instance, been admirably exemplified recently in the study of concerted reactions[8], and in the interpretation of photoelectron spectra, which have proven immensely useful in the study of halogen-containing compounds (see section I. A. 3).

Semi-empirical methods which explicitly take into account all valence electrons of a molecule and generally start out with an SCF calculation are finding increased application. They are proving useful for a semi-quantitative interpretation of many molecular properties. In all of these procedures certain integrals are neglected, others are calibrated on atomic

data and possibly on one or more test-molecule(s). Depending on the approximations and the parametrization, different designations have found common usage: CNDO [9-11] (complete neglect of differential overlap), INDO [12] (intermediate neglect of differential overlap), NDDO [13] (neglect of diatomic differential overlap), PNDO [14] (partial neglect of differential overlap), MINDO [15] (modified intermediate neglect of differential overlap). For an assessment of the respective merits and shortcomings of these methods the reader is referred to the literature, and also to some recent reviews[16,17].

2. Some spectroscopic properties

In this section we briefly mention some spectroscopic properties of halogen-containing compounds which are of general interest, but which will not be treated in more detail in the following parts of this chapter. In some cases recent and extensive reviews already exist, as indicated.

a. Nuclear quadrupole resonance (*n.q.r.*). Nuclei having a spin larger than $\frac{1}{2}\hbar$, as do chlorine, bromine and iodine, possess a non-spherical charge distribution, which implies the existence of an electric nuclear quadrupole moment. Due to this a nucleus may only take on certain orientations with respect to a surrounding inhomogeneous electric field. The coupling energy is proportional to the quadrupole moment and to the electric field gradient at the nucleus. As the nuclear spin is fixed with respect to the nuclear quadrupole moment, its orientational energy also depends on the electric field gradient. At given frequencies, lying in the radiofrequency range, nuclear resonance transitions between the different orientational substates, or quadrupole levels, can be induced. From these frequencies the relative value of the electric field gradient at the nucleus may be deduced and conclusions drawn on the electronic charge distribution in the vicinity of the nucleus[18]. This provides a means of evaluating the participation of halogen *p* orbitals in bonding. Such measurements require relatively large samples of material in the solid state. A review on n.q.r. and its application to chemistry has been given by Lucken[19].

b. Mössbauer spectroscopy of bonded iodine[20,21]. The exact frequency of the 57·6 KeV gamma rays emitted by the ^{127}I nucleus depends on its molecular environment. The chemical information obtainable from such a Mössbauer spectrum is derived from the quadrupole splitting, which gives an estimate of the extent to which iodine *p* orbitals participate in the filled molecular orbitals of the system, and the isomer shift, which measures the *s* electron density. It appears that in iodobenzene, for instance, the best description for the electronic structure of iodine is pure *p* bonding[21]. Though the magnitude of the quadrupole coupling is only determined to an

accuracy of $\sim 0{\cdot}5\%$[20], hence less precisely than with n.q.r., Mössbauer spectroscopy has the advantage of also yielding its sign[21].

c. Fluorine nuclear magnetic resonance. The only naturally occurring isotope of fluorine, ^{19}F, has a nuclear spin of $\frac{1}{2}\hbar$, like the proton. Its g-value is also not very different, the n.m.r. frequency in a 10 kilogauss field being 40·055 Mc/s, as compared to 42·576 Mc/s for the proton. Observation of ^{19}F n.m.r. is therefore relatively easily accessible with standard equipment. These spectra may show large chemical shifts and spin coupling constants, both between different fluorine nuclei and between fluorine and hydrogen. It appears that the magnetic shielding of the ^{19}F nucleus decreases with increasing electronegativity of the atom to which the fluorine is bonded[22]. In the series CH_3F, CH_2F_2, CHF_3 the fluorine chemical shifts in p.p.m. with respect to CF_4 are + 210·0, + 80·9, + 18·2 respectively[23,24]. For a general review see reference 24.

In the frame of LCAO–MO theory the expression for the constant for indirect F—F coupling is made up of orbital (OB), spin dipolar (SD) and Fermi contact (FC) terms[25,26]. An interpretation of a variety of experimental data from this point of view is to be found in reference 27.

d. The heavy-atom effect and the study of triplet states. Spin–orbit coupling increases in heavy atoms (see also sections I. B. 1 and III. A) and, to a varying degree, in molecules containing such atoms. It is well known, for instance, that aromatic molecules substituted with iodine, bromine or even chlorine atoms show an enhanced phosphorescence. Spin–orbit coupling is responsible for singlet–triplet mixing, making a non-radiative intersystem crossing from higher singlet states to the triplet states of the molecule, in particular to the lowest triplet state, more probable. The probability for phosphorescence, or the radiative transition from the lowest triplet state to the singlet ground state, grows accordingly. Beside intramolecular, or internal spin–orbit effects, as mentioned, the presence of surrounding solvent molecules containing heavy atoms may have a similar influence on a solute molecule. This is termed the solvent- or external heavy-atom effect. For a review see reference 28.

The classification and assignment of molecular triplet states are of considerable general interest. This aim may be pursued by studying the fine structure of phosphorescence spectra and of triplet–triplet absorption spectra. Electron spin resonance also has become an important tool, in particular the measurement of zero-field splittings[28]. Recently a combination of both approaches has been developed, designated as phosphorescence–microwave double-resonance spectroscopy[29] (p.m.d.r.). It consists of saturating the transitions between the zero-field sublevels of the lowest triplet state with microwave radiation of appropriate frequency

and observing the concomitant changes in the selectively polarized phosphorescence from these individual sublevels. For an application to the lowest triplet state of *p*-dichlorobenzene, see reference 30.

e. The haloketone effect in optical activity. The measurement of the 300 nm $n \rightarrow \pi^*$ Cotton effect of the carbonyl chromophore has found wide application in determining the absolute configuration and the position of substituents in asymmetric ketones. The main characteristics of this effect are summarized by the well-known sector rules, be it an octant[31–33] rule or quadrant[34–37] rule. Djerassi and coworkers have empirically found that axially (as opposed to equatorially) located α-halogen substituents exert a very strong influence both on the wavelength of the $n \rightarrow \pi^*$ transition and on the magnitude of the o.r.d. or c.d. curve[38]. The introduction of the halogen substituent may even reverse the sign of the $n \rightarrow \pi^*$ Cotton effect. Interestingly, however, the contribution of a dissymmetrically located fluorine substituent to the rotational strength of this transition appears to be opposite in sign to that of other atoms in similar position, such as carbon, chlorine, bromine or iodine[31,38,39]. Bouman and Moscowitz[33] conclude that the fluorine anomaly cannot be explained if the effect of the fluorine atom on the carbonyl chromophore is treated merely as an electrostatic perturbation. The present author has tried to give a tentative answer to this question by considering the n-π mixing as arising through overlap with a substituent orbital. The mixing coefficient is shown to be inversely proportional to the difference between the effective ionization potential of this orbital (fluorine 2*s*, 2*p*, say) and of the carbonyl n orbital[36]. It is conceivable that this difference is of opposite sign in the case of fluorine, as compared to chlorine, bromine or iodine.

In the following sections we will see that the fluorine anomaly is not restricted to the realm of optical activity. It appears very strikingly in photoelectron spectra, for instance.

3. Photoelectron (p.e.) spectroscopy

Although the photoelectric effect has been known for almost a century[40], its systematic application to the study of molecules is recent[41–45]. This development was only made possible by important progress in the conception and design of spectrographs on the one hand, and by significant advances in the quantum-mechanical description of molecular electronic structure on the other.

When a photon hits a molecule with sufficient energy $h\nu$ to ionize it, the kinetic energy of the ejected electron E may be expressed as

$$E = h\nu - W \tag{1a}$$

where W is the work required to extract the electron and bring it to infinity. In turn W may be written as

$$W = I_A + \Delta E_{vib} + \Delta E_{rot} \tag{1b}$$

where I_A designates the adiabatic ionization potential, that is, the energy difference between the neutral and ionized molecules, both at the lowest vibrational–rotational levels of their ground states (see Figure 1). ΔE_{vib}

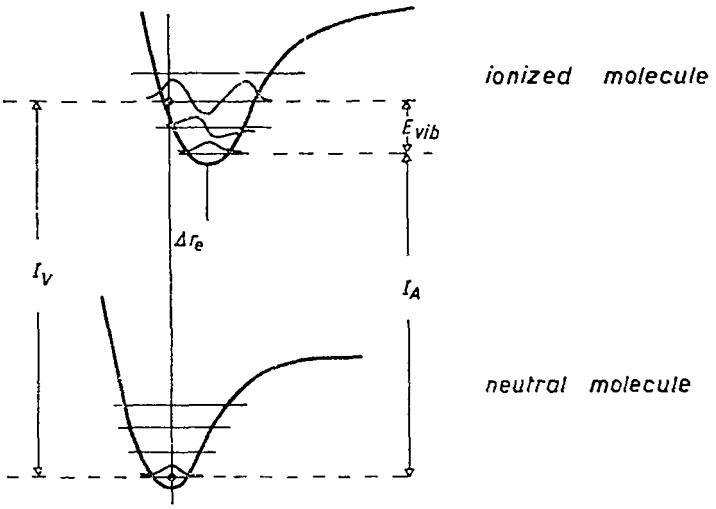

FIGURE 1. Illustration of the vertical and adiabatic ionization potential, I_V and I_A for a diatomic molecule. Δr_e represents the difference in equilibrium geometry between neutral molecule and radical cation.

and ΔE_{rot} are the differences in vibrational and rotational energy. Of course $|I_A| \gg |\Delta E_{vib}| \gg |\Delta E_{rot}|$, the accurate measurement of these quantities depending on the resolving power of the apparatus and the nature of the spectrum.

The probability f of photoionization may be described in the same terms as the probability for ordinary absorption. Within the Born–Oppenheimer approximation one may write for a transition from electronic state i, vibrational state ν to electronic state j, vibrational state μ[46,47]

$$f_{i\nu,j\mu} = 4{\cdot}703 \times 10^{29} . \nu_{ij} . |\bar{M}_{ij}|^2 . |S_{\mu\nu}|^2 \tag{2}$$

ν_{ij} is the average frequency of the transition in cm^{-1}. $\bar{M}_{ij}$ designates the electronic transition moment in electrostatic units averaged over the normal vibrations of the initial, or ground state, and $S_{\mu\nu}$ stands for the overlap integral between the vibrational wavefunctions of the initial and final state.

In other words, photoelectronic transitions also obey the Franck–Condon principle[48]. The most probable electronic transition is the one which does not entail any change in the nuclear coordinates and corresponds to a vertical excitation energy or ionization potential I_V (see Figure 1). Within an electronic band in the spectrum the relative intensity of the vibrational lines should be given by the magnitude of the Franck–Condon factors $|S_{\mu\nu}|^2$. Absorption spectra show the vibrational spacings of the final (upper) state.

The extent of vibrational structure in photoelectron spectra depends very much on the nature of the electron which has been removed. The more bonding (or antibonding) an electron, the more will its removal affect the potential curve (or, in general, energy hypersurface) governing the motion of the nuclei. This in turn will change the equilibrium nuclear geometry and will lead to vibrational progressions in the spectrum. It is therefore, on the other hand, to be expected that the ejection of a non-bonding electron will not lead to significant dimensional changes of the molecule and consequently, by the Franck–Condon principle, to a single sharp line[49].

The Franck–Condon principle gives a means of rationalizing ΔE_{vib} in the p.e. spectrum. Koopmans' theorem[50] provides a way of predicting the vertical ionization potential I_V (see Figure 1); the energies of the Hartree–Fock SCF orbitals of the neutral molecule are generally good approximations for these ionization potentials. This in turn permits the assignment of a given photoelectron band as the ejection of an electron from a particular SCF orbital and consequently to deduce the symmetry of the electronic state of the resulting ion. Even if, due to the neglect of electronic reorganization upon ionization, and of correlation effects, the agreement between Koopmans' theorem and experiment cannot possibly be exact, the energetic sequence of the ionized states is almost always correctly predicted.

At this point we wish to make some remarks which are perhaps not of immediate concern to the experimental chemist, but which we deem extremely important from a theoretical point of view: in recent years much attention has been given to so-called localized orbitals[51–53]. From a mathematical point of view these localized orbitals provide just as acceptable solutions for the molecular SCF problem as the usual delocalized or canonical ones. It appears that they may give an intuitively more appealing picture of the charge distribution of individual electrons and be better suited than canonical orbitals as a starting point to take into account electron correlation. They possibly provide a means of defining wavefunctions for certain limited groups of atoms and of transferring these wavefunctions from one molecule to another, without the necessity of performing elaborate calculations. In this sense some doubt has been cast

on the physical significance and usefulness of canonical SCF orbitals, as compared to the localized ones. Photoelectron spectroscopy, on the other hand, shows these doubts to be completely unfounded in relation to ionization. As Brundle, Robin and Basch remark[54]: 'The canonical Hartree–Fock orbitals for the neutral species are uniquely defined as those orbitals (within the basis of all occupied MO's in the parent molecule) which best represent the electron charge density the molecule would lose for each electron, were that electron to be removed; information about the ejected electron's wavefunction is unambiguously built into the neutral molecule canonical Hartree–Fock MO's.'

We may add that delocalized orbitals are also well suited for the description of electronic spectra and for understanding the symmetry principles in concerted reactions.

B. Electronic Properties of the Molecules F_2, Cl_2, Br_2 and I_2

A meaningful comparison of the electronic properties of the carbon–halogen bonds C—F, C—Cl, C—Br, C—I requires a study of the halogen molecules themselves. The data given and discussed in this section are to be understood in this sense.

The halogen atoms all lack one electron to fill their respective valence shells. In an elementary but illustrative way[55] the electronic energy levels of the diatomic halogen molecules may be understood as shown in Figure 2

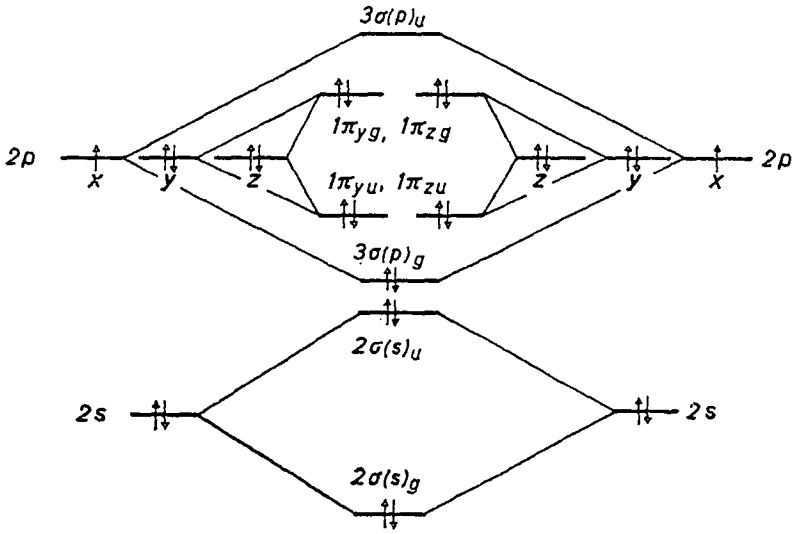

FIGURE 2. The sequence of orbitals in the fluorine atom and molecule, according to a simple energy level scheme.

for the example of fluorine. From this scheme one predicts the decreasing energy sequence of the filled valence orbitals to be $1\pi_g$, $1\pi_u$, $3\sigma_g$, ... By Koopmans' theorem[50] the ionization potentials are expected to be

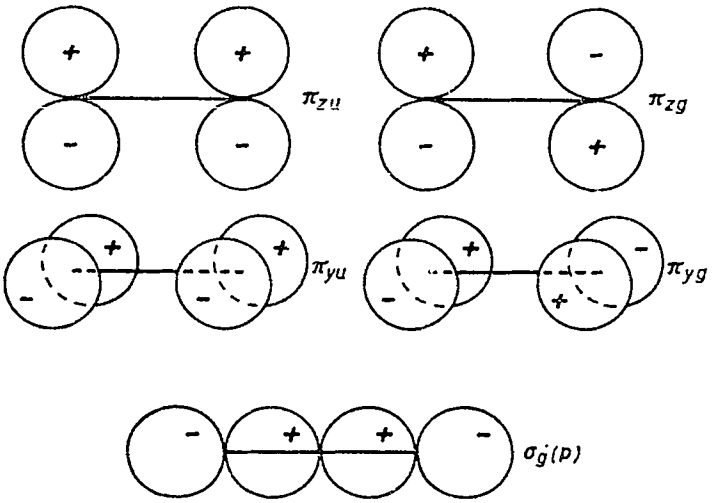

FIGURE 3. A simplified representation of some orbitals of π and σ symmetry.

approximately equal to the energies of the Hartree–Fock SCF orbitals. Consequently the first ionization of F_2 should go to the $^2\Pi_g$ state of the ion F_2^+, the next ionizations to the state $^2\Pi_u$, followed by $^2\Sigma_g$. Recent photoelectron (p.e.) spectra of the halogens[56] indicate that this sequence is indeed found in F_2 as well as in the molecules Cl_2, Br_2 and I_2. The numerical values of the ionization potentials are given in Table 1b. As is to be expected, they decrease on going from F_2 to I_2. One notices that in a given molecule the average value of the potentials for ionization to the states $^2\Pi_g$ and $^2\Pi_u$, $\frac{1}{2}(I_1 + I_2)$, lies very close to the corresponding atomic ionization potential (Table 1a). The difference of 0·1–0·2 eV is not far from the

TABLE 1a. Properties of the halogen atoms

Experimental property	F	Cl	Br	I
First atomic ionization potential (eV)	17·418[a]	13·01[a]	11·84[a]	10·454[a]
Atomic electron affinity (eV)	3·448[b]	3·613[b]	3·363[b]	3·063[b]

[a] $X(^2P_{\frac{3}{2}}) \rightarrow X^+(^3P_2)$. C. E. Moore, *Natl. Bur. Std. (U.S.) Circ.*, **467**, Vol. 3 (1958); see also R. W. Kiser, *Tables of Ionization Potentials*, Dept. of Chemistry, Kansas State University, Manhattan, Kansas, 1960.

[b] R. S. Berry and C. W. Reimann, *J. Chem. Phys.*, **38**, 1540 (1963).

TABLE 1b. Properties of the halogen molecules

Experimental property	F_2	Cl_2	Br_2	I_2
Internuclear distance r_e (Å)	1·435[a]	1·988[a]	2·283[a]	2·666[a]
First ionization potential to ionic state $^2\Pi_g$, I_1 (eV)	15·70[b]	11·49[b]	10·51, 10·90[b,e]	9·34, 9·97[d,e]
Second ionization potential to ionic state $^2\Pi_u$, I_2 (eV)[j]	18·4[c] 18·98[d]	14·0[c] 14·43[d]	12·5[c] 13·08[d]	10·8, 11·6[c,e] 11·03, 11·82[e]
Electron affinity A (eV)	3·08[f]	2·38[f]	2·51[f]	2·58[f]
Dissociation energy D_e (eV)	1·65[g]	2·5143[g]	1·991[h]	1·555[h]
Vibrational frequency ω_e (cm^{-1})	892·1[a]	564·9[a]	323·2[a]	214·6[a]
Nuclear quadrupole coupling constants (Mc/s)	—	$^{35}Cl_2$ 108·95[i]	$^{79}Br^2$ 765·86[i]	$^{127}I_2$ 2156·0[i]

[a] Reference 46, pp. 501–581.
[b] Reference 56, resolved 0—0 band of p.e. spectrum.
[c] Onset values.
[d] Band maxima.
[e] Reference 56, resolved $^2\Pi_{\frac{3}{2}}$ and $^2\Pi_{\frac{1}{2}}$ lines; see also reference 73.
[f] Reference 66.
[g] Reference 61 and references cited therein.
[h] Reference 46, pp. 501–581, from $D_0^0+\frac{1}{2}\omega_e$.
[i] Reference 19, p. 289, solid-state data.
[j] By the term 'second ionization potential' we here refer to the energy of the second p.e. band. In general, as in the present case, it corresponds to single ionization to an excited state of the mono-cation and not to double ionization.

experimental uncertainty of p.e. spectra. This finding lends support to the naïve picture of the top-filled orbitals π_g and π_u being symmetrically located in their energies with respect to the atomic orbitals np_y or np_z of which they are composed. The energy splitting between the π_g and π_u orbitals is expected to be roughly proportional to the overlap integral $\langle np_{za} | np_{zb} \rangle$, the suffixes a and b designating the atomic centres.

As the top-filled π_g orbital is antibonding the π_u orbital is bonding, and as in the halogen molecules there are as many electrons in the one as in the other, the net effect of these π electrons is a non-bonding one by cancellation. One expects the resulting bonding contribution to come mainly from the electron pair in the top-filled σ_g orbital. Consequently it appears that the single bond drawn by the chemist, F—F, Cl—Cl, Br—Br, I—I, is an appropriate representation of the valence situation.

Ab initio calculations of the electronic properties of the halogen molecules are quite numerous in the case of fluorine, scarce in the case of chlorine[57] and, to the author's knowledge at the time of writing, only one calculation has ever been performed on both Br_2 and on I_2[58].

One notices in the case of F_2 that calculations of an improved degree of sophistication and accuracy do not automatically lead to better results, in fact sometimes even to predictions which contradict the much more naïve picture discussed above and supported by experimental evidence. For instance, in an *ab initio* calculation following the Hartree–Fock–Roothaan procedure[59] the energetic sequence of highest-filled orbitals is (in eV) $1\pi_g$ (−18·03), $3\sigma_g$ (−20·29), $1\pi_u$ (−21·91), and the dissociation energy D_e is found to be negative, namely −1·63 eV, the experimental value being +1·65 eV. The best value of D_e for F_2 obtained by the Hartree–Fock method is −1·37 eV[60]. Correlation effects play a decisive role in the electronic structure of the fluorine molecule. By taking these into account, as with the optimized valence configuration method[61], positive values for D_e close to the experimental ones are found. The experimental dissociation energy of F_2 is extremely low, compared for instance to the one for nitrogen of 7·519 eV or for oxygen of 5·178 eV *[62]. Chlorine, with the highest dissociation energy among the halogens[61,63], shows a value which still lies well within the energy spectrum of visible radiation. The photochemical reactivity of the halogens is well known. The primary process of dissociation under light of relatively long wavelength is commented upon in basic textbooks. In the chlorine molecule a satisfactory calculation of D_e to date still seems elusive. Recent valence bond calculations on the one hand[57] and SCF results on the other[61] lead to computed results of 0·71 eV and 0·87 eV respectively, compared to the experimental value of 2·51 eV (Table 1b).

* From $D_0^0 + \omega_e/2$.

In view of advances in mass spectroscopic and molecular beam techniques it is also of interest to get an idea of the dissociation energy of the positive and negative molecular ions. In this connexion the following relations between dissociation energies*, lowest ionization potentials I and electron affinities A are useful[61, 64, 65]:

$$D_e(X_2^-) = D_e(X_2) + A(X_2) - A(X) \tag{3a}$$

$$D_e(X_2^+) = D_e(X_2) - I(X_2) + I(X) \tag{3b}$$

By definition in this context:

$$I(X_2) = E_+(r_e^+) - E(r_e) \tag{4a}$$

$$A(X_2) = E(r_e) - E_-(r_e^-) \tag{4b}$$

where $E(r_e)$, $E_+(r_e^+)$ and $E_-(r_e^-)$ designate the electronic energies of X_2, X_2^+ and X_2^- respectively, at the corresponding equilibrium distance (see Figure 4)†. Electron affinities of halogen molecules have recently been

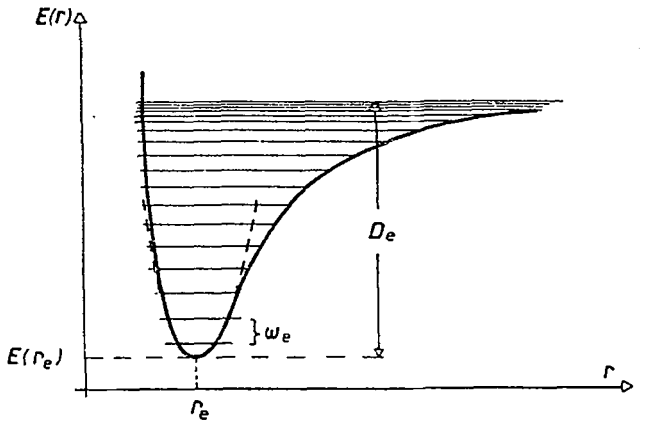

FIGURE 4. Illustration of the binding energy D_e and the vibrational frequency ω_e.

experimentally determined by assessing the charge transfer threshold in halogen ion–halogen molecule[66] or alkali atom–halogen molecule[67, 68] collisions of the types

$$Y^- + X_2 \longrightarrow X_2^- + Y$$

and

$$M + X_2 \longrightarrow X_2^- + M^+$$

* The dissociation energy D_e referred to the potential minimum is also called binding energy.

† I as defined here and I_A, the adiabatic ionization potential, are related by $I_A = I + \frac{1}{2}(\omega_e^+ - \omega_e)$, neglecting terms due to anharmonicity of vibration.

Previous estimates were obtained from charge-transfer spectra for Cl_2, Br_2 and I_2[69] and from the appearance potential of the F_2^- ion in mass spectra[70].

While the dissociation energy measures the depth of the minimum of the potential energy curve, the vibrational frequency ω_e gives an indication of the shape in the vicinity (see Figure 4) of the minimum. One notices from F_2 to I_2 a very marked decrease of ω_e, as simultaneously the equilibrium distance r_e increases.

In the $^2\Pi$ states of the molecular cation the molecule possesses a resulting electronic orbital angular momentum around the internuclear axis, as well as an electronic spin angular momentum. This leads to spin–orbit coupling and a splitting into two different substates $^2\Pi_{\frac{1}{2}}$ and $^2\Pi_{\frac{3}{2}}$, depending on the value of the total electronic angular momentum. The high value of the spin–orbit coupling constant in Br_2 and particularly I_2 illustrates its strong dependence on nuclear charge Z. For a hydrogenic state of given quantum numbers n, l the spin–orbit coupling constant is proportional to Z^4. In a many-electron atom or molecule an effective screened nuclear charge must be taken. The increase is therefore much attenuated, but still important, namely roughly of the order of Z^2.

The electronic absorption spectra of the halogen molecules have been the aim of intense study, but are difficult to characterize in a concise way.

TABLE 1c. Properties of the halogen molecule cations

Experimental property $^2\Pi_g$ state	F_2^+	Cl_2^+	Br_2^+	I_2^+
Internuclear distance r_e (Å)	1·326[a,c]	1·892[b,c]	—	—
Dissociation energy D_e (eV)	3·37[d]	4·03[d]	3·32[d,e]	2·67[d,e]
Vibrational frequency ω_e (cm^{-1})	1054·5[a,c]	645·6[b,c]	376·0[b,c]	—
Spin–orbit coupling constant ζ (cm^{-1})	337 ± 40[c]	645 ± 40[c]	2820 ± 40[c]	5125 ± 40[c]

[a] T. L. Porter, *J. Chem. Phys.*, **48**, 2071 (1968).
[b] F. P. Hubermann, *J. Mol. Spectry.*, **20**, 29 (1966).
[c] Reference 56.
[d] Rough estimate from the relation $D_e(X_2^+) = D_e(X_2) - I(X_2) + I(X)$; see also reference 73.
[e] Value for $^2\Pi_{\frac{1}{2}}$ state.

TABLE 1d. Properties of the halogen molecule anions

Experimental property	F_2^-	Cl_2^-	Br_2^-	I_2^-
Dissociation energy D_e (eV)	1·28[a]	1·28[a]	1·14[a]	1·08[a]

[a] Estimate from the relation $D_e(X_2^-) = D_e(X_2) + A(X_2) - A(X)$; see also reference 61.

In F_2 one finds only continuous absorption, with a maximum at about 34,500 cm^{-1}. Absorption continua set in at 20,850 cm^{-1} in Cl_2 and at 19,580 cm^{-1} in Br_2[62]. For further details see for instance reference 71. A recent and very thorough discussion of the electronic structure and spectrum of iodine is given by Mulliken[72].

Before turning to the carbon–halogen bond, a glance at the halogen hydrides is instructive (see Table 1e). The first ionizations are in general to

TABLE 1e. Properties of the hydrogen halides

Experimental property	HF	HCl	HBr	HI
Ionization potential	16·06[a]	12·80[a]	11·87[a]	10·75[a]
Dipole moment (Debye) gas	1·736[b]	1·034[b]	0·828[c]	0·448[c]

[a] Reference 73, adiabatic values, average of $^2\Pi_{\frac{3}{2}}$ and $^2\Pi_{\frac{1}{2}}$ lines.
[b] A. L. McClellan, *Tables of Experimental Dipole Moments*, W. H. Freeman and Co., San Francisco, 1963.
[c] F. A. Van Dijk and A. M. Dymanus, *Chem. Phys. Letters*, 5, 387 (1970).

the $^2\Pi$ state of the ion. The ionization potential of HF is 1·35 eV lower than the first atomic ionization potential of fluorine, whereas in HI the deviation from the atomic value changes sign and is only −0·30 eV. The dipole moment decreases likewise on going from HF to HI, showing the attenuated effect of the hydrogen atom in the higher hydrogen halides.

II. ALIPHATIC CARBON–HALOGEN COMPOUNDS

A. Alkyl Halides

1. The electronic properties of halomethanes

Photoelectron spectroscopy has recently proved very useful in the study of the carbon–halogen bond within simple homologous series and/or in systems of relatively high symmetry. Assignments of p.e. bands may sometimes be made with limited computational effort and provide a meaningful insight into the electronic structures of both the neutral molecule and the ion. At first we want to compare the p.e. spectra of the fluoromethanes with computed data[54,74]. Then the correlation with the spectra of the derivatives of the higher halogens will be discussed[75,76].

It is perhaps instructive to begin by looking at some structural properties[77] (Table 2). In particular we note the decrease of the C—F bond length on going from CH_3F to CF_4 by the amount of almost 0·07 Å, which indicates an increase in C—F bonding. This change is paralleled by the trend in the

first ionization potential (Table 3b). *Ab initio* calculations[54,74] predict the highest occupied orbitals in CH_3F to be of symmetry e (point group C_{3v}) and to be quite strongly antibonding along the C—F bond (Table 4a). On going from CH_3F to CF_4 the contribution of the top-filled orbital gradually

TABLE 2. Experimental bond lengths r in Å, bond angles θ, and C—F stretching force constants k in mdyn/Å in the fluoromethanes, from reference 77

	CH_4	CH_3F	CH_2F_2	CHF_3	CF_4
r (CH)	1·085	1·105	1·091	1·098	—
r (CF)	—	1·385	1·358	1·332	1·317
θ (HCH)	109·47°	109·9°	112·1°	—	—
θ (FCF)	—	—	108·2°	108·8°	109·47°
k_{C-F}	—	5·8	—	8·1	9·2

TABLE 3a. Experimental vertical ionization potentials in eV, from reference 75

	CH_3F	CH_3Cl	CH_3Br	CH_3I
I_1 (e)	13·04	11·30, 11·32	10·54, 10·86	9·54, 10·16
I_2 (a_1)	17·06	14·42	13·49	12·50
I_3 (e)	17·06	15·40	15·08	14·80
I_4 (a_1)	23·4	21·5	19·9	19·6
Δ_1 (cm^{-1})[a]	—	630 ± 40	2560 ± 30	5050 ± 40

[a] Reference 76.

See also references 54 and 45, Chap. 8.

The symbol $I_1(e)$ designates the potential of the first p.e. band, corresponding to ionization from the top-filled degenerate orbitals of symmetry e; $I_2(a_1)$ stands for the potential of the second p.e. band, corresponding to ionization from the next orbital of symmetry a_1 etc. Δ_1 indicates the spin–orbit splitting in the first p.e. band. Under CH_3Cl, CH_3Br and CH_3I the energies of the resolved $^2E_{\frac{3}{2}}$ and $^2E_{\frac{1}{2}}$ peaks of this first band are given.

TABLE 3b. First vertical ionization potentials in eV of halomethanes

	F	Cl	Br	I
CH_3X	13·04e	11·31e	10·70e	9·85e
CH_2X_2	13·29b_1	11·40$b_2 + a_2$	10·61b_2	9·46b_2
CHX_3	14·80a_1	11·48a_2	10·47a_2	—
CX_4	16·23t_1	11·69t_1	10·54t_2	—

Data and assignments from Reference 75. Averaged values within a p.e. band.

The letters after the numbers indicate the symmetry of the orbital from which ionization occurs.

becomes non-bonding. The experimental first ionization potential then also increases from 13·04 eV to 16·23 eV, a value not very far from the first ionization potential of the neutral fluorine atom. The calculated effective atomic charges (Table 4a) remain relatively constant on the fluorine atoms

TABLE 4a. Computed overlap populations of top-filled SCF–MO and total effective atomic charges, q

	CH_4	CH_3F	CH_2F_2	CHF_3	CF_4
C—F overlap[a]	—	−0·228	−0·142	−0·119	0·000
q_C[b]	−0·305	−0·034	+0·224	+0·530	—
q_F[b]	—	−0·212	−0·200	−0·208	—

[a] Reference 54.
[b] Reference 74.

TABLE 4b. Dipole moments of fluoromethanes in Debye units

	CH_3F	CH_2F_2	CHF_3
Experimental[a]	1·85	1·97	1·65
Ab initio SCF–MO[a]	2·43	2·61	2·21
Ab initio SCF–MO[b]	2·597	2·812	2·245

[a] Reference 74.
[b] Reference 54.

($\sim -0{\cdot}2$), at the expense of the carbon atom, which becomes increasingly positive: perfluorination on one carbon centre appears to make that centre very electron deficient.

The p.e. data on the higher halomethanes contrast with those on the fluoromethanes in two interesting ways: the first ionization potentials in CH_3Cl, CH_3Br, CH_3I are not very far from those in Cl_2, Br_2, I_2, respectively (Tables 1b and 3a). In CH_3F, however, it is about 2·7 eV lower than in F_2. Secondly, on going from CH_3Cl to CCl_4 or from CH_3Br to CBr_4 the first ionization potential does not change appreciably, in contrast to the series CH_3F to CF_4 (Table 3b).

To what extent are the electrons in the top-filled e orbitals of CH_3Cl, CH_3Br or CH_3I 'non-bonding' halogen np electrons? Only a detailed calculation could give a quantitative answer. From the ionization potentials one would assume these orbitals to be more weakly antibonding along C—X (X = Cl, Br, I) than in CH_3F. On the other hand, it also appears

that the bonding properties along C—X do not change as much on going from CH_3X to CX_4 than in the case of the fluorine compounds.

One notices (Table 3a) that the first p.e. band $I_1(e)$ is split by an amount of about 600 cm^{-1} in CH_3Cl, 2500 cm^{-1} in CH_3Br and 5000 cm^{-1} in CH_3I. This splitting (Δ_1) is due to spin–orbit coupling and is of the same order of magnitude as in the parent halogen molecules. An interesting observation has been made and interpreted by Brogli and Heilbronner[80] by studying the p.e. spectra of alkyl monobromides and monoiodides of lower symmetry, in particular of symmetry C_s. If the symmetry axis along the carbon–halogen bond is less than threefold the degeneracy of the e orbitals is lifted and the orbital angular momentum strongly quenched. Consequently one would expect spin–orbit coupling and the concomitant splitting Δ to decrease. Yet this is not observed and the splitting Δ persists undiminished in compounds such as

Brogli and Heilbronner were able to show that this apparent anomaly is due to differences in conjugation of the halogen np orbitals with the alkyl orbitals in and perpendicular to the plane of symmetry. Their simplified model also permits a rationalization of changes in the vibrational fine structure.

It is interesting to note that spin–orbit coupling effects should be smaller in the p.e. spectrum of $CHBr_3$, for instance, than in that of H_3CBr, in spite of the same overall symmetry and of the fact that bromoform contains more heavy atoms[75]. However, none of these atoms lie on a higher ($n \geqslant 3$) axis of rotation, in contrast to methyl bromide. On the other hand, degenerate bands may in general also be split by Jahn–Teller interaction.

From the relatively high ionization potentials it is to be expected that the fluoromethanes absorb at short wavelengths (Table 5). It is found that throughout the series, with the exception of CF_4, the first absorptions appear at about 30,000 cm^{-1} or 3·5–4 eV below the first ionization potential.

TABLE 5. First vertical ionization potential compared to longest-wavelength u.v. absorption (of Rydberg type) in cm^{-1} (from reference 54)

	CH_4	CH_3F	CH_2F_2	CHF_3	CF_4	CH_3CH_3
First ionization	109,400	105,200	107,000	119,800	130,500	97,500
Absorption to 3s	78,000	76,000	75,500	87,000	—	68,000
Absorption to 3p	—	83,500	83,500	95,500	110,000	75,800

Brundle, Robin and Basch[54] assign the first and second absorptions in CH_3F, CH_2F_2 and CHF_3 as Rydberg transitions to 3*s* and 3*p* orbitals, respectively. In CF_4 no transition to 3*s* is reported.

Among other properties, the particular nature of the carbon–fluorine bond is also exhibited by the stretching force constant (Table 6a), which is

TABLE 6a. Carbon–halogen stretching force constants in mdyn/Å, and characteristic frequencies in cm^{-1} (from reference 78)

	F	Cl	Br	I
>C—X	5·96[a]	3·64	3·13	2·65
	1100	650	560	500

[a] See also Table 2.

TABLE 6b. Proton chemical shifts referred to CH_4 in p.p.m. for gaseous monohalo-alkanes (from reference 79)

		F	Cl	Br	I
$H_3C—X$		−4·00	−2·71	−2·32	−1·85
$\overset{II}{H_3}\overset{I}{CH_2}C—X$	I	−4·23	−3·22	−3·12	−2·97
	II	−1·14	−1·29	−1·47	−1·66

very much higher than in corresponding bonds with other halogens. The strongly polarizing influence of fluorine is shown by the proton chemical shifts in monohalogenated alkenes. Interestingly, however, the deshielding effect of fluorine appears to be less long-range than that of iodine (Table 6b).

In view of the importance of radical reactions, comparisons between halomethanes and halomethyl radicals are of immediate interest. Studies of bond dissociation reactions indicate[81] that the dissociation energies of carbon–hydrogen and carbon–bromine bonds to form CBr_3 radicals are about 13–17 kcal/mole lower than the dissociation energies for carbon–hydrogen and carbon–bromine bonds to form CH_3 radicals. This coincides with the observation made by matrix i.r. spectra[82] that the C—Br stretching force constants of CBr_3 are higher than either those of CBr_4 or of $HCBr_3$. Likewise, bond dissociation energies indicate that dibromomethyl is electronically stabilized[82,83], though to a lesser degree than tribromomethyl. Similar findings are made with the corresponding chlorine

compounds, leading to the conclusion that an analogous stabilization of radicals prevails[32]. It seems that in general alkyl radicals are stabilized by chlorine and bromine, in the sense that $\dot{C}X_3$ lies energetically less far above CX_4 than $\dot{C}H_3$ lies above H_3CX, and $\dot{C}X_3$ lies energetically less far above HCX_3 than $\dot{C}H_3$ lies above CH_4 etc. This systematic trend is not observed for the corresponding fluorine compounds. It appears that trifluoromethyl and difluoromethyl are scarcely stabilized in the sense here mentioned[82,83]. In the absence of detailed calculations it is not easy to put the finger on the exact reason for the basic difference between bromo-, chloro- (and presumably also iodo-) methyl radicals, on the one hand, and the fluoromethyl radicals, on the other. It may be due to the very high electronegativity and the lack of easily accessible *d* orbitals for bonding in fluorine.

The determination of the geometry, i.e. planarity or non-planarity, of halomethyl radicals has also been tackled by electron spin resonance[84]. While CH_3 is planar[85], CF_3 is not[86]. From the magnitude of the coupling constants in e.s.r. spectra one predicts CH_2Cl to be nearly planar[87], $CFCl_2$ to be more pyramidal than CCl_3[88,89]. On the other hand, from the interpretation of vibrational spectra, both CBr_3 and CCl_3 appear to be pyramidal, with bond angles intermediate between tetrahedral and planar[82] (see also Table 7).

TABLE 7. Properties of halomethyl radicals

	Geometry	Valence angles	Stabilization
CH_3	Planar	120° [a]	
CF_3	Pyramidal	~115° [b,c]	None[c]
		>109° [c]	
CCl_3	Pyramidal	<120°	~12 kcal/mole[c]
		>109° [c]	
CBr_3	Pyramidal	<120°	~12 kcal/mole[c]

[a] Reference 85.
[b] Reference 86.
[c] Reference 82.

2. The inductive effect and the dipole moments of alkyl halides

The *ab initio* computations of molecular dipole moments are fraught with difficulties even for the simplest of alkyl halides, the fluoromethanes (see Table 4b, section II. A. 1). The results of SCF calculations appear to be numerically too large and they probably depend quite strongly on the choice of basis functions. We do not want to deal here at length with the results obtained by more approximate quantum mechanical procedures,

such as the CNDO method[90], although their agreement with experiment, for reasons hard to analyse precisely, is rather better. Instead, we will go back about twenty years and look at a model for the inductive effect which, though admittedly crude and semi-empirical, permits *a posteriori* to rationalize a quite wide variety of data on the dipole moments of more complicated alkyl halides[91,92]. In particular, a recent application has been made to various chloroethanes[93].

The theory starts out from a knowledge of bond longitudinal polarizabilities, Slater-type electron screening constants and covalent radii. It uses the notions of net charge, total net charge and effective nuclear charge. One considers each bond A—B in the molecule as being essentially made up of two electrons. These electrons may be described by a bond orbital, for instance

$$\phi_{A-B} = a\chi_A + b\chi_B \tag{5}$$

χ_A and χ_B being appropriate atomic orbitals. We define as the net charges on atoms A and B respectively, due to the bond A—B,

$$q_{A-B} = -2e(a^2 + abS) + e \tag{6a}$$

$$q_{B-A} = -2e(abS + b^2) + e = -q_{A-B} \tag{6b}$$

S stands for the overlap integral between χ_A and χ_B and e for the positive elementary charge. This reflects the idea that originally each atom contributes one electron to the bond and, depending on the coefficients a, b, gets a certain amount of electronic charge back. The coefficients a, b may conceivably be calculated using an MO procedure. On the other hand, the net charges may also be assessed empirically, applying formula (10) to appropriate molecules of known dipole moment, as is done in reference 91.

The total net charge on each atom is the sum of the individual bond contributions. For instance, in the case of CH_3X:

$$Q_H = q_{H-C}, \quad Q_C = 3q_{C-H} + q_{C-X}, \quad Q_X = q_{X-C} \tag{7a}$$

Of course

$$3Q_H + Q_C + Q_X = 0 \tag{7b}$$

The total net charge on each atom is not an exact measure for the screening of the nuclear charge. The effective nuclear charge Z_A is made up of a part which is constant for a given atom, on going from one molecule to another, z_{0A}, and a part depending on the total net charge.

$$Z_A = z_{0A} + (s_A/e)\, Q_A \tag{8}$$

where s_A stands for Slater's screening constant[94]. The next quantity of importance is the longitudinal polarizability of a given bond, α^l_{A-B},

which may be inferred from experiment[95] and which is assumed constant on going from one molecule to another. The dipole moment induced in the bond A—B may be expressed as

$$\mu_{A-B} = \alpha^{l}_{A-B} . F \tag{9}$$

where F is an effective or average field strength along the bond. It seems reasonable to write

$$\mu_{A-B} = -q_{A-B} . r_{A-B} = \alpha^{l}_{A-B}\left(\frac{Z_A e}{R_A^2} - \frac{Z_B e}{R_B^2}\right) \tag{10}$$

where r_{A-B} is the bond length and R_A, R_B designate the covalent bond radii of atoms A and B. Expression (10) represents a set of coupled equations, one for each bond in a molecule, subject to the condition (7b) that the sum of total net charges be zero. Using the experimental dipole moments of the molecules CH_3X, say, for calibration, the equations (10) provide a means of predicting the dipole moments and charge distributions of numerous other haloalkanes to a satisfactory degree of accuracy (see Tables 8 and 9).

TABLE 8. Average bond properties

A—B	Bond lengths[a] r_{A-B} (Å)	Bond longitudinal polarizabilities[b] α^{l}_{A-B} ($\times 10^{24}$ cm^3)	Covalent radii[c] R_B (Å)	Bond dipole moments[d] μ_{A-B} (D)	van der Waals radii[e] W_B (Å)
C—H	1·091	0·79	0·30	0·4	1·2
C—C	1·541	1·88	0·771	0	—
C—F	1·381	0·96	0·64	1·41	1·35
C—Cl	1·767	3·67	0·99	1·46	1·80
C—Br	1·937	5·04	1·14	1·38	1·95
C—I	2·135	8·09	1·33	1·19	2·15

[a] Paraffinic bond lengths. *Tables of Interatomic Distances*, (Ed. L. E. Sutton), The Chemical Society, London, 1958.
[b] Reference 91.
[c] Reference 91.
[d] C. P. Smyth, *Dielectric Behavior and Structure*, McGraw-Hill Book Company, New York, 1955, p. 244.
[e] L. Pauling, *The Nature of the Chemical Bond*, 3rd ed., Cornell University Press, Ithaca, N.Y., 1960.

TABLE 9. Calculated and measured dipole moments, in Debye units—vapour phase, unless otherwise stated

	Calculated	Measured	Reference
CH_3F	1·81	1·81	91
CH_3Cl	1·86	1·86	91
CH_3Br	1·78	1·78	91
CH_3I	1·59	1·59	91
CH_2F_2	1·91	1·96	91[a]
CH_2Cl_2	1·63	1·57	91
CH_2Br_2	1·48	1·43	91
CH_2I_2	1·23	1·08–1·14 solution	91
CHF_3	1·53	1·59	91
$CHCl_3$	1·12	1·01–1·15	91
$CHBr_3$	0·98	0·90–1·3	91
CHI_3	0·78	0·80–1·0 solution	91
C_2H_5F	1·95	1·92, 1·96	92
C_2H_5Cl	2·02	2·00–2·05	92
C_2H_5Br	1·95	1·99–2·02	92
C_2H_5I	1·82	1·87–1·93	92
CH_3CH_2Cl	1·86	1·75–2·09	93[b]
CH_3CHCl_2	1·79	2·07–3·33	93[b]
CH_3CCl_3	1·55	1·79–2·03	93[b]
CH_2ClCCl_3	1·58	1·44 solution	93[b]
$CHCl_2CCl_3$	1·09	0·92	93[b]
CCl_3CCl_3	0·0	0·0	93[b]
CH_2ClCH_2Cl	1·03 (25°C)	1·13–1·84	93[b]
$CH_2ClCHCl_2$	1·30 (90°C)	1·25–1·42	93[b]
$CHCl_2CHCl_2$	1·09 (130°C)	1·29, 1·37	93[b]

[a] See also A. L. McClellan, *Tables of Experimental Dipole Moments*, W. H. Freeman, San Francisco, 1963.
[b] And references cited therein.

In the ethyl (and higher) alkyl halides in which the resulting dipole moment varies with conformation, an averaging has to be carried out over the potential for internal rotation: adopting a purely classical approach one writes

$$\langle\mu^2\rangle = \int_0^{2\pi} \mu^2(\phi) \exp\{-E(\phi)/kT\}\,\mathrm{d}\phi \Big/ \int_0^{2\pi} \exp\{-E(\phi)/kT\}\,\mathrm{d}\phi$$

Obviously in these cases a temperature dependence of the molecular dipole moment must be and actually is observed.

3. Barriers to internal rotation in haloethanes

In view of the very large amount of computer time required for *ab initio* calculations on large molecules, predictions, or rather rationalizations, of the barriers to internal rotation in haloethanes must today still mainly be based on a more empirical frame of reference. If the lack of deeper insight is partly compensated by conceptual simplicity, the aims of the experimental chemist may be served just as well.

Scott and Scheraga[96] have proposed a procedure for calculating barriers to internal rotation[97] based mainly on two effects, namely 'exchange interaction' of the electrons in bonds adjacent to the bond about which internal rotation occurs and 'non-bonded' or van der Waals interactions. All bond distances and bond angles, with the exception of the angle of internal rotation ϕ, are considered fixed in the molecule. The conformational energy $E(\phi)$ is expressed as

$$E(\phi) = \tfrac{1}{2}E_0(1+\cos 3\phi)+\sum_{ij}\{a_{ij}\exp(-b_{ij}r_{ij})-c_{ij}r_{ij}^{-6}+d_{ij}r_{ij}^{-1}\} \quad (11)$$

where the first term on the right-hand side represents the 'exchange interaction', while the second term sums up the 'non-bonded interactions' between all pairs of atoms i, j whose relative distance of separation r_{ij} depends on ϕ. Within molecules of the same class, such as substituted ethanes, the quantity E_0 is taken as constant. The parameters a_{ij}, b_{ij} and c_{ij} characterize a van der Waals potential[98] and $d_{ij}r_{ij}^{-1}$ stands for an additional Coulombic potential due to the interaction of atomic charges. Table 10 summarizes values for these parameters and Table 11 gives data

TABLE 10. Parameters for the non-bonded potential functions as given by reference 96—energies in kcal/mole, distances in Å (see formula 11)

Interaction i j	a_{ij}	b_{ij}	c_{ij}	d_{ij}
H···H	$9{\cdot}17\times10^3$	4·54	45·2	0
H···F	$1{\cdot}69\times10^4$	4·57	62·7	0
H···Cl	$3{\cdot}90\times10^4$	4·15	321	0
H···Br	$2{\cdot}18\times10^4$	3·66	465	0
F···F	$6{\cdot}02\times10^4$	4·60	118	14·4[a]
F···Cl	$1{\cdot}47\times10^5$	4·18	527	4·09[a]
Cl···Cl	$3{\cdot}14\times10^5$	3·75	2520	1·16[a]
Br···Br	$3{\cdot}46\times10^4$	2·78	5180	0

[a] Value for the case where the halogen atom is attached to carbon, as in haloethanes.

on barriers to internal rotation. The calculations by Mark and Sutton[93] follow exactly the procedure of Scott and Scheraga with two exceptions. (a) To obtain the Coulombic parameters d_{ij} they explicitly take into account the atomic charges as derived by the method described in the preceding section II. A. 2. (b) Scott and Scheraga adopt for E_0 the value 3·11 kcal/mole, Mark and Sutton 2·9 kcal/mole.

TABLE 11. Barriers to internal rotation in kcal/mole

Molecule	Experimental	Calculated (Scott and Scheraga[a])	Calculated (Mark and Sutton[b])	Calculated (CNDO[c])
CH_3CH_3	2·70–3·10[a]	3·29		2·18
CH_3CH_2F	3·30[c]	3·31		2·00
CH_3CHF_2	3·18	3·33		1·88
CH_3CF_3	3·48	3·35		1·76
CF_3CH_2F	4·58			1·46
CF_3CHF_2	3·51			1·22
CF_3CF_3	3·92	4·35		1·07
CH_3CH_2Cl	3·7[b]	3·44	3·0	
CH_3CHCl_2	3·5	3·56	3·1	
CH_3CCl_3	2·8	3·73	3·3	
CCl_3CH_2Cl	10·0		8·7	
CCl_3CHCl_2	14·2		14·1	
CCl_3CCl_3	17·5[b]; 12·0[a]	20·89	19·6	

[a] Reference 96.
[b] Reference 93.
[c] Reference 99.

In general, we notice in Table 11 that the barrier heights significantly deviate from a value around 3–4 kcal/mole only in cases where Cl···Cl interaction is present, that is, when relatively 'bulky' substituents are on both carbon atoms. In the case of the fluoroethanes, application of the semi-empirical quantum chemical CNDO procedure fails to predict the correct trend[99]. *Ab initio* SCF calculations have been performed on different conformations of 3-fluoropropene[100] to assess theoretically the barrier to internal rotation around the C—C single bond.

Experimentally, barrier heights may be determined from microwave data for molecules with permanent dipole moments, or from far infrared spectra. In other cases one must rely on the results of electron diffraction measurements or on thermodynamic data. In recent years ultrasonic absorption techniques[101] have met with some success and the application

of nuclear magnetic resonance appears to gain in importance[102]. A case in point is that of perhalogenated ethanes containing different combinations of fluorine, chlorine and bromine atoms. To obtain the barriers from microwave or infrared data for such complicated asymmetric tops is exceedingly difficult. The temperature dependence of the fluorine nuclear magnetic resonance, on the other hand, may be more easily interpreted to estimate these barriers. Newmark and Sederholm[103] have studied the fluorine n.m.r. spectra of such molecules as $CFCl_2$—$CFCl_2$, CF_2Br—CCl_2Br, CF_2Br—$CFBr_2$, CF_2Br—CFBrCl, CFClBr—CFClBr and CF_2Br—CHBrCl. Applying absolute reaction rate theory[104], they find free energies of activation for the transitions between different rotamers of the order of 7–12 kcal/mole. These free energies of activation may, with some reserve, be equalled with torsional barriers.

B. Halogenated Ethylenic Compounds

1. The electronic properties of some halogenated ethylenes from p.e. spectra

As in the case of the alkyl halides, photoelectron spectroscopy reveals some highly interesting details on the electronic structure of halogenated ethylenes. Table 12 gives the values for the first and second vertical

TABLE 12. First and second vertical ionization potentials of halogenated ethylenes

	$I_1(\pi)$	$I_2(\sigma)$	Reference
$H_2C{=}CH_2$	10·51[a]	12·38[a]	45
	10·6	12·85	106
$H_2C{=}CHF$	10·58	13·79	106
cis-HFC=CHF	10·43	13·97	106
trans-HFC=CHF	10·38	13·90	106
$H_2C{=}CF_2$	10·72	14·79	106
$F_2C{=}CHF$	10·53	14·64	106
$F_2C{=}CF_2$	10·52	15·95	106
$F_2C{=}CHCl$	10·04	12·15	105
$F_2C{=}CFCl$	10·24	13·01	105
$F_2C{=}CCl_2$	9·84	12·14	105
$H_2C{=}CHCl$	10·18	11·72	105
cis-HClC=CHCl	9·83	11·71	105
trans-HClC=CHCl	9·81	11·86	105
$H_2C{=}CCl_2$	10·00	11·67	105
$Cl_2C{=}CHCl$	9·65	11·73	105
$Cl_2C{=}CCl_2$	9·51	11·38	105

[a] Adiabatic values.

ionization potentials of the fluorinated and chlorinated species and we wish to comment on some significant points.

Unquestionably the first ionization in ethylene at 10·51 eV (adiabatic) is from the $\pi (1b_{3u} = 1b_{zu})^*$ orbital[45], firstly because the vibrational fine structure of the p.e. band appears to show characteristic strong excitation of the totally symmetric C—C stretching mode of the ion in conjunction with the twisting vibration, secondly from the energetic sequence of SCF orbitals in the neutral molecule and Koopmans' theorem.

On similar grounds it is concluded that the p.e. bands occurring between 10·38 and 10·72 eV in the fluoro compounds[105, 106], between 9·51 and 10·18 eV in the chloro species[105], also correspond to ionization from the respective highest filled orbital of symmetry π. Interestingly, the first ionization potentials in the fluoro compounds are all very close to the value in ethylene and scarcely depend on the number of fluorine atoms present. In the chloro compounds the first ionization potential is lowered with respect to ethylene by about 0·4 eV when there is one chlorine atom, by 0·6–0·8 eV when there are two, by 0·95 when there are three and by about 1·1 eV in the tetrachloro case. This lowering may be explained by the conjugation of the halogen $3p_z$ atomic orbital of chlorine with the π_z orbital of the C=C bond[105]. In the fluorinated species, because of the high ionization potential of the fluorine atom, the corresponding conjugative effect is smaller and the inductive effect is larger than in chlorine, tending to keep the first ionization potential close to the value of the unsubstituted compound (see also Figure 5).

The relative insensitivity of the first ionization potential of ethylene towards fluorination is contrasted by the drastic stepwise increase of the second ionization potential, which in the molecular orbital picture corresponds to the ionization from an orbital of symmetry σ. This finding has been termed the perfluoro effect[106]. It parallels the trend observed for the first ionization potential in the fluoromethanes (see section II. A. 1) and reveals the strong inductive effect of fluorine on σ MO's (see Figure 6). On a computational level it is conceivably mirrored by a growing presence of fluorine atomic orbitals in the corresponding σ molecular orbital. In the extreme case of tetrafluoroethylene the second ionization potential lies 0·3 eV below the first one of tetrafluoromethane and 0·2 eV above the first ionization potential of F_2.

In the chlorinated compounds, on the other hand, the second ionization

* For the irreducible representations of the point group D_2, B_1, B_2, B_3, we here adopt the convention B_x, B_y, B_z in accordance with references 113 and 114. In reference 94, p. 386, and reference 112, however, one finds another convention, B_z, B_y, B_x.

potential changes only slightly within the series, in analogy to the first ionization potential of the chloromethanes. In fact, all the values differ by at most 0·4 eV from the first ionization potential of the molecule Cl_2 (see Table 1b). They all lie below the second ionization potential of

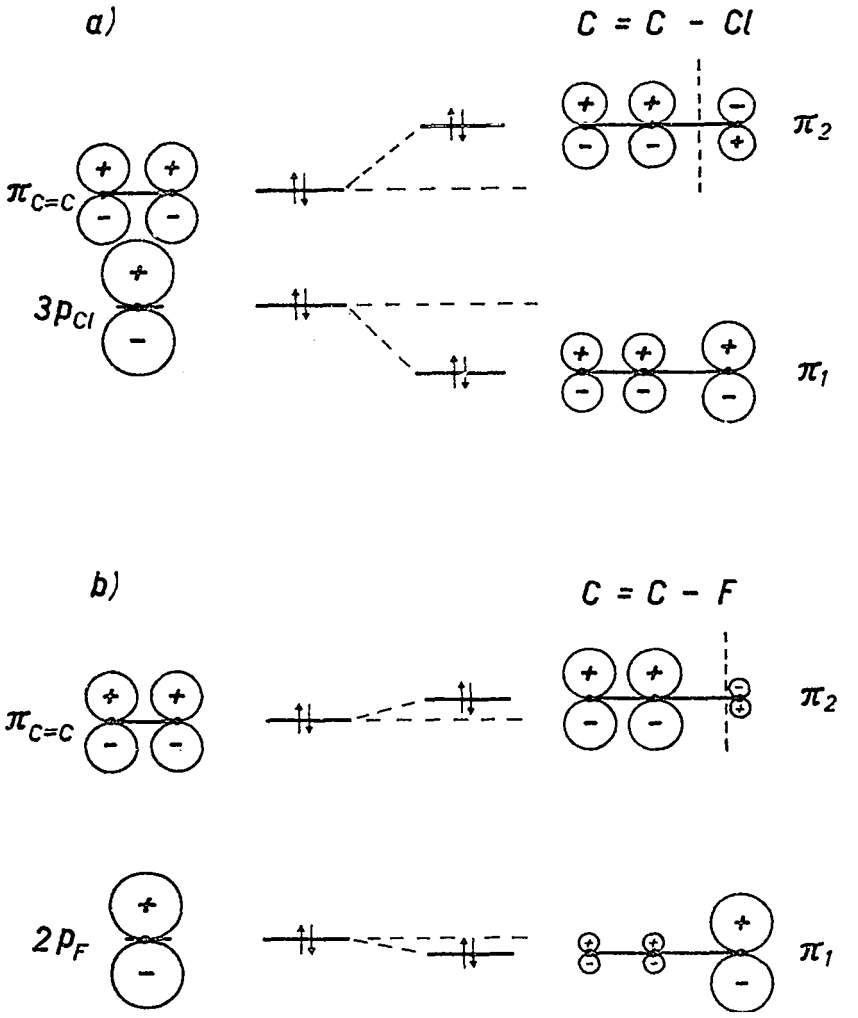

FIGURE 5. (a) The destabilizing influence of chlorine by conjugation with the highest filled π orbital of ethylene. Note the node bisecting the C—Cl bond in π_2. (b) Because of the higher ionization potential of fluorine, i.e. its lower $2p$ level, the conjugative effect is much less pronounced. The inductive effect is here disregarded. In neither case (a) nor (b) does the lower π level, π_1, correspond to the second ionization potential. The second ionization potential corresponds in both cases to removal of a higher-lying σ electron.

unsubstituted ethylene. Obviously, the σ molecular orbitals from which these ionizations occur must contain substantial contributions from the $3p$, originally non-bonding, chlorine orbitals. However, in contrast to the fluorinated species, the inductive effect must here be of lesser importance.

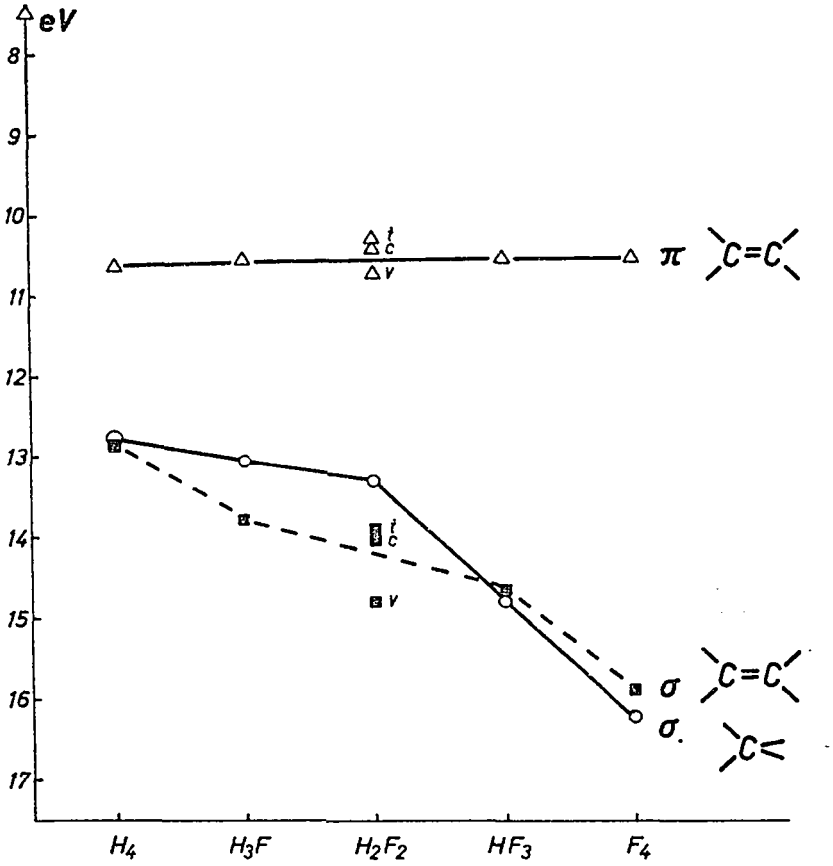

FIGURE 6. The perfluoro effect: ○, the first ionization potential of the fluoromethanes; ▣, the second ionization potential of the fluoroethylenes; △, the first ionization potential of the fluoroethylenes, which is scarcely affected; *t*, *c*, *v* mean *trans*, *cis*, *vicinal*, respectively.

In the halogen molecules X_2 the highest filled π molecular orbitals are doubly degenerate and antibonding (see Figures 2 and 3). In halogenated ethylenes a degeneracy of the two top filled orbitals is ruled out by lack of cylindrical symmetry. However, the highest filled π orbital, and the highest σ orbital at least, should be antibonding along the C—X bond(s). Along the C—C bond these orbitals are of course expected to be bonding.

From the study of a Rydberg series in the electronic spectrum of C_2Cl_4, which converges to a first adiabatic ionization limit at 9·33 eV (corresponding to the vertical ionization potential of 9·51 eV in the p.e. spectrum), Humphries, Walsh and Warsop[107] conclude that, relative to the ground state of the molecule, the upper Rydberg states and the ground state of the $C_2Cl_4^+$ ion have increased C—C bond lengths and slightly decreased C—Cl bond lengths. From an application of the Franck–Condon principle they deduce the values of $+(0{\cdot}11 \pm 0{\cdot}01$ Å) for the change of the C—C bond lengths and $-(0{\cdot}03 \pm 0{\cdot}015$ Å) for the C—Cl bonds in the ground state of the ion, as compared to the ground state of the neutral molecule.

These results may be qualitatively understood by the fact that upon removal of an electron from the top filled π orbital the bond order of the C—C bond decreases, while the one of the C—Cl bonds increases. The bond length should increase with decreasing bond order and vice versa. For a detailed account of bond length–bond order relationships see reference 109. Coulson and Luz[108] have investigated the question more quantitatively considering also electrostatic and exchange interactions and they conclude that bond order changes indeed account primarily for the experimental result.

2. The electronic spectra of halogenated ethylenes

To what extent and in what manner do the electronic spectra of halogenated ethylenes differ from the spectrum of ethylene itself? A difficulty in interpreting these spectra comes from the fact that even the longest-wavelength bands strongly overlap. In ethylene it is generally concluded[110, 111] that the broad band, consisting of a very long progression ($f \approx 0{\cdot}3$) starting at or above 2150 Å and attaining a maximum at about 1620 Å, is the V←N transition, corresponding to $\pi_z \rightarrow \pi_z^*$ excitation, of symmetry $^1B_{xu}$ in the planar molecule. It appears from the vibrational fine structure that much of the long-wavelength intensity of the transition comes from the molecule being in a non-planar conformation where one CH_2 group is twisted with respect to the other one. A series of sharp doublets, starting at 1750 Å, is attributed to a first Rydberg $\pi_z \rightarrow \sigma^*(3s)$ transition ($f \approx 0{\cdot}03$). It is followed by higher transitions of the Rydberg type converging at the adiabatic ionization limit of 10·51 eV. Recently Buenker, Peyerimhoff, Hsu and Kammer[112-114] have, from *ab initio* calculations, come to a somewhat modified interpretation of the broad 2150–1620 Å V←N band system. They conclude that non-vertical transitions are responsible for the absorption maximum around 1620 Å, the molecule in the excited state being in a twisted conformation. Moreover, two excited singlet states have to be considered to interpret this band. As

hitherto assumed, the state termed V_u, corresponding to $^1B_{xu}(\pi_z \rightarrow \pi_z^*)$ in the planar molecule and in addition the V_g state corresponding to $^1B_{xg}(\pi_z \rightarrow 3p_y)$ has also to be taken into account[115]. As the molecule gets twisted, the angle θ going from 0° to 90°, the point group of the molecule changes: $D_{2h} - D_2 - D_{2d}$. The $^1B_{1g}(^1B_{xg}) - {}^1B_1 - {}^1B_2$, V_g state always lies energetically below the $^1B_{1u}(^1B_{xu}) - {}^1B_1 - {}^1A_2$, V_u state[113]. The $V_g \leftarrow N$ transition, though magnetic dipole allowed and electric dipole forbidden for $\theta = 0$, gains electric dipole allowedness for $0° < \theta < 90°$, reaching a maximum at about 40°. This transition therefore also contributes intensity to the band in question. For a detailed theoretical discussion of the vibrational fine structure see reference 114.

A systematic experimental study of the u.v. spectra of fluoroethylenes was recently carried out by Bélanger and Sandorfy[116]. It is shown that these spectra may be well correlated with that of ethylene. With decreasing wavelength the main sequence of transitions is, according to the assignment of these authors, a sharp Rydberg $3R \leftarrow N$ band followed by a broad $\pi \rightarrow \pi^*$ absorption, leading into a series of higher Rydberg transitions. Table 13 only accounts for the lowest part of the spectra. With increasing fluorination the $3R \leftarrow N$ band is pushed to the red. Interestingly, a similar

TABLE 13. The longest-wavelength transitions in halogenated ethylenes in Å and their assignment (only the onset of the Rydberg bands is indicated)

	$\pi \rightarrow \sigma^*(3s)$		$\pi \rightarrow \pi^*$		$\pi \rightarrow \sigma^*(3p)$	
$H_2C{=}CH_2$[a]	$3R \leftarrow N$	1744	$V \leftarrow N$	Max. 1620	$3R' \leftarrow N$	<1620
$H_2C{=}CH_2$[b]	$3R \leftarrow N$	1744	$V_u \leftarrow N$	$\leqslant 1620$	$V_g \leftarrow N$	$\geqslant 1620$
$H_2C{=}CHF$[c]	$3R \leftarrow N$	1776	$V \leftarrow N$	Max. 1665	$3R' \leftarrow N$	1532
cis-HFC=CHF		1910		Max. 1585		1586
trans-HFC=CHF		1775		Max. 1665		1502
$H_2C{=}CF_2$		1840		Max. 1650		1568
$F_2C{=}CHF$		1907		Max. 1600		1555
$F_2C{=}CF_2$		1945		Max. 1395		1547
$H_2C{=}CHCl$[d]	3, $4R \leftarrow N$	1750	$V \leftarrow N$	Max. 1840	Higher Rydberg	1585
trans-HClC=CHCl[d, e]		1800		Max. 1950		1528
$Cl_2C{=}CCl_2$[d, f]		<2000		Max. 1970	Max. 1615;	1573

[a] References 110 and 111.
[b] References 112–114; see explanation in text.
[c] Reference 116.
[d] Reference 110, pp. 536 ff.
[e] Reference 112.
[f] Reference 107.

more pronounced trend is observed with increasing methylation of ethylene[117–119]. Now, however, while in tetramethyl ethylene the first ionization potential is 8·53 eV (determined by electron impact)[120], in the tetrafluoro compound it is practically the same as in unsubstituted ethylene. So the mechanism of the red-shift may be a different one. The maximum of the $\pi \rightarrow \pi^*$ band occurs in mono-, di- and trifluorinated ethylenes around 1600 Å, as in ethylene itself. Tetrafluoroethylene is an exception in that this band is found at 1395 Å. As in the case of the red-shift of the 3R←N band, this blue-shift of the $\pi \rightarrow \pi^*$ absorption cannot be attributed to a change in the energy of the π orbital. Bélanger and Sandorfy[116] consider the possibility that when the last hydrogen of ethylene is substituted by fluorine the potential barrier to torsion becomes so high that the excited state remains coplanar and strongly antibonding with a correspondingly high energy. It may also have to do with the very low energy (see Table 12) of the highest σ orbital. INDO–CI calculations[121] show that in all fluoroethylenes there is an interaction between a $\sigma\sigma^*$ configuration and the pure $\pi\pi^*$ configuration, thereby lowering the V($\pi \rightarrow \pi^*$) excited state. In the tetrafluoro compound the $\sigma\sigma^*$ configuration is energetically so high as to be of vanishing influence.

It is hard to give a simple account of the spectra of the chloroethylenes[107, 110, 122]. Some rudimentary data are given in Table 13. A basic analogy to the ethylene spectrum appears to be maintained. A marked red-shift of the V←N maximum is encountered, as compared to ethylene. Of interest is a recent study of the vacuum u.v. spectra of several chlorofluoroethylenes[123]. An attempt is made to correlate the V←N data of these compounds with that of the chloroethylenes on the one hand, the fluoroethylenes on the other. The selective influence of the different F and Cl substituents on the energies of the π and π^* orbitals is considered. Among the conclusions by Scott and Russell[123]: the initial large destabilization of the π orbital energy of ethylene on chlorine substitution (see Tables 12 and 13 and Figure 5) is present in the chlorofluoroethylenes. The initial large stabilization of the π^* orbital energy observed in the chloroethylenes is not present in the chlorofluoroethylenes.

C. The Electronic Structure of Halogenated Acetylenes

An important feature of acetylene and its halogenated derivatives is the linear equilibrium geometry of the electronic ground state. The vibrational and rotational fine structure of the longest-wavelength absorption band beginning around 2400 Å leads to the conclusion that the first excited state of acetylene is bent, however, having C_{2h} symmetry (*trans* form)[124]. The electronic spectra of chloro- and bromoacetylene have been studied by

Thomson and Warsop[125,126]. In chloroacetylene there are two electronic transitions above 2000 Å, namely around 2500 Å and 2250 Å respectively, also leading to non-linear excited states. These bands probably both correspond to $\pi \rightarrow \pi^*$ excitations. Below 2000 Å there appear several Rydberg transitions to linear excited states. The spectrum of bromoacetylene is analogous to that of the chlorine compound, but shifted slightly to the red[126,127]. The interpretation of the recorded bands in terms of intravalence or Rydberg transitions is similar to the chlorine case. The maintenance of linearity in the Rydberg transitions lets one assume that the ionized species will also be linear. This is beautifully confirmed by the photoelectron spectra.

Heilbronner and coworkers[128-130] have measured the photoelectron spectra of mono- and dihalogen acetylenes and have interpreted their results in a most complete and elegant fashion. The sequence and symmetry of the highest filled molecular orbitals of the neutral molecules follow from elementary group theory and simple energetic considerations. In the monohalogen compounds of symmetry $C_{\infty v}$ the sequence, diminishing in energy, is π, π, σ, σ ..., while in the dihalogen species of symmetry $D_{\infty h}$ one finds $\pi_u, \pi_g, \pi_u, \sigma_g, \sigma_u$ .... In this sense it is possible, even in the absence of more quantitative computations, to assign the photoelectron bands quite in detail, if perhaps tentatively (see Table 14 and Figures 7a, 7b). The confirmation has to come from a study of the fine structure. The electron configuration of the ion obtained by ionizing an electron from the molecular orbital π_i in the neutral molecule gives rise to two substates of total angular momentum $\frac{3}{2}\hbar$ and $\frac{1}{2}\hbar$ respectively, energetically separated due to spin–orbit coupling (see also section I. B and section II. A. 1 and reference 2, p. 10). Besides the vibrational structure, more or less present in all bands, the spin–orbit splitting between these two $^2\Pi_{\frac{3}{2}}^{(i)}$ and $^2\Pi_{\frac{1}{2}}^{(i)}$ states comes out very strikingly in the higher halogen derivatives[128,129]. The magnitude of the splitting Δ_i for a given band is experimentally given as the energy difference of two characteristic sharp peaks:

$$\Delta_i = I_{\frac{3}{2}i} - I_{\frac{1}{2}i} \tag{12}$$

The average ionization potential I_i (which, by Koopmans' theorem is considered equal to the SCF energy of orbital π_i), listed in Table 14, is the average value

$$I_i = \tfrac{1}{2}(I_{\frac{3}{2}i} + I_{\frac{1}{2}i}) \tag{13}$$

Theoretically, the magnitude of Δ_i is roughly equal to[128]

$$\Delta_i \approx \zeta' \sum_p Z_p^2 \, c_{ip}^2 \tag{14}$$

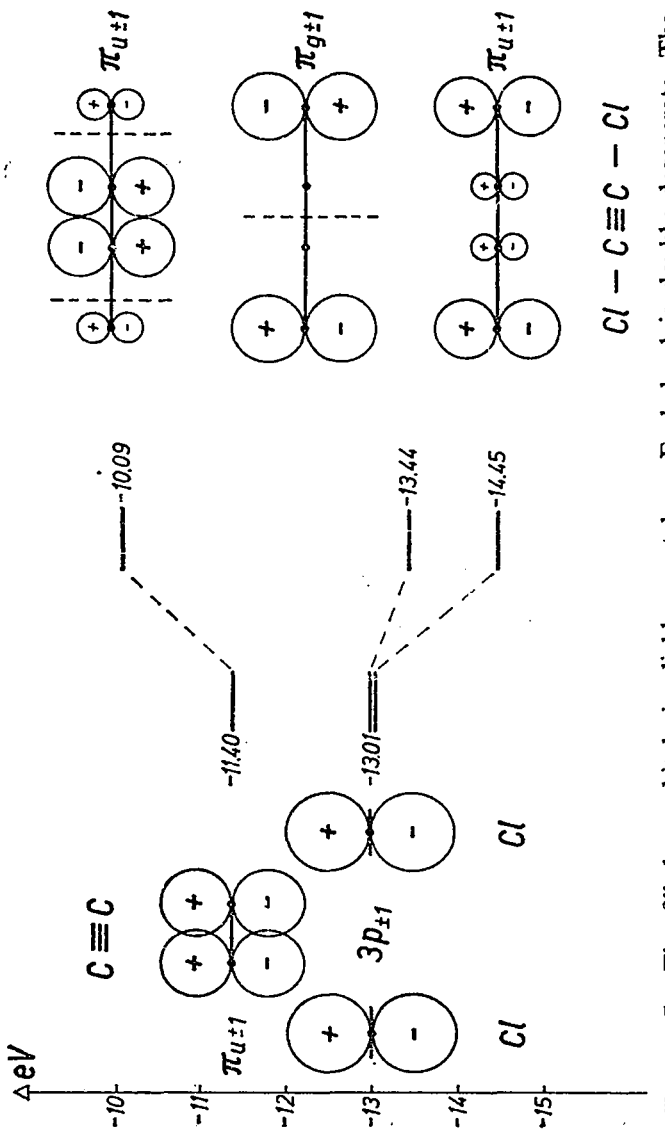

FIGURE 7a. The filled π orbitals in dichloroacetylene. Each level is doubly degenerate. The highest orbital contains a relatively small chlorine contribution. Note the node across both C—Cl bonds. (See also reference 128.)

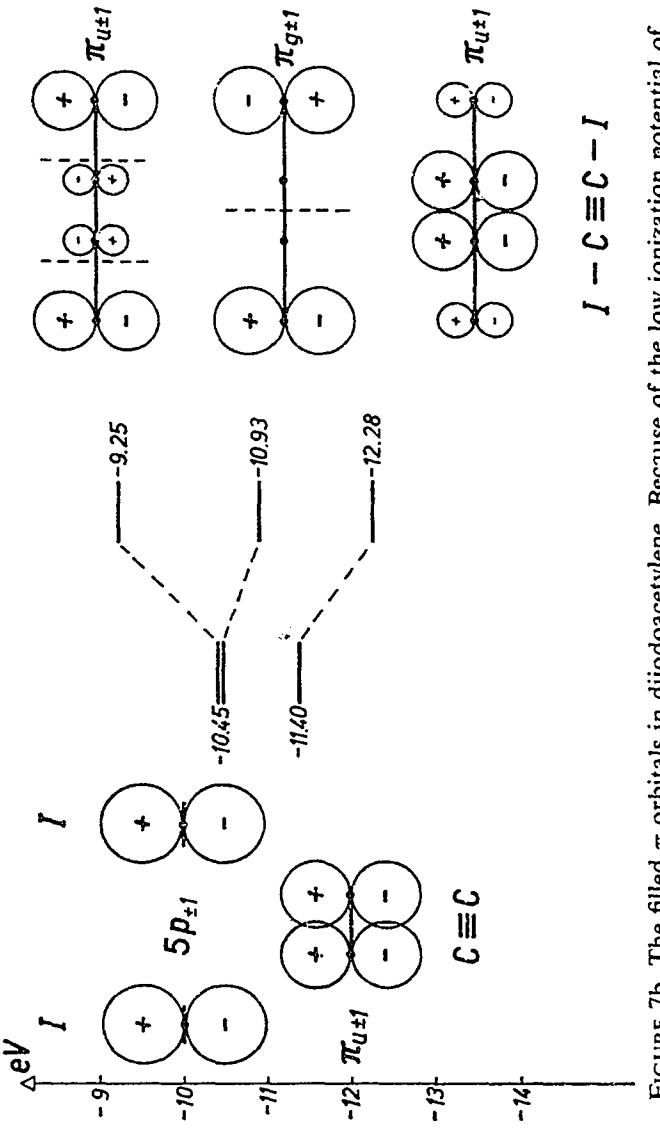

FIGURE 7b. The filled π orbitals in diiodoacetylene. Because of the low ionization potential of iodine the highest π orbital shows a relatively large iodine contribution. (See also reference 128.)

where Z_p is the nuclear charge of the pth atom in the linear molecule, c_{ip} is the LCAO coefficient on atom p of the molecular orbital π_i and ζ' is a constant. Contributions from atoms H, C and even F are negligible, for Cl they become measurable, for Br and I they are large, as in the halogen

TABLE 14. Average vertical ionization potentials of halogenated acetylenes from Heilbronner and coworkers[a] and, for comparison, of acetylene[b], the halogen molecules[c] and some interhalogen compounds[d]

	I_1	I_2	I_3	I_4	I_5
HC≡CH[b]	π_u 11·40	σ 16·44	σ 18·42		
F_2[c]	π_g 15·70	π_u 18·98			
HC≡CF[a]	π 11·26	σ? 17·8	π ?		
Cl_2[c]	π_g 11·49	π_u 14·43			
HC≡CCl[a]	π 10·63	π 14·08	σ 16·76	σ 18·10	
ClC≡CCl[a]	π_u 10·09	π_g 13·44	π_u 14·45	σ_g 16·76	σ_u 17·81
Br_2[c]	π_g 10·71	π_u 13·08			
HC≡CBr[a]	π 10·31	π 13·00	σ 15·99	σ 17·6	
BrC≡CBr[a]	π_u 9·77	π_g 12·26	π_u 13·38	σ_g 15·64	σ_u 16·90
I_2[c]	π_g 9·66	π_u 11·43			
HC≡CI[a]	π 9·94	π 12·08	σ 14·86	σ 17·4	
IC≡CI[a]	π_u 9·25	π_g 10·93	π_u 12·28	σ_g 14·22	σ_u 15·48
ClBr[d]	(π 11·1)				
ClC≡CBr[a]	π 9·98	π 12·64	π 14·08	σ 16·07	σ 17·47
ClI[d]	(π 10·31)				
ClC≡CI[a]	π 9·60	π 11·66	π 13·85	σ 14·88	σ 17·21
BrI[d]	(π 9·98)				
BrC≡CI[a]	π 9·51	π 11·46	π 13·03	σ 14·71	σ 16·35

[a] References 128, 129.
[b] References 45, 106 and C. Baker and D. W. Turner, *Chem. Comm.*, 797, 1967.
[c] Reference 56.
[d] R. W. Kiser, *Tables of Ionization Potentials*, Dept. of Chemistry, Kansas State University, Manhattan, Kansas, 1960; electron impact data.

molecules themselves. The fact that Δ_i depends on the coefficients c_{ip} is of interest in discussing the relative differences between the π orbitals.

Figures 7a and 7b show in a qualitative fashion the shapes of the three highest occupied orbitals in Cl—C≡C—Cl and I—C≡C—I (for details

on the following σ orbitals, see reference 128). The orbitals are pairwise degenerate*:

$$\pi_{+1} = \frac{1}{\sqrt{2}}(\pi_y + i\pi_z) \tag{15a}$$

$$\pi_{-1} = \frac{1}{\sqrt{2}}(\pi_y - i\pi_z) \tag{15b}$$

Each orbital is doubly occupied in the ground state of the neutral molecule. In all molecules X—C≡C—X the second highest pair of molecular orbitals $\pi_g \pm 1$ practically consists only of halogen $np_{\pm 1}$ orbitals, because of the node bisecting the molecule. Accordingly, the corresponding coefficients are large and for a given compound one should find $\Delta_2 > \Delta_1, \Delta_3$ (see Table 15), in agreement with experiment. Looking at the iodine compound, one deduces that the top π_u orbital contains a stronger iodine contribution than the lower one, leading to the conclusion $\Delta_1 > \Delta_3$, which is also verified

TABLE 15. Absolute values in eV of spin–orbit splittings between $^2\Pi_{\frac{1}{2}}$ and $^2\Pi_{\frac{3}{2}}$ states—data on halogenated acetylenes are from Heilbronner and coworkers[a]; Δ_i refers to ith ionized state (see Table 14)

	Δ_1	Δ_2	Δ_3
Cl[b]	0·11		
Cl_2[c]	0·08		
HCl[b]	0·10		
HC≡CCl[a]	—	~0·08	
ClC≡CCl	—	~0·10	
Br[b]	0·46		
Br_2[c]	0·35	~0·26	
HBr[b]	0·32		
HC≡CBr[a]	0·14	0·13	
BrC≡CBr	0·20	0·29	0·13
I[a, b]	0·94		
I_2[c]	0·64	~0·79	
HI[b]	0·66		
HC≡CI[a]	0·41	0·23	
IC≡CI	0·44	0·60	0·21

[a] References 128 and 129.
[b] Reference 73.
[c] Reference 56.

* The x-axis coincides with the molecular axis.

experimentally. In the chlorine compound one would expect the reverse to be the case, only the effect does not seem to be measurable. The potential for ionization from the π_g orbital lies in all symmetric dihalogenated acetylenes at about 0·4 eV above the first atomic ionization potential of the corresponding halogen atom (see Tables 1a and 14).

We notice that, as in the halogenated ethylenes (see section II. B. 1) the highest occupied π molecular orbital is antibonding along a C—X bond, which implies that the overlap population, or the contribution to the bond order, is negative. Consequently one expects these bonds to be shortened upon Rydberg excitation or ionization of one electron out of this top π orbital. Heilbronner, Muszkat and Schäublin[130] have estimated the interatomic distances in monohaloacetylene radical cations from the vibrational fine structure of the photoelectron spectra. By the Franck–Condon principle, and assuming the ionization to proceed from the lowest vibrational level of the neutral molecule in its ground state, only totally symmetric vibrations will show up in these spectra. In analogy to Smith and Warsop[131] Heilbronner and coworkers proceed as follows: the vibration in question is identified from the vibrational spacings, based on a normal co-ordinate analysis of the neutral molecule. This presupposes that the vibrational frequencies do not change drastically upon ionization and that the linearity of the molecular geometry remains unaffected. The intensity of the vibrational sub-bands is considered to be proportional to the Franck–Condon factors. From an analytical expression for these factors[132] the relative change in the equilibrium value of the normal co-ordinate in question is assessed and transformed into changes in internal co-ordinates. The results so obtained from the photoelectron band of lowest energy are[130]: $\Delta r_{C-F} = -0{\cdot}062$ Å, $\Delta r_{C-Cl} = -0{\cdot}067$ Å, $\Delta r_{C-I} = -0{\cdot}078$ Å. On the other hand, the C≡C bond length increases by the respective amounts +0·053 Å, +0·026 Å, +0·025 Å.

Ab initio SCF calculations on HC≡CF and HC≡CCl have been performed by McLean and Yoshimine (cited in reference 133) and on the dihalogenated species by Straub[134]. Results of some n.q.r. measurements are to be found in reference 135.

III. AROMATIC CARBON–HALOGEN COMPOUNDS

A. The u.v. Spectra of Halogen-substituted Benzene

The influence of a substituent on the π electrons of an aromatic system, such as benzene or naphthalene, may, to a first approximation, be subdivided into an inductive effect and a resonance, or conjugative effect[136]. From that viewpoint the inductive effect of a substituent corresponds to

the influence of a perturbing electrostatic potential field on the π electrons of the unsubstituted molecule. A strongly electronegative substituent will, for instance, increase the effective positive nuclear charge of the carbon atom C′ to which it is attached. In the language of simple Hückel theory the absolute value of the corresponding Coulomb integral will be increased: $|\alpha_{C'}| > |\alpha_C|$. However, in the molecular orbital itself no explicit cognizance is taken of the substituent orbital(s). The resonance effect, or effect of conjugation on the other hand, takes into account the capacity of the substituent itself to contribute electrons to the π electron system. In the case of halogen each substituent contributes two electrons originally located in np_z orbitals which are perpendicular to the plane of the molecule. The region over which the π electrons are delocalized is consequently extended. In the language of simple Hückel theory there is a non-vanishing resonance integral $\beta_{C'X}$ between the substituent and the adjacent carbon atom C′, and the molecular orbitals explicitly contain halogen np_z contributions.

It was recognized a long time ago[137] that the electronic spectrum of benzene cannot possibly be understood on a simple one-electron basis, on account of the degeneracy of the Hückel orbitals e_{1g}^+ and e_{1g}^-, e_{2u}^+ and e_{2u}^-. The π electrons have to be regarded as an inseparable system, that is, the mutual influence of the electrons must be considered explicitly by means of configuration interaction. Although, in those substituted benzene derivatives in which there remain only twofold axes of symmetry, this degeneracy is more or less strongly lifted, electron interaction remains a very important effect.

Starting from Hückel molecular orbitals for benzene and the lowest, quadruply degenerate, singly excited configurations built therefrom[137], the influence of (i) electron interaction, (ii) the inductive effect of one or more substituents and (iii) the resonance effect of these substituents may, within the frame of perturbation theory, be taken into account in a sequence of computational steps.

One procedure, applicable to substituents of weak conjugative influence, may be as follows. Let (i) electron interaction split the degeneracy of the lowest singly excited configurations. One obtains the singlet states $^1B_{2u}$ (responsible for the ^1L_b band), $^1B_{1u}$ (responsible for the ^1L_a band) and $^1E_{1u}$ (the final states of the ^1B absorption). The (ii) inductive effect of one or more substituent(s) is now treated as a perturbation[138]. According to the symmetry of this perturbation, these states in second-order perturbation theory mix differently with each other, with the ground state $^1A_{1g}$, and possibly with higher excited benzene states. From the shifted energy levels and modified transition moments the spectral changes are predicted.

A further development in the application of perturbation theory consists in explicitly including the states of the substituent in the calculation, as well as charge-transfer states between substituent and benzene nucleus[139-142]. On this basis Petruska[140], for instance, distinguishes between the following[141]: (iia) The first-order inductive perturbation. In the case of multiple substitution the contribution of each substituent is additive and independent of its relative position. (iib) The second-order inductive perturbation. It is a measure of the mixing of the benzene ring states with each other. In the case of multiple substitution these second-order terms add vectorially, that is, they are dependent upon the relative position of substituents. (iii) The second-order conjugative perturbation. It is a measure of the mixing of pure benzene states with the ring-to-substituent charge-transfer states. For multiply-substituted species these terms are scalarly additive, as are the terms (iia). Quantitatively Petruska finds for the shift $\Delta\nu$ of the non-degenerate band ^1L_b:

$$-\Delta\nu = \sum_m l_m + |\sum_m v_m \exp(2\pi i m/3)|^2 - 0{\cdot}2\,|\sum_m v_m(-1)^m|^2 \qquad (16)$$

where l_m and v_m are parameters characteristic of the substituent attached to carbon atom m in the benzene ring ($m = 1, \ldots, 6$). Obviously l contains the contributions (iia) and (iii), while v stands for (iib). These parameters may be either calculated or calibrated on some chosen species.

TABLE 16. Petruska's[140] parameters for benzene substitution

Substituent	l (cm^{-1})	v (cm^{-1})
F	50	17·0
Cl	935 (840 *ortho*)	11·0
Br	975	11·0
I	1000	15·0
CH_3	560 (405 *ortho*)	8·0
NH_2	3550	21·0

Values of l and v for halogen substitution as obtained by Petruska[140] are given in Table 16. They reflect the following relative influences.

Second-order inductive effect: $NH_2 > F > I > Cl, Br > CH_3$

Resonance or conjugative* effect: $NH_2 > I \gtrsim Cl, Br > CH_3 > F$

* The terms 'inductive' and 'resonance' as used from a MO-theoretical and spectroscopic point of view in this chapter cannot be directly identified with the more chemical definitions, as found, for instance, in C. K. Ingold, *Structure and Mechanism in Organic Chemistry*, 2nd. ed., Cornell University Press, Ithaca, New York, 1969.

As an illustration of the strong second-order inductive effect of fluorine, note the relative shift $\Delta\nu$ in the ^1L_b band of 1,3- and 1,4-difluorobenzene (Table 17). Compare it with the data on the corresponding Cl and Br compounds.

With the development of digital computers the P method[143, 144] has found increasing application in the study of substituted aromatic systems. This procedure starts out from molecular orbitals extending over all the π centres of the molecule, including all substituent atoms. These MO's are made self-consistent (SCF) by an iterative procedure. From these orbitals singly excited configurations are constructed. The excited states are obtained by letting all those configurations which fall within an appropriate energy range interact with each other. The advantage of the P method is that it can treat weak and strong substituents on exactly the same formal basis[145]. It has the disadvantage of making an intuitively useful qualitative distinction between different types of interaction more difficult than the perturbation methods. The P method may possibly be somewhat more accurate than the better perturbation procedures, but less suited to relate directly spectral changes within a homologous series.

For an application of the P method to some fluorobenzenes see reference 146.

For recent investigations on the triplet states of halogen-substituted benzenes see section I. A. 2. d and, for instance, references 147–149.

B. The p.e. Spectra of Halogen-substituted Benzene

Turner[150] reports the photoelectron spectra of benzene and of a number of halobenzenes. In benzene the first, 9·24 eV, band is unquestionably due to ionization from the top filled $\pi_2(e_{1g}^+)$, $\pi_3(e_{1g}^-)$ orbitals. Recently Brundle, Robin and Kuebler[151] have reinterpreted the second band at 11·49 eV in the light of a comparison with hexafluorobenzene. It appears that ionization from a $\sigma(e_{2g})$ level is responsible. A number of calculations indeed predict a σ orbital to lie energetically between the π orbitals. Such a result was obtained for the first time by extended Hückel calculations[7]. Ionization from the lowest $\pi_1(a_{2u})$ orbital should give rise to the 12·3 eV band.

In monohalobenzenes similar bands occur, although somewhat shifted in energy. A splitting of the first band into two components seems to confirm that the degeneracy between π_2 and π_3 has been lifted. In addition to the bands resembling the ones in benzene some sharp peaks are observed, at 13·7 eV in fluorobenzene, 11·3 and 11·7 eV in chlorobenzene, 10·6 and 11·2 eV in bromobenzene, 9·6 and 10·5 eV in iodobenzene. Turner attributes these bands to ionization from 'non-bonding' molecular orbitals containing significant halogen *np* contributions. In Figure 8 we

TABLE 17. U.v. spectroscopic data from reference 140: wavelengths λ, frequency shifts with respect to benzene $\Delta\nu$, oscillator strengths f (subdivided into a purely vibronic and purely electronic part) (spectra were all recorded in alkane solvents)

	^1L_b			^1L_a		^1B	
	λ (Å)	$-\Delta\nu$ (cm^{-1})	$f(\times 10^4)$	λ (Å)	$-\Delta\nu$ (cm^{-1})	λ (Å)	$-\Delta\nu$ (cm^{-1})
C_6H_6	(37,850 cm^{-1})		16+0	(48,780 cm^{-1})		(54,050 cm^{-1})	
	2640	0		2050	0	1850	0
C_6H_5F	2660	270	17+70	2060	200	1840	−300
1,3-$C_6H_4F_2$	2655	200	17+68				
1,4-$C_6H_4F_2$	2735	1290	17+205				
C_6H_5Cl	2715	1030	18+12	2165	2500	1910	1700
1,2-$C_6H_4Cl_2$	2772	1850	20+20	2220	3700	1965	3200
1,3-$C_6H_4Cl_2$	2780	1900	20+18	2215	3600	1975	3400
1,4-$C_6H_4Cl_2$	2815	2340	20+42	2285	5000	1945	2600
C_6Cl_6	3035	4920	24+0	2450	8000	2190	8400
C_6H_5Br	2720	1070	18+10	2210	3500	1920	2000
1,2-$C_6H_4Br_2$	2775	1850	20+14				
1,3-$C_6H_4Br_2$	2785	1950	20+24				
1,4-$C_6H_4Br_2$	2825	2450	20+32				
C_6H_5I	(2730)	(1200)	20+30	2300	5300	1960	3000
$C_6H_5CH_3$	2685	610	21+10	2110	1400	1900	1400
$C_6H_5NH_2$	2955	4000	20+224	2395	7000	1980	3600

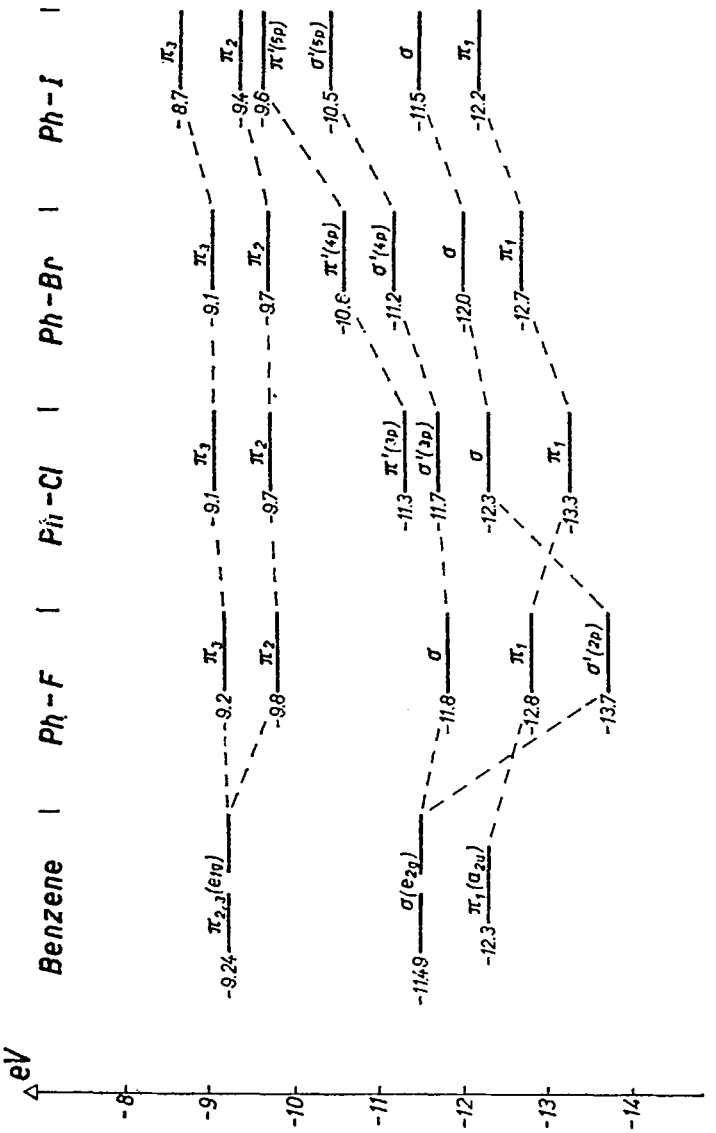

FIGURE 8. Orbital energy levels in benzene and monohalogenated benzenes. The data on benzene stem mainly from reference 150, those on the substituted benzenes from reference 151. The interpretation and assignments are based partly on reference 150, partly on reference 151, and are, for the rest, somewhat speculative.

have identified the negative value of the vertical ionization potentials with the energy of the SCF orbital from which by Koopmans' theorem an electron is assumed to be ionized. Our assignment of the 'non-bonding' levels as a higher one of symmetry π and a lower one of symmetry σ and the correlation of σ levels is somewhat speculative. In the absence of *ab initio* calculations on such large systems, some good CNDO-type calculations or even EH calculations may shed some light on this question.

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The Chemistry of The Carbon-Halogen Bond: Part 1
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CHAPTER 2

Structural chemistry of the C—X bond

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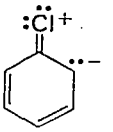
I. INTRODUCTION

The lengths of carbon–carbon bonds vary from 1·54 Å* for the single bond in diamond and alkanes, through 1·34 Å for the double bond in alkenes, to 1·20 Å for the triple bond in acetylenic compounds[1]. Intermediate lengths are found for the bonds in aromatic compounds (1·39 Å in benzene derivatives) and for formally single bonds, such as the central bonds in 1,3-butadiene, $CH_2{=}CH{-}CH{=}CH_2$ (1·48 Å) and butadiyne, $HC{\equiv}C{-}C{\equiv}CH$ (1·38 Å). The reduction in bond distances from alkanes to alkenes to alkynes has been interpreted in terms of increasing π-bond character (e.g. reference 2), with partial multiple-bond character

* Throughout this chapter mean bond distances will be quoted to the nearest 0·01 Å. Individual bond lengths determined from microwave spectra are usually accurate to about 0·001 Å for molecules of the complexity described here; from electron-diffraction of gases the accuracy is several thousandths of an Ångström. The accuracy of X-ray diffraction results is given in terms of the standard deviation, e.g. bond length = 1·857 Å, standard deviation (σ) = 0·007 Å, written as 1·857 (7) Å. Common statistical practice is to take only differences greater than about 3σ as being highly significant, so that standard deviations quoted throughout this chapter are approximately tripled before the significance of bond length differences is discussed.

for the single bond in butadiene. It has long been recognized[3,4,5], however, that the effective covalent radius of carbon varies with its state of hybridization, so that some of the bond length differences are a result of this effect. It has been proposed that in fact electron-delocalization effects are unimportant in classical molecules, the bond lengths in them being determined solely by the state of hybridization of carbon[6,7]. The lengths of formally single bonds, such as the central bonds in butadiene and butadiyne, can be rationalized solely in terms of smaller covalent radii for C(sp^2)- and C(sp)-hybridized atoms than for the C(sp^3) atoms in alkanes; use of the covalent radii C(sp^3) = 0·77 Å C(sp^2) = 0·74 Å, C(sp) = 0·69 Å permits an explanation of formally single C(sp^n)—C(sp^n) bond distances completely in terms of hybridization differences and also accounts for some of the shortening in multiple bonds. The controversy over the relative importance of hybridization and electron-delocalization in influencing carbon–carbon bond lengths has been summarized[8].

Similar bond length variations are found for carbon–halogen bonds[1], with ranges 1·38–1·32 Å for C—F, 1·78–1·64 Å for C—Cl, 1·94–1·79 Å for C—Br and 2·14–1·99 Å for C—I. Decreases in the C—Cl bond distances in chlorobenzenes (given as 1·70 Å in reference 1, but see section II, B) and chloroalkenes (1·72 Å), in comparison with similar bonds in saturated aliphatic chlorine compounds (1·77 Å), have been interpreted in terms of about 10–20% double-bond character for the C—Cl bonds[2], resulting from conjugation of an unshared pair of electrons of the chlorine atom with the double bond or aromatic nucleus:



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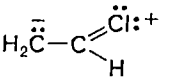


(2)

Nuclear quadrupole coupling constants, however, indicate only about 5% double-bond character in molecules such as vinyl chloride[9,10] and variations of C—X bond lengths (Table 1) have been correlated satisfactorily

TABLE 1. C(sp^n)—X bond distances (Å)

	% s-character	X = H	C(sp^3)	F	Cl	Br	I
C(sp^3)—X	25	1·10	1·54	1·38	1·78	1·94	2·14
C(sp^2)—X	33	1·08	1·51	1·33	1·74	1·89	2·09
C(sp)—X	50	1·06	1·46	1·27	1·64	1·79	1·99

with changes in hybridization of the carbon atom[7], linear relationships being found (Figure 1) between bond length and percentage *s*-character of carbon. The correlation lines for the carbon–halogen bonds are approximately parallel, and the fact that they are not parallel to the C—C and

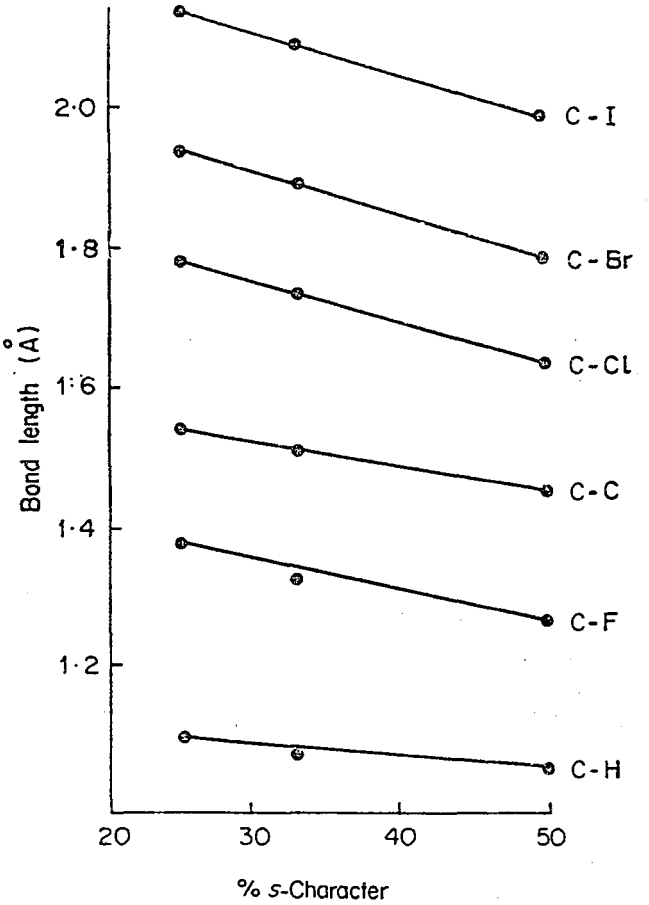


FIGURE 1. Relation between C—X bond distance and % *s*-character of the carbon atom.

C—H lines has been rationalized on the basis of an expected non-additivity of covalent radii and in terms of details of the overlap of atomic orbitals[7].

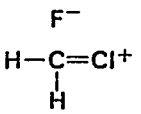
Further lesser variations in C—X bond lengths have been related to the electronegativities of the other atoms bonded to the carbon atom[11]. Thus (Table 2), the C—F bond length decreases from 1·385 Å in CH_3F to

1·323 Å in CF_4; the C—Cl distance from 1·781 Å in CH_3Cl to 1·751 Å in CF_3Cl and to 1·766 Å in CCl_4. The effect is most marked with the strongly electronegative fluorine atom. The effect has again been attributed to

TABLE 2. Dependence of C(sp^3)—X bond distances (Å) on electronegativity of other substituents

	X = F	X = Cl		
	R = F	R = F	R = Cl	R = CH_3
CH_3—X	1·385	1·781	1·781	1·781
RCH_2—X	1·358	1·759	1·772	1·788
R_2CH—X	1·332	—	1·762	1·798
R_3C—X	1·323	1·751	1·766	1·803

double-bond characters as high as 20%[2], resulting from structures such as **3**, but is also explicable in terms of hybridization changes at the carbon



(3)

atom, in this case small second-order effects[11]: the strongly electronegative fluorine atom attracts the *p*-electrons of the carbon atom, resulting in more *s*-character in, and thus shorter, C—X bonds.

The variation in C—Cl distances in methyl, ethyl, *i*-propyl and *t*-butyl chlorides (Table 2)[12,13] might also be explained on the basis of electronegativity differences, but it has been considered that electron-delocalization, hybridization, electronegativity and steric effects are all inadequate to explain the variation in the bond lengths in this series of molecules. It has been suggested that the increase in C—Cl bond length from CH_3Cl to *t*-BuCl is consistent with increasing ionic character, but it is difficult to place the arguments on a quantitative basis[13].

In order to account for variations in carbon–halogen bond distances it is probably necessary to consider one or several of the following possible effects:

(i) hybridization of the carbon atom;

(ii) hybridization of the halogen atom, although it is difficult to estimate this effect;

(iii) electron-delocalization of halogen lone-pairs, resulting in contributions from structures with C=X^+ arrangements;

(iv) electronegativity differences, which lead to second-order changes in hybridization;

(v) ionic character in the carbon–halogen bond;

(vi) intramolecular steric effects;

(vii) intermolecular interactions in the solid state.

The data presented in Tables 1 and 2 suggest that hybridization of the carbon atom is the major influence on the carbon–halogen bond lengths, with minor variations resulting from any or all of the other effects. It seems appropriate then to discuss the lengths of carbon-halogen bonds in terms of variation in the hybridization of the carbon atom, with double-bond character and other effects playing a more minor role. In the following survey of carbon–halogen bonds, no attempt has been made to be completely comprehensive, but a selection of bond distances in various types of molecular system has been chosen to illustrate the ranges of C—X distance found in various bonding situations. Where possible these have been chosen from more recent accurate structural analyses, although the accuracy is often not very high for bonds involving the heavier halogens, Br and I. Carbon–chlorine bonds are discussed first, since a large number of fairly accurate values are available covering a wide range of distances, followed by C—Br and C—I bonds, for which the available measurements are usually less accurate. Finally a description is given of variations of C—F bonds, which are related to the strongly electronegative character of the fluorine atom.

II. CARBON–CHLORINE BONDS

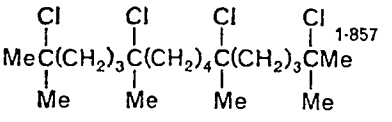
A. Saturated Compounds

The carbon–chlorine bond lengths in simple aliphatic chloro-compounds are in the range 1·75–1·78 Å, a mean value of 1·767 Å being quoted in reference 1. Some recent X-ray crystal studies of more complex molecules have revealed C—Cl distances which are somewhat longer than this range, with values as high as 1·86 Å having been reported (Table 3). It is difficult to find any systematic correlation between the variation in C—Cl bond distances and the various factors outlined in section I. In **4**, where all the C—Cl bonds are 1·857 Å (Table 3), the Cl—C—C angles are in the range 105·3–107·6°, which could indicate less than normal *s*-character in the C—Cl bonds and hence account at least qualitatively for their increased length in comparison with other C—Cl bonds. It is difficult to extend such correlations to other compounds in Table 3. Some of the molecular skeletons are subject to considerable strain, e.g. **7** and **8**, as evidenced also by C—C bond distances as long as 1·593 Å in **7** and

TABLE 3. C—Cl bond distances (Å) in aliphatic compounds

Compound	C—Cl	Reference
2,6,11,15-Tetrachloro-2,6,11,15-tetramethylhexadecane (4)	1·857 (7)	14
trans-2,5-Dichloro-1,4-dioxan	1·845 (6)	15
2,3-Bis-(*cis*-4-chloro-1-methylcyclohexyl)-*trans*-2-butene (5)	1·837 (7) 1·809 (9)	16
α-Chlorotropane (6)	1·834 (3)	17
cis-2,3-Dichloro-1,4-dioxan	1·819 (9) 1·781 (7)	18
3,6-Dichloro-11,12-benzotetracyclo-[5.3.2.$0^{2,6}$.$0^{3,8}$]dodecan-9-one (7)	1·814 (5) 1·800 (6)	19
t-Butyl chloride	1·803	12
iso-Propyl chloride	1·798	13
3,4,5-Trichlorotetra-cyclo-[4.4.0.$0^{3,9}$.$0^{4,8}$]decan-2-one (8)	1·795 (6) 1·754 (4) 1·753 (5)	20
Ethyl chloride	1·788	13
Dichloromalonamide, $Cl_2C(CONH_2)_2$	1·781 (2)	21
8,8-Dichloro-4-phenyl-3,5-dioxa-bicyclo[5.1.0]octane (9)	1·78 (2) 1·77 (2)	22
Various simple chloroparaffins	1·751–1·781, mean 1·767	1
Chlorocyclopropane	1·740	23
1,1-Dichlorocyclopropane	1·734	24

1·574 Å in **8**. Of the three C—Cl bonds in **8**, one is 0·04 Å longer than the other two, the only distinction being that the long bond involves a carbon atom with a hydrogen atom attached. Again it is possible to make some rationalization in terms of electronegativity and hybridization differences, but it is difficult to extend the arguments on a general basis.



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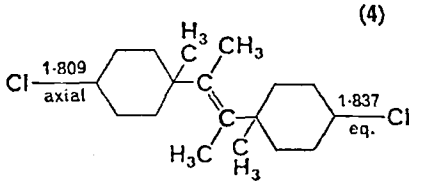

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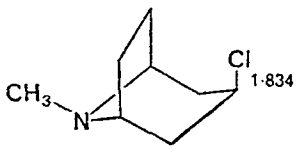
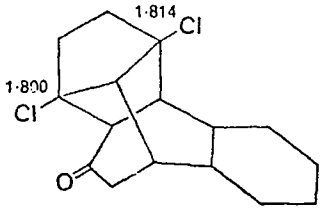


(6)

Two of the compounds in Table 3 each contain one axial and one equatorial chlorine atom. In *cis*-2,3-dichloro-1,4-dioxan the C—Cl distances are 1·819 and 1·781 Å for the axial and equatorial chlorines respectively, while in **5** the distances are 1·809 and 1·837 Å for axial and equatorial C—Cl bonds. The axial bond is thus longer in one case and shorter in the other, and it is difficult to account for these differences in bond lengths.

The long C—Cl distance of 1·857 Å in **4** has been ascribed to molecular packing forces in the crystal, which contains relatively short Cl···H intermolecular contacts, the shortest being 2·7 Å, in comparison with the



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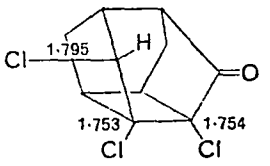

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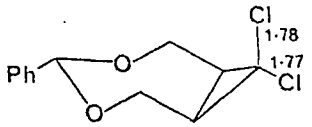

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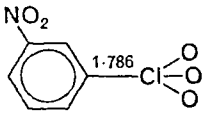


(10)

sum of the van der Waals radii of 3·0 Å. It is difficult to describe such effects quantitatively. Many chlorine-containing molecules exhibit Cl···Cl intermolecular distances in the crystal which are shorter than the van der Waals contact of 3·6 Å, with distances as short as 3·3 Å being observed[25]. These interactions may have an influence on the C—Cl bond lengths, but again a general correlation is not readily apparent. Crystals of dichloromalonamide for example contain an extremely short intermolecular Cl···Cl contact of 3·10 Å, but the C—Cl distances seem quite normal, 1·781 Å (Table 3).

Although a general correlation of C—Cl bond distances with bonding features does not seem evident, two significant points emerge from the data in Table 3. The C—Cl bond lengths found in compounds with angles close to the tetrahedral value are often longer than those found for apparently similar hybridization situations in simple molecules (1·75–1·78 Å), with lengths as great as 1·86 Å being observed. The detailed values of the bond lengths are probably dependent on other factors such as intra- and intermolecular steric effects and ionic character which are difficult to

describe quantitatively. The second point is that C—Cl bonds in cyclopropane derivatives appear to be shorter (1·73–1·74 Å) than normal. This is probably a result of greater *s*-character in the C—Cl bonds, and possibly also some π-bonding between the chlorine atoms and the ring, the cyclopropane ring having some properties which are similar to those of a double bond[26].

B. *Aromatic Compounds*

Carbon–chlorine bond distances have been measured in a large number of aromatic molecules and a representative listing is given in Table 4. The mean C(arom)—Cl distance in a typical aromatic chlorocompound is

TABLE 4. C—Cl bond distances (Å) in aromatic compounds

Compound	C—Cl	Reference
3-Nitroperchlorylbenzene (**10**)	1·786 (10)	27
N-Methyl-*p*-chlorobenzaldoxime	1·768 (7)	28
2-Chloro-4-nitroaniline	1·766 (9)	29
1,3-Di-*p*-chlorophenyl-2-triethyl-carbinyl-4-ethyl-5,5-diethyl-1,3-diaza-2,4-diborolidine	1·764 (6)	30
Bis-(5-chlorosalicylaldoximato)copper(II)	1·762 (11)	31
N-5-Chlorosalicylideneaniline	1·752 (6)	32
2-Chloro-5-nitrobenzoic acid	1·753 (6)	33
p-Chloroaniline	1·75 (1)	34, 35
1-(2,6-Dichlorobenzyl)-6-hydroxy-1,4,5,6-tetrahydro-nicotinamide dihydrate	1·748 (4)	36
2,5-Dichloroaniline	1·744 (12)	25
2,6-Dichloro-4-nitroaniline	1·743 (4)	37
N-(*p*-Chlorophenyl)-α-isopropyl-β-phenyl-β-lactam	1·741 (3)	38
Ammonium chloranilate monohydrate	1·741 (6)	39
p-Dichlorobenzene	1·74 (1)	40
1,4,5,8-Tetrachloronaphthalene	1·74 (1)	41
9,10-Dichloroanthracene	1·74 (2)	42
4-Acetyl-2′-chlorobiphenyl	1·738 (10)	43
2-Chloro-*N*-salicylideneaniline	1·737 (3)	44
trans-pp′-Dichloroazobenzene	1·737 (4)	45
o-Chlorobenzoic acid	1·737 (7)	46
4,4′-Dichlorodiphenylsulphone	1·736 (7)	47
Di-*p*-chlorophenyl hydrogen phosphate	1·736 (13)	48
o-Chlorobenzoylacetylene	1·734 (6)	49
1-(4-chlorobenzyl)-1-nitroso-2-(4,5-hydro-2-imidazolyl)-hydrazine monohydrate	1·732 (12)	50
2-Chlorotropone	1·73	51
2,6-Dichloro-4-diazo-2,5-cyclohexadien-1-one	1·73	52
syn-p-Chlorobenzaldoxime	1·728 (6)	53

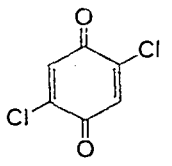
TABLE 4 (*cont.*)

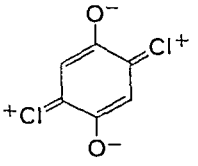
Compound	C—Cl	Reference
Chloranilic acid dihydrate	1·720 (6)	54
2-Chloro-3-hydroxy-1,4-naphthoquinone	1·72	55
Chloranilic acid (**12**)	1·717 (6)	54, 56
Chlorobenzoquinones: tetrachloro	1·714	57, 58
2,3-dichloro	1·715 (5)	
chloro	1·717 (4)	
2,5-dichloro	1·717 (3)	
2,6-dichloro	1·727 (5)	
N,N,N′,N′-Tetramethyl-*p*-diaminobenzene-chloranil	1·716 (7)	59
Tetrachlorohydroquinone	1·70–1·74	60, 61, 62
Pentachlorophenol	1·67–1·73	61, 63
2-Chloro-3-amino-1,4-naphthoquinone	1·71	64
2-Chlorothiophene	1·71	65
Tetrachlorophthalic anhydride	1·705	66
1,2,3,4-Tetrachloro-di-*n*-propylcalicene	1·705 (7)	67
1,2,3,4-Tetrachlorobenzo[g]sesquifulvalene	1·704	68
4,4′-Dichloro-3,3′-ethylenebis-sydnone (**14**)	1·678 (3)	69

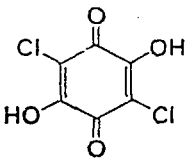
about 1·74 Å, with most of the accurate values lying in the range 1·73–1·75 Å (Table 4). This average value is longer than that of 1·70 Å listed for the standard C(arom)—Cl in previous compilations of bond distances (e.g. reference 1), but is very close to the length quoted[7] for the C(sp^2)—Cl single bond, 1·736 Å, which suggests that these C—Cl bonds have little if any double-bond character. The longest C(arom)—Cl distance observed is in 3-nitroperchlorylbenzene (**10**), 1·786 (10) Å; it is reasonable to ascribe this long bond to an increased single-bond radius for the chlorine atom, as a result of increasing substitution[27]. Only a few other bonds are longer than the average range, and it is difficult to account for these increases. In 2-chloro-4-nitroaniline, for example, the distance is 1·766 (9) Å, while in the rather similar 2,6-dichloro-4-nitroaniline, the length is the more normal 1·743 (4) Å. The hybridization at the carbon atoms is rather similar in all the compounds, nearly all the C—CCl—C angles being slightly greater than 120°, with no obvious correlation between angles and C—Cl bond distance.

A second group of compounds has C—Cl distances in the range 1·70–1·72 Å, mean about 1·71 Å. These are mainly quinones, and the shorter C—Cl distances are possibly explicable in terms of resonance involving structures such as **11b** for 2,5-dichlorobenzoquinone (**11a**), and **12b** for chloranilic acid (**12a**). Some support for these structures with

C=Cl double bonds is found by the observance of a more normal C—Cl bond distance, 1·741 (6) Å, in the chloranilate ion (**13**), possibly because the major contributing structures are **13a** and **13b**, giving the delocalized π-systems in **13c**. It has been pointed out that most of the molecules with


(11a)


(11b)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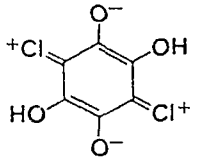
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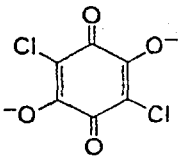
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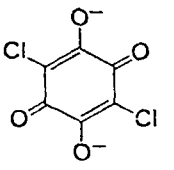
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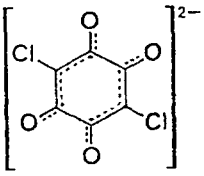
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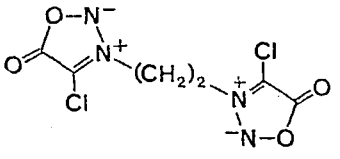
(14)

the shorter C—Cl bonds have *ortho* chlorine substituents, and the shortening may result from some type of interaction between the chlorine atoms[66]. The shortest C—Cl bond found among aromatic compounds is 1·678 (3) Å in the sydnone (**14**), and this shortening is probably due to considerable delocalization of the chlorine lone-pair electrons onto the positive nitrogen atom[69].

C. Ethylenic and Acetylenic Compounds

Olefinic C—Cl bonds average 1·72 Å[1] and at acetylenic carbon atoms the C—Cl distances are about 1·64 Å[1]. The reductions from the range found in saturated molecules (section II. A) are explicable largely in terms of hybridization changes at the carbon atom (see section I).

In conclusion the ranges of C—Cl bond distances found are 1·75–1·86 Å in saturated compounds, 1·73–1·74 Å in cyclopropane derivatives, 1·74 Å in most aromatic molecules, but about 1·71 Å in chlorobenzoquinones and some other polychlorinated molecules, 1·72 Å at ethylenic carbon atoms, and 1·64 Å at acetylenic carbon atoms. The gross differences are explicable on the basis of hybridization differences at the carbon atoms; more subtle minor variations are probably related to any or all of electron-delocalization, electronegativity differences, intra- and intermolecular steric effects and ionic character, and it is difficult to make quantitative correlations.

III. CARBON–BROMINE AND CARBON–IODINE BONDS

Carbon–bromine and carbon–iodine bond distances have generally been measured with less accuracy than carbon–chlorine lengths, so that many observed minor variations cannot be considered to be statistically significant. The variations in bond distance again seem to be chiefly related to hybridization of the carbon atom (Table 1, see section I). The C—Br bond length is about 1·94 Å in saturated molecules, about 1·89 Å at ethylenic carbon atoms, and about 1·79 Å at acetylenic carbon atoms. The quoted average C—Br bond distance in aromatic molecules[1] is 1·85 Å, but this value seems low in the light of recent work, a length of about 1·89 Å having been found in several compounds, e.g. 1·886–1·896 (16) Å in 2,4,6-tribromoaniline[70], 1·91 (3) Å in the *O-p*-bromobenzoate of batrachotoxinin A[71], 1·905 (15) Å in the *p*-bromobenzoyl derivative of ε-caesalpin[72], 1·892 and 1·904 (10) Å in 5-(6′-bromo-3′-ethyl-2′-methylbenzimidazolium) barbiturate[73], and 1·897 (18) Å in the bromoindole derivative of 3β-methoxy-21-keto-Δ^{13}-serratene[74].

The C—I bond distance has been observed as 2·14–2·21, 2·09, 2·05 and 1·99 Å in paraffinic, olefinic, aromatic and acetylenic environments respectively (Table 1, section I)[1].

IV. CARBON–FLUORINE BONDS

The lengths of carbon–fluorine bonds are influenced by the strongly electronegative character of the fluorine atom. In monofluoro paraffinic compounds the C—F bond distance is about 1·39 Å (Table 5), although

one distance as long as $1{\cdot}43 \pm 0{\cdot}02$ Å has been reported, for *t*-butyl fluoride[77]. In polyfluorinated molecules the C—F length is decreased to about 1·33 Å (Table 5). In addition other C—X bonds (X = Cl, Br, I) are shortened by the presence of fluorine atoms in the molecule. These bond length shortenings are certainly related to the highly electronegative nature of the fluorine atom, and may be rationalized either in terms of

TABLE 5. Variation of C—F bond distances (Å)

	Monofluoro compounds	Polyfluoro compounds
C(sp^3)—F	1·39	1·33
C(sp^2)—F	1·34	1·31
C(sp)—F	1·27[a]	—

[a] References 75 and 76.

ionic, doubly bonded structures or of hybridization variations resulting from the electronegativity differences (see section I). The C—F bond distances are also influenced by the state of hybridization at the carbon atom, decreasing to about 1·34 Å and 1·31 Å for C(sp^2)—F bonds in mono- and polyfluoro compounds respectively, and to about 1·27 Å for C(sp)—F bonds (Table 5).

Within each group of compounds the C—F bond distances are remarkably constant. C(arom)—F bond lengths, for example, are all very close to 1·33 Å[1]; a recent X-ray study[78] of tetra(pentafluorophenyl)-cyclotetraphosphane gives a range of 1·328–1·342 (5) Å for ten independent C(arom)—F bond lengths, with a mean of 1·337 Å.

V. CONCLUSION

The full range of carbon–halogen bond distances is summarized in Table 6. It is apparent that there are wide and interesting differences among the bonds of each type; the variations are almost as large as those observed

TABLE 6. Summary of C—X bond distances (Å)

	C—F	C—Cl	C—Br	C—I
Paraffinic	1·32–1·39	1·75–1·86	1·94	2·14–2·21
Aromatic	1·33	1·74 (1·71)	1·89	2·09
Olefinic	1·31–1·34	1·72	1·89	2·05
Acetylenic	1·27	1·64	1·79	1·99

for C—C bonds, in spite of the fact that there are no unexcited structures with C=X as for C=C in alkenes. The grosser variations are explicable in terms of hybridization changes at the carbon atom, but it is difficult to account quantitatively for the more minor variations, which probably result from one or more of the effects outlined in section I.

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CHAPTER 3

Analysis of organic halogen compounds

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I. INTRODUCTION

A. Uses of Halogenated Compounds

A brief consideration of the main fields of application of organic halogen compounds* should be helpful for visualizing the type of analytical problems to which they give rise.

(i) Synthetic organic chemistry has made ample use of halogen compounds as agents for the attachment of alkyl and aryl groups, as viable intermediates in the introduction of unsaturation, etc.[1,2].

(ii) Much of the pioneering and subsequent work on the theoretical aspects related to the electronic and geometric properties of organic molecules has been done on organic halides[3,4]. The early studies on mechanisms of aliphatic and aromatic substitution were also largely concerned with organic halides[5]. Work in these fields is still very active today.

(iii) Despite the abundance of halogens as a constitutive element of the biosphere, only a few dozen really natural organic halogen compounds are known. Among these, the only ones of outstanding importance are the iodinated derivatives of tyrosine. On the other hand, many metabolic products derived from pesticides, drugs and test organic compounds have been isolated from living matter.

(iv) Many organic halides have pharmacological importance, although their action is usually related to the presence of other functional groups in the molecule[6].

(v) The field of pesticides produces many examples of organic halides, mainly chlorides, and to a much lesser extent fluorides, bromides and iodides[7,8].

(vi) In the high-polymer field the importance of polychloroprene, polyvinylchloride and polytetrafluoroethylene need not be emphasized[9]. The

* When speaking about organic halogen compounds in the present chapter, only C–halogen compounds other than acyl halides and their thiono or imino analogues are considered, although part of the discussion that follows also applies to the latter compounds.

flame-retardant properties of halogen compounds, especially brominated compounds, have found application in the textile, plastics, elastomer and wood industries[8].

(vii) Various halogenated compounds have found applications as solvents for reactions, extractions, dry cleaning and solvent dyeing, as media for solid separations and as refrigerating media[8,10].

The basic research and development work implied in all the fields just described was accompanied by a parallel search for analytical methods. These ranged from routine quality control to trace analysis of pesticide residues in tissues, from the interpretation of spectra to the isolation and characterization of undesirable trace by-products of similar structure to the main product.

The variety and extension of these problems is enormous and comprises many thousands of references to original works. In the present chapter we intend to discuss briefly a number of outstanding methods and to mention others which are of less importance from the point of view of their past application, but which are of potential applicability in the future. Shortage of space does not allow to go deep into the principles governing the methods but we hope that the present work will inspire some new ideas in the analytical field.

B. General Comments on Halogen Analysis

The analytical problems posed by the organic halides in principle involve four sets of procedures, one for each element. It is fortunate, however, that the sets for chlorine, bromine and iodine have much in common and only problems involving fluorine usually require methods that do not apply to the other halogens. It is for this reason that the word 'halogen' will usually refer to Cl, Br and I while the inclusion of F will always be expressly mentioned.

Two important areas of development can be pointed out among the methods of halogen analysis. One is the shrinking of the sample size or halogen concentration necessary in order to attain results. Another important trend concerns the analysis of two or more halogens present in the same sample, especially when their proportions are very disparate. This is the result of the methodology involving *mineralization* of the organic halogen, which is usually followed by determination methods that do not distinguish between the various halogens. As previous mineralization is one of the most important and convenient methods for halogen determination, discriminative instrumentation is being developed for the finishing steps. Powerful discriminative methods are nuclear activation, various kinds of emission and absorption spectrometries and titrations

with 'specific halide electrodes'. Similar developments have occurred in some methods that are intrinsically incapable of distinguishing among halogens and do not require mineralization of the sample.

Nearly all reactions of the organic halo moiety involve the rupture of the C–halogen bond, and in most cases this occurs rather sluggishly, with yields lower than quantitative. This rules out derivatization as a way to quantitative analysis for all but a few classes of compounds.

Table 1 lists some references to treatises and textbooks dealing with organic analysis, where organic halides are discussed to various extents.

TABLE 1. A guide to textbooks and treatises on the analysis of organic compounds

Type of analysis	Reference
A. *Chemical methods*	
1. Qualitative	
Halogen detection	11–16
Specific compound detection	12, 15, 17
Compound identification	11–14, 16, 19
2. Quantitative	
Halogen determination	14, 16, 18, 20–23
Specific compound determination	16, 17, 21
B. *Physical methods*[a]	16, 18, 24–30

[a] Works dedicated to a specific method appear in the pertinent sections.

II. ELEMENTARY ANALYSIS

The methods causing minimal sample disruption, described in section II. A–C, have several intrinsic advantages. (i) Manipulations of the sample are reduced to those of fitting its size to the instrument requirements. (ii) Dangers of contamination or losses can be considerably reduced. (iii) The bulk may serve as the sample in continuous set-ups. (iv) The same sample may be used for further analytical purposes. The most outstanding methods of this type involve high energy irradiation which causes small alterations in the sample that can be measured only with sensitive physical devices. Besides the methods described immediately below, electron capture may be included; however, the main application of this procedure is found in the field of gas chromatography and will be dealt with in section III. A. 2. c.

The methods described in sections II. D and E, on the other hand, entail the destruction of the sample. Nevertheless, the amounts of material

required are very small and usually may be taken from bigger samples intended for other purposes. Sections II. F and G deal respectively with the conversion of organic into inorganic samples and with the halogen analysis of the latter.

A. X-Ray Spectroscopy

X-Ray techniques are potentially of wide practical applicability[31]. The routine determination of halogens can be carried out with high efficiency down to fractions of 1%, thus attaining obvious advantages over the usual chemical procedures. A peculiarity of X-ray spectra is their near independence of the chemical state of the element (see below, however).

An X-ray photon absorbed by an atom promotes its potential energy according to the rules of quantum mechanics and produces a characteristic spectrum for each element. These are called edge spectra due to their peculiar shape, namely a curve growing continuously with the wavelength until a transition is reached, when a very steep drop (edge) takes place, the

TABLE 2. Some absorption edges of the organic elements[32]

Element	Edge	Wavelength (Å)	Energy (keV)
H	None		
C	*K*	43·68	0·2838
N	*K*	~31·2	~0·397
O	*K*	23·32	0·5317
P	*K*	5·784	2·1435
S	*K*	5·0185	2·47048
F	*K*	~18	~0·69
Cl	*K*	4·3971	2·8196
	M_I	417	0·0297
Br	*K*	0·9204	13·470
	L_I	6·959	1·781
	N_I	399	0·0311
I	*K*	0·37381	33·1665
	L_{II}	2·5542	4·8540
	$M_{IV,V}$	19·66	0·6161
	$N_{IV,V}$	224	0·0552
	O_I	444	0·0279

same trend being repeated several times, depending on the element. In Table 2 the main absorption edges of the organic elements are summarized. In order to determine an element the absorption intensity is measured on both sides of the edge and the jump compared with a standard[32,33]. The

edges commonly used are *K* and *L*, but specific problems may require the use of other edges.

The measurement of polychromatic X-ray absorption, corresponding to ordinary colorimetry, has been applied to chlorine-containing polymers, where it was shown that the absorption is proportional to the chlorine content[34]. Based on the same principle, a method has been proposed for controlling the thickness of polyvinylchloride sheet continuously[34].

Emission X-ray spectroscopy is also a very useful analytical tool. It has lately acquired a high degree of sophistication both in instrumentation and in its range of applications[35]. Three types of spectra can be distinguished[36].

Photoelectron spectra measure the energy of electrons emitted after a photon of known energy impinged on the sample[37]. The energy difference between the emitted electron and the exciting X-ray photon is an approximate measure of the binding energy of the electron, while the emitted intensity measures the probability of the process. A direct correlation can be established between photoelectron spectra and absorption spectra. This type of emission spectra can be extended to the far ultraviolet region where better resolution and more information on molecular structure can be obtained[38].

Photon spectra (emission spectra, fluorescence spectra) arise when an electron of an outer shell fills the vacancy left by the electron emitted in the photoelectron processes. These transitions are accompanied by photon emission of characteristic wavelengths and intensities. Analytically the most useful lines are the *K* lines[39], arising from the transition of an *L* shell electron to a *K* shell vacancy[32] (for example bromine-containing drug traces in serum excreta, and tissues can be determined at the level of a few p.p.m. or less[40]). However, other lines can now be used[35]. X-Ray fluorescence spectra may vary with the chemical state, as the energy levels of *L* and *M* electrons vary with chemical binding in small atoms.

Chlorides have been determined indirectly by precipitating the silver salt and measuring the *K* line of silver[41]. Fluorine cannot be determined in conventional X-ray spectrographs, but, after conversion to fluoride ion (section II. C), it can be quantitatively precipitated from its solutions in trace amounts with lanthanum nitrate, and determined by measuring at a La–L_α line[42].

Auger spectra arise when an electron of an outer shell fills the vacancy left in an inner shell by the photoelectron process, and the energy difference is spent by the emission of a second electron. These spectra are also sensitive to the chemical state if they involve valence shell electrons[35, 43]. Auger spectra are suitable for the analysis of light atoms, including fluorine.

B. Electron Microprobe Analyser

This is a highly sophisticated instrument capable of analysing elements in microscopic samples[44,45]. The samples are scanned by a very narrow beam of electrons (beam diameter often less than 1 μ) and the X-ray emission is measured and recorded. For the halogens the limits of detectability are about 10^8 atoms. A particle of 1 μ diameter should contain at least about 2% of F, 0·2% of Cl or Br and 0·07% of I[45].

The use of the microprobe analyser for organic and biological samples has also received some attention[31]. A very recent development combines the features of the electron microprobe analyser and the mass spectrograph, where many advantages in sensitivity, range of elements and potential applications are gained. The applicability of this instrument, the *ion microprobe*, to organic and biological samples is still to be explored[46].

C. Nuclear Activation

Treatment of samples with high energy particles or electromagnetic radiation may produce nuclear reactions leading to the formation of radioactive isotopes. Strictly speaking no manipulations of the sample should be required, other than proper size adjustments and encapsulation, either before or after irradiation. In this case purely instrumental methods can be applied, which allow the introduction of automation in routine analysis. On the other hand, pre- or post-treatment might be advantageous due to the nature of the matter analysed[47], thus converting the method into a destructive one. Nuclear activation is a very convenient method for trace analysis[28] of organic compounds and of biological matter[48–50].

Losses of halogen by volatilization are observed on irradiation of biological samples, which necessitates special containers for long irradiation times[51]. Some matrices frequently present in inorganic and biological samples interfere with the trace analysis of many elements, including the halogens. This is due to a large extent to the presence of sodium chloride and other salts in the matrix as illustrated in Table 3[52]. The background

TABLE 3. Detection limits (p.p.m.) of the halogens in various matrices[52]

Matrix	F	Cl	Br	I
Whole blood	30	—	—	4
Urine	30	—	—	0·1
Milk	10	—	—	2
Tap water	3	—	0·1	0·3
'Pure' water	2	0·0007	0·04	0·0009
Polyethylene vessels	0·2	0·02	0·01	0·002

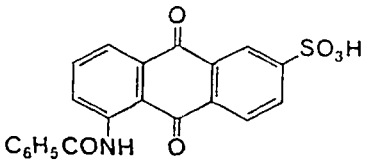
activities limit the use of neutron activation coupled with paper or thin-layer chromatography in the trace analysis of chlorine and bromine derivatives in drugs[53]. The activation of paper chromatograms has been reviewed[54].

The choice of one among the many activation techniques that have been proposed depends on various factors: (i) number of analyses, (ii) radiation sources available, (iii) counting devices available, (iv) elements required and (v) nature of matrix and trace elements.

The nuclear activation method is recommended only for large numbers of samples, where the outlay and labour spent in establishing the appropriate routines are paid off by the efficiency attained.

Among the many possibilities of activation shown in Table 4 some require nuclear reactors, while others are satisfied with more humble devices which may be installed almost everywhere. Furthermore, the choice of a certain activating reaction is made in order to improve the resolution of the pertinent element from the rest of the sample. Thus, for example[55], bromine and fluorine can be determined in samples of biological origin, containing C, H, O, P, S, Mg, Ca, Fe, K, Na and Cl by γ-ray activation as the threshold energies of $^{19}F(\gamma, n)^{18}F$ and $^{81}Br(\gamma, n)^{80}Br$ are respectively $-10{\cdot}4$ and $-10{\cdot}0$ MeV, while the other nuclides need higher energies to become activated.

The pre- and post-treatment of samples are necessary in many cases[47] and involve problems of contaminations and losses. For example, if sodium is present in the original sample in high concentrations it interferes with halogen determinations. It may be separated from its solutions by adding 5-benzamidoanthraquinone-2-sulphonic acid (**1**)[88]. Post-treatment



(1)

may be a very involved process[86, 89] as exemplified in Figure 1. A simple post-irradiation manipulation consists of separating by gas chromatography and counting before the gas chromatograph detector. One of the obvious and immediate advantages gained by such a procedure is the elimination of non-volatile contaminants[90].

Nuclear activation reactions that have been proposed for analytical purposes are summarized in Table 4, and the modes of decay of the nuclides together with references to applications are listed in Table 5.

TABLE 4. Nuclear activation reactions of the halogens[49, 56]

Reaction[a]	Reference[b]	Reaction[a]	Reference[b]
$^{19}F(\gamma,n)^{18}F$	55, 57–60	$^{19}F(n,\gamma)^{20}F$	59
$^{19}F(p,\alpha)^{16}O$	59	$^{19}F(^2H,^3H)^{18}F$	59, 61
$^{19}F(p,^3H)^{17}F$	61	$^{19}F(^3He,n\alpha)^{17}F$	59, 69–71
$^{19}F(p,pn)^{18}F$	59, 61	$^{19}(^3He,\alpha)^{18}F$	59, 61, 69–72
$^{19}F(p,^2H)^{18}F$	59	$^{19}F(^3He,^3H)^{19}Ne$	59, 61, 69
$^{19}F(p,n)^{19}Ne$	61	$^{19}F(^3He,2p)^{20}F$	59, 69
$^{19}F(n,\alpha)^{16}N$	59, 62–64	$^{19}F(^3He,n)^{21}Na$	59, 61, 69
$^{19}F(n,2n)^{18}F$	59, 62, 65, 66	$^{19}F(^3He,\gamma)^{22}Na$	61
$^{19}F(n,p)^{19}O$	59, 62, 64, 67, 68	$^{19}F(\alpha,n)^{22}Na$	59
$^{35}Cl(\gamma,n)^{34m}Cl$	55, 57, 58	$^{35}Cl(^3He,\alpha n)^{33}Cl$	69
$^{35}Cl(p,pn)^{34m}Cl$	56	$^{35}Cl(^3He,\alpha)^{34,\,34m}Cl$	39, 70
$^{35}Cl(n,\alpha)^{32}P$	67, 73	$^{35}Cl(^3He,3p)^{35}S$	69
$^{35}Cl(n,2n)^{34}Cl$	74	$^{35}Cl(^3He,^3H)^{35}Ar$	69
$^{35}Cl(n,2n)^{34m}Cl$	67, 74	$^{35}Cl(^3He,2p)^{36}Cl$	69
$^{35}Cl(n,p)^{35}S$	73	$^{35}Cl(^3He,n)^{37}K$	69
$^{35}Cl(^3He,2\alpha)^{30}P$	69, 70	$^{35}Cl(^3He,p)^{37}Ar$	69
$^{37}Cl(p,n)^{37}Ar$	67	$^{37}Cl(^8He,\alpha 2p)^{34}P$	69
$^{37}Cl(n,\alpha)^{34}P$	67	$^{37}Cl(^3He,\alpha 2n)^{34,\,34m}Cl$	69, 70
$^{37}Cl(n,p)^{37}S$	67, 73, 74	$^{37}Cl(^3He,\alpha p)^{35}S$	69
$^{37}Cl(n,\gamma)^{38}Cl$	64, 75	$^{37}Cl(^3He,\alpha)^{36}Cl$	69
$^{37}Cl(n,\gamma)^{38m}Cl$	76	$^{37}Cl(^3He,^3H)^{37}Ar$	69
$^{37}Cl(^3He,3\alpha)^{28}Al$	69	$^{37}Cl(^3He,2p)^{38}Cl$	69
$^{37}Cl(^3He,2\alpha)^{32}P$	69	$^{37}Cl(^3He,2n)^{38}K$	69, 70
		$^{37}Cl(^3He,p)^{39}Ar$	69
$^{79}Br(\gamma,n)^{78,\,78m}Br$	57, 58	$^{79}Br(n,n')^{79m}Br$	64, 79
$^{79}Br(\bar{p},n)^{79}Kr$	77	$^{79}Br(n,\gamma)^{80}Br$	79, 80
$^{79}Br(n,\gamma)^{76}As$	78	$^{79}Br(n,\gamma)^{80m}Br$	56, 80
$^{79}Br(n,2n)^{78}Br$	79		
$^{81}Br(\gamma,\alpha)^{77}As$	81	$^{81}Br(n,2n)^{80m}Br$	67
$^{81}Br(\gamma,n)^{80,\,80m}Br$	57, 58	$^{81}Br(n,\gamma)^{82}Br$	75
$^{81}Br(p,pn)^{80,\,80m}Br$	82	$^{81}Br(^2H,p)^{82}Br$	83
$^{81}Br(n,\alpha)^{78}As$	67		
$^{127}I(\gamma,2n)^{125}I$	84	$^{127}I(n,2n)^{126}I$	67
$^{127}I(\gamma,n)^{126}I$	57, 58, 84	$^{127}I(n,p)^{127}Te$	85
$^{127}I(p,n)^{127}Xe$	77	$^{127}I(n,\gamma)^{128}I$	64, 85, 86
$^{127}I(n,\alpha)^{124m}Sb$	56	$^{127}I(^2H,2n)^{127}Xe$	87

[a] In a nuclear reaction X(*a*, *b*)Y, nuclide X is irradiated with *a*, yielding *b* and nuclide Y. *n* = neutron; *p* = proton; α = α-particle; γ = γ-ray; ^2H, ^3H and ^3He are nuclei.

[b] For possible interferences, consult reference 56.

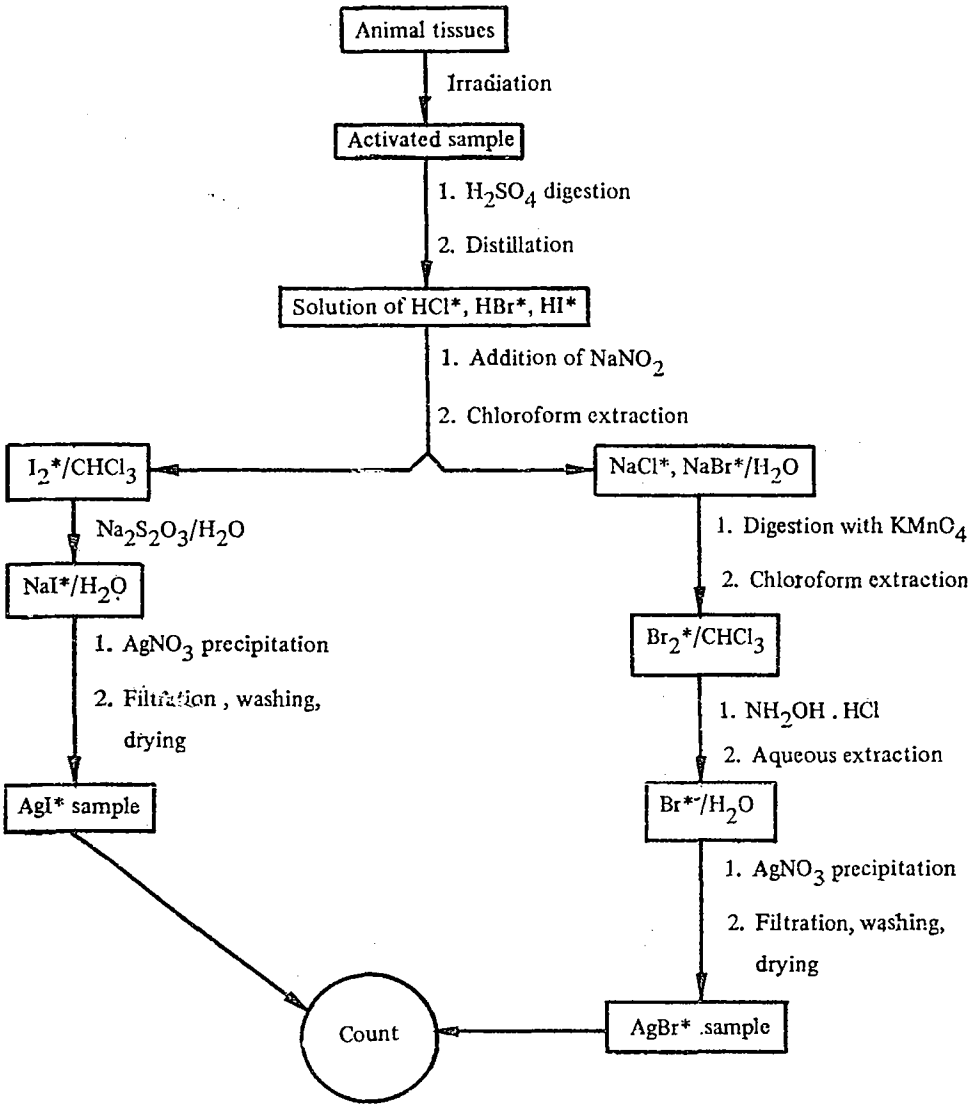


FIGURE 1. Determination of Br and I in animal tissues by nuclear activation[89].

TABLE 5. Decay modes of the halogen nuclear products[a]

Nuclide	Half lifetime	Particles[b]	Transitions[c]	Photons[d]	Reference to applications[e]
^{16}N	7·35 s	β^-		A few γ's	62, 66, 91
^{19}O	29 s	β^-		A few γ's	66, 68, 92
^{17}F	66 s	β^+		AR	69
^{18}F	109·7 min	β^+	EC	AR	55, 60, 66, 69
^{20}F	11·4 s	β^-			65, 66
^{19}Ne	17 s	β^+		AR	
^{21}Na	23 s	β^+		AR	69
^{22}Na	2·58 year	β^+	EC	AR, a few γ's	
^{32}P	14·3 day	β^-			
^{34}P	12·4 s	β^-		A few γ's	66
^{35}S	88 day				
^{37}S	5·06 min	β^-		A few γ's	
^{34}Cl	1·56 s	β^+		AR	
^{34m}Cl	32·0 min	β^+	IT	AR, several γ's	55, 66
^{38}Cl	37·3 min	β^-		A few γ's	51, 93, 94
^{38m}Cl	1·0 s			A γ-ray	76
^{37}Ar	35 day		EC	An X-ray	
^{76}As	26·5 h	β^-		Many γ's	
^{77}As	38·8 h	β^-		A few γ's	
^{78}As	91 min	β^-		Many γ's	
^{78}Br	6·4 min	β^+	EC	AR, a few γ's	55, 68, 79
^{78m}Br					95
^{79m}Br	4·8 s				68, 79
^{80}Br	17·6 min	β^+, β^-	EC	AR, a few γ's	80, 96, 97
^{80m}Br	4·4 h		IT	A few X-rays	80
^{82}Br	35·5 h	β^-		A few γ's	51, 96–99
^{79}Kr	34·9 h	β^+	EC	AR, a few γ's and an X-ray	
$^{124m_1}Sb$	93 s	β^-	IT	A few γ's	
$^{124m_2}Sb$	21 min		IT	An X-ray	
^{127}Te	9·4 h	β^-		A few γ's and an X-ray	
^{125}I	60 day		EC	An X-ray	
^{126}I	13 day	β^+, β^-	EC	AR, a few γ's	55
^{128}I	25·1 min	β^+, β^-	EC	AR, a few γ's	85, 86, 100
^{127}Xe	36·4 day		EC	A few γ's and an X-ray	

[a] Most data were taken from reference 10.

[b] The β^+ particle is accompanied by the annihilation radiation (AR), which is a γ-ray of 0·511 MeV energy. The β^- particles may have energies up to about 4·5 MeV. For the actual values see reference 10.

[c] EC = orbital electron capture; IT = isomeric transition to a lower energy state. Both processes are accompanied by photon emission (for actual energy values see reference 10).

[d] The photons may range from γ-rays of about 4 MeV down to X-rays (for actual energies see reference 10). AR = annihilation radiation.

[e] Mainly of applications involving organic halogen. A wide bibliographic compilation of examples and methods is given in reference 101.

D. Emission Spectra

1. Organic molecules

The spectrophotometry of flames is potentially a method of 'fingerprint' identification and determination of organic compounds. In an oxygen–hydrogen burner the organic sample undergoes fragmentation and electronic transitions take place in the fragments that are accompanied by emission in the u.v.-visible region. Unfortunately, most assignments pertain to C, C—H and C—N fragments[102,103]. The method has been coupled to gas chromatographic separation and C—Cl bands were assigned at 277 and 279 nm[103].

Another type of emission spectrometry which can be coupled with gas chromatography is that of a helium plasma, where several emission lines may be useful in quantitative analysis of S, P and the halogens down to a few nanograms of the elements[104,105]. By direct current discharge generation of the He plasma, detection limits of 10^{-13} g/s have been obtained, measuring the atomic spectra of the elements as follows: F at 6902·5 Å, Cl at 7256 Å, Br at 7348·6 Å and I at 6082·5 and 5464·6 Å. The lines for F, Cl and Br give good discrimination when more than one halogen is present in the plasma, while those of I have poor selectivity[105]. Similar studies were also reported for argon plasmas[106].

2. Metal-sensitized spectra

Both organic matter and the salts resulting from mineralization procedures described in section II. F can produce spectra belonging to the excitations of metallic ions in flames or plasmas. Potassium iodide can be determined in the presence of large amounts of potassium chloride in a hollow-cathode light source[107,108]. The possibilities of iodine compound analysis by emission in a copper hollow cathode have been explored[109].

Fluorides can be determined by following the depression in the atomic absorption of Mg in an air–coal gas flame. The ions NO_3^-, Cl^-, Br^-, I^-, NH_4^+ and K^+ caused no interference but PO_4^{3-} and SO_4^{2-} did so markedly[110]. Airborne organic fluorine has been determined by the SrF excitation in a flame with detection limits of about 50 μg/l[111].

The time-consecrated Beilstein test[112] has been adapted for detection in gas chromatography by burning the compounds over a copper gauze in an oxygen–hydrogen flame and measuring the emitted intensities at 394 or 526 nm (interference filters). Cl, Br and I compounds behave differently from F or non-halogen compounds and the sensitivity is in the nanogram range[113].

Sensitizing with indium seems to give better results: organochloro[114], organobromo[115,116] and organoiodo[117] compounds can be determined by

passing organic vapours over an indium surface before burning in an oxygen–hydrogen flame, and measuring the intensity of the lines at 359·9 nm for InCl[118], 372·7 nm for InBr and 409·9 nm for InI[117] either spectrophotometrically or by using the appropriate interference filter. This method has also been coupled with gas chromatographic separation, measuring at 360 nm, where distinctinve response was obtained for Cl, Br and I, but not for F. Interference is observed for S but not for P and the detection limits are about 0·1 p.p.m. of halogen in organic matter[119].

An important development of gas chromatography regarding its application to pesticide trace analysis was the introduction of halogen-sensitive flame ionization detectors (see section III. A. 2. c). Based on a similar design, alkali salt-sensitized flame photometers have been devised which can also be used as flame ionization detectors. In a detector fitted with a sodium sulphate pellet the Na emission at 589 nm (interference filter) was measured. The response for light organic halides was Cl < Br < I and the discrimination from non-halogen matter was excellent, as is dramatically illustrated in Figure 2, where both photometric and ionization responses

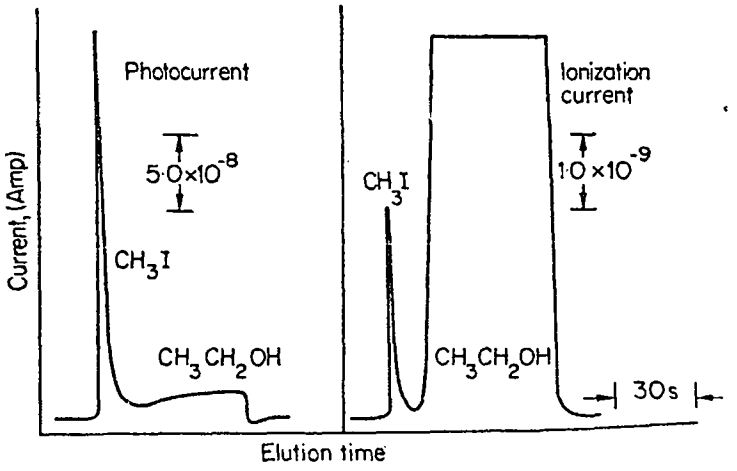


FIGURE 2. Comparison of photometric and ionization current response in a detector fitted with a sodium sulphate pellet. Sample: 5 μl of 0·0010% methyl iodide in ethanol[120]. Reproduced by permission of the American Chemical Society from A. V. Novak and H. W. Malmstadt, *Anal. Chem.* **40**, 1108 (1968).

were measured for the same sample[120]. The effects of various working parameters were tested for flames sensitized with Li_2SO_4, Na_2SO_4 and K_2SO_4, measuring at 671, 589 and 769 nm respectively and the sodium salt was found to be best. The response was log–log linear for Cl, Br and I

compounds but not for F compounds. It was always the poorest for F compounds, while for Cl and Br it varied according to the type of compound and the basis of computation (e.g. response/ng or response/nmole). Nitriles and nitro compounds have only a weak response, and, in general, the method is 1000–5000 times more sensitive for Br and Cl compounds than for non-halogen compounds[121].

E. Mass Spectra

This method allows us, in general, to obtain the elementary analysis of all the fragments produced by electron impact on volatile organic molecules, including the molecular ion, and in the case of non-volatile materials it allows detection of the presence of many elements down to a certain concentration limit. Organic halides are especially suited for these methods. Applications concerning structural elucidation will be given in section V. C.

1. High resolution mass spectrometry

The total and the fractional part of the m/e value of the molecular peak (M) can be used to determine the elementary formula of the molecule by finding the n_i values that best satisfy equations (1) and (2) simultaneously,

$$M = \sum_i n_i m_i \tag{1}$$

$$\text{Fractional part of } M = \text{Fractional part of } \left\{ I + \sum_i n_i (m_i - i) \right\} \tag{2}$$

where n_i is the number of atoms with mass number i and atomic mass m_i (see Table 6), and I is an arbitrarily large integer.

2. Chlorine and bromine multiplets

The natural abundances of isotopes stand approximately in the ratio of 3 : 1 for chlorine and 1 : 1 for bromine (Table 6). The record in a mass spectrum corresponding to an ion containing c atoms of chlorine and b atoms of bromine will consist of $b+c+1$ lines spaced at 2 mass unit intervals. The relative abundances of the multiplet components can be calculated as follows: develop the expression on the left-hand side of equation (3), formally as though the indices b and c were exponents (but write them as subscripts). For each term of the summation compute the z_i values according to equation (4), list the z_is in order of increasing magnitude and finally compute the statistical weights w_j of the peaks by adding all coefficients a_i that correspond to the same value of z_i, as in equation (5). For example, the computation for an ion containing Cl_2Br_2 is shown in Table 7.

TABLE 6. Properties of the naturally occurring isotopes of the organic elements[a]

Isotope	Atomic mass[b]	Natural abundance (%)	Nuclear spin (I)[c]	Quadrupole moment (Q)[d]
^{1}H	1·007825	99·985	1/2	—
^{2}H	2·01410	0·015	1	$2·77 \times 10^{-3}$
^{12}C	12·00000	98·89	—	—
^{13}C	13·00335	1·11	1/2	—
^{14}N	14·00307	99·63	1	$7·1 \times 10^{-2}$
^{15}N	15·00011	0·37	1/2	—
^{16}O	15·99491	99·759	—	—
^{17}O	16·99914	0·037	5/2	-4×10^{-3}
^{18}O	17·99916	0·204	—	—
^{19}F	18·99840	100	1/2	—
^{31}P	30·97376	100	1/2	—
^{32}S	31·97207	95·0	—	—
^{33}S	32·97146	0·76	3/2	$-6·4 \times 10^{-2}$
^{34}S	33·96786	4·22	—	—
^{36}S	35·96709	0·014	—	—
^{35}Cl	34·96885	75·53	3/2	$-7·97 \times 10^{-2}$
^{37}Cl	36·96590	24·97	3/2	$-6·21 \times 10^{-2}$
^{79}Br	78·9183	50·54	3/2	0·33
^{81}Br	80·9163	49·46	3/2	0·28
^{127}I	126·9044	100	5/2	−0·69

[a] From reference 10.
[b] Based on the arbitrarily assigned mass 12·00000 for $^{12}_{6}C$, in the physical scale.
[c] In units $h/2\pi$.
[d] In units of 10^{-24} cm^2.

TABLE 7. The statistical weights (w_j) of the quintet corresponding to an ion containing Cl_2Br_2

z_t	Terms with equal z_k	m/e	w_j	
			Approximate	Precise[a]
	$(3\,^{35}Cl+{}^{37}Cl)_2(^{79}Br+{}^{81}Br)_2 =$ $(9\,^{35}Cl_2+6\,^{35}Cl^{37}Cl+{}^{37}Cl_2)$ $(^{79}Br_2+2\,^{79}Br^{81}Br+{}^{81}Br_2) =$			
4	$9\,^{35}Cl_2{}^{79}Br_2+$	M	9	9·82
6	$18\,^{35}Cl_2{}^{79}Br^{81}Br+6\,^{35}Cl^{37}Cl^{79}Br_2+$	$M+2$	24	25·61
8	$9\,^{35}Cl_2{}^{81}Br_2+12\,^{35}Cl^{37}Cl^{79}Br^{81}Br+$ $^{37}Cl_2{}^{79}Br_2+$	$M+4$	22	22·95
10	$6\,^{35}Cl_2{}^{37}Cl^{81}Br_2+2\,^{37}Cl_2{}^{79}Br^{81}Br+$	$M+6$	8	8·17
12	$^{37}Cl_2{}^{81}Br$	$M+8$	1	1·00

[a] Computed by developing

$$\left(\frac{75·53}{24·47}\,^{35}Cl+{}^{37}Cl\right)_c\left(\frac{50·54}{49·46}\,^{79}Br+{}^{81}Br\right)_b=\sum_{i=1}^{I}a_i\,^{35}Cl_{\alpha_i}{}^{37}Cl_{\beta_i}{}^{79}Br_{\gamma_i}{}^{81}Br_{\delta_i}$$

instead of equation (3).

$$(3\,^{35}Cl+{}^{37}Cl)_c(^{79}Br+{}^{81}Br)_b = \sum_{\substack{i=1 \\ I=(b+1)(c+1)}}^{I} a_i\,{}^{35}Cl_{\alpha_i}{}^{37}Cl_{\beta_i}{}^{79}Br_{\gamma_i}{}^{81}Br_{\delta_i} \quad (3)$$

$$z_i = \alpha_i + 3\beta_i + \gamma_i + 3\delta_i \quad (4)$$

$$w_j = \sum_{z_i=\text{constant}} a_i \quad (j = 1, 2, \ldots, b+c+1;\ z_1 \leqslant z_2 \leqslant \ldots \leqslant z_I) \quad (5)$$

The statistical weights calculated from the actual isotope abundances do not differ much from those found by the approximate method. Not all the peaks of a multiplet are always easily recognized, as they may be lost in the background noise; e.g. the heaviest peak of the Cl_4 quintet has less than 1% of the intensity of the most abundant peak as the intensities are in the ratio of 8 : 108 : 54 : 12 : 1. The Cl, Br content of a molecule can be found by fitting the multiplet shape to one of the entries of a table computed as described above for various values of b and c (see, for example, reference 122).

3. Carbon isotope peaks

With fluorine and iodine no halogen multiplet analysis is possible. However, the isotopic peaks of other elements, especially carbon, may be of help in detecting the presence of and even determining such halogens, as the $M+1$ peak has an intensity much lower than the one that could be expected from a halogen-free compound of molecular weight M. Thus, for example, for iodobenzene, $M = 204$, the ratio of the $M+1$ to the M peak is 6·1% and that of the $M+2$ to the M peak is 0·2%. On the other hand, for C—H—O compounds the same ratios can be[27] 11–17% and 1·3–1·5% respectively, depending on the oxygen content.

4. Spark source mass spectrometer

Ordinary mass spectrographs require the introduction of the sample into the ionization chamber in a volatilized form; however, the mass spectra of non-volatile compounds can also be obtained. The compound is mixed with a conducting substance thus forming an electrode, which on sparking emits ionized particles in the source section of the mass spectrograph. The sensitivity of this method is comparable to that of neutron activation, or better, especially with fluorine compounds[28,123,124].

F. Organic Halogen Mineralization

The simplest detection and determination methods based on chemical reactions entail the conversion of organically bound halogen atoms into elementary halogen or halide anions. Once this step has been accomplished the analytical finishing is an *inorganic* analysis problem. However, many

of the finishing methods have been designed to solve specific problems posed by mineralized organic systems and therefore deserve special attention (section II. G).

The choice of the proper decomposition method depends on various considerations:

(i) *Properties of the sample*: Most mineralization methods give good results with 'easy' samples say, for example, a steroidal halide. On the other hand, with highly halogenated samples, volatile liquids or gases the choice has to be made *ad hoc*.

(ii) *Kind of halogen*: Not all mineralization procedures are suited for determination of all the four halogens.

(iii) *Sample size*: The sample may belong either by fate or by design to one of the classes ranging from macro down to submicro.

(iv) *Administrative requirements*: The necessity of establishing efficient routines may arise to cope with long runs of samples of the same type. Automation of at least part of the analytical process may become necessary and critical in the choice.

(v) *Equipment*: The existence in a laboratory of obsolete equipment in good working condition may often dictate the analytical procedure, especially if an alternative choice is expensive.

(vi) *Skill and personal taste of operators*: Analysts tend to develop special attachments to certain methods and become very proficient in them, while other methods of comparable quality become rejected for reasons belonging to the realm of psychology rather than chemical science.

The mineralization step of an organic elementary analysis and the finishing steps have been reviewed[11–15,20–23,125].

I. Combustion tube

a. Oxygen combustion. A series of variations of the classical semimicro combustion method of Pregl[20] have been proposed for determining all four halogens. The sample is burnt in an oxygen stream at high temperatures (900–1000°) and the products are carried by the stream and passed through an aqueous solution of hydrogen peroxide, with or without an alkali. The organic halogen is converted to the elementary form, possibly with a small amount of the hydrogen halide, and converted to the latter form in a collecting solution, as shown in reaction (6), or to the corres-

$$X_2 + H_2O_2 \longrightarrow 2\,HX + O_2 \qquad (6)$$

ponding salt in the presence of alkali. Fluorine is reactive enough to yield HF directly with water (equation 7).

$$2\,F_2 + 2\,H_2O \longrightarrow 4\,HF + O_2 \qquad (7)$$

Reduction of the combustion gases by sodium bisulphite has also been applied[126]. Whenever HX production is to be ensured prior to dissolving the combustion gases, wet oxygen can be used to provide the hydrogen needed[127,128]. Wet oxygen combustion has also been used for F determination in biological samples[129].

Among the variations proposed are empty tube combustions[130], platinum catalysed combustions[131], alumina plates[132], sintered quartz plates[133], etc. Determinations at the submicro level has been carried out[134].

The importance of the oxygen combustion tube stems from the possibility of adapting it to automatic systems (see section II. G. 9), and to simultaneous halogen-C-H analysis[135,212].

b. Hydrogen combustion. Pyrolysis in hydrogen atmosphere converts halogen to hydrogen halide, sulphur to hydrogen sulphide and phosphorus to phosphine[136]. The latter two products interfere with halide titration but they may be eliminated if combustion is carried out in the presence of nickel catalysts. Hydrogen combustion is used in commercial instruments for automatic halogen analysis (section II. G. 9).

2. Oxygen flask combustion

The first determinations of this type were performed in the last century[137], but, except for some sporadic applications, the method remained unchanged until the fifties, when Schöniger adapted it for determinations of sulphur and the halogens in the micro scale[138–140]. He showed that the method can be as accurate as other more lengthy microanalytical methods

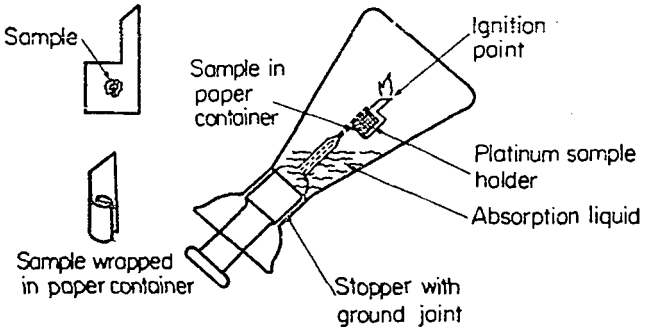


FIGURE 3. Oxygen combustion flask. Reproduced by courtesy of A. H. Thomas Co.

now used. In the authors' laboratory this method has been applied for several years with good results even with samples containing more than 60% halogen by weight.

The Schöniger procedure is as follows: the sample is weighed into a small filter paper container which is folded and clamped in a platinum

gauze holder; the paper is ignited and rapidly introduced into an 'iodine flask' filled with oxygen and containing the absorbing solution. The flask is tilted so that the solution forms a seal (Figure 3). The combustion is complete in 5–10 s, and then the flask is shaken for a few minutes to complete the absorption of the combustion gases and the solution is ready for the end determination.

A large number of modifications of the method and the main points to which attention should be paid have been reviewed[141]. Some variations are summarized in Table 8.

TABLE 8. Modifications of the oxygen flask combustion method

Type of variation	Remarks	Reference
1. *Sample size*		
(a) Macro	5 l flask, infrared ignition	142
	Flowing oxygen combustion	143
	Oxygen Parr bomb	144, 181
(b) Semimicro	Ordinary Schöniger method	141
(c) Micro	Ordinary Schöniger method	141
	Air-filled flask with steel sample holder for field detection problems	145
(d) Submicro	Special design flask ('hot flask combustion')	23, 148
2. *Accuracy and applicability*		
(a) Micro	Using potentiometric finish	22
(b) Submicro	Using chemical and potentiometric finish	21, 23
3. *Special handling of samples*		
(a) Liquids	Sample in capillaries, in a special platinum holder	147
	Hot flask	148
	Sample in capsules of cellulose, polyethylene or gelatine	149, 154
(b) Thermally unstable compounds	Electric ignition	150
(c) Combustion without containers	Combustion in furnace at 850°	148
(d) Explosive compounds	Heating coil, screen protection[a]	152
4. *Modifications due to the halogen content*		
(a) Fluorine compounds	Additives for aiding complete combustion[b]:	
	sucrose	154
	sodium peroxide	155

TABLE 8 (*cont.*)

Type of variation	Remarks	Reference
	potassium chlorate	156
	paraffin wax	157
	dodecyl alcohol	151, 158
	Combustion in quartz flasks	146, 154, 266
	Distillation after combustion	127
	Combustion in polypropylene flasks	160
	Combustion in polycarbonate flasks	158
	Semimicro to micro samples	161
	Submicro samples	156
	Determination in chromatographic spots	162
(b) Chlorine compounds	Absorption in dilute alkaline hydrogen peroxide[c]	138
	Absorption in pure water	163
(c) Bromine compounds	Absorption in dilute alkaline hydrogen peroxide[d]	138
	Absorbing reagent for highly brominated compounds:	
	hydrazine sulphate	163, 167
	sodium borohydride	159,164
	Absorption in buffered sodium hypochlorite for highly chlorinated bromine compounds[e]	138
(d) Iodine compounds	Absorption in dilute alkaline hydrogen peroxide	138
	Absorption in sodium carbonate solutions (ng range)	165
	Various reductive absorption reagents:	
	hydrazine	166
	hydroxylamine	166
	sodium borohydride	159
	Poly(methyl methacrylate) sample holder	166

[a] The jacket described in reference 153 has been used in our laboratories for several years.

[b] Trifluoroacetic acid derivatives have been satisfactorily analysed in our laboratories without additives (see also reference 168). Open-chain fluorides such as poly(tetrafluoroethylene) have been found to decompose quite readily, whereas highly fluorinated ring compounds are difficult to decompose and more energetic combustion methods are recommended[141].

[c] Although peroxide is not strictly necessary[163] it is useful in converting nitrogen and sulphur combustion products into nitrate and sulphate respectively[141].

[d] This reagent is adequate for many organic bromine compounds of low or moderate halogen content.

[e] $Br_2 + 5\ ClO^- + H_2O \rightarrow 2\ BrO_3^- + 5\ Cl^- + H^+$. See section II. G. 4.

3. Oxygen–hydrogen flame

This technique is suitable for the combustion of large samples in which trace elements have to be determined. Several designs were proposed to fit the requirements of sample volatility and size[169–171]. Thus, determination of chlorine traces in petroleum[172], various halogens in viscous polybutylene fraction[173] and general organic halogen microanalysis[174] have been proposed.

The method is potentially very suitable for automated semi-continuous analysis, especially of fluids, and developments should be expected in this direction.

4. Fusion methods

Samples which are difficult to mineralize thoroughly by the oxygen combustion methods are conveniently decomposed by fusion with metals, oxides or strong oxidants. The main disadvantages of such methods are that they usually require a subsequent work-up of the sample before the end analysis and they yield solutions with large amounts of salts other than those stemming from the organic sample. On the other hand, fusion methods have long been applied to heteroatom detection in organic compounds due to their easy adaptability to fast manipulations in devices as simple as test tubes. The subject has been reviewed[15].

a. Sodium peroxide in the Parr bomb[175]. Determination of all halogens can be made by fusion of the organic sample with sodium peroxide. The method is best suited for the macro to semimicro range, and a large excess of sodium salts is produced during the work-up of the fusion materials*. Several modifications have been proposed in order to improve the results[180, 182, 185], e.g. adding ethylene glycol to the fusion mixture.

b. Fusion with metals, oxides and carbonates. This is the most widely recommended method for detection of organic halogen in semimicro-sized samples[11–15]. Some applications have been also made in quantitative analysis. The methods are summarized in Table 9. The fused mass is usually dissolved in water and interfering anions such as sulphide, cyanide and thocyanate are expelled from the solution, leaving the halides. Instead of expelling those ions the halides may be oxidized to the free halogen form and detected as described in section II. D. 5. This may be

* Although its accuracy for bromine determinations has been doubted[176], it is the authors' experience that bromine can be adequately determined in organic samples, e.g. in routine determination of brominated wood[177–179], where Schöniger's method failed because of the low combustibility of the samples[179]. Activation analysis[80] also gave good results.

done conveniently with manganese dioxide, potassium permanganate or sulphochromic mixture[12,192] affording very sensitive detection tests (see section II. G. 5).

TABLE 9. Fusion agents for organic halide analysis

Fusion agent	Type of analysis	Reference
Sodium	Detection	11–15, 183
	Determination	184
Sodium with ethylene glycol	Determination	182
Potassium	Detection	186
	Determination	234
Magnesium with potassium carbonate	Detection	188
Zinc with potassium carbonate	Detection	189
Sodium carbonate	Detection	12
Sodium carbonate with dextrose	Detection	190
Calcium oxide	Determination	191

5. Oxidative digestions

These consist of treating the organic or biological sample with strongly oxidizing solutions that are capable of totally disrupting the structure, leaving the halogens in their halide or free halogen forms.

The classical Carius method[193,194], consists of digesting in nitric acid in a sealed tube at high temperatures, and has been for many years the most popular procedure. The chromic acid digestion is carried out in a distillation apparatus; it consists of a treatment with concentrated mineral acid in the presence of potassium dichromate and silver dichromate, where the halogen produced is carried by a stream of oxygen into a sodium hydroxide solution containing hydrogen peroxide[195]. After the proper dilutions and reductions the halide solutions are ready for the end determinations. Many sensitive spot tests for the halogens follow sulphochromic acid digestion[12].

6. Reductive digestions

These procedures are milder than the oxidative digestions, leading to the conversion of organic halogen and other heteroatom functions to the corresponding hydride or salt, while the organic skeleton undergoes only relatively slight changes. Catalytic hydrogenations with Raney nickel in alkaline medium[196], treatment with the sodium diphenyl reagent[197] or sodium borohydride and palladium[198,199] have been proposed for halogen determinations.

The reduced organic skeleton can be used in identification and structure assignment problems, as discussed in sections III. A. 2. b and IV. D.

7. Solvolytic digestions

Treatment with strongly basic solutions brings about elimination or displacement of organic halide by the base anion. Determination procedures have been proposed based on displacement by sodium dissolved in ethanol (the Stepanow method)[200], liquid ammonia[201], amines (see end of section IV. A) or potassium hydroxide[202]. Detection by the use of alcoholic silver nitrate[11–15] is also based on electrophilically catalysed solvolysis. These methods of mineralization fail to be quantitative in many types of organic halides, and strongly depend on the molecular structure as shown in section IV. A.

8. Photolysis

Irradiation with u.v. light causes the breaking of C–halogen bonds liberating atomic halogen that may react *in situ* with many test reagents. This property has been applied to sensitive visualization tests in paper and thin-layer chromatography, as shown in section III. A. 1.

A mineralization method for organic halogen determination has been proposed, based on decomposition of a small sample (~ 1 mg) sealed in a quartz ampoule and strongly irradiated by a xenon lamp for a few seconds up to a few minutes (iodo compounds decompose the fastest and fluoro compounds the slowest). The organic halogen is converted to a mixture of free halogen and hydrogen halide which can be subsequently absorbed in an appropriate medium prior to titration[203].

G. Finishing Procedures for Mineralized Samples

The result of the mineralization step considered in section II. F is a solution containing the halogens in the halide or elementary form, accompanied by other compounds resulting from the sample destruction and mineralizing agents. The finishing step consists of the analysis (quantitative or qualitative) of the mineralized halogen and choice of the adequate method depends much on the nature of the mineralized solution. The subject has been reviewed[11–15, 20–23, 125].

1. Alkalimetric and acidimetric titrations

If the receiving solution of a combustion set-up has a known amount of alkali, the excess can be titrated with acids in the presence of methyl red indicator, as was done with the nitric acid–dichromate digestion[204].

For chloride or bromide determinations of compounds containing sulphur or nitrogen, mercuric oxycyanide is added and the alkali hydroxide produced according to reaction (8) can be titrated with standardized acid[138,205].

$$2\,Hg(OH)CN + 2\,NaX \longrightarrow Hg(CN)_2 + HgX_2 + 2\,NaOH \qquad (8)$$

$$(X = Cl, Br)$$

After oxygen combustion and absorption in water, hydrogen fluoride can be determined by acidimetry[206] when no other acid-producing elements are present. Of course all these methods yield 'total' halide results. When more than one halogen is present in the sample the separation procedures described in sections II. G. 6–8 have to be applied.

2. Precipitation methods

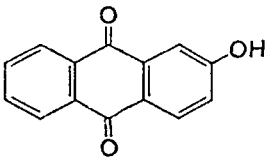
a. Fluoride. Micro and semimicro determinations of this halide can be performed by precipitating as lead chlorofluoride[161,207]. The composition of the precipitate is variable and therefore a strict routine of analysis is advised, and either expulsion of interfering ions[161] or volatilization of the fluorine might be advisable[208]. These procedures are, however, cumbersome and titrations with lanthanum(III) nitrate are recommended. Quantitative precipitations of fluoride with lanthanum(III) are also possible[42]. The precipitation methods for fluoride ions have been reviewed[209].

b. Chloride, bromide and iodide. Silver halide precipitations were used after all classical mineralization procedures both for detection[11–15] and determination problems[20–23]. The method is free from interference but it is tedious and its precision relatively poor[210]. Best quantitative results are obtained with chloride and bromide, while iodide falls behind owing to its low conversion factor.

Direct absorption by silver of the halogen formed in the combustion tube was already introduced in the last century[211] and has been further modified and improved for use in the micro scale[212,213]. The halogen is absorbed on a silver sponge which can be weighed at the end of combustion. Absorption on lead dioxide has also been proposed[214]. These methods are of advantage only when simultaneous elementary analyses including the halides have to be performed in the same combustion train.

3. Detection and determination of halides with the aid of colour indicators

a. Fluoride. After fusion the presence of fluoride can be detected by its decolorizing effect on the complex formed between zirconium(IV) and



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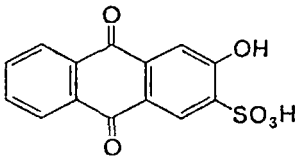


(3)

alizarin (2) [12]. The most widely investigated titrant for fluorides is thorium(IV) nitrate using as indicator sodium alizarinsulphonate (3), which is adequate for all mineralization procedures yielding fluoride[157, 208, 215, 217]. Some restrictions of this method are:

(i) The stoicheiometric relation of reaction (9) is not followed strictly. This requires the use of calibration curves.

$$Th(NO_3)_4 + 6\,F^- \longrightarrow ThF_6^{2-} + 4\,NO_3^- \qquad (9)$$

(ii) Sodium alizarinsulphonate is also an acid–base indicator changing its colour from yellow in acidic solution to violet in alkaline solution. Therefore the appropriate buffer should be used to allow a good end-point in fluoride titration (change from yellow to red).

(iii) Nitrogen and other halogens do not interfere with the titration but sulphate, phosphate, arsenate and most metals do.

Other titrants forming stable complexes with fluoride ions are cerium(III) nitrate[218], zirconium(IV) chloride[219] and aluminium chloride[220]. The visual methods for detection and titration of fluoride have been reviewed[209].

Table 10 summarizes reagents that have been proposed for photometric fluoride determinations. These methods are based on the sequestering ability of fluoride on metal ions thus forming complexes which are more stable than those between the metal ion and the organic dye. Fluorine complex formation is accompanied by a corresponding reduction of the absorption intensity of the organo-metal complex but may be accompanied by adsorption of the dye on the metal fluoride precipitate forming thus a *lake* of characteristic colour[209].

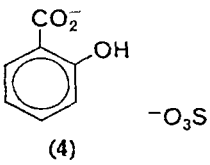
Fluoride ion in the μg/l range inhibits the rate of reaction (10), catalysed by Zr^{IV} ion, thus affording a sensitive kinetic method of fluoride determination[228].

$$BO_3^- + 2\,I^- \xrightarrow{Zr^{IV}} BO_3^{3-} + I_2 \qquad (10)$$

b. Chloride, bromide and iodide. The direct colorimetric determination of halides has been paid scarce attention. Nile blue sulphate or chloride

TABLE 10. Reagents for spectrocolorimetry of fluoride ion

Reagent		Remarks	Reference
Metal ion	Organic ligand		
Fe^{III}	Salicylate (4)		154
Zr^{IV}	SPADNS (5)	Absorption at 540–590 nm	221
Ce^{III}	Alizarin (2)	Absorptions at 538 and 567–568 nm. At pH 4·3 alizarin-fluorine blue is formed and measured at 610 nm	221
La^{III}	Alizarin (2)	A method for ultramicro determinations	221, 222
La^{III}	Chloranilate (6)		223
Th^{IV}	Chloranilate (6)		893
Al^{III}	Eriochrome cyanine R (7a)	Adequate for up to 20 μg	224
Zr^{IV}	Eriochrome cyanine R (7a)	Adequate for traces up to 2·5 μg	155, 221, 222 225
Zr^{IV}	Calcein blue (8)	Down to 10^{-7}M	226
Th^{IV}	Xylenol orange (7b)	0·7–10 μg	221
Zr^{IV}	Xylenol orange (7b)	5–50 μg/l	227



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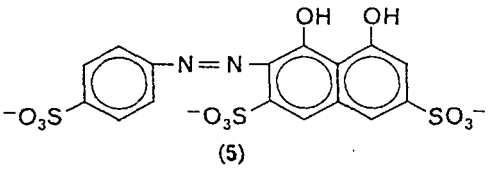

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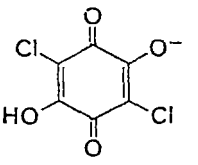

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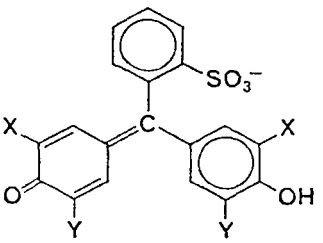
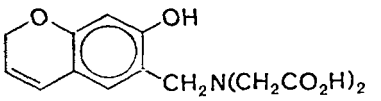


(7a, X = CO_2^-; Y = CH_3)
(7b, X = $CH_2N(CH_2CO_2^-)_2$; Y = CH_3)
(7c, X = Br; Y = Cl)



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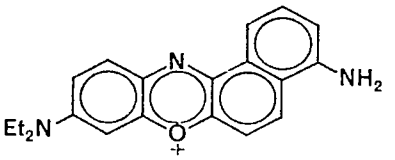
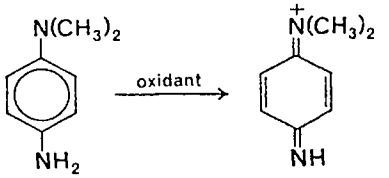


(9)

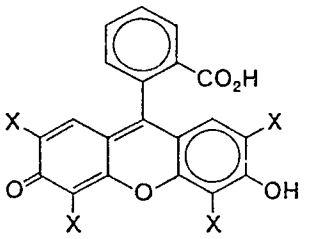
(9) forms salts with bromide or iodide which can be extracted into organic solvents and determined spectrophotometrically[229]. The spectrophotometric measurement of hexachloroferrate ions[230] may be developed into a general colorimetric method for chlorides. Iodide catalyses the formation of Prussian blue, affording a very sensitive method for determination of this ion (see section II. G. 6). Copper(II) oxidizes *N,N*-dimethyl-*p*-phenylenediamine (reaction 11) yielding Wuster's red (**10**+**11**). The



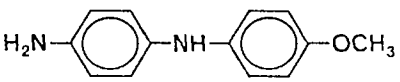
(10) (11) (11)

reaction is inhibited, however, by the copper(I) produced, unless halides or pseudohalides are present, as these anions combine strongly with copper(I). This reaction system has been developed into a semiquantitative indicator method[231].

Argentometry by Mohr's method[232], although still in use after more than a century, is not suitable for micro scale analysis. Addition of organic adsorption indicators is made in order to facilitate the end-point observation: fluorescein (**12a**) is long in use[233], variamine blue B (**13**) was used in micro-titrations[234] and dithizone (**14**) in aqueous acetone titrations[235]. The subject has been reviewed[233].



(12a, X = H)
(12b, X = Br)



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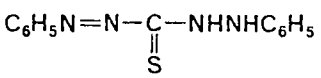


(14)

Mercuric halides, formed according to reaction (12), do not precipitate from solution but are dissociated to a very limited extent. This allows easy end-point visualization in titrations with mercury(II) nitrate by means of the intensely coloured complexes of Hg^{II} with diphenylcarbazide (**15**)

$$Hg^{2+} + 2X^- \longrightarrow HgX_2 \qquad (12)$$

or diphenylcarbazone (**16**) [236]. The reaction is pH-dependent and good results are obtained only within rather narrow limits, e.g. in water at pH 1·5–2 [237].

$C_6H_5NHNHCONHNHC_6H_5$ (**15**) $\qquad$ $C_6H_5N{=}NCONHNHC_6H_5$ (**16**)

The method is suitable for finish after most mineralization procedures. A convenient modification is to carry out the titration in 80% ethanol[238]. Many adaptions have been proposed in the micro scale[126, 239, 240]. The subject has been reviewed[233, 241–243].

4. Amplification reactions

Bromide and iodide may be oxidized to the corresponding halates, thus enlarging sixfold their conversion factor. Bromide is oxidized with sodium hypochlorite at pH 5–7 (equation 13), the excess reagent is destroyed with sodium formate, iodide and acid added (equation 14) and the iodine titrated. This is the classical van der Meulen method, which has been modified for semimicro work[244]. Iodide interferes in the method.

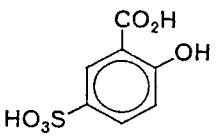
$$Br^- + 3\,ClO^- \longrightarrow BrO_3^- + 3\,Cl^- \qquad (13)$$

$$BrO_3^- + 6\,I^- + 6\,H^+ \longrightarrow 3\,I_2 + Br^- + 3\,H_2O \qquad (14)$$

Iodide and iodine are converted into iodate by bromine according to reactions (15) and (16) respectively. The excess bromine is then removed by formic acid, sulphosalicylic acid (**17**) or oxine (**26**)[262], and the iodine liberated according to reaction (17) is detected or determined as required.

$$I^- + 3\,Br_2 + 3\,H_2O \longrightarrow IO_3^- + 6\,Br^- + 6\,H^+ \qquad (15)$$

$$I_2 + 5\,Br_2 + 6\,H_2O \longrightarrow 2\,IO_3^- + 10\,Br^- + 12\,H^+ \qquad (16)$$



(**17**)

$$IO_3^- + 5\,I^- + 6\,H^+ \longrightarrow 3\,I_2 + 3\,H_2O \qquad (17)$$

None of the other halogens interferes. No direct amplification reaction for chloride has been proposed, and the indirect methods[244, 245] are of no advantage.

5. Free chlorine, bromine and iodine

Mineralization procedures leading to the free halogen afford very sensitive detection methods by means of colour reactions, which are summarized in Table 11. Many such reactions are sensitive to about 2 μg or less of halogen in the sample.

TABLE 11. Colour reactions for free halogen detection

Reagent	Recommended for	Colour reaction	Reference
Iodide-starch	Cl_2, Br_2, I_2	Colourless to blue	246
Thio-Michler's ketone (**18**)	Cl_2, Br_2, I_2	Brown-yellow to blue	12
N,*N*-Dimethyl-*p*-phenylene-diamine (**10**)	Cl_2, Br_2, I_2	Colourless to red	12
Diphenylamine	Cl_2, Br_2, I_2	Colourless to blue[a]	12
Congo red (**19**)–H_2O_2	Cl_2	Red to blue	192
o-Tolidine (**19′**)[e]	Cl_2 + Br_2 mixtures	Colourless to yellow	248
Fluorescein (**12a**)	Br_2	Yellow to red[b]	192
Fuchsin (**20**)-bisulphite (leuco-form)	Br_2	Colourless to blue	249
α-Naphthoflavone (**21**)	Br_2, I_2	Colourless to orange-red (Br_2) or to blue-violet (I_2)	250
Tetrabase (**22**)	I_2	Colourless to blue[c]	192
Sodium nitrite[d]	I_2	Yellow to brown, measured at 455 nm	199

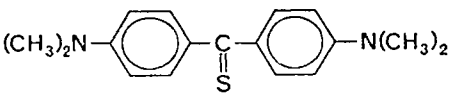
[a] Under certain conditions the method becomes specific for chlorine.

[b] The reaction entails conversion to eosin (**12b**). Iodine interferes by yielding the tetraiodo analogue (erythrosine). See section II. D. 8. b.

[c] The other halogens interfere. However, freshly prepared chloramine-T (**23**) solutions transform iodide to iodine[251] without oxidizing **22**. This is a very sensitive method.

[d] This reagent converts iodide into iodine which is measured photometrically.

[e] This is a quantitative photometric method.



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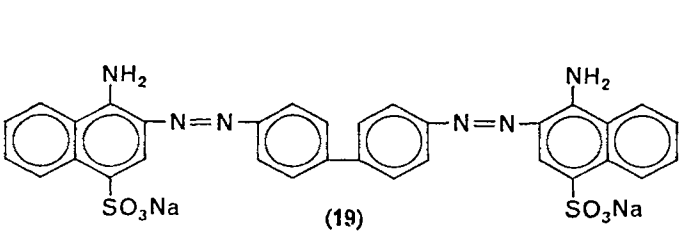

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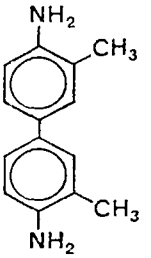

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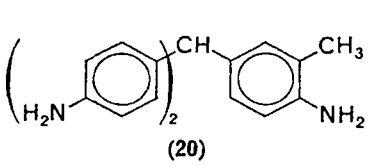

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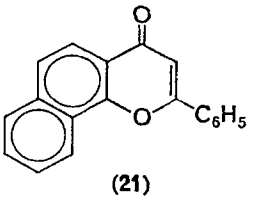

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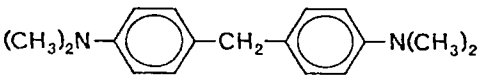

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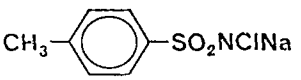


(23)

6. Chromatography of the halide anions

Halide ion separation has been effected on thin layers made of ion exchange resins[252], keratin[253] and silica gel, the latter being the most widely studied[254, 255]. Development has been done in the form of alkali or ammonium halides with aqueous solvents[253] or with amine-containing alcoholic solvents[254]. The R_f values found in the latter case follow the order

$$I^- > SCN^- > Br^- > Cl^- > N_3^- > Fe(CN)_6^{3-} \sim Fe(CN)_6^{4-} > CN^- > F^-$$

Spot visualization can be done by any of the following reagents[254]:

(i) An acid–base indicator with transition point at sufficiently high pH, which has been just over-neutralized with alkali, e.g. bromocresol purple (**7c**), with transition from pH 5·2 yellow to pH 6·8 purple will show pale spots on a purplish background due to the acidic reaction of all ammonium halides[256].

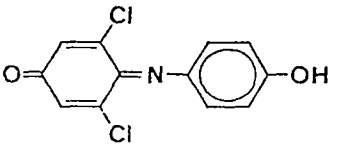
(ii) Ammoniacal silver nitrate–fluorescein spray will show the halide spots after u.v. irradiation[254].

(iii) Zirconium–alizarin complex decolorates in the presence of fluoride showing a pale spot[257].

(iv) A ferricyanate–arsenite spray will reveal iodide as a blue spot, as iodide catalyses reaction (18) leading to the formation of Prussian blue[192]. In fact this principle has been developed into a very sensitive colorimetric method for iodide determination (0·01–0·10 μg/ml range)[258].

$$Fe^{III} + As^{III} \xrightarrow{\text{iodo compounds}} Fe^{II} + As^{V} \qquad (18)$$

(v) 'Dichlorophenolindophenol' (**24**)–silver nitrate shows pink spots on a pale blue background. The spots turn to brown on exposure to sunlight[259].



(24)

Many of the visualizing agents shown in Table 15 are also suitable for the halides.

7. Electrometric halide determinations

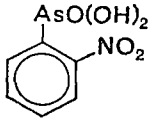
a. General comments. A great variety of instrumental methods have been applied to halide determinations which include the photometric methods of section II. G. 3. However, of more extended application are the various electrometric methods due to their accuracy, specificity, simplicity and adaptability to the requirements of routine analysis[21]. These instruments are capable of effecting analysis of each halide present in a mixture without requiring chemical separation, especially when they are present in similar proportions (see also section II. G. 8). The recent development of *specific halide electrodes* as discussed below is noteworthy. Some electrometric methods for the halides are summarized in Table 12. The electrometric methods for fluorine have been reviewed[209].

b. Halide responsive electrodes. The supporting theory and analytical applications of ion-selective electrodes have been the subject of intense research activity in the past few years and will probably continue in the future with added momentum[272–276]. In addition, instrumentation manufacturers have introduced commercial versions of these tools. The new electrodes markedly influenced the techniques of end-determination of halides, especially when several halogens had to be determined in the same sample. Between the hitherto developed ion-selective electrodes there are several types designed to measure activity of individual halides in solution or one halide in the presence of a high excess of the others.

TABLE 12. Electrometric methods for halide analysis

Method	Remarks	Range	Ref.
	1. *Fluoride*[a]		
Potentiometry (null-point)	Titrations with Ce^{IV}. The Ce^{IV}–Ce^{III} redox potential is lowered by fluoride complex formation	>5 mM	260, 261
Potentiometry	Titrations with $AgNO_3 + Th(NO_3)_4$, Pt and calomel electrodes, optimum results at pH 7·2. All four halides can be determined	Semimicro	317
High frequency titration	Titrations with La^{III} or Sr^{II}	Semimicro	216
Polarography	Displacement by F^- of *o*-nitrobenzene-arsonic acid (**25**) from its complex with Th^{IV}; the reduction of **25** is measured	2–10 μg	264
Amperometry	Titrations with $Th(NO_3)_4$, rotating Al electrode		265
	2. *Chloride, bromide and iodide*[a]		
Potentiometry	See second entry of fluorides above		
Potentiometry (null-point)	Ag–AgCl electrodes	~15 p.p.m.	132
Potentiometry	Three separate titrations: (i) total halide, (ii) chloride after oxidation of Br^-, I^-, (iii) iodide after oxidation of I^- to iodate (section II. G. 8. b)	Semimicro	262
Potentiometry	See above (fluorides)		185, 266
Polarization techniques	$AgNO_3$ titration	1–200 μg I^- 1–100 μg Br^-	267 268
Potentiometry	Cl^- and Br^-; Pt electrode	10^{-6}–10^{-3}M	263
Amperometry	Mercury pool and calomel–sodium nitrate electrodes	<100 μM	131
Coulometry	With biamperometric end-point	~100 μmole	269
Coulometry	Different conditions required for every halide. Automatic system	~1 μmole	270
Coulometry	In acetic acid with potentiometric end-point. Automatic system	15–75 nmole	271

[a] Titrations and potentiometric determinations with specific electrodes are discussed in section II. G. 7. b.



(25)

The halide-responsive electrodes can be used essentially in two ways (resembling the use of the glass electrode in pH measurements): they can be calibrated to read directly the concentrations and their potential vs. log [Hal$^-$] response has been found to be linear over a wide range of concentrations (see Figures 4 and 5). They can also be used for potentiometric titrations. These procedures require only a pH-meter with an

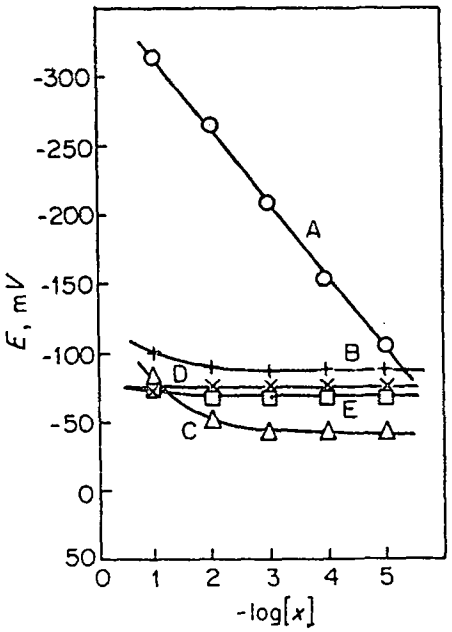


FIGURE 4. Potentiometric selectivity of a Pungor-type I$^-$ membrane electrode to I$^-$ in I$^-$—Cl$^-$ and I$^-$—Br$^-$ binary mixtures. Reference electrode Ag—AgCl (0·1) electrode with KNO_3 salt bridge: A, calibration graph for I$^-$ electrode; B, 10^{-5}M KI in Br$^-$ solution; C, 10^{-6}M KI in Br$^-$ solution; D, 10^{-5}M KI in Cl$^-$ solution; E, 10^{-6}M KI in Cl$^-$ solution; when X is Cl$^-$ or Br$^-$ [274]. Reproduced by permission of the Society for Analytical Chemistry from E. Pungor and K. Toth, *Analyst*, **95**, 1132 (1970).

expanded millivolt scale and a reference electrode. Measurement with ion-specific electrodes is rapid, non-destructive, and the sample does not need pretreatment and therefore automated analytical methods are extremely simple to design[277]. Halide electrodes which were developed during the last few years are insensitive to cations and various anions and are more resistant to surface poisoning than the traditional silver–silver halide electrodes. They do not need preconditioning or anodizing treatment and, most importantly, they can be used in the presence of oxidizing agents[278].

Since some of the theoretical approaches[274] and some phenomena are not yet fully understood[272], the classification of the types of ion-specific electrodes is still contradictory. However, according to their construction they can be divided into three main classes[274]:

(i) *Homogeneous membranes*, containing the material that is responsible for their electrochemical behaviour. This material can be a polymer, a pastille pressed from smaller particles or a slice cut from a single crystal.

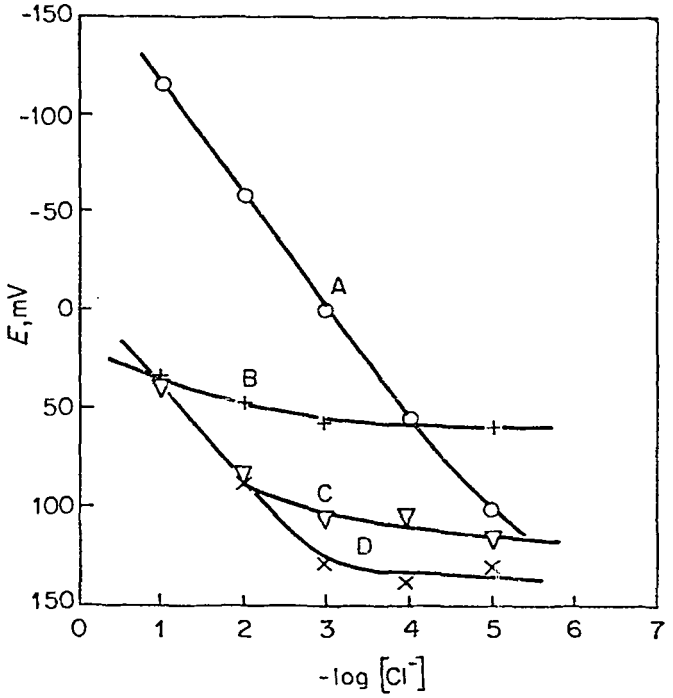


FIGURE 5. Potentiometric selectivity of a Pungor-type Br^- membrane electrode to Br^- in Br^-—Cl^- binary mixtures. Reference electrode Ag—AgCl (0·1) with KNO_3 salt bridge: A, calibration graph for Br^- electrode; B, 10^{-4}M Br^- in Cl^- solution; C, 10^{-5}M Br^- in Cl^- solution; D, 10^{-6}M Br^- in Cl^- solution[274]. Reproduced by permission of the Society for Analytical Chemistry from E. Pungor and K. Toth, *Analyst*, **95**, 1132 (1970).

(ii) *Heterogeneous membranes*, consisting of an electrochemically active material, such as silver halide salts, and an inert binding material, which gives the membrane the required mechanical properties. Pungor and coworkers[274] have found a satisfactory way of immobilizing fine particles of precipitate in a coherent, silicone rubber matrix.

(iii) *Ion-exchange membrane electrodes* represent another class of ion-selective electrodes suitable for halide measurements. The major subgroups of this class are the liquid ion-exchange membranes and the solid-state electrodes. The sensitivity of liquid ion-exchange membranes for measurements of iodide and chloride[280] and chloride alone was studied[281].

The response of solid-state electrodes was found to be superior to that of the liquid ion-exchange electrodes. The sensitivity and selectivity of Pungor-type specific halide electrodes are shown in Figures 4 and 5. The break points of the extrapolated lines give the activities of the interfering ions, while the ratio of activities of the pertinent ion to the other ion should give the selectivity constant.

Each Pungor-type electrode is best suited for measurement of the halide common with the precipitate of the membrane[272]. Thus, the silver iodide membrane electrode gives the Nerstian response to iodide over a wide concentration range, but to a lesser extent to chloride ion.

Pungor-type electrodes made of lanthanum(III), thorium(IV) and other rare earth precipitates were examined[282]. The response was found to be in the 10^{-2}–10^{-4} M fluoride range.

The solid-state homogeneous electrodes or crystalline membrane electrodes for chloride, bromide and iodide ions using solid cast pellets of silver halides as the active membrane have no advantage of sensitivity or selectivity over the heterogeneous Pungor-type electrodes, but may have better durability and faster response, which is important for analytical purposes[272]. Among them, the iodide-selective electrode was studied in detail[283]. The single crystal rare earth fluoride electrodes[284] have received a great deal of attention because of the difficulties present in fluoride determinations and the outstanding selectivity of these membranes[285,286]. Hydroxide seems to be the only major interfering ion in measurements with these electrodes. The activity calibration curve shows that the electrode follows a Nerstian behaviour with fluoride concentrations as low as 10^{-5}M and a useful non-Nerstian response at least at 10^{-6}M, at the proper pH[272]. The useful pH range for measurements is limited by formation of hydrogen fluoride in the acidic region and the electrode response to the hydroxide in the alkaline region. The electrode was later modified[287] for measurements of 10 μl samples.

Of the several types of solid-state membrane electrodes for chloride, bromide and iodide the silver sulphide membrane electrode seems to be the most advantageous for analytical work. There are two versions of this type of electrode: the heterogeneous Pungor-type[274,279] consisting of silver sulphide dispersed in silicone rubber, and the homogeneous type[288] similar to a conventional glass electrode, with its membrane made of a

disc-shaped section of crystalline silver sulphide. Studies on these electrodes for measurement of chloride in strongly oxidative media showed excellent results[289]. Successive titration of chloride, bromide and iodide with silver nitrate using Pungor[279] and homogeneous[290] electrodes were performed.

Some applications of ion-selective electrodes to end determinations of halogens in organic compounds are listed in Table 13.

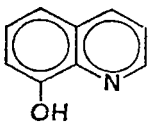
8. Halide mixture analysis

a. Some chemical separation schemes. The frequently used procedure of determining *total halide* followed by successive subtractions of single halide determinations accumulates the experimental errors of all the preceding determinations in the remainder. It is therefore important to develop reliable specific methods for each halide. Although such procedures exist, their applicability is not general for all possible concentration ratios and when the latter are very disproportionate strong interferences occur[309].

For fluoride the methods described in sections II. G. 2. a and 3. a should suffice for detection and determination in all mixtures. Nor does fluoride interfere with the other halides in the various separation methods. For these reasons fluoride is not considered in the mixtures mentioned below.

Chloride can be detected by the special diphenylamine test[310] (Table 11). Permolybdic acid oxidizes bromide and iodide to the free elements* which are captured by sulphosalicylic acid (**17**) in solution. This leaves only chloride for detection by precipitation[311]. Chloride determination can be effected after oxidation of bromide and iodide according to reaction (19), carried out in the presence of oxine (**26**) which removes free halogen until all bromide and iodide ions are consumed[262].

$$2\,X^- + H_2O_2 + 2\,H^+ \xrightarrow[X=Br,I]{} X_2 + 2\,H_2O \qquad (19)$$



(26)

Bromide can be detected after oxidation with sulphochromic mixture by the fuchsin-bisulphite method[249] (Table 11) with no interference from chlorine or iodine, or after oxidation by permolybdic acid (chloride is

* Iodine is further oxidized, partially or totally, to iodate, depending on the procedure.

TABLE 13. Some applications of halide responsive electrodes

Halide	Origin of sample	Electrode type	Procedure	Range	Reference
F^-	Organic fluorides	Eu-doped LaF_3 single crystal	Direct reading	Micro	146, 160, 291
F^-	Biological materials	Eu-doped LaF_3 single crystal	Direct reading	10^{-5}–10^{-2}M	202, 292
F^-	Organic fluorides	Eu-doped LaF_3 single crystal	Titration with La^{3+}, Th^{4+} or ZrO^{2+}	Micro and semimicro	151, 158, 293, 294
F^-	Vegetation	Eu-doped LaF_3 single crystal	Direct reading	1–10 μg	295
F^-	Standard solutions	Eu-doped ThF_4 single crystal	Direct reading	0·02 mole	276, 299
Cl^-	Organic chlorides	Ag_2S homogeneous	Titration with $AgNO_3$	10–100 μg	296
Cl^-	HCl in PVC production	Liquid–liquid	Continuous potentiometry	0–1110 p.p.m.	297
Cl^-	Water	Heterogeneous	Direct reading	$\geqslant 10^{-4}$M	298
Cl^-	Biological fluids	Pungor	Direct reading or titration with $AgNO_3$	10^{-5}M	300
Cl^-	Pharmaceuticals	Pungor	Direct reading or titration with $AgNO_3$	10^{-4}M	301
I^-	Standard solutions	AgI homogeneous	Direct reading	0·1–10 p.p.m.	302
I^-	Organic materials	AgI homogeneous	Potentiometry	Micro	303
I^-	Standard solutions	Organic liquid phase	Direct reading	$\geqslant 10^{-6}$M	304
Cl^-, Br^-, I^-	Standard solutions	Heterogeneous	Direct reading	$\geqslant 10^{-6}$M I^-, $\geqslant 10^{-5}$M Br^-, $\geqslant 10^{-4}$M Cl^-	305
Cl^-, Br^-, I^-	Standard solutions or after combustion	Na^+-sensitive glass electrode	Direct reading	5×10^{-4}–5×10^{-3}M	306
Cl^-, Br^-, I^-	Standard solutions	AgCl, AgBr, AgI single crystals	Successive titrates	Micro	290
Cl^-, Br^-, I^-	Standard solutions	Ag_2S single crystal	Titration with $AgNO_3$	40–1500 n-equiv.	307
Cl^-, Br^-, I^-	Standard solutions	Homogeneous and heterogeneous	Direct reading	0·02 mole	276
Cl^-, Br^-, I^-	Pharmaceuticals	Pungor	Direct reading or titrations with $AgNO_3$	10^{-3}M	308

unaffected and iodide is totally converted to iodate) by the fluorescein test[312] (Table 11). Bromine determinations in the presence of chlorides are based on conversion to bromates (reaction 13). In the presence of iodides the iodate value is deducted from the total halate value obtained after hypochlorite treatment, or from total halide minus chloride minus iodide[244].

Iodide is converted to iodine by fresh chloramine T (23) and detected by reaction with tetrabase[313] (Table 11) or by the catalysis of reaction (18). Determination is done after oxidation to iodate by bromine according to reaction (15)[244].

b. Application of electrometric methods. These are convenient because iodide, bromide and chloride can be titrated in the same aliquot, but they may give erratic results especially in argentometric potentiometry[309]. At a very early stage[314] it was observed that the results are dependent on the ratios of solubility products of the various silver halides.

The end-point errors in this method when determining mixtures of chlorides and bromides were later discussed[315]. It was shown that silver halides form mixed crystals or undergo flocculation and an appreciable amount of chloride is precipitated together with bromide before the first end-point is reached. Positive errors from 1 to 20%, depending upon the conditions, have been observed for the bromide end-point[315].

The errors increase in determinations of very dilute halide mixtures. The coprecipitation, however, does not affect the total halide value of two or even three halides in admixture.

In spite of these difficulties, the potentiometric titration of mixtures of halides with silver nitrate, using a silver wire as the indicating electrode and a calomel electrode as the reference electrode, connected to one another with a potassium nitrate–agar bridge, is a very favoured technique, and a correction was proposed to account for the coprecipitation of bromide and chloride ions[316].

Satisfactory results were obtained in our laboratories on mixed halogen-containing samples with the titrant being added at a constant rate.

If all four halogens are present in the same sample the fluoride can be determined by any specific method and the other three halides by subsequent potentiometric titration with silver nitrate[266] or by potentiometry with a mixed titrant containing thorium and silver nitrate at a platinum electrode[317].

Amperometric titrations with silver nitrate with rotating platinum electrode[167] or at a quiet mercury pool at +0·15 V were tried[131]. In order to determine I^- in presence of Cl^- and Br^- it was found necessary to titrate I^- in ammoniacal solution and then complete the determination of

two other halides by titrating in acid solution. However, during the titration in ammoniacal solution a small excess of silver nitrate is always present and therefore very small amounts of Br^- in the presence of large amounts of I^- cannot be determined.

Coulometry was used[318] to determine mixtures of iodide and bromide or iodide and chloride with better accuracy than the argentometric titrations. Bromide–chloride mixtures cannot be analysed very accurately because of the great codeposition of silver halides. The introduction of halogen-specific electrodes did not improve the potentiometric titrations of mixtures of halides with silver nitrate (see bottom entries of Table 13).

9. Some remarks on automated organic halogen analysis

Most continuous automated analysis devices[319] are developed *ad hoc* for quality control in processes, making use of one or more physical properties of the system. In the case of the organic halides such properties could be, for example, density, refractive index, X-ray and u.v. absorbance. Except in the latter case, these are usually higher for the organohalogens than for most organic compounds. These properties apply both to the neat compounds and to their solutions.

On the other hand, automated elementary analysis of organic halogen has not been widespread in spite of the large number of instruments that perform automated C, H, N analysis.

One set-up for automated organic halogen titration[128, 320, 321] which has been developed commercially is depicted schematically in Figure 6. The sample is vaporized in the inlet and carried into the combustion tube either by an inert gas or the combustion gas or both. The pyrolysis is performed at 800–1100° and the halogen converted into a mixture of hydrogen halide and the free element in case of oxygen combustion. Some of these combustion tubes are capable of pyrolysing up to 0·5 mg/s of hydrocarbons. The combustion gases are bubbled through the electrolyte (70% acetic acid) contained in the titration cell. A certain level of silver ions is maintained in the solution at the expense of the silver anode (reaction 20). If the silver-cation level in the solution is lowered by halide introduction (reaction 21) the sensor-reference electrode system will trigger off reaction (20), until the silver-ion level is restored and the current taken to implement reaction (20) is recorded. The microcoulometer is capable of determining halogen at the nanogram level[136]. An extensive bibliography of applications of this instrumentation is available[322].

$$Ag^0\,(\text{anode}) \longrightarrow Ag^+\,(\text{solution}) + e^- \qquad (20)$$

$$Ag^+\,(\text{solution}) + Hal^-\,(\text{solution}) \longrightarrow AgHal\,(\text{precipitate}) \qquad (21)$$

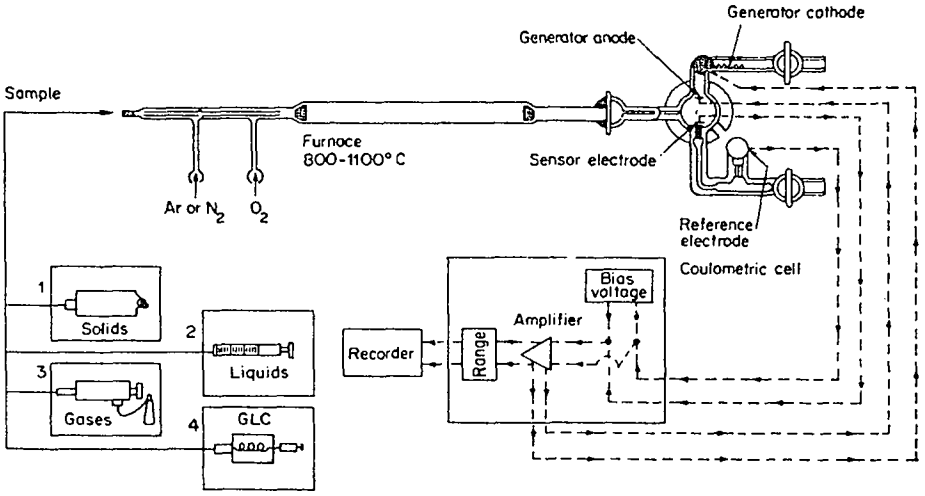


FIGURE 6. Automatic microcoulometric titration system for organic halides[322]. Reproduced by courtesy of Dohrmann Instruments Co.

Another variation of automated analysis coupled with gas chromatographic separation is also commercially available[323]. It consists essentially of a device where the chromatography effluent is mixed with hydrogen, a furnace where the reductive pyrolysis yields hydrogen halide, a bubbler where the combustion gases are absorbed in a stream of de-ionized water and an electrolytic conductivity detector[324] where the solution is measured. The system, which is capable of measuring halogen in the $< 10^{-7}$ g range[325], is shown schematically in Figure 7.

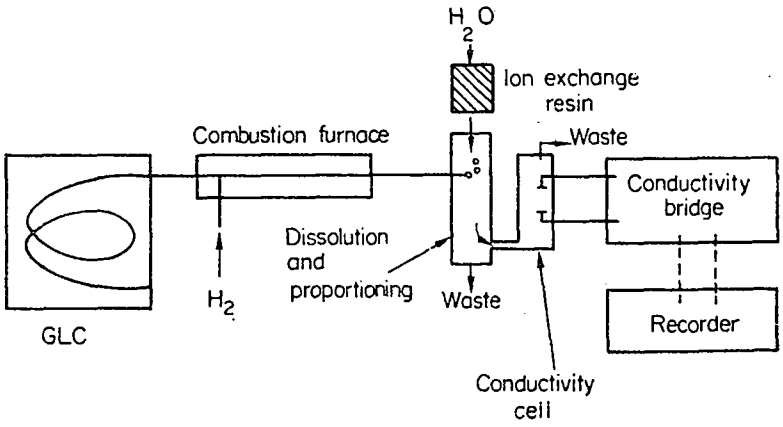


FIGURE 7. Electrolytic conductivity detector for automatic analysis of organic halides[323]. By courtesy of Tracor Inc.

III. MOLECULAR ANALYSIS

A. Distribution Properties

1. Thin-layer chromatography

This separation technique[326] provides an excellent means of preliminary or final detection of specific compounds, detection of halogenated components of a mixture and a preliminary step for their determinations.

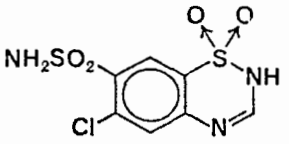
The most widespread solid phase is silica gel[326]; however, basic ion exchange resins such as Dowex I, Permutit ES, Amberlite IRA-400 and BioRad AG 1-X8 have been proposed for organic halogen separation[327,328]. Some examples of the application of the thin-layer chromatography method are listed in Table 14 and the visualization reagents for organic halides are summarized in Table 15.

A useful technique for the separation of olefinic compounds consists of brominating them during the chromatography development[353]. Thus, Δ^5-3β-hydroxysterols (**33**) are converted to the corresponding dibromides which migrate faster, while sterols with the double bond at another position remain near the start[357], e.g. small amounts of 5α-cholestan-3β-ol (**34**) could be detected in the presence of a large excess of cholesterol

TABLE 14. Some applications of thin-layer chromatography to the separation and detection of organic halides

Type of compound	Visualization reagents[a]	Reference
Monohalogenated anilines[b]		329
Halogenated pyridines		330
Halogenated bactericides	1	331
Bromoureides[c] and their metabolites	7, 9	332–335
Chlorothiazide (**27**) and hydrochlorothiazide (**28**) derivatives[d]		334, 336, 337
Iodinated amino acids (**29a, b**; **30a, b, c**) and derived hormones	3, 4	338–341
Bromosulphalein (**31**) and its metabolites		338, 342–344
Chlorinated pesticides	2, 5, 7, 8, 10–13	345–351
Olefins after bromination	10, 14	348, 352–357

[a] Numbers refer to entry of Table 15.
[b] The R_f values follow the sequence *ortho* > *meta* > *para*, frequently found for non-polar substituents in primary aromatic amines.
[c] Used as hypnotics.
[d] Used as diuretics.



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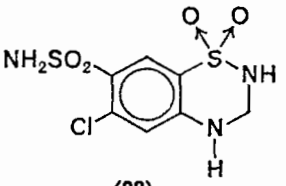

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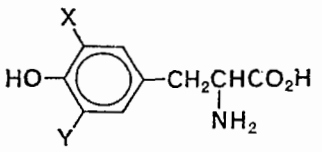
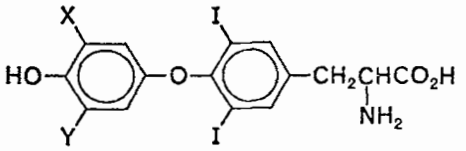


(29a; X = I, Y = H)
(29b; X = Y = I)



(30a; X = Y = H)
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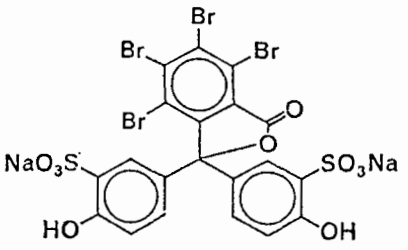

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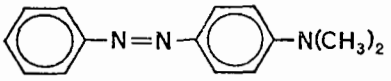
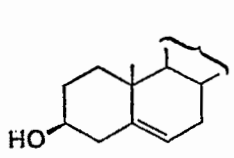


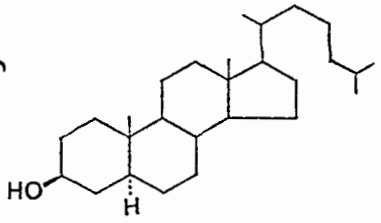
(32)

(35)[355]. *In situ* bromination may be helpful in separating saturated from unsaturated lipids[353, 354, 356] and sorbic acid (36) from benzoic acid used in foodstuffs[348].

Cumulative bibliography on the subject has been compiled[363–365].



(33)



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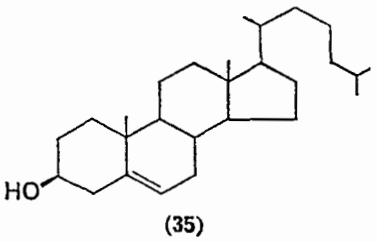


(35)

$CH_3CH{=}CHCH{=}CHCO_2H$

(36)

2. Gas chromatography

a. The column. It is possible to identify an unknown by various methods[366, 367]. Studies were made of the principles that may guide the selection of stationary liquid phases, but the theory is not very accurate and is only a guiding rule[368]. For instance[369], fluoro compounds should pass faster through the column than hydrocarbons of similar volatility, because F, being larger than H, will hinder the approach between the solute and the stationary liquid phase, thus lowering the interactions.

TABLE 15. Visualization reagents for organic halides[a]

No.	Reagent	Remarks	Ref.
1	U.v. irradiation	A general procedure that reveals many organic compounds by fluorescence, fluorescence-quenching or photochemical formation of coloured compounds	349
2	*o*-Tolidine (**19'**) followed by u.v. irradiation (254 nm)	Green spots after 1 min with chlorinated pesticides. Detection limit 0·5–1 μg	358
3	Starch mixed in the layer, and u.v. irradiation (254 nm)	After a few minutes iodo compounds yield blue spots	339
4	$FeCl_3 + K_3[Fe(CN)_6] + As_2O_3$	In the presence of iodo compounds reaction (18) is catalysed yielding blue spots. Reveals 2 ng of thyroxine (**30c**)	192, 359
5	Br_2, $AgNO_3$, fluorescein (**12a**), followed by u.v. irradiation	By treating with one solution after the other in the prescribed order red spots of eosin (**12b**) reveal the presence of chlorinated (or brominated) hydrocarbons[b]	346
6	$Ce(SO_4)_2 + H_2SO_4$	Iodo compounds	346
7	*N*,*N*-Dimethyl-*p*-phenylenediamine (**10**) followed by u.v. irradiation	Organic halides yield red spots as they liberate free halogen (see Table 11)	351
8	Diphenylamine + $ZnCl_2$ followed by heating	Chlorinated insecticides yield coloured spots	360
9	Fluorescein (**12a**)–H_2O_2	Bromo compounds yield red spots of eosin (**12b**)	361
10	Methyl yellow (**32**) followed by u.v. irradiation	Chlorinated hydrocarbons yield red spots due to chlorine liberation	362
11	$AgNO_3$, formaldehyde, followed by u.v. (sunlight) irradiation	After several steps, dark grey spots appear on a light grey background	347
12	$AgNO_3$, 2-phenoxyethanol, followed by u.v. irradiation	Dark spots	350
13	$AgNO_3$, H_2O_2 followed by u.v. irradiation	Dark grey spots on light grey background	347
14	Antimony(III) chloride	α,β-Dibromo compounds give colour spots	352
15	Nuclear activation	Visualization by radio-autography	53

[a] A compilation of visualization techniques is given in reference 349.
[b] Exposure to iodine vapours is more sensitive than this visualization procedure[346].

Following the same ideas, hydrocarbon-type liquid phases would be useful for separating fluorocarbons of close boiling points while fluorinated stationary phases are less effective for this purpose[370,371].

The interaction of chlorobenzene with various stationary phases was investigated[372]. Both nematic and smectic liquid crystals were found to have some discriminating capacity for the isomers of disubstituted benzenes including some halogenated compounds[372,373].

Aluminas modified by various inorganic compounds have proved to be useful in hydrocarbon separations[374]. Aromatic halogen compounds are also separated satisfactorily; however, alkyl halides decompose to various extents. Clathrate-forming transition metal complexes were also studied as stationary phases for aromatic compounds[375].

Table 16 lists some stationary phases which were recommended especially for halogenated compounds.

TABLE 16. Stationary phases useful for halogen compounds[a]

Stationary phase	Maximum operational temperature (°C)	Recommended use
Dibenzyl ether	80	Chlorine compounds
Dialkyl phthalates (semipolar)	175	Chlorine compounds
Silicone oils (non-polar)	200	General use
Igepol 880[b]	200	Aromatic chlorine compounds
Fluorosilicone oils (polar)	250	General use
Perfluorocarbons (freons)		Retain fluorine compounds and let through alkanes
Carbowaxes[c] (polar)	250	General use
Apiezons[d] (non-polar)	300	High-boiling compounds
Tricresyl phosphate[e]		Alkyl iodides

[a] From reference 375.
[b] Nonylphenoxypolyethyleneoxyethanol.
[c] Polyethyleneglycols.
[d] High molecular weight hydrocarbons.
[e] From reference 64.

b. Pre-column treatment. In order to simplify mixture resolution, identification and structure elucidation various reactions have been carried out, in special devices, just before injection into the resolving column[367,376]. For example[377], in a series of three columns, the first impregnated with neutral silver nitrate, the second with concentrated sulphuric acid and the third with disodium hydrogen phosphate, reaction (22) takes place with *sec*-alkyl bromides (above 30° also with *t*-alkyl bromides) in the first column, the olefin and nitric acid being removed in the second and third

$$\begin{matrix} RCHCH_2R' \\ | \\ Br \end{matrix} + AgNO_3 \longrightarrow RCH{=}CHR' + AgBr + HNO_3 \qquad (22)$$

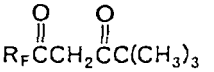
columns respectively. This leaves primary and tertiary alkyl bromides for the chromatography.

An interesting general technique also applicable to organic halides is the so-called carbon skeleton chromatography[378-380]. The sample is treated with catalysts that leave only the skeleton or a degraded skeleton. Chromatography of the resulting mixture shows the structures to which the functional groups were attached. Some of the reactions shown in section IV. D are suitable for skeleton chromatography.

c. Detectors. Electron-capture detectors are responsive to organic halogen compounds and only a few other organic structures produce a response, e.g. nitro, cyano, polycyclic aromatic compounds[367]. These detectors have long been used in pesticide trace analysis[381]. The response of fluoro compounds is the lowest among the organic halides; however, it varies over several orders of magnitude depending on the presence of saturation or other halogens as shown in Figure 8[382]. The response of iodo compounds is about three times that of the analogous chloro compounds. Low molecular weight halo compounds, especially fluoro compounds, are best detected by use of dual techniques, e.g. electron capture combined with flame ionization detectors. An important application of the electron-capture detector is the analysis of compounds lacking response by forming responsive derivatives[383]. Table 17 lists some examples of such derivatives.

TABLE 17. Electron-capture responsive derivatives for gas chromatography

Original compounds	Derivative	Reference
Transition metal ions	Trifluoroacetylacetone complex	383, 384
	Hexafluoroacetylacetone complex	383, 384
	Perfluoroacylpyvalylmethanes (37)	385
Sterols, amines, alcohols, phenols	*N*- or *O*-chloroacetyl	386, 387
Alcohols, phenols, amino acid *n*-butyl esters	*N*- or *O*-pentafluoropropionyl	387–389
Amines, alcohols, phenols	*N*- or *O*-chlorodifluoroacetyl	387
Amino acid *n*-butyl esters	*N*-trifluoroacetyl	386, 388, 389
Amphetamine and ephedrines	*N*-pentafluorobenzoyl	390
Phenethylamine, catecholamines	*N*-perfluoroacyl and *N*-perfluoroalkylidene	391, 392
Carbamate pesticides	*N*-Trifluoroacetyl	393



(37)

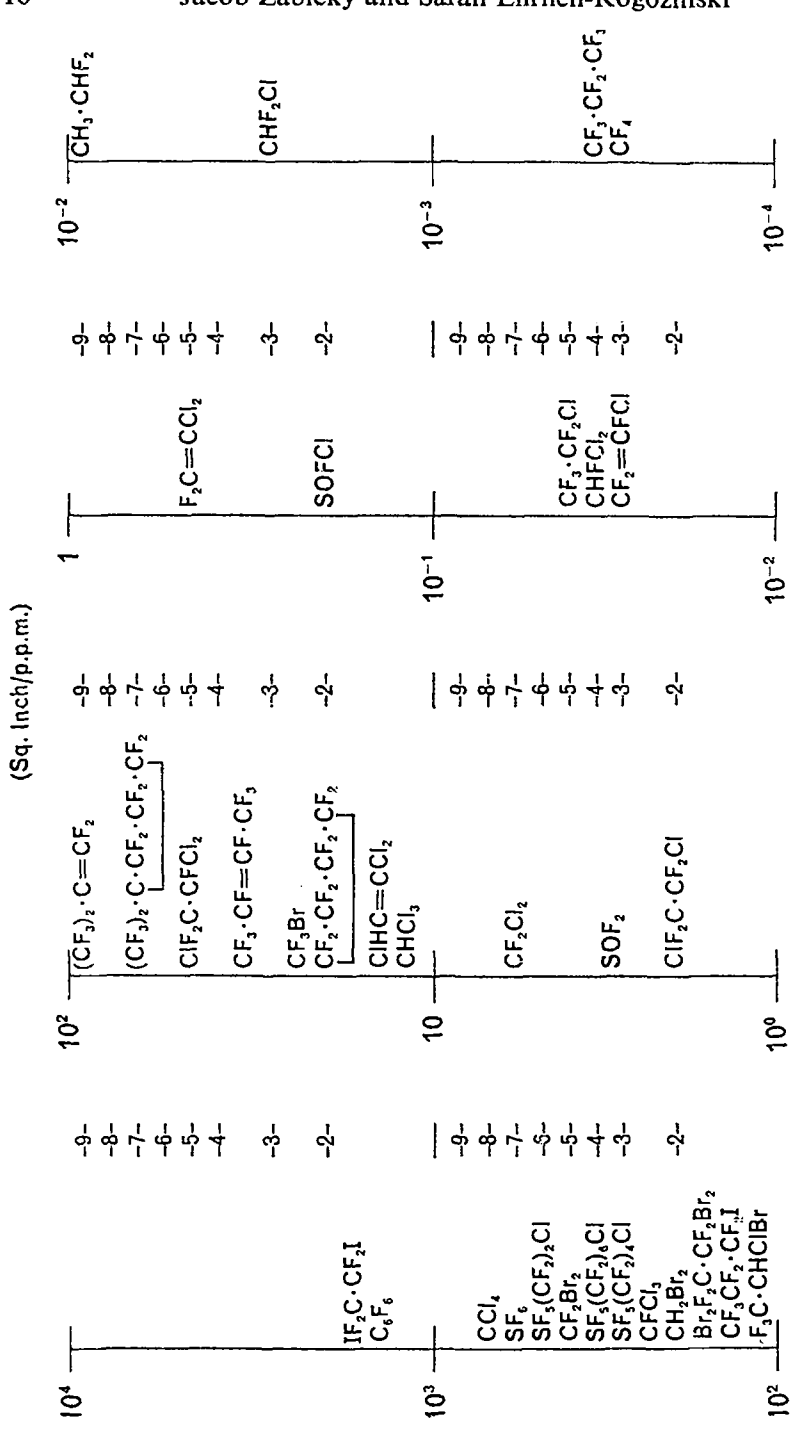


FIGURE 8. The dependence of electron-capture detector response on the structure of organic fluoro compounds[382]. Reproduced by permission of the American Chemical Society from C. A. Clemons and A. P. Altschuler, *Anal. Chem.*, **38**, 133 (1966).

Flame ionization detectors can be modified so that they become especially sensitive to organic halogens (not fluorine), phosphorus, nitrogen, arsenic and sulphur compounds[394-396] with sensitivity in the nanogram region[395]. This is accomplished by introducing an alkali salt in the detector. Several factors are important in determining the response of the alkali flame ionization detectors[397,398]: the type of alkali salt, the gas flow and the geometry of the detector. Thus, for example, using the rubidium sulphate pellet modification shown in Figure 9 one can obtain

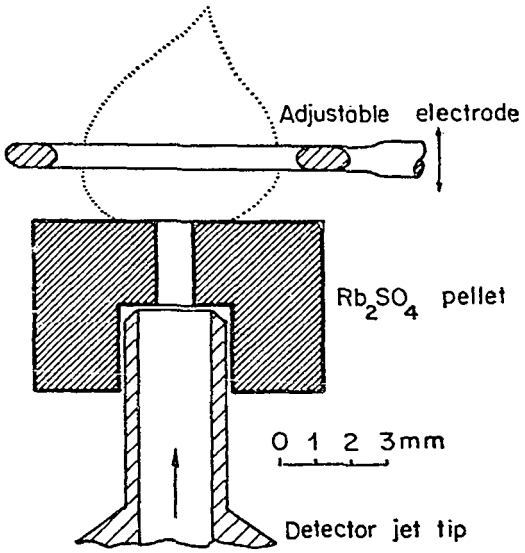


FIGURE 9. Alkali flame detector modification for attaining selective response with various hetero-elements[397]. Reproduced by permission of Elsevier Publishing Co. from S. Lakota and W. A. Aue, *J. of Chromatogr.*, **44**, 472 (1969).

negative currents for chloro and bromo compounds, and positive currents for iodo, nitrogen and phosphorus compounds when the gap between the electrode and the pellet is narrow. Figure 10 shows how the response for the various elements changes on widening this gap, with that of bromine changing sign. In this fashion various pesticide types can be distinguished. A typical chromatogram for a mixture of three phenyl halides is shown in Figure 11.

Metal-sensitized flame photometric detectors were discussed in section II. D. 2, and the electrolytic conductivity detector in section II. G. 9. Reviews on gas chromatographic detectors appeared in references 399 and 400.

d. Coupling to other instrumental methods. The choice among several couples depends on the demands of speed, resolution and the economic possibilities[401]. For coupling to slow-scanning instruments the interrupted elution gas chromatography technique has been developed[401]. The most

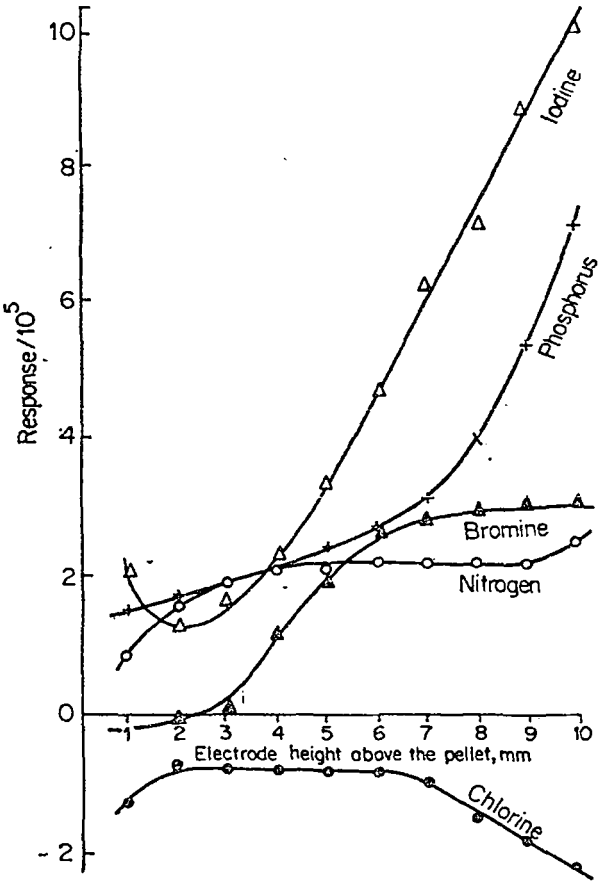


FIGURE 10. Effect of electrode height (in Figure 9) on the response of the alkali flame detector[397]. Reproduced by permission of Elsevier Publishing Co. from S. Lakota and W. A. Aue, *J. of Chromatogr.*, 44, 472 (1969).

important couple is a mass spectrometer (for example, reference 402) but other less expensive instruments have been applied, e.g. improved i.r. spectrophotometers equipped with long path cells[403], u.v. spectrophotometers (for example, the alkyl iodides with less than six carbon atoms have been distinguished[379]) and nuclear magnetic resonance spectroscopy with multiple scanning[404].

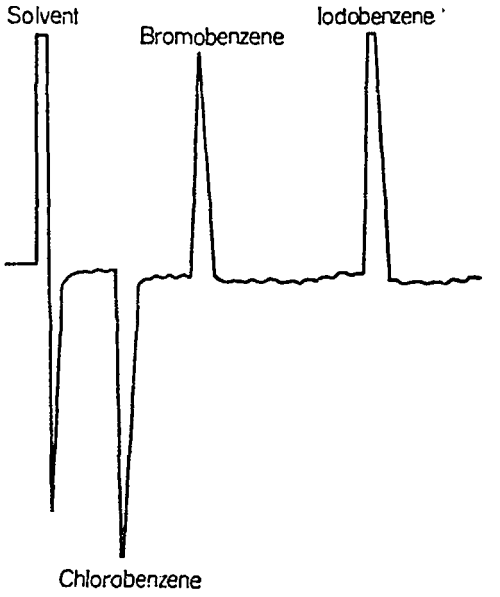


FIGURE 11. A typical chromatographic trace for a mixture of organic halides using the alkali flame detector of Figure 9. The sign of the bromobenzene peak can be inverted by narrowing the electrode gap (Figure 10)[397]. Reproduced by permission of Elsevier Publishing Co. from S. Lakota and W. A. Aue, *J. of Chromatogr.*, **44**, 472 (1969).

3. Phase solubility titrations

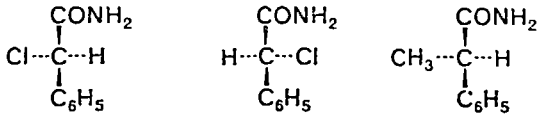
This technique[405] is of practical importance for determining the composition of liquids containing specific organic halogen compounds, as these are usually much less soluble in hydroxylic solvents and water. For example[406], mixtures of alcohols with bromobenzene, 1,2-dibromoethane, chloroform[406], dichloromethane and allyl bromide[407] have been titrated with water until the appearance of turbidity. The end-point is evaluated according to calibration curves with an average absolute error of less than 1%.

4. Quasiracemic mixtures

Some physical properties of the mixtures of two compounds of similar structure can be used to correlate their configuration. This method has been occasionally applied for configuration assignments of organic halides Thus (+)-chlorosuccinic acid and (−)-bromosuccinic acid* have long been

* (+) and (−) denote the sign of the optical rotations under certain experimental conditions.

known to form a molecular compound[408], and this can be interpreted as proof for their opposite configurations. Solid solutions are formed by (−)-2-chloro-2-phenylacetamide (**38**) with (+)-2-phenylpropionamide (**40**), while **39** forms a molecular compound with **40**, and therefore **38** and **40** have the same configuration. In this particular case the melting points of the mixtures showed their different nature[409].



(38) **(39)** **(40)**

Quite generally, if a mixture of two similar compounds shows an i.r. spectrum[410,411] or an X-ray diffraction pattern[411–413] which is the sum of the two simple spectra or patterns, while on changing one of the components by its enantiomorph new lines are obtained, then it can be concluded that a molecular compound has been formed in the latter case, and that the compounds of the second mixture have opposite configuration.

B. Spectral Properties

Several types of spectra are dependent on the structure of the molecule as a whole. Inasmuch as these spectra reveal details of the halogen and its near proximity they will be treated in other sections. Outstanding among the spectral techniques are the following:

(i) X-Ray crystallography is one of the ultimate tools for structural analysis. In fact the presence of halogen atoms is very helpful in solving such problems, but their usefulness decreases with increasing halogenation. This method is becoming more accessible to the average organic chemist: nevertheless, it is not applied as a first choice due to its inherent difficulties. Further details for the application of X-ray crystallography in organic compounds are found elsewhere[414].

(ii) Mass spectrometry gives a fingerprint of the organic molecule. This can be applied in pesticide residue analysis[402,415]. The application to elementary analysis is treated in section II. E, and to structural analysis in section V. C.

(iii) The interpretation of microwave spectra presents no immediate analytical value. On the other hand, this method may be introduced as a highly discriminating way of detecting known compounds in the gaseous state[416]. The readily accessible region is in the 10,000–50,000 MHz range of frequencies with a line width of 0·1 MHz. This allows about 4×10^5

different spectral lines to be distinguished. If the main lines and their approximate intensities for every compound of interest are known it is almost certainly possible to detect every such compound, in spite of partial line overlaps. Spectral tabulations can be found in reference 417.

(iv) The emission spectra of flames and plasmas mentioned in section II. D. 1 can be used as detection and determination means for many classes of compounds.

(v) The so-called fingerprint region of the i.r. spectrum affords a convenient means of identification of specific organic compounds. Large collections of spectra are available and they are coupled with indices of the absorption bands[418,419]. Applications of i.r. spectroscopy to structure elucidation are found in section V. E.

IV. FUNCTIONAL ANALYSIS BY CHEMICAL METHODS

The halide functions have two main peculiarities in their chemical reactions: (i) the great majority of reactions involve substitution or elimination of the halogen, and only a few yield adducts preserving both the organic radical and the halogen (e.g. Grignard-type reactions), and (ii) most organic halides react slowly with yields lower than quantitative. Hence, information on stereochemistry or the site of attachment may be lost after a reaction and quantitative analysis via derivative formation is usually precluded. Derivative formation implies in fact the conversion of an analytical problem into a new one. This is done to provide additional information leading to the solution of the original problem.

The classical methods always aimed at the formation of solid derivatives which were identified by their melting points. At present this is not necessary, as the derivative may be characterized or identified spectroscopically, and sometimes without even bothering to obtain a clean sample (which is required for melting point determination). Furthermore, the application of chromatographic separations and spectral methods allows the use of derivatizing reactions affording yields that are far from quantitative.

Many derivatives have been proposed by analysts and some have justly acquired widespread acceptance. On the other hand, the methods of organic synthesis continuously introduce new reagents and procedures for performing delicate and discriminating reactions[1,2]. Attention is called to such innovations as possible sources of inspiration for the search of new useful analytical tools.

Table 18 presents a concordance of reagents according to their chemical type and should be helpful in discerning whether a certain chosen method

TABLE 18. Reagents for derivatizing carbon–halogen compounds[a]

A. Elementary reagents

Chlorine: **ox** (205), (206)
Copper: **red** (175)
Devarda's alloy (Cu—Al—Zn): **red** (174)
Hydrogen: **nhr** (76), (86); **red** (154), (157), (158), (177)
Lithium: **red**[b] (144), (169), (173); **d2x** (184)
Lithium–sodium alloy: **met** (88)
Magnesium: **d2x** (184), (197); **met** (87), (89), (91)–(95), (97), (98), (139), (184); **red**[c, d] (139), (167); **dhx** (167)
Nickel: **red**[d]; **nhr** (76)
Palladium: **red** (154), (177)
Platinum: **nhr** (86)
Sodium: **red**[b] (161), (170)
Sulphur: **nhr**[e]
Zinc: **d2x** (178)–(183); **red** (154), (159)
Zinc–copper couples: **d2x** (195); **red** (146), (147)

B. Acids, oxides, hydroxides and alkoxides

Anion exchange resins (OH^- form): **c–c** (65); **dhx** (106)
Chlorosulphonic acid: **nhr** (207)
Chromium trioxide: **ox** (198)
Nitric acid: **nhr**[f] (208)
Potassium bicarbonate: **dhx** (122)
Potassium *t*-butoxide: **dhx** (100), (101), (105), (127); **red** (172); **ox** (201)
Potassium carbonate: **c–c**[g]
Potassium ethoxide: **dhx**[g] (100)
Potassium 3-ethyl-3-pentoxide: **dhx** (100)
Potassium hydroxide: **c–s** (37); **dhx** (99), (122), (123), (126); **ns**[h] (26), (32)
Silver oxide: **c–c** (119); **dhx** (114); **ns** (32)
Sodium 2-*n*-butylcyclohexanolate: **dhx** (103)
Sodium ethoxide: **dhx** (104)
Sodium hydroxide: **c–c** (26); **c–o** (33); **c–s** (35), (38); **dhx**[g] (99), (102); **ns** (25)

C. Metal amides, carbonyls and hydrides

Dicobalt octacarbonyl: **c–c** (96)
Lithium aluminium hydride: **red** (145)
Lithium dicyclohexylamide: **dhx** (105), (197)
Lithium diethylamide: **dhx** (120)
Nickel tetracarbonyl: **red** (141), (160)
Potassium amide: **dhx** (115); **c–c** (131)
Sodamide: **dhx** (116)–(118), (128)–(130)
Sodium hydride: **nhr** (46)
Sodium borohydride: **red** (143)

D. Salts

Ammonium thiocyanate: **ns** (85)
Benzyltrimethylammonium mesitoate: **dhx** (134)
Calcium carbonate: **dhx**[i]
Chromium(II) salts: **d2x** (186), (187); **red** (148)–(150), (156), (187); **c–c** (187)
Formaldehyde sodium sulphoxylate: **red** (157)–(158)
Lead tetraacetate: **c–o** (43)
Lithium bromide: **dhx**[i]
Lithium carbonate: **dhx** (133)
Magnesium iodide: **ns**[j]
Mercury(II) halides: **met** (95)

TABLE 18 (*cont.*)

D. Salts (cont.)

Potassium carbonate: **dhx**[g]
Potassium iodide: **ns**[k]
Potassium permanganate: **nhr** (37)
Potassium persulphate: **ox** (202)
Silver acetate: **c–o** (44)
Silver chromate: **ox** (198)
Silver 3,5-dinitrobenzoate: **c–o** (40)
Silver nitrate: **dhx**[i]; **ns** (29)–(31)
Silver nitrite: **ns** (79)
Silver tetrafluoroborate: **c–c** (57); **c–o** (124); **ns** (124); **ox** (200)
Silver *p*-toluenesulphonate: **c–o** (41); **dhx**[i]
Silver trifluoroacetate: **ns** (28)
Sodium acetate: **c–s** (36); **dhx** (113)
Sodium azide: **ns** (84), (86)
Sodium bicarbonate: **c–n** (53); **dhx**[i]; **ox** (42)
Sodium cyanide **ns** (83)
Sodium iodide: **d2x** (185); **ns** (74), (82), (83)
Sodium nitrite: **ns** (79), (81)
Sodium thiocarbonate: **ns** (39)
Sodium thiosulphate: **ns** (77)
Tallium(I) bromide: **met** (94); **red** (93)
Tetraethylammonium chloride: **dhx**[i]
Zinc chloride: **ns** (24)

E. Organometallic compounds

Allylsodium: **c–c** (76)
Butyllithium: **dhx** (165); **red** (165)
Dimethylcopperlithium: **c–c** (69)–(71)
Disodium naphthalene: **d2x** (189)
Disodium phenanthrene: **d2x** (189)
3-Lithio-1-(trimethylsilyl)propyne: **c–c** (68)
Lithium acetylide: **c–c** (72)
Lithium diphenylamide: **dhx** (105)
Methyllithium: **c–c** (168); **dhx** (166), (167); **red** (166)–(168)
Methylmagnesium bromide: **red** (142)
Phenylthiomethyllithium: **c–c** (73)
Sodium methylsulphinyl methide: **d2x** (188); **red** (162)–(164)
Tri-*n*-butyltin hydride: **red** (140), (155), (171); **dhx**[g]

F. Amines, amides, hetarenes and hydrazine derivatives

Amines: **c–n** (54)
2-Aminofluorenone: **c–n** (53)
Ammonia: **c–n** (47), (49); **nhr** (203); **ns** (207)
Aniline: **c–n**[m]
Benzenesulphonamides (variously substituted): **c–n**[i] (52)
Benzenesulphonhydrazide: **c–n** (52); **red** (52)
t-Butylamine: **dhx** (108)
s-Collidine: **dhx**[o]
1,2-Diaminoethane: **c–c** (72)
1,5-Diazabicyclo[4.3.0]non-5-ene: **dhx**[o]
Dicyclohexylethylamine: **dhx** (109)
N,*N*-Diethylaniline: **dhx** (107)
Diisopropylethylamine: **dhx** (109)
N,*N*-Dimethylaniline: **red** (151)
2,4-Dinitrophenylhydrazine: **dhx** (135)
Ethyl carbamate: **c–n** (57)
Ethyl carbazate: **dhx**[i]
Hydrazine: **nhr** (27); **red**[d]
N-Phenylmorpholine: **dhx** (107)
Phthalimides (variously substituted): **c–n**[n] (55)
Pyridine: **dhx**[e, o] (112)
Quinoline: **dhx**[o] (112)
Saccharin: **c–n**[n]
Semicarbazide: **dhx**[i]
Sulphonamides (variously substituted): **c–n**[n] (56)
Tri-*n*-butylamine: **dhx** (137)
Triethylamine: **dhx** (121), (125), (137)
Tetraethylammonium chloride: **dhx**[i]

TABLE 18 (*cont.*)

G. Organophosphorus compounds

Hexamethylphosphoric triamide: **c–c** (72); **dhx** (111), (130), (138)
Hexamethylphosphorous triamide: **c–p**[p] (62)
Triethyl phosphate: **c–n** (53); **dhx** (53)
Triethyl phosphite: **c–p**[p] (60); **d2x** (192)
Triisopropyl phosphite: **d2x** (192)
Trimethyl phosphite: **dhx** (110)
Triphenylphosphine: **c–p**[p] (52), (58), (153); **d2x** (191); **red** (52), (152), (176)

H. VIth group element compounds

4,5-Dihydro-2-mercaptoimidazole: **c–s**[k]
Dimethylsulphonium methylide: **c–c** (75)
Dimethyl sulphoxide: **ox** (42), (199)–(201)
2,4-Dinitrothiophenol: **c–s** (37)
Diphenyl selenide: **d2x** (190)
Diphenyl telluride: **d2x** (190)
Ethylmercaptan: **red** (150)
Formaldehyde sodium sulphoxylate: **red** (157), (158)
6-Nitro-2-mercaptobenzothiazole: **c–s** (38)
Sodium methylsulphinylmethide: **d2x** (188); **red** (162)–(164)
Thiourea: **c–s** (34)–(36)

I. Miscellaneous organic compounds

Aryl isocyanates: **c–c** (89)
Benzene: **as** (203)
Benzoic acid: **red** (175)
t-Butanol: **red** (172)
Diethyl malonate: **c–c**[p] (66)
Ethanol: **d2x** (193)
Isopropenyl acetate: **nhr** (45)
Methyl borate: **c–b**[q] (91)
Methyl fluorene-9-carboxylate: **c–c** (64)
Phenol (variously substituted): **as** (26); **c–o** (33)
Picric acid: **nhr**[k, q] (34)
2-Pyridinecarboxaldehyde: **nhr** (48)
Sodium 1,2-naphthoquinone-4-sulphonate: **nhr** (80), (85)
Trimethyl borate: **as** (91)

[a] Numbers refer to numbered reactions in this chapter. The following abbreviations are used:

as: aromatic substitution;
c–b: reaction leading to a C—B bond formation;
c–c: reaction leading to a C—C bond formation;
c–n: reaction leading to C—N bond formation;
c–o: reaction leading to a C—O bond formation;
c–p: reaction leading to a C—P bond formation;
c–s reaction leading to a C—S bond formation;
d2x: formation of an unsaturation or a cycle at the expense of two halogen atoms;
dhx: dehydrohalogenation;
met: metallation;
nhr: non-halogen reaction;
ns: nucleophilic substitution;
ox: oxidation;
red: reduction, formation of a C—H bond at the expense of a C-halogen bond.

should show interference by the various components expected to be present in a problem sample. It is regretted that space shortage does not allow us to give more details on the analytical scope of the reactions shown below.

A. Direct Displacement of the Halides

The overall reaction (23), where Y is usually a proton, a metal cation or a void group, is the basis of many usual procedures for obtaining derivatives.

$$R{-}X + Y{-}Z{-}R' \longrightarrow R{-}Z{-}R' + X^- + Y^+ \qquad (23)$$

Aliphatic halogens α to an unsaturated group are easily removed by solvolysis or nucleophilic reagents yielding alcohols, ethers, esters and other derivatives. This allows determination of activated halides in the presence of simple alkyl or aryl halides which are more stable to mild treatment. For example, 2-bromo-2-methylhexanoic acid is rapidly hydrolysed in water at 25°, thus allowing the determination of the halide ion liberated. Allyl, benzyl, benzhydryl and trityl halides are also quickly hydrolysed; but more slowly in the presence of electronegative groups (see, for example, reference 420). Aryl halides become susceptible to facile nucleophilic substitution on introducing electronegative groups in the ring[421], to the extent that they become useful as derivating reagents for the amines[422].

The kinetics and steric behaviour of displacement reactions[5] have been extensively discussed for many types of halides and their application to analytical problems has been reviewed[423,424]. The reactions shown in section IV. C. 2, namely cyclizations involving elimination of hydrogen halide, can be considered as halide displacement reactions where the displacing moiety happens to be part of the same molecule.

1. Hydrolytic displacement

This type of derivative formation occasionally yields analytically useful results. Compounds of general formula $X{-}CH_2CH_2{-}Y$ release acetaldehyde on fusion with zinc chloride according to reaction (24). The

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[b] Mentioned in sections IV. B and IV. D. 1. c.
[c] Mentioned in section IV. D. 1.
[d] Mentioned in section IV. D. 1. e.
[e] Mentioned in section IV. F. 2.
[f] Mentioned in section IV. F. 1.
[g] Mentioned in section IV. C. 2.
[h] Mentioned in section IV. A. 1.
[i] Mentioned in section IV. C. 5.
[j] Mentioned in section IV. D. 2. a.
[k] Mentioned in section IV. A. 3.
[l] Mentioned in section IV. A. 4.
[m] Mentioned in section IV. A. 5.
[n] See Table 19.
[o] Mentioned in section IV. C. 1.
[p] Usually followed by other reactions.
[q] Mentioned in section IV. A. 2.

acetaldehyde can be detected by the Rimini test (formation of blue-to-violet-coloured complexes with sodium nitroprusside (**41**) in the presence of amines affording a very sensitive detection test for such structures[12].

$$X{-}CH_2CH_2{-}Y \xrightarrow{ZnCl_2} CH_3CH{=}O \qquad (24)$$

(X, Y = halogen, OR, NR_2, SR)

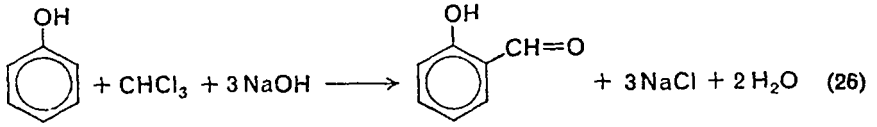
$Na_2[Fe(CN)_5NO]$

(41)

Some highly halogenated compounds undergo the haloform reaction (25), which can be followed by salicylaldehyde (**43**) formation if carried out in the presence of phenol (reaction 26). Reaction (27) yields fluorescent salicylaldazine (**44**) when salicylaldehyde is treated with hydrazine[12]. For example, chloral (**42**, X = Cl) and bromal (**42**, X = Br) undergo these reactions. Optically active 1-bromo-1-chloro-1-fluoro-acetone yields optically active 1-bromo-1-chloro-1-fluoromethane[425].

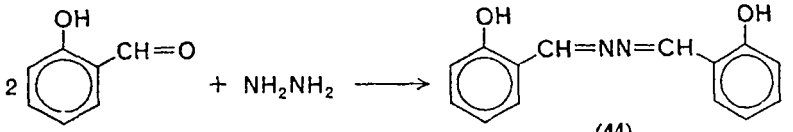
$$CX_3CH{=}O + NaOH \longrightarrow CHX_3 + HCO_2Na \qquad (25)$$

(42)



(26)

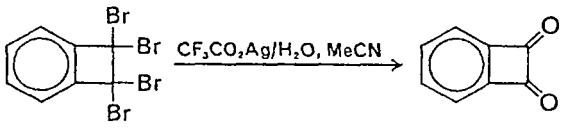
(43)



(27)

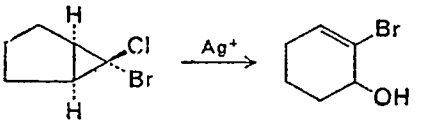
(43) **(44)**

gem-Dibromides are hydrolysed to the ketones in the presence of silver trifluoroacetate (reaction 28)[426] or a base such as potassium hydroxide[427].



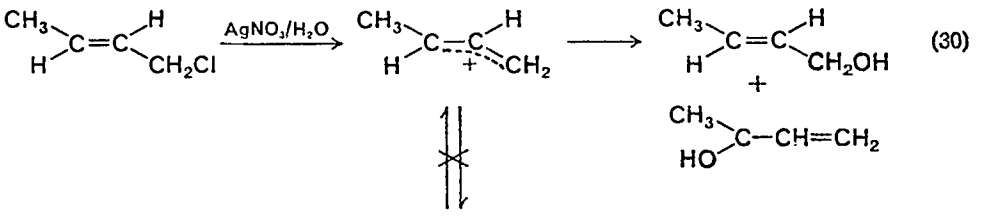
(28)

Silver ions catalyse the hydrolysis of the *endo* halogen in *gem*-dihalocyclopropanes bringing about a rearrangement (reaction 29)[428].

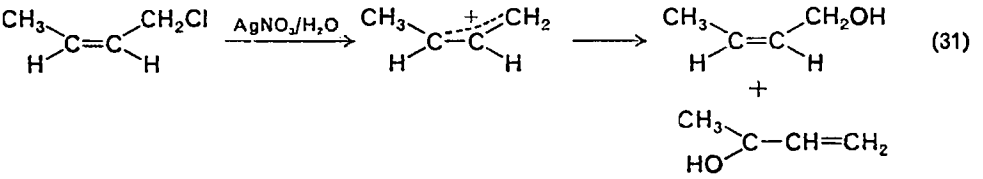


(29)

Allyl halides, solvolysed through a carbonium ion intermediate, undergo anionotropic rearrangements leading to mixtures of alcohols. The *cis* or *trans* configuration of the allyl halide can be, nevertheless, partially preserved (reactions 30, 31)[429]. The stereochemistry of hydrolytic

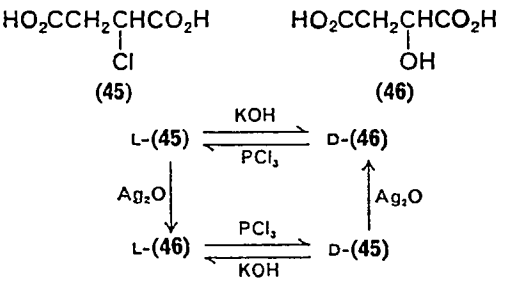


(30)



(31)

displacements depends on the reagents used. A classic example[430,431] is shown in reaction (32).



(32)

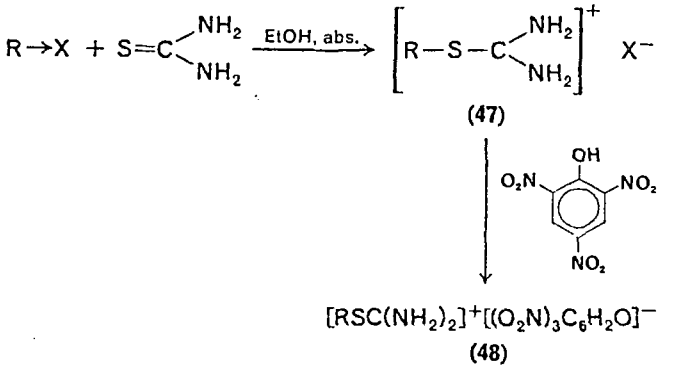
2. Ether formation

Phenols with alkyl halides in basic solution yield aryl alkyl ethers (reaction 33). The proper choice of the aryl group allows the formation of crystalline derivatives, or the further complexation of the aromatic ether with picric acid. Thus triiodophenol[432], *p*-hydroxybenzoic acid[433], *p*-hydroxydiphenylamine[434] and β-naphthol[11,14,19] have been proposed for this purpose.

$$R{-}X + HOAr \xrightarrow{NaOH} ROAr \qquad (33)$$

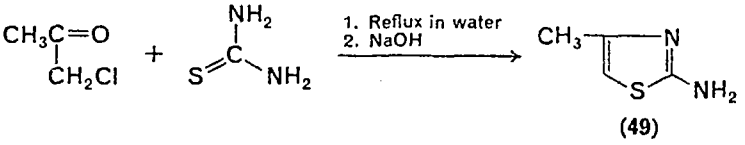
3. Thioethers and similar derivatives

Alkyl halides combine with thiourea[11, 14, 19, 435] to give *S*-alkylthiouronium salts (**47**) which on addition of picric acid yield the corresponding picrates (**48**) (reaction 34). α-Haloketones yield with thiourea substituted

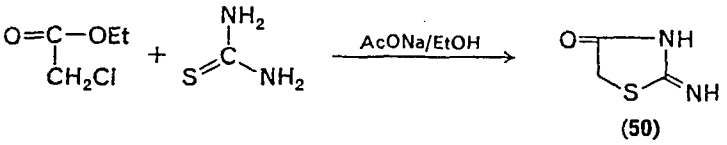


(34)

2-aminothiazoles (**49**) as shown in reaction (35)[436]. Similarly, α-halo esters yield pseudohydantoins (**50**), with loss of the alcoholic moiety of the ester (reaction 36)[437].

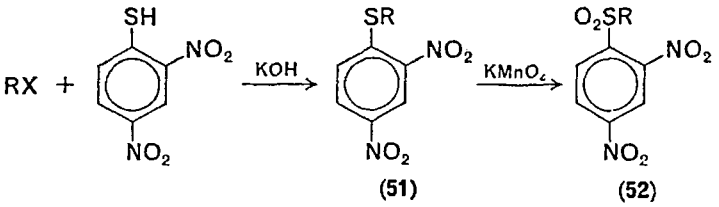


(35)



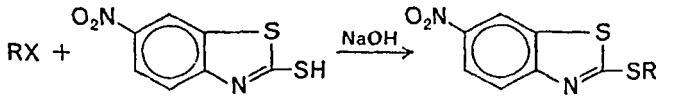
(36)

Thioethers derived from alkyl bromides and iodides can be formed with 2,4-dinitrothiophenol. Alkyl chlorides react if potassium iodide is added to the mixture. The thioether **51** can be oxidized to the corresponding sulphone **52** (reaction 37)[14, 19, 438, 439].



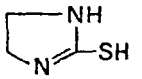
(37)

Alkyl halides can be derivatized with 6-nitro-2-mercaptobenzothiazole (53) as shown in reaction (38). This reagent is recommended for dihalides[14, 19, 440, 441]. The picric acid complex of the thioether formed from



(38)

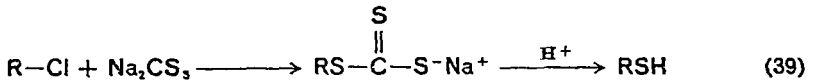
(53)



(54)

an alkyl halide and 4,5-dihydro-2-mercaptoimidazole (54) has been also proposed for derivatization[442].

Alkyl halides heated with sodium thiocarbonate yield the corresponding

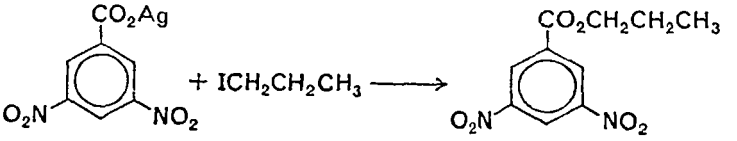


(39)

thiols (reaction 39)[443]. Dithioethers are formed from primary alkyl halides with thiosulphate (see reactions 77–78).

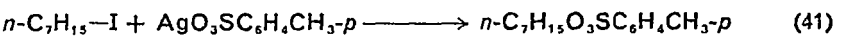
4. Ester formation

3,5-Dinitrobenzoates are formed from alkyl iodides as shown in reaction (40), but results are unsatisfactory with alkyl chlorides and bromides[14, 444].

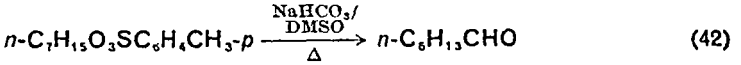


(40)

Primary alkyl halides yield with silver *p*-toluenesulphonate the corresponding tosylate (reaction 41) which can be further oxidized to an aldehyde on heating with dimethyl sulphoxide (reaction 42, similar to reaction 200)[445]. Secondary and tertiary alkyl halides yield olefins under the same conditions of esterification[446], unless the reaction is carried out at very low temperatures[447].

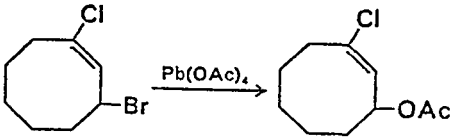


(41)



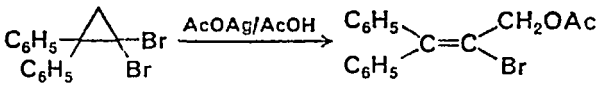
(42)

Lead tetraacetate displaces bromine preferentially, forming acetates (reaction 43), and is better than silver acetate for this purpose[448].



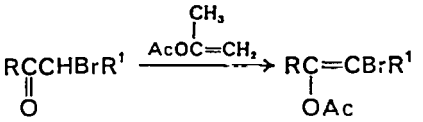
(43)

Silver acetate causes a substitution–rearrangement process on *gem*-dihalocyclopropanes yielding allyl esters (reaction 44)[449].

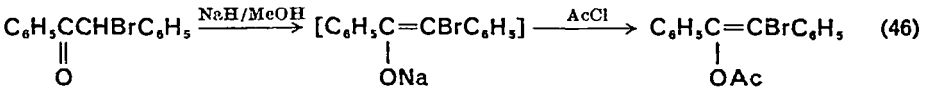


(44)

It is possible to convert an α-haloketone to the corresponding enol ester without touching the halogen by treating either with isopropenyl acetate (reaction 45)[1] or with sodium hydride (reaction 46)[450].



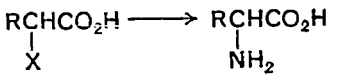
(45)



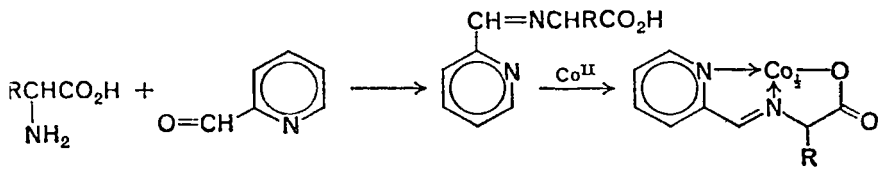
(46)

5. *N*-Substitution of amines

α-Halo acids are converted by ammonia to the corresponding amino acid (reaction 47) which can be detected as the cobalt(II) complex of the Schiff base with 2-pyridinecarboxaldehyde (reaction 48)[192,247].



(47)

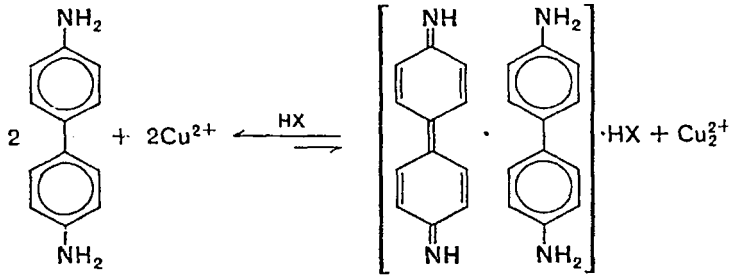


(48)

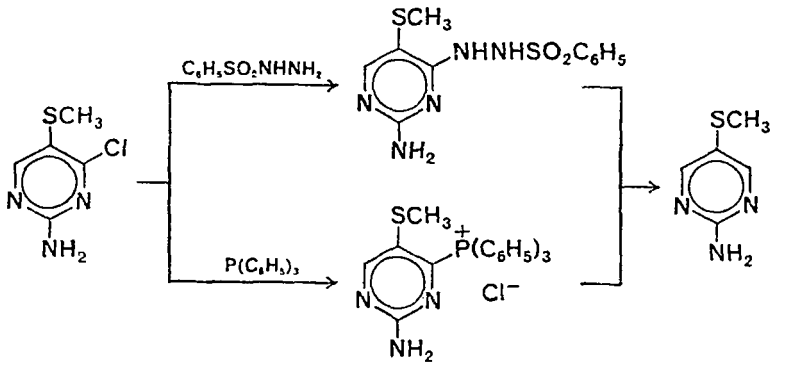
A sensitive detection method for the haloforms consists of heating with ammonia, thus forming hydrogen cyanide (reaction 49) which can be revealed by pushing the equilibrium (51) towards benzidine blue (55) formation, due to removal of copper(I) ions according to reaction (50)[12].

$$CHX_3 \xrightarrow[X=Cl,\,Br,\,I]{NH_3/\Delta} HCN + 3\,NH_4Cl \qquad (49)$$

$$Cu_2^{2+} + 2CN^- \longrightarrow Cu_2(CN)_2 \qquad (50)$$

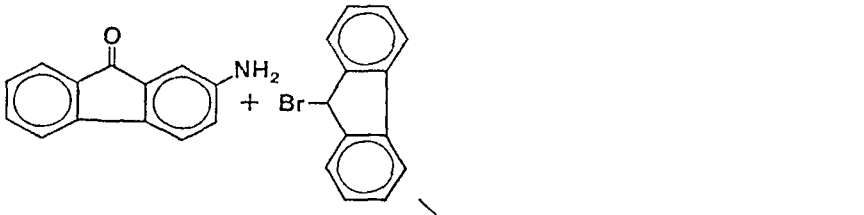


Benzenesulphonhydrazide with certain heterocyclic halogen compounds yields the corresponding *N*-aryl derivative which, on heating with alkali, releases the reduced heterocyclic system (reaction 52)[451]. Alternatively the same reduction can be carried out with triphenylphosphine (reaction 52).

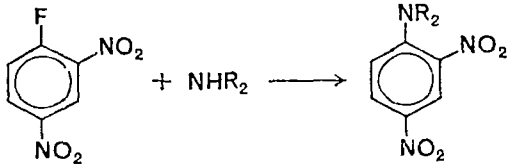


Alkyl and aryl bromides or iodides alkylate weakly basic amines in the presence of triethyl phosphate, as shown in reaction (53)[434].

Aromatic halides substituted with electronegative groups combine with primary and secondary amines[421, 422] (reaction 54).

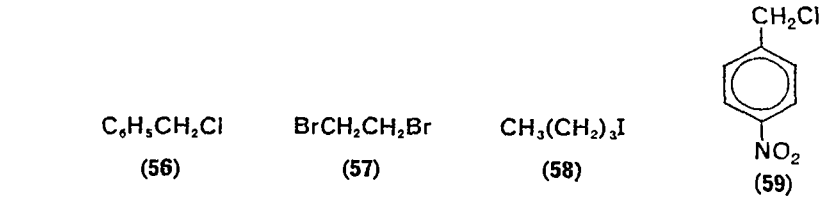


(53)



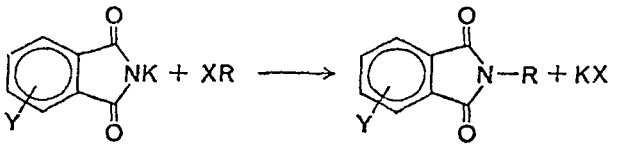
(54)

A determination method for alkyl halides consists of refluxing the sample in aniline for 3–30 min, depending on reactivity, and the anilinium salts being titrated with sodium methoxide. Compounds **56–61** yielded quantitative results with the proposed procedure. On the other hand, amyl bromide (**62**) showed a deviation slightly larger than 1% and cetyl bromide (**63**) failed to yield quantitative results, even after 1 h reflux[452]. A modification for the higher alkyl iodides has also been proposed[453].

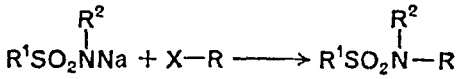


6. *N*-Substitution of amides

Alkyl halides combine with the alkali salts of variously substituted phthalimides (reaction 55) and sulphonamides (reaction 56). Table 19



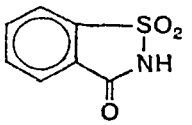
(55)



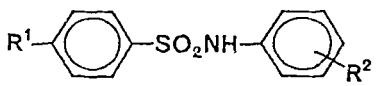
(56)

TABLE 19. Imides and sulphonamides recommended for derivatizing alkyl halides

Reagent	Reference
3-Nitrophthalimide	14, 19, 454
4-Nitrophthalimide	14, 19, 455
Tetrachlorophthalimide	14, 19, 456
Saccharin (64)	14, 457
p-Bromobenzenesulphon-*p*-anisidide (65, $R^1 = Br$; $R^2 = p\text{-}OCH_3$)	14, 458
p-Toluenesulphotoluidides (65, $R^1 = CH_3$; $R^2 = o\text{-}, m\text{-}, p\text{-}CH_3$)	14, 459



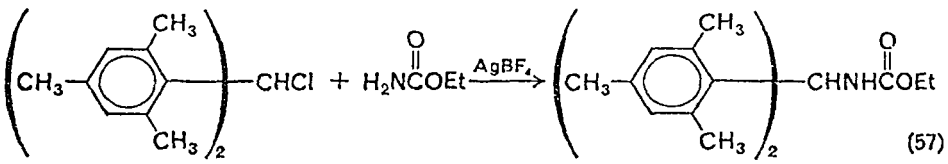
(64)



(65)

lists some of these reagents which have been proposed for use in analytical problems.

Benzhydryl halides can react with ethyl carbamate in the presence of silver tetrafluoroborate (reaction 57)[460].



(57)

7. Derivatization via *P*-alkylation (Wittig-type reactions)

Alkyl halides react with phosphines and phosphites to yield ylides (e.g. **66**) which may react further in many ways. Of special interest are the derivatives with carbonyl compounds[1,461] described for triphenylphosphine

in reactions (58–59) and the reductive dehalogenations discussed in section IV. D. 2. a. The usual reactivity for the halides is I > Br > Cl.

$$R^1R^2CH{-}X + P(C_6H_5)_3 \longrightarrow R^1R^2CH{-}\overset{+}{P}(C_6H_5)_3 \xrightarrow{\text{base}} R^1R^2\overset{-}{C}{-}\overset{+}{P}(C_6H_5)_3 \quad (58)$$

(66)

$$R^1R^2\overset{-}{C}{-}\overset{+}{P}(C_6H_5)_3 + O{=}CR^3R^4 \longrightarrow R^1R^2C{=}CR^3R^4 + OP(C_6H_5)_3 \quad (59)$$

(66)

Modifications of the Wittig reaction have been proposed involving the use of triethyl phosphite (reactions 60–61)[462,463] or hexamethylphosphorous

$$C_6H_5CH_2Cl + P(OEt)_3 \longrightarrow C_6H_5CH_2\overset{+}{P}(OEt)_3Cl^- \xrightarrow{\Delta} C_6H_5{-}CH_2\overset{O}{\overset{\|}{P}}(OEt)_2 \quad (60)$$

$$C_6H_5CH_2\overset{O}{\overset{\|}{P}}(OEt)_2 + C_6H_5CH{=}CHCH{=}O \xrightarrow{MeO^-/DMF} C_6H_5CH{=}CHCH{=}CHC_6H_5 \quad (61)$$

triamide (reactions 62–63)[464]. The latter reagent yields hexamethylphosphoric triamide (67) which is water-soluble.

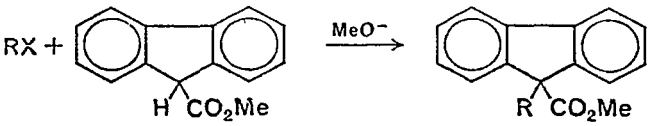
$$C_6H_5CH_2Br + P(NMe_2)_3 \longrightarrow C_6H_5CH_2\overset{+}{P}(NMe_2)_3Br^- \xrightarrow{MeO^-} C_6H_5\overset{-}{C}H\overset{+}{P}(NMe_2)_3 \quad (62)$$

$$C_6H_5\overset{-}{C}H\overset{+}{P}(NMe_2)_3 + C_6H_5CH{=}O \longrightarrow C_6H_5CH{=}CHC_6H_5 + O{=}P(NMe_2)_3 \quad (63)$$

(67)

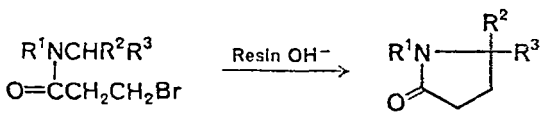
8. C-Alkylation of carbanions

Methyl fluorene-9-carboxylate undergoes alkylation at the 9-position with alkyl halides (reaction 64)[14,465].



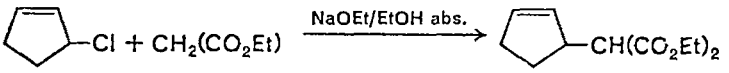
(64)

N-Substituted ω-haloacylamides cyclize to lactams in the presence of strong base ion exchange resins (reaction 65)[466]. Ethyl malonate reacts



(65)

with alkyl halides (reaction 66)[467]. This reaction may be followed for example by derivatizing with urea to a barbituric acid (reaction 67)[468].



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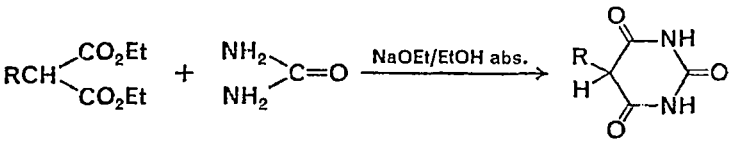
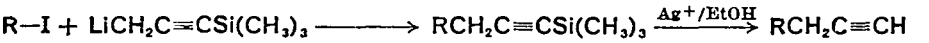


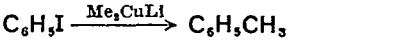
(67)

Primary halides yield terminal acetylenes by reaction (68) with 3-lithio-1-(trimethylsilyl) propyne[469].

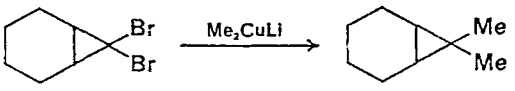


(68)

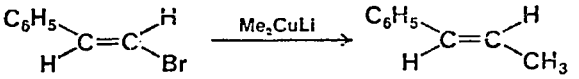
Dimethylcopperlithium is capable of introducing a methyl group in place of a halogen in aryl, vinyl and alkyl halides, as illustrated in reactions (69–71) respectively[470].



(69)

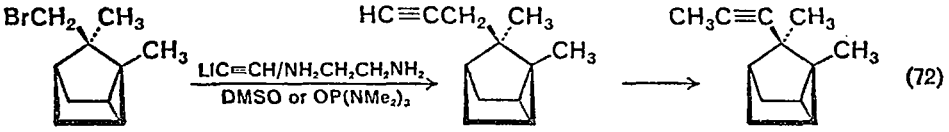


(70)



(71)

Lithium acetylide is capable of introducing the acetylene moiety in alkyl halides having the neopentyl structure, which are usually difficult to substitute. The terminal acetylenes (**68**) can be isomerized to the non-terminal form (**69**) (reaction 72)[471].



(68) (69)

(72)

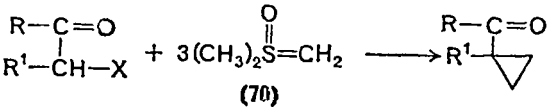
Primary alkyl bromides and iodides can be converted into the homologous phenyl thioethers (reaction 73) or further into the homologous alkyl iodides (reaction 74) by treatment with phenylthiomethyllithium. If

the halide happens to be allylic the reaction becomes easier, but suitable acceptors of HI and I_2 have to be added to the reaction mixture in order to avoid double-bond migrations[472].

$$n\text{-}C_{10}H_{21}I + C_6H_5SCH_2^-Li^+ \longrightarrow n\text{-}C_{11}H_{23}SC_6H_5 \quad (73)$$

$$n\text{-}C_{11}H_{23}SC_6H_5 \xrightarrow{CH_3I,\ NaI/\ DMF} n\text{-}C_{11}H_{23}I \quad (74)$$

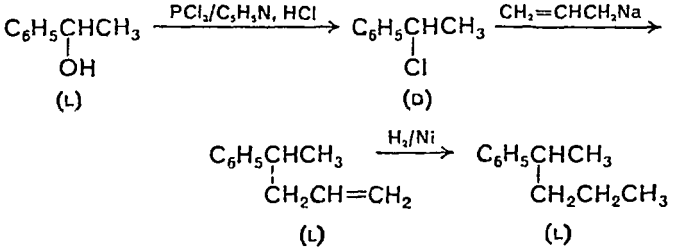
Dimethyloxosulphonium methylide (**70**) yields acylcyclopropanes with α-halo carbonyl compounds (reaction 75)[473].



(75)

(70)

Alkyl alkali metals produce the halogen displacement usually accompanied by Walden inversion, a fact which may be helpful in assigning absolute configurations (see, however, reference 474). For example, the configuration of 2-phenylpentane was correlated with that of α-phenethol via a halogenated intermediate of known configuration, as shown in reaction (76)[475]. See also reactions (119–121, 131).

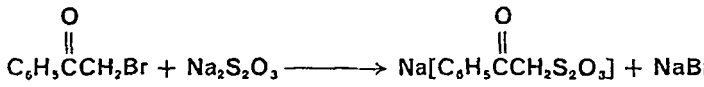


(76)

(L) (D) (L) (L)

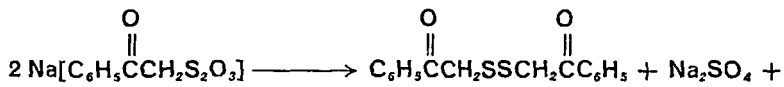
9. Miscellaneous nucleophilic substitutions

Primary alkyl halides yield Bunte salts (**71**) on treatment with thiosulphate (reaction 77). These derivatives undergo further decomposition, releasing sulphur dioxide (reaction 78) that may be detected by its smell or reductive properties[12, 192, 476].



(77)

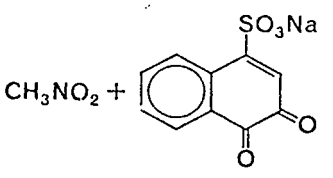
(71)

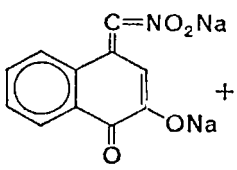


(78)

Alkyl iodides treated with sodium nitrite yield the corresponding nitroalkanes (reaction 79). Methyl iodide can thus be detected if its product is further treated with sodium 1,2-naphthoquinone-4-sulphonate (**72**) in alkaline medium, yielding a coloured compound (reaction 80)[192]. The same method may be applied for the detection of monohaloacetic acids, as these yield nitromethane on heating with sodium nitrite (reaction 81)[477]. Silver nitrite is also effective in reaction (79) with primary halides[478].

$$R{-}I + NaNO_2 \longrightarrow R{-}NO_2 + NaI \qquad (79)$$





+ Na_2SO_3 (80)

(72)

$$XCH_2CO_2H + NaNO_2 \longrightarrow O_2NCH_2CO_2H \longrightarrow CH_3NO_2 + CO_2 \qquad (81)$$

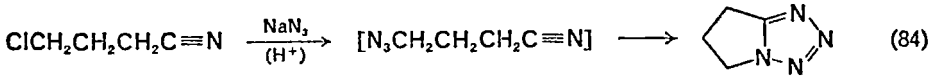
Alkyl and aryl halides that are susceptible to nucleophilic substitution can be converted to the corresponding iodides by treatment with sodium iodide in various solvents, as shown in reaction (82)[479–481]. Sodium iodide

$$R{-}Hal + NaI \longrightarrow R{-}I + NaHal \qquad (82)$$

is a helpful catalyst in the conversion of benzyl chlorides to their corresponding cyanides (reaction 83)[482].

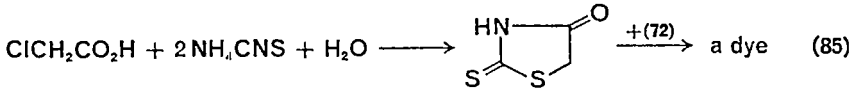
$$p\text{-}MeOC_6H_4CH_2Cl + NaCN \xrightarrow{NaI/Me_2CO} p\text{-}MeOC_6H_5CH_2CN \qquad (83)$$

The azide ion is similar to iodide, but usually more effective, in displacing organic halogen (including iodine)[483]. An additional advantage is that the organic azido group may undergo thermal rearrangements and cyclizations involving other properly situated groups in the molecule[483, 484], yielding derivatives with analytically useful properties, as in reaction (84)[484]. α-Haloacetic acids yield rhodanine (**73**) on treatment with am-



(84)

monium thiocyanate. The product reacts with **72** to give a blue-violet coloration (reaction 85)[12].



(85)

(73)

Displacement by strong nucleophilic electrolytes usually involves a Walden inversion[5]. This fact may be helpful in correlating the absolute configuration of an alkyl halide with that of a known compound. For example, α-phenethyl chloride was correlated with α-phenethylamine[485] as shown in reaction (86).

$$\underset{\text{(D)}}{C_6H_5\overset{Cl}{\overset{|}{C}}HCH_3} \xrightarrow{NaN_3} \underset{\text{(L)}}{C_6H_5\overset{N_3}{\overset{|}{C}}HCH_3} \xrightarrow{H_2/Pt} \underset{\text{(L)}}{C_6H_5\overset{NH_2}{\overset{|}{C}}HCH_3} \qquad (86)$$

B. *Displacement via Organometallic Intermediates*

The formation of Grignard reagents is the first step for multiple possibilities of derivatization. Although reaction (87) constitutes the most widely used method for organometal intermediate formation, treatment of alkyl or aryl halides with lithium, lithium–sodium alloys or butyllithium yields the corresponding lithio compound, e.g. as shown in reaction (88)[1,2].

$$R{-}X + Mg \longrightarrow R{-}MgX \qquad (87)$$

$$R{-}X + Li/Na \longrightarrow R{-}Li + NaX \qquad (88)$$

Among the derivatives recommended for organic halides[11,14,19] are conversions into anilides[486,487], toluides and α-naphthalides[486]. These are prepared by reacting the organometallic intermediate with the corresponding aryl isocyanate, as shown in reaction (89). The anilides resulting from allyl halides can be converted into crotonic anilides by treatment with acid (reaction 90)[487].

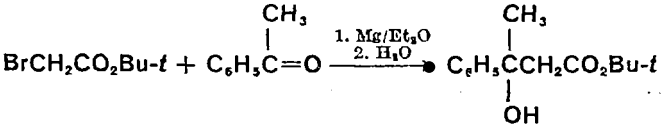
$$R{-}MgX + ArN{=}C{=}O \longrightarrow \overset{O}{\overset{\|}{R}}CNHAr \qquad (89)$$

$$CH_2{=}CHCH_2\overset{O}{\overset{\|}{C}}NHAr \xrightarrow{H^+} CH_3CH{=}CH\overset{O}{\overset{\|}{C}}NHAr \qquad (90)$$

Aromatic Grignard reagents may be converted into phenols by means of methyl borate (reaction 91)[488].

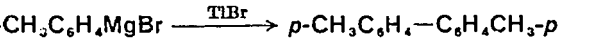
$$C_6H_5MgBr + B(OMe)_3 \xrightarrow{H^+/H_2O} C_6H_5B(OH)_2 + (C_6H_5)_2BOH \xrightarrow{H_2O_2} C_6H_5OH \qquad (91)$$

Reformatsky-type reactions can be carried out with Mg instead of Zn if the *t*-butyl ester of the α-halo acid is used, e.g. reaction (92)[489].

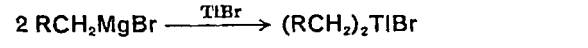


(92)

Aryl Grignard reagents with no *ortho* substituents undergo high yield biaryl formation on treatment with thallium(I) bromide (reaction 93). Secondary alkyl Grignard reagents give a similar reaction in about 50% yield and primary alkyl or *ortho* substituted aryl Grignard reagents give dialkylthallium(III) bromides (reaction 94)[490], or the analogous diarylthallium(III) compounds.

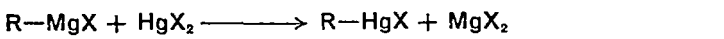


(93)

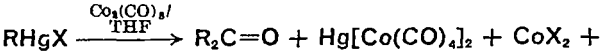


(94)

Other organometallic derivatives obtained via Grignard reagents are halomercury compounds (reaction 95), which have been recommended for identification purposes[11,14,19]. The organomercury halides can be further reacted in the presence of dicobalt octacarbonyl to yield a ketone (reaction 96)[491].

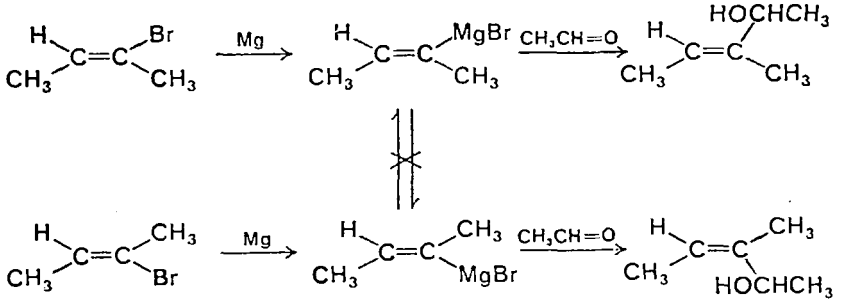


(95)



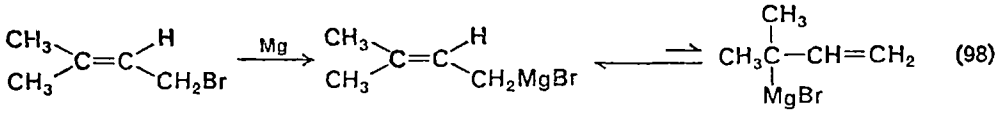
(96)

The stereochemistry of various classes of halides is preserved when converted into organometallic derivatives and further reacted, thus allowing the establishment of useful correlations[429,492]. Vinyl halides preserve their *cis* or *trans* configuration on passing through an anionic form (e.g. Grignard reagents, reaction 97)[493]. Allyl halides, on the other



(97)

hand, may undergo cationotropic rearrangements which have to be considered when derivatizing via organometallic intermediates (e.g. reaction 98)[494]. Cyclopropyl halides also preserve their configuration on metallation with magnesium[492].



(98)

C. Elimination of Hydrogen Halide

Such eliminations can be selective for certain types of halides and the spectral properties of the products may be helpful in structural elucidation of the parent halide.

1. Alkyl halides

Alkali hydroxides and alkoxides bring about dehydrohalogenation under various conditions depending on the substrate. When two elimination products are possible, hydroxides tend to obey Saytzeff's rule (reaction 99); however, the yield of the anti-Saytzeff products varies with the nature of the base, as shown in reaction (100)[495–498].

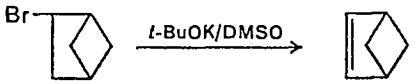
$$(CH_3)_2CBrCH_2CH_3 \xrightarrow{\text{base}} (CH_3)_2C{=}CHCH_3 \qquad (99)$$

$$CH_3CBrCH_2CH_3 \xrightarrow{\text{base}} CH_2{=}CCH_2CH_3 \qquad (100)$$

$$\begin{vmatrix} CH_3 & & CH_3 \end{vmatrix}$$

EtOK,	30%
t-BuOK,	72·5%
Et_3COK,	88·5%

Dehydrohalogenations with potassium *t*-butoxide proceed smoothly in dimethyl sulphoxide solvent, e.g. reaction (101)[499].



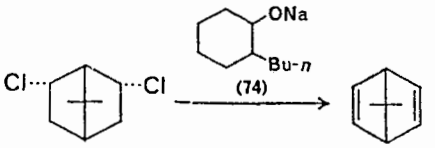
(101)

Good yields are obtained in the same solvent in dehydrochlorinations with sodium hydroxide or ethoxide (reaction 102)[500].

$$(C_6H_5)_3CCH_2CH_2Cl \xrightarrow[\text{DMSO}]{\text{NaOH/}} (C_6H_5)_3CCH{=}CH_2 \qquad (102)$$

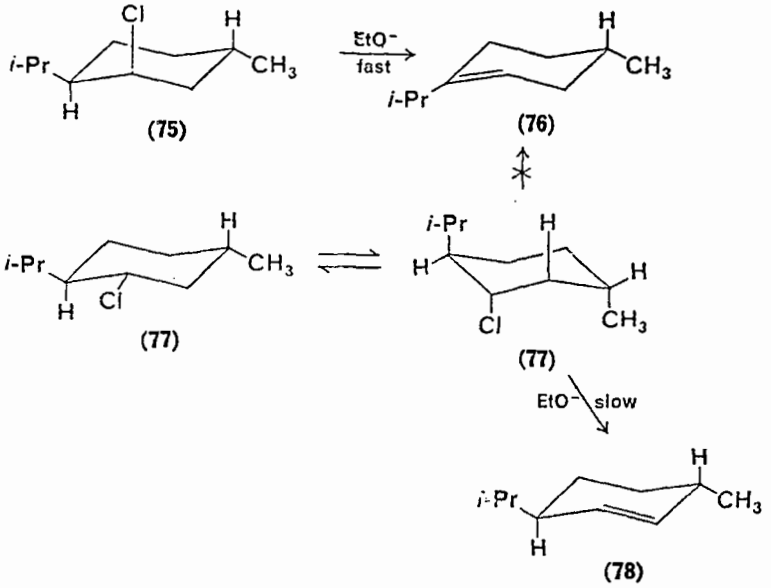
(90%)

Sodium 2-*n*-butylcyclohexanolate (**74**) is effective in dehydrohalogenating compounds even in cases where potassium *t*-butoxide and lithium diethylamide (see below) fail, e.g. reaction (103)[501].



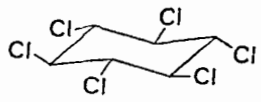
(103)

In cyclic compounds *trans*-diaxial eliminations are favoured, especially if they conform to the Saytzeff rule and a *t*-hydrogen is eliminated; on the other hand, axial-equatorial or diequatorial eliminations are very sluggish. Reaction (104) illustrates the production of 3-menthene (**76**) from neo-



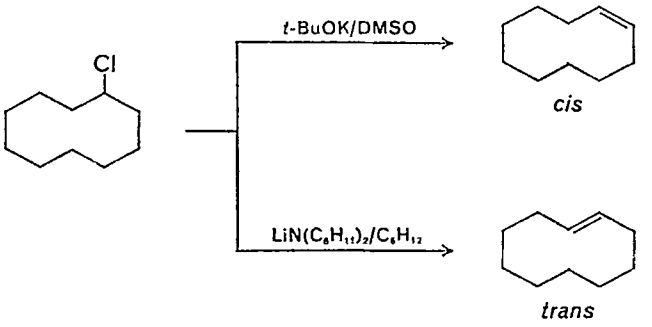
(104)

menthyl chloride (**75**) according to Saytzeff's rule, while the anti-Saytzeff product 2-menthene (**78**) is produced from the anomeric menthyl chloride (**77**)[502]. Similarly, the all-equatorial isomer of hexachlorocyclohexane (**79**), is by far the most resistant to alkaline solvolysis[503].



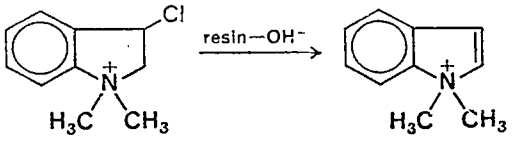
(79)

The stereochemistry of the resulting olefins depends on the dehydrohalogation reagent[497, 498, 504], as shown, for example, in reaction (105).



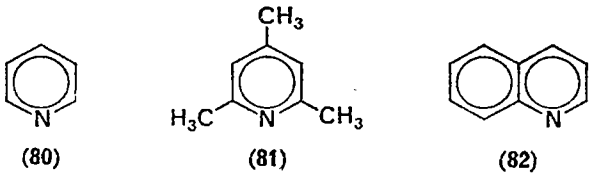
(105)

Organic halides containing the quaternary ammonium moiety can be dehydrohalogenated by treatment with strongly basic resins (reaction 106). Treatment with bases in solution brings about elimination reactions involving the quaternary ammonium function[505].

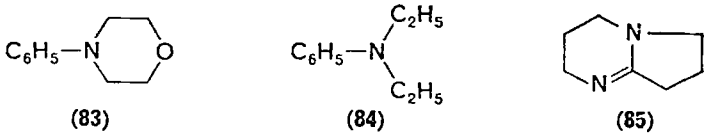


(106)

Amines and nitrogen-containing aromatic heterocycles can be used for effecting dehydrohalogenations. These are mild bases which need either harsh conditions or the presence of easily removable proton or halogen in the substrate. These properties allow selective removal of halogen atoms in polyhalogenated compounds. Heating in the presence of heterocyclic compounds such as pyridine (**80**), *s*-collidine (**81**) and quinoline (**82**) has long been used for this purpose[1].

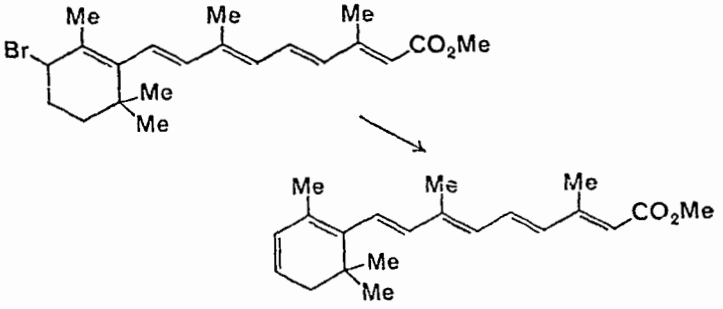


(80) (81) (82)



(83) (84) (85)

N-Phenylmorpholine (**83**) acts like *N*,*N*-diethylaniline (**84**) but is purified more easily. They can both be used for allylic halides (reaction 107)[506]. A very effective dehydrohalogenating reagent is 1,5-diazabicyclo[4.3.0]non-5-ene (**85**)[507].



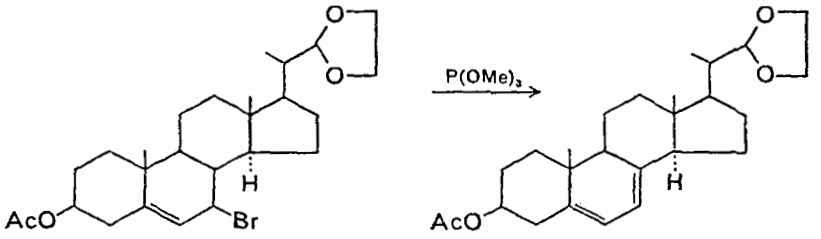
(107)

Other useful amine bases for alkyl halide dehydrohalogenation are *t*-butylamine (e.g. reaction 108 [508]), dicyclohexylethylamine, diisopropylethylamine (e.g. reaction 109 [509]) and triethylamine[1]. α-Haloketones, on the other hand, are reduced in the presence of dialkylanilines (see section IV. D. 1. b).

$$CCl_3CH_2\underset{\displaystyle Br}{\underset{|}{C}}HB(OC_4H_9)_2 \xrightarrow{t\text{-}BuNH_2} CCl_3CH{=}CHB(OC_4H_9)_2 \qquad (108)$$

$$CH_3CH_2O\underset{\displaystyle Cl}{\underset{|}{C}}HCH_3 \xrightarrow[\text{or } i\text{-}Pr_2NEt]{(C_6H_{11})_2NEt} CH_3CH_2OCH{=}CH_2 \qquad (109)$$

Trimethyl phosphite catalyses dehydrohalogenation on refluxing in xylene (reaction 110)[510].

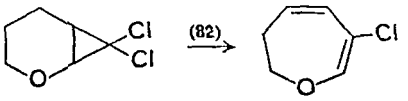


(110)

Primary alkyl bromides undergo dehydrobromination on heating with hexamethylphosphoric triamide, yielding terminal alkenes (reaction 111)[511]. *gem*-Dihalocyclopropanes undergo elimination–rearrangement

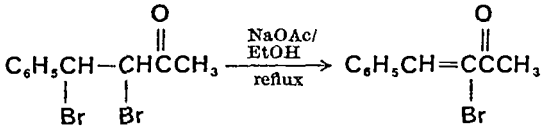
$$RCH_2CH_2{-}Br \xrightarrow{O{=}P(NMe_2)_3} RCH{=}CH_2 \qquad (111)$$

via vinyl halide intermediates on heating with bases such as pyridine (**80**) or quinoline (**82**)[512,513], e.g. reaction (112)[512].



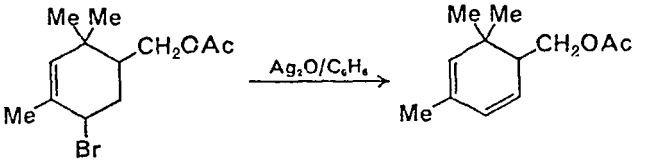
(112)

Refluxing *vic*-dibromides in the presence of ethanolic sodium acetate yields vinyl bromides (reaction 113)[514].



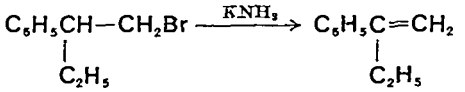
(113)

Silver oxide converts allylic halides slowly into conjugated dienes (reaction 114)[515]. Alkali amides cause dehydrohalogenations, but no



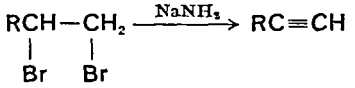
(114)

excess should be used in order to avoid rearrangements (reaction 115)[516].

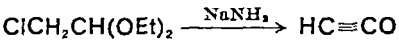


(115)

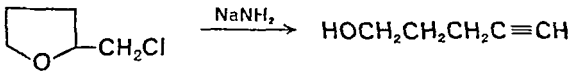
vic-Dibromides are converted to the corresponding acetylenes (reaction 116)[517]. Similarly, β-haloethers also yield acetylenes (reactions 117[518] and 118[519]).



(116)



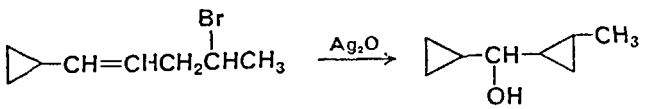
(117)



(118)

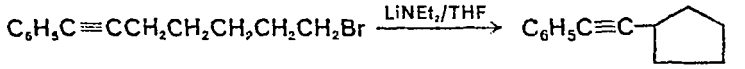
2. Cyclization of alkyl halides

Unsaturated alkyl halides and halogenated compounds containing suitable functional groups dehydrohalogenate forming cyclic compounds on treatment with various reagents. Homoallylic halides yield cyclopropanes with silver oxide or potassium carbonate (reaction 119)[520].



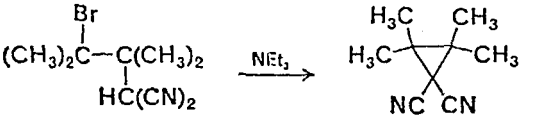
(119)

Lithium diethylamide has been used to cyclize acetylenic halides as shown in reaction (120)[521]. Tri-*n*-butyltin hydride gives similar results[522].



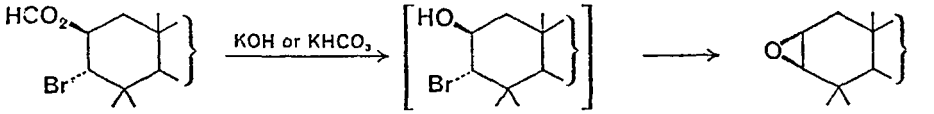
(120)

Triethylamine also is capable of causing cycloalkyl formation, if both the halogen and the departing proton are sufficiently activated, as in reaction (121)[523] (see also section IV. A. 8).



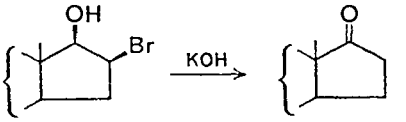
(121)

Halohydrins or their formates in the *trans*-diaxial conformation yield epoxides with bases (reaction 122)[524–526]. The stereoselectivity of this reaction is high[428]. *Trans*-diequatorial halohydrins may also undergo this cyclization[524].



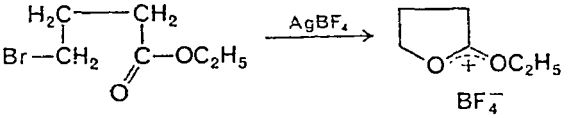
(122)

Halohydrins with the *cis* configuration yield carbonyl compounds (reaction 123)[524,527].



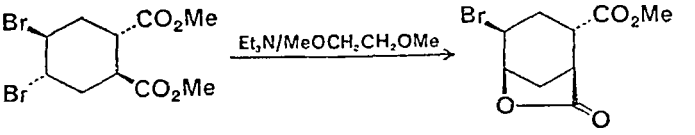
(123)

Silver tetrafluoroborate with alkyl halides can effect *O*-alkylations of ethers, ketones, esters and alkyl carbonates to yield tertiary oxonium salts. If the substrate is a bromo ester a heterocyclic compound is formed (reaction 124)[528].



(124)

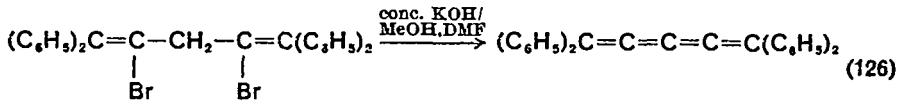
Triethylamine may cause the lactonization of γ-bromo acids (reaction 125)[529].



(125)

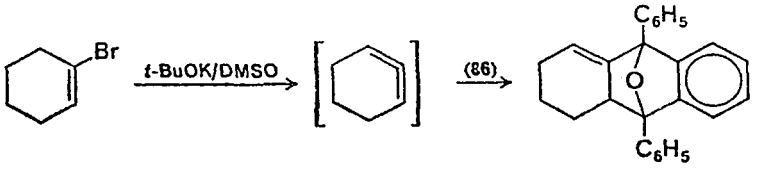
3. Vinyl halides

Displacement and elimination reactions are more difficult to carry out with these compounds than with alkyl halides and more drastic treatment is therefore required. Treatment with hydroxide or alkoxide yields allenes (reactions 126[530] and 127[531,532]). Reaction (127) is not, however, without

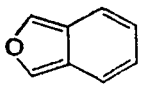


(126)

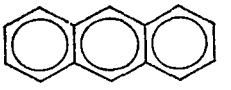
complications[533,534]. Trapping of allenes can be done *in situ* by conjugated diene reagents such as 1,3-diphenylisobenzofurane (**86**)[531,532], as shown in reaction (127).

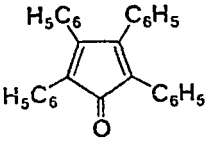


(127)



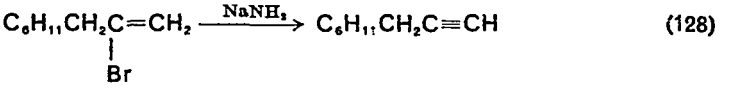
(86)


(87)



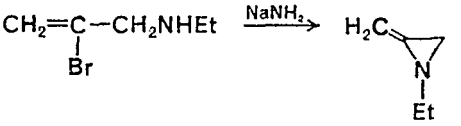
(88)

Sodamide converts vinyl halides into acetylenes[517] (reaction 128).



(128)

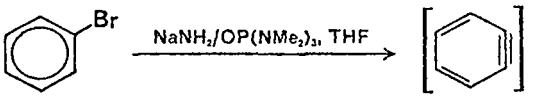
On the other hand, compounds with a 2-halo-3-amino-propene partial structure form aziridines with sodamide (reaction 129)[535].



(129)

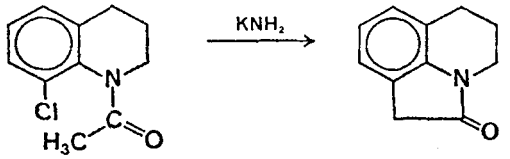
4. Aryl halides

These compounds require specially drastic conditions to eliminate hydrogen halide and produce an aryne, e.g. reaction (130)[536,537]. The



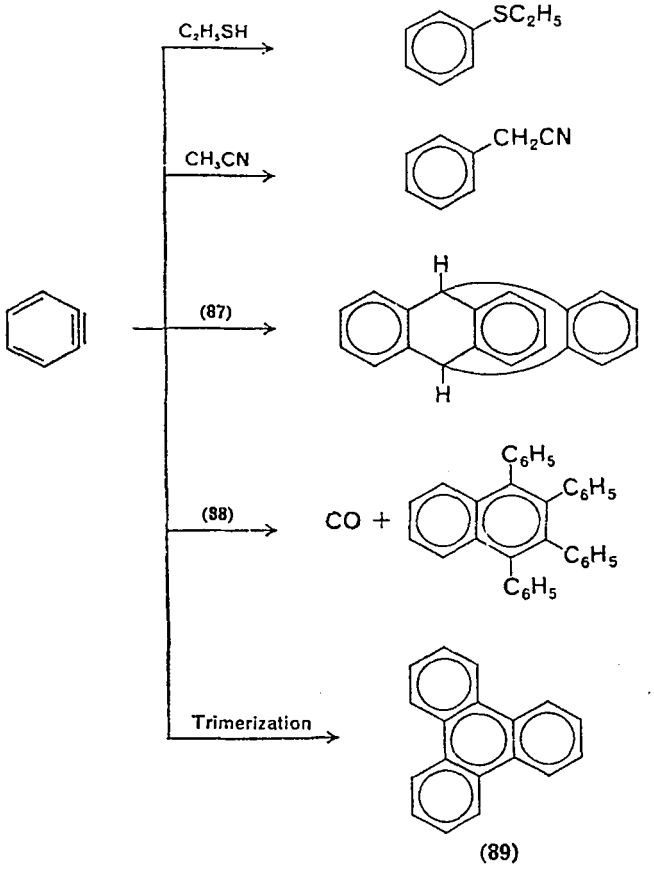
(130)

dehydrohalogenation product is, however, a very reactive intermediate capable of further reaction, either intramolecularly with a suitable situated substituent (reaction 131)[538] or with other reagents such as



(131)

mercaptans, acetonitrile[536, 537], or dienic systems, e.g. anthracene (**87**)[539], tetraphenylcyclopentadienone (**88**)[540], with itself forming triphenylene (**89**)[541], as shown in reactions (132a–e).



(132a)

(132b)

(132c)

(132d)

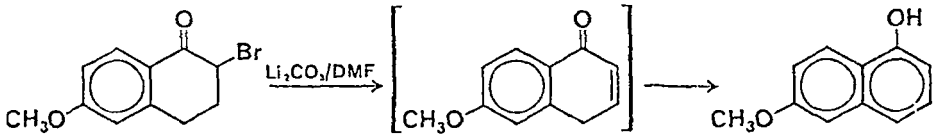
(132e)

(89)

5. α-Halocarbonyl compounds

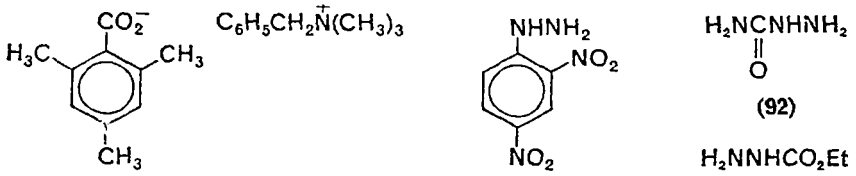
These compounds dehydrohalogenate with relative ease as compared to saturated alkyl halides. Among reagents that have been used for this

purpose are ethanolic silver nitrate[542], weak bases like sodium bicarbonate[543,544], lithium carbonate (reaction 133[545], see also reaction 201), or



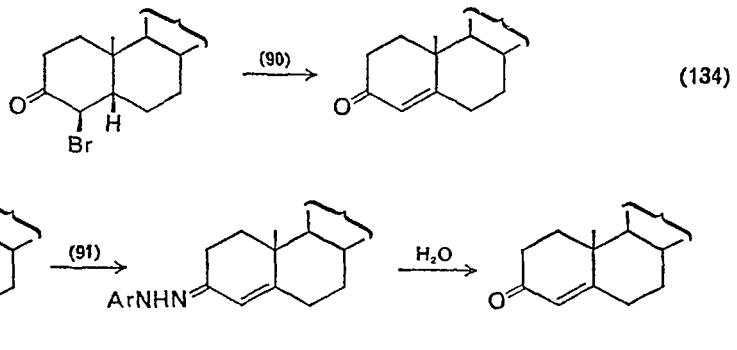
(133)

calcium carbonate[546] and salts such as lithium bromide[547], tetraethylammonium chloride[548] or benzyltrimethylammonium mesitoate (**90**) (reaction 134[549]). Reagent **90** effected the elimination from a *cis* conformation under mild conditions, while the former weak bases usually



(90) (91) (92) (93)

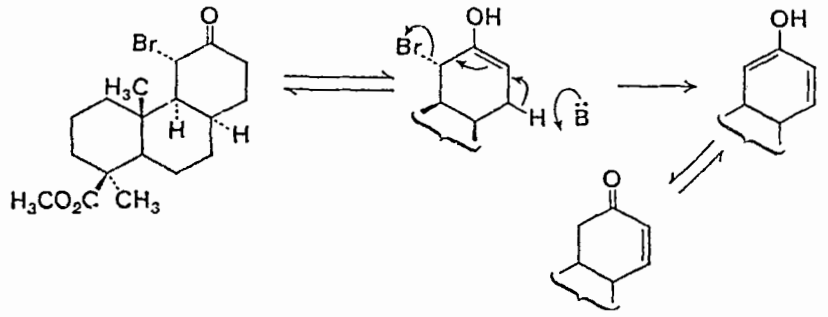
require a *trans*-diaxial conformation. Other similar reagents are hydrazine derivatives such as 2,4-dinitrophenylhydrazine (**91**), semicarbazide (**92**) and ethyl carbazate (**93**)[550–553] (reaction 135).



(134)

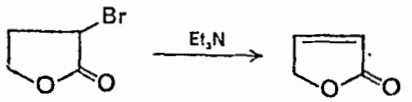
(135)

The eliminations performed in aprotic solvents may take a 1,4-pathway if no neighbouring *trans*-axial hydrogen is present. This may be confusing when the halogen substitution site is to be assigned (reaction 136)[554].



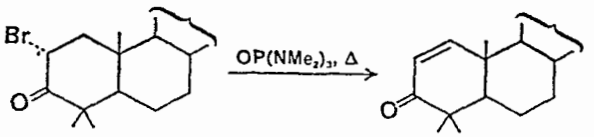
(136)

Amines are also capable of dehydrohalogenating α-haloketones and α-haloesters, e.g. tri-*n*-butylamine[555] and triethylamine (reaction 137)[556].



(137)

Hexamethylphosphoric triamide dehydrohalogenates on heating both α-haloketones and α-halo esters as shown in reaction (138)[557].



(138)

D. Reduction

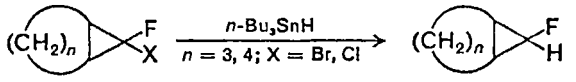
Two main types of derivatives can be obtained from reductive treatment, namely compounds where a hydrogen atom takes the place of the halogen and compounds where an unsaturation is formed in place of two monovalent oxidizing leaving groups, of which at least one is halogen. Polarographic reductions are described in section V. B.

1. Substitution of halogen by hydrogen

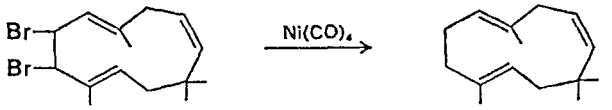
a. Alkyl halides. These can be reduced by magnesium in the presence of isopropanol[558]. Very stable halides can be reduced by this method, however, fluoro compounds are less reactive. This is in fact a particular case of the general reduction of Grignard reagents with active hydrogen compounds (reaction 139).

$$R{-}MgX + H{-}Y \longrightarrow RH + MgXY \qquad (139)$$

Tri-*n*-butyltin hydride (reaction 140[559], see also reactions 155 and 171) and nickel tetracarbonyl (reaction 141[560], see also reaction 159) reduce halides without touching the skeleton structure.

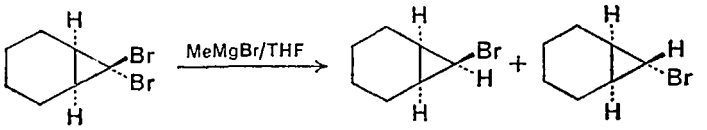


(140)



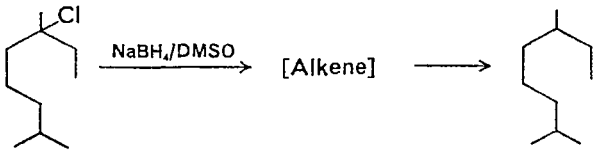
(141)

Methylmagnesium bromide is capable of effecting non-stereospecific monodehalogenations in *gem*-dihalocyclopropanes (reaction 142[561]).

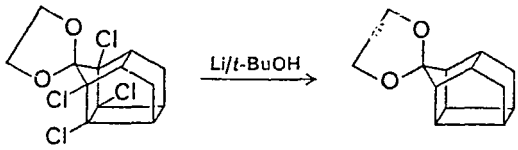


(142)

Sodium borohydride in dimethyl sulphoxide reduces alkyl halides. Optically active *t*-alkyl halides produce a racemic compound, probably as shown in reaction (143)[562]. Lithium in *t*-butyl alcohol reduces alkyl halides leaving the skeleton intact (reaction 144)[563].

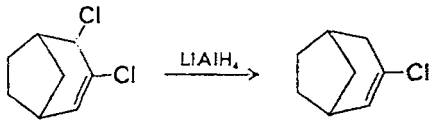


(143)



(144)

Alkyl halides can be reduced without touching less reactive halogens by means of lithium aluminium hydride (reaction 145)[1]. With the same reagents α-bromohydrins yield the alcohol[564].



(145)

Propargyl halides undergo a reduction with zinc–copper couple which is accompanied by rearrangement to allenes (reaction 146)[565]. Bromoform yields acetylene on heating with zinc–copper couple (reaction 147)[12]. Carbon tetrachloride and tetrabromide give the same reactions but are less sensitive[12].

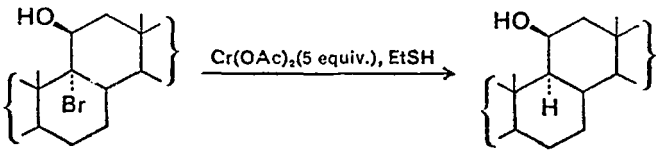
$$CH_3\underset{\displaystyle Cl}{\underset{|}{C}}HC{=}CCH_2CH_2OAc \xrightarrow{Zn-Cu} CH_3CH{=}C{=}CHCH_2CH_2OAc \qquad (146)$$

$$2\,CHBr_3 \xrightarrow{Zn-Cu} C_2H_2 + 3\,ZnBr_2 \qquad (147)$$

Chromium(II) salts are capable of reducing alkyl halides in high yields[566], e.g. reaction (148). The course of the reaction may lead to dimerization (reaction 149). Bromohydrins usually undergo other types of reduction, as will be shown in section IV. D. 2. a; however, in the presence of a hydrogen donor such as a mercaptan, the hydroxyl group is left intact (reaction 150)[525, 567].

$$CH_3CH_2CH_2Br \xrightarrow{Cr(ClO_4)_2,\ NH_2CH_2CH_2NH_2/aq.\ DMF,\ N_2} CH_3CH_2CH_3 \qquad (148)$$

$$(C_6H_5)_2CHBr \xrightarrow{CrSO_4/aq.\ DMF,\ N_2} (C_6H_5)_2CHCH(C_6H_5)_2 \qquad (149)$$

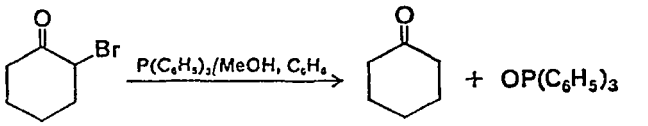


(150)

b. α-Halo ketones and α-halo acids. These undergo many reactions which are impossible with ordinary alkyl halides. α-Bromo and α,α-dibromo ketones are reduced by dimethylaniline (reaction 151)[568].

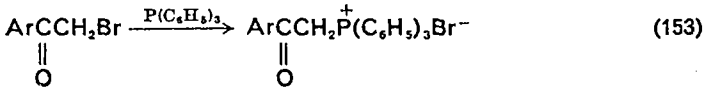
$$p\text{-}BrC_6H_4\overset{\displaystyle O}{\overset{\|}{C}}\underset{\displaystyle Br}{\underset{|}{C}}HCH_3 \xrightarrow{C_6H_5NMe_2} p\text{-}BrC_6H_4\overset{\displaystyle O}{\overset{\|}{C}}CH_2CH_3 \qquad (151)$$

Triphenylphosphine reduces secondary and tertiary α-haloketones (reaction 152)[569]. On the other hand, phenacyl halides yield quaternary



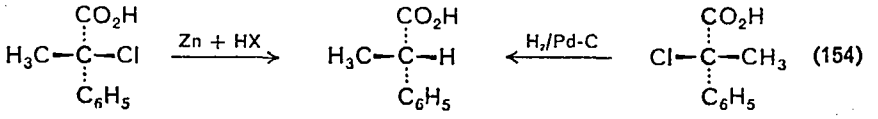
(152)

phosphonium salts (reaction 153)[570].



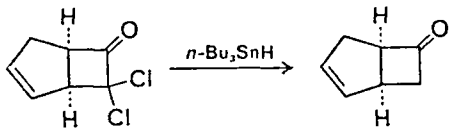
(153)

Catalytic hydrogenation of α-haloketones has to be carried out in the presence of a base such as triethylamine, in order to avoid catalyst poisoning[571]. Catalytic reduction of α-chloro-α-phenylpropionic acid in the presence of palladium is carried out with inversion of configuration while reduction with nascent hydrogen preserves the configuration (reaction



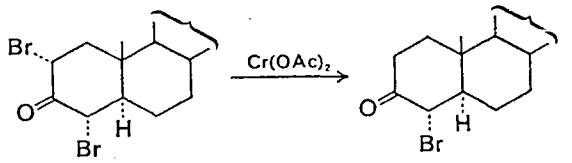
(154)

154)[572]. Tri-*n*-butyltin hydride effects dehalogenations without touching the skeleton structure (reaction 155)[573].



(155)

Chromium(II) salts can be used for stepwise reduction of α-bromoketones (reaction 156)[574].



(156)

Nascent hydrogen produced by zinc in acid solution or fomaldehyde sodium sulphoxylate (reaction 157) can lead to α-halocarbonyl reduction[12, 575]. This has been used for specific detection of chloral and bromal[12],

$$HOCH_2SO_2Na + H_2O \longrightarrow HOCH_2SO_3Na + 2\,H^\circ \qquad (157)$$

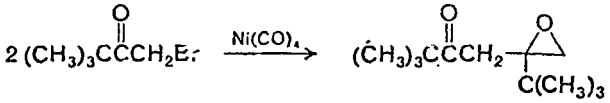
$$CX_3CH{=}O \xrightarrow[X=Cl,\,Br]{H^\circ} CH_3CH{=}O + 3\,HX \qquad (158)$$

in which reduction (158) is followed by the Rimini test for aldehydes. γ-Bromo-α,β-unsaturated carbonyl compounds (ketones and esters) are

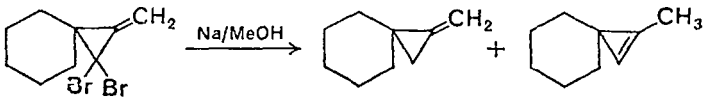
reduced and rearranged simultaneously to the corresponding β,γ-unsaturated compound, with zinc in protonic solvents (reaction 159)[576, 577].

$$(CH_3)_2\underset{\displaystyle Br}{\underset{|}{C}}CH{=}CHCO_2Et \xrightarrow{Zn/AcOH} (CH_3)_2C{=}CHCH_2CO_2Et \qquad (159)$$

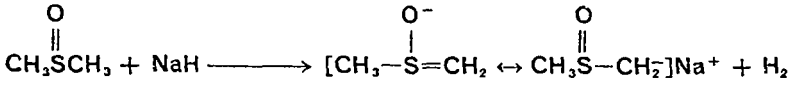
Nickel tetracarbonyl effects reductive dimerization of α-bromoketones (reaction 160)[578, 579], to yield β-epoxyketones.

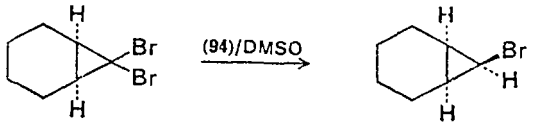


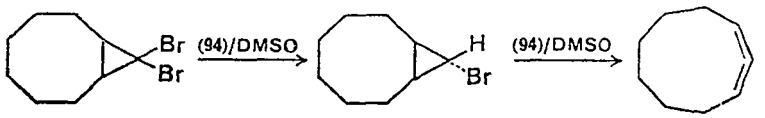
c. gem-*Dihalocyclopropanes.* Various effective ways of performing reduction of such halogen atoms are known: lithium in *t*-butyl alcohol, sodium in liquid ammonia and sodium in methanol are the most commonly used. The latter reagent is known to cause double-bond migration to a certain extent (reaction 161)[449].



Sodium methylsulphinylmethide (**94**) is obtained *in situ* on dissolving sodium hydride in dimethyl sulphoxide (reaction 162). This reagent can reduce *gem*-dihalocyclopropanes stepwise (reactions 163 and 164). If

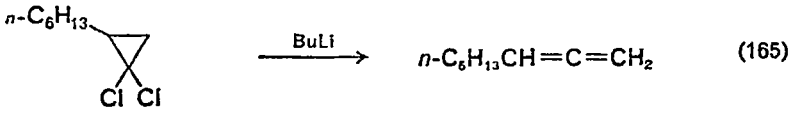






steric conditions allow, excess reagent brings about allene formation (reaction 164)[449].

Alkyllithium reagents convert *gem*-dihalocyclopropanes directly into allenes (reactions 165 and 166). In the case of bicyclo[*n*.1.0] compounds good results are obtained for $n \geqslant 6$ (reaction 167)[449]. Tetraalkyl-*gem*-dibromocyclopropanes yield with methyllithium bicyclo[1.1.0]butanes (reaction 168)[580].



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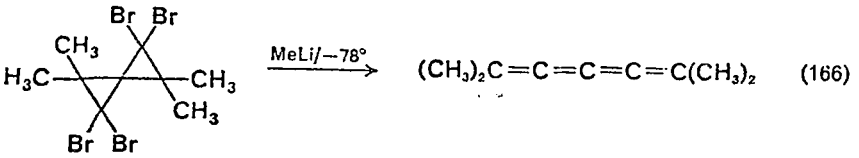
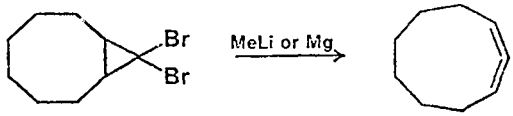
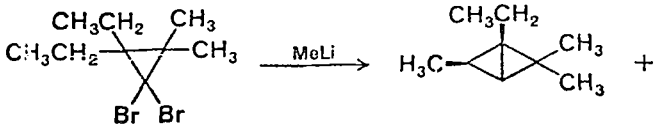
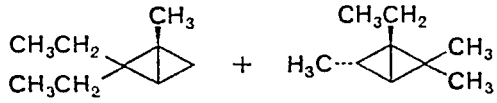


(166)



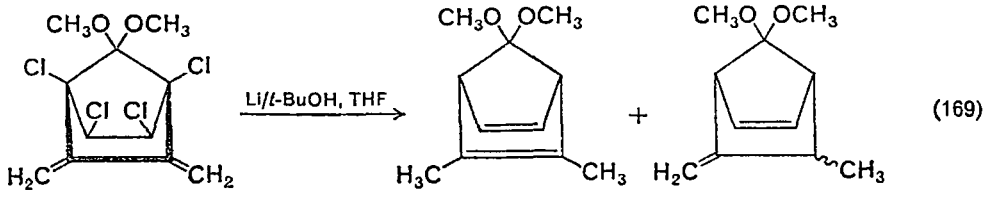
(167)





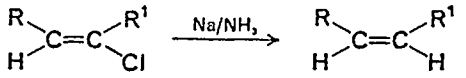
(168)

d. Vinyl halides. Both lithium[581] and sodium[582] in *t*-butyl alcohol are capable of reducing vinyl halides without disrupting the skeleton; however, some overhydrogenation and double-bond migration (reaction 169)[583]



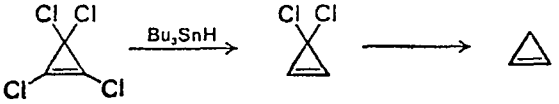
(169)

may occur. The *cis* or *trans* configuration of vinyl halides is preserved on reducing with sodium in liquid ammonia (reaction 170)[584].



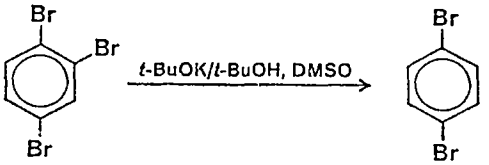
(170)

Tributyltin hydride also leaves the skeleton untouched (reaction 171)[559, 585].



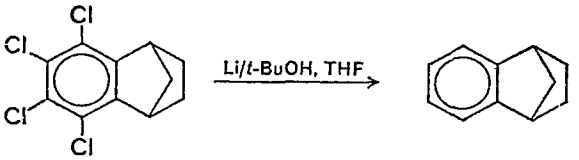
(171)

e. Aryl halides. Monodebromination or monodeiodination of *vic*-dihalides is performed by potassium *t*-butoxide (reaction 172)[586].



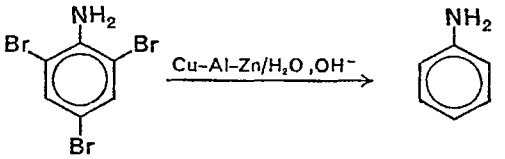
(172)

Lithium in *t*-butyl alcohol is capable of dehalogenating polyhaloaromatic compounds (reaction 173)[587].



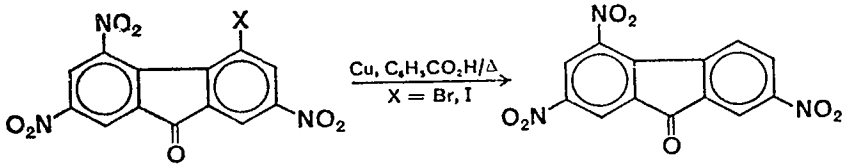
(173)

Halogenated anilines are reduced by Devarda's alloy in alkali solution (reaction 174)[588].



(174)

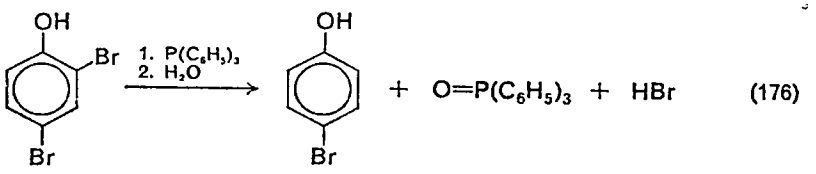
Aromatic nitro compounds are dehalogenated by copper powder in the presence of molten benzoic acid (reaction 175)[589] and by hydrazine in the presence of Raney nickel[590]. Magnesium in isopropanol is very effective in



(175)

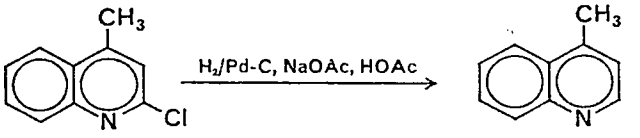
dehalogenations[558] (see also section IV. D. 1. a), but fluorobenzene is inert towards this reagent.

Triphenylphosphine reduces halides *ortho* or *para* to phenol groups, the former being preferred (reaction 176)[591].



(176)

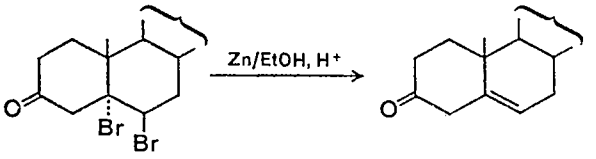
Reaction (52) affords a reduction method for certain heterocyclic halides. Catalytic hydrogenation in the presence of a base can also be applied for these compounds (reaction 177)[592].



(177)

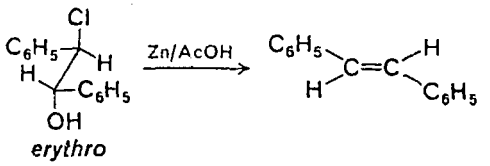
2. Reductive eliminations

a. vic-*Dihalides and halohydrins.* (i) Various metals effect reduction leading to multiple-bond formation: zinc powder in a protonic solvent under acidic conditions attacks *vic*-dihalides and halohydrins of *trans*-diaxial configuration (reactions 178–180)[593–595]; however, some instances of *cis*-halohydrin reduction are known[596]. These reductions have been widely applied in the steroid field[597]. Also β-bromo ethers can be similarly reduced (reaction 181)[598]. Vinyl halides do not react under these conditions (e.g. reaction 182)[582], but they may be reduced with zinc under conditions conducent to free radical formation (reaction 183)[599].

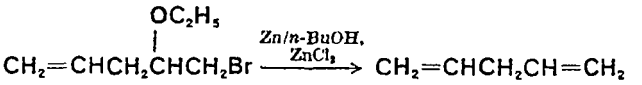


(178)

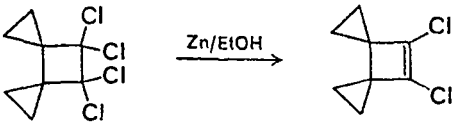
$$CCl_3{-}CClF_2 \xrightarrow[ZnCl_2]{Zn/MeOH,} CCl_2{=}CF_2 \qquad (179)$$



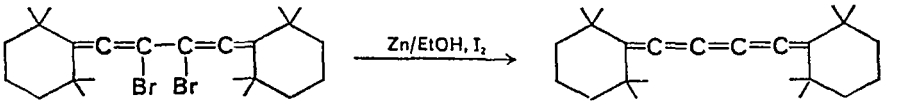
(180)



(181)

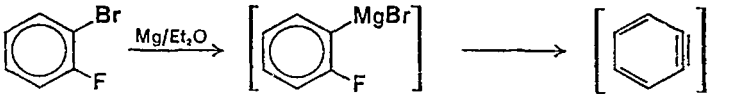


(182)



(183)

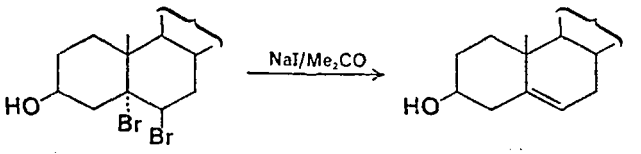
Magnesium can cause dehalogenation in many types of *vic*-dihalides via Grignard intermediates. When the substrate is aromatic (reaction 184)[539]



(184)

the resulting benzyne can be further trapped as shown in reactions (132a–e). Lithium reacts similarly to magnesium with aromatic dihalides[541].

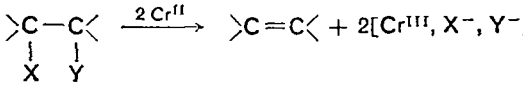
(ii) Reducing salts such as magnesium iodide[600] and sodium iodide (reaction 185)[601, 602] also yield olefinic products. Only the *trans*-diaxial form of a steroid, (**95**), reacts[603].



(95)

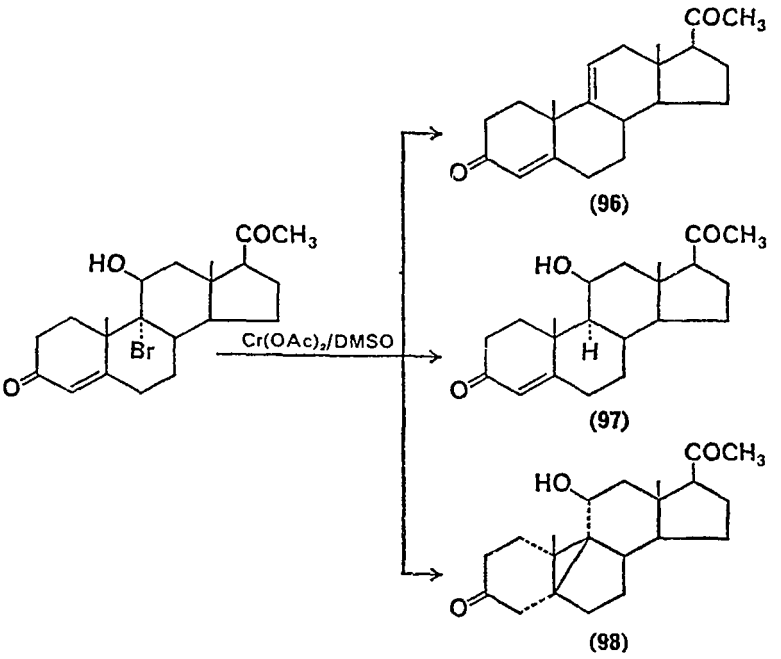
(185)

Chromium(II) salts are also useful reducing agents, both for *vic*-dihalides and bromohydrins (reaction 186)[604]. Reaction (187) shows that besides the



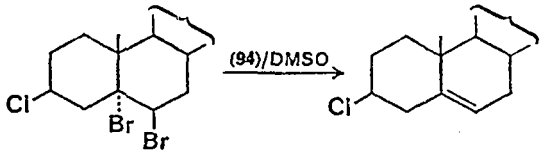
(186)

normal route leading to **96**, bromine replacement[605] yielding **97** (cf. reaction 150) and rearrangement to **98**[605, 606] also take place.



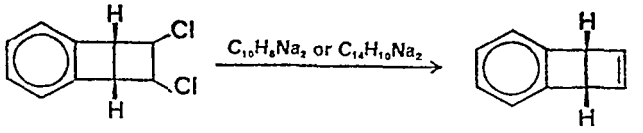
(187)

Sodium methylsulphinylmethide (**94**) is capable of dehalogenating *vic*-dibromides without touching other isolated alkyl halides (reaction 188[607], see also reactions 162–164).



(188)

(iii) Disodium phenanthrene and disodium naphthalene are useful in debrominating *vic*-dihalobenzocyclobutanes (reaction 189)[608, 609].



(189)

(iv) Diphenyl selenide and diphenyl telluride can be used to dehalogenate *vic*-dibromides (reaction 190)[610]. The dibromo reagent obtained can be regenerated with bisulphite.

$$C_6H_5CH(Br)-CH(Br)CO_2H \xrightarrow{(C_6H_5)_2Se} C_6H_5CH=CHCO_2H + (C_6H_5)_2SeBr_2 \quad (190)$$

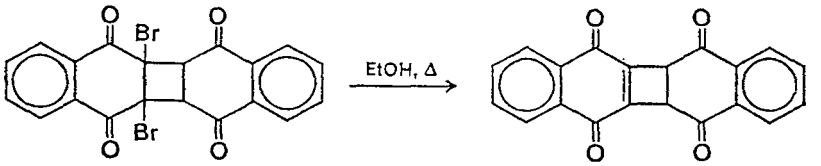
(v) Triphenylphosphine acts in a way similar to reaction (190) to yield olefins with many classes of *vic*-dihalides[611-613] (e.g. reaction 191).

$$CCl_3CCl_2\overset{O}{\overset{\|}{C}}CCl_2CCl_3 \xrightarrow{2\,(C_6H_5)_3P} CCl_2=CCl\overset{O}{\overset{\|}{C}}CCl=CCl_2 + 2\,(C_6H_5)_3PCl_2 \quad (191)$$

Triethyl phosphite[614] and triisopropyl phosphite[615] also dehalogenate alkylene *vic*-dihalides (reaction 192). The condition for this reaction is the presence of electronegative substituents attached to the Hal—C—C—Hal central structure[614].

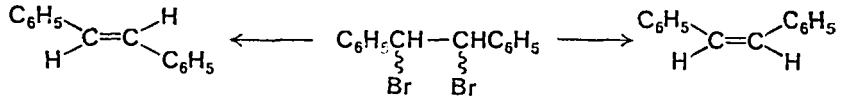
$$BrCH_2CHBrCN \xrightarrow{P(OEt)_3} CH_2=CHCN \quad (192)$$

(vi) *vic*-Dihalides are debrominated on heating in ethanol solvent (reaction 193)[616]. A faster reduction is attained in the presence of bases[617].



(193)

The stereoselectivity of various reducing agents mentioned above has been studied in the debromination of stilbene dibromides (reaction 194)[618].

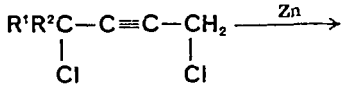


(194)

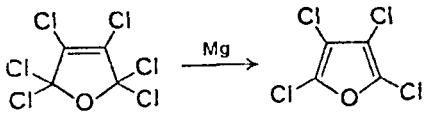
b. telo-*Dihalides.* These compounds lead to the formation of cycles or, if suitable unsaturated chains are interposed between the halogen-bearing carbon atoms, to the shifting and increasing of unsaturation. These reactions are conveniently carried out with metals. Thus zinc–copper couples cause cyclization of 1,3-dibromopropanes to the corresponding cyclopropane (reaction 195)[619]. Dehalogenation of 1,4-dichloro-2-alkynes

$$C_6H_5CH(Br)CH_2CH_2(Br) \xrightarrow{Zn-Cu} C_6H_5-\triangleleft \quad (195)$$

leads to cumulenes (reaction 196)[620], and of 1,4-dichloro-2-alkenes to 1,3-butadienes (reaction 197)[621].



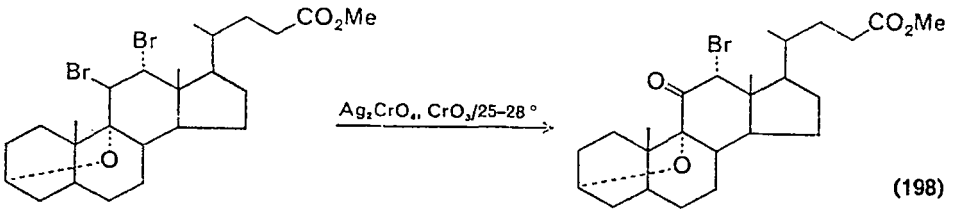
(196)



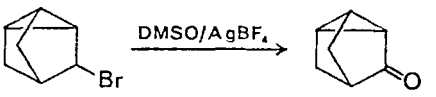
(197)

E. Oxidation

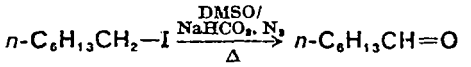
Only a few oxidative processes seem to have potential analytical value in organic halide analysis. Silver chromate oxidizes β-bromoethers to α-alkoxyketones (reaction 198)[622]. Dimethyl sulphoxide oxidizes *sec*-alkyl bromides to ketones (reaction 199)[623], and primary alkyl halides to



(198)

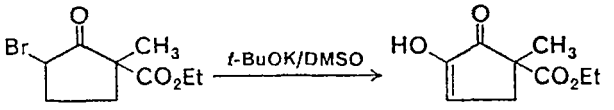


(199)



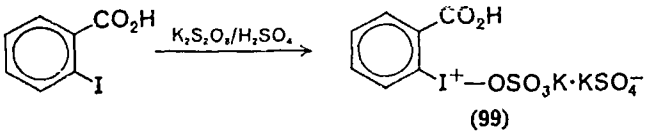
(200)

aldehydes (reaction 200)[624]. Silver salts catalyse these oxidations. Dimethyl sulphoxide oxidizes cyclic α-bromoketones as shown in reaction (201)[427].

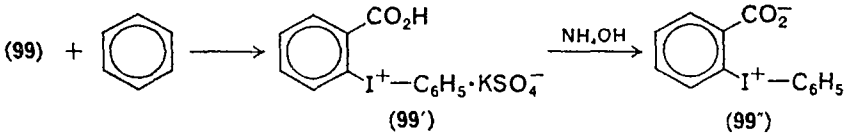


(201)

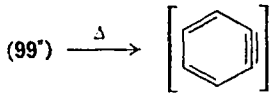
Iodo compounds are capable of easy binding to organic radicals yielding stable iodonium compounds (**99′**, **99″**). Thus *o*-iodo aromatic carboxylic acids can be converted into benzynes via oxidation with potassium persulphate by the reaction sequence (202–204)[625]. Steps (202–204) are applicable to all aromatic compounds containing no reducing functional groups other than iodo.



(99) (202)



(99′) (99″) (203)



(204)

Conversion to iodoso compounds (**101**) by reactions (205–206) has been proposed for identification of aromatic iodo compounds[626]. The process involves the intermediate formation of aryl iodochlorides (iodoarene dichlorides, **100**).

$$Ar{-}I + Cl_2 \longrightarrow Ar{-}ICl_2 \qquad (205)$$

$$\underset{\textbf{(100)}}{Ar{-}ICl_2} + 2\,NaOH \longrightarrow \underset{\textbf{(101)}}{Ar{-}IO} + 2\,NaCl + H_2O \qquad (206)$$

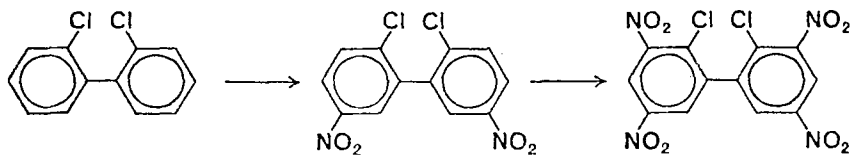
F. Miscellaneous Reactions

1. Aryl halides

Reaction with chlorosulphonic acid affords sulphonyl chlorides which are converted to the corresponding sulphonamides on treatment with ammonia (reaction 207)[11,14,19,627]. When X = I in reaction (207) ring chlorination also takes place. Fluorobenzene, iodobenzene, *o*-dichlorobenzene and *o*-bromochlorobenzene all yield sulphones with chlorosulphonic acid at 50°.

$$XC_6H_5 \xrightarrow{ClSO_3H} p\text{-}XC_6H_4SO_2Cl \xrightarrow{NH_3} p\text{-}XC_6H_4SO_2NH_2 \qquad (207)$$

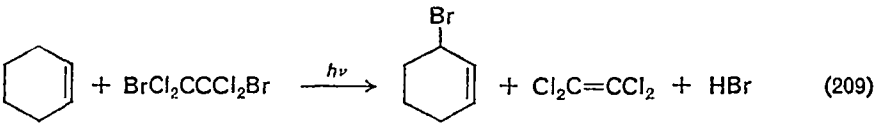
Nitration affords useful derivatives for identification purposes (reaction 208)[11,14,19].



(208)

2. Polyhalogenated compounds

Strong heating of polyhalogenated organic compounds (e.g. CCl_4) on finely powdered solids such as SiO_2, SnO_2, ThO_2, etc. brings about liberation of free halogen[192] that can be detected by the methods of Table 11. The presence of hydrogen in polyhalogenated compounds can be ascertained if hydrogen sulphide is liberated on fusion with sulphur[628]. Polychlorinated compounds containing a few bromine atoms and no hydrogen are brominating agents under photolytic conditions[629]. Benzylic or allylic hydrogens are displaced in chain reactions by the bromine liberated, and therefore compounds containing such hydrogens can be placed in the irradiated sample for bromine scavenging (reaction 209)[630].



(209)

Polyhalogenated aromatic compounds yield a colour reaction on treatment with pyridine and aqueous alkali (the Fujiwara reaction[631]). Various modifications have been proposed both for submicro scale detection[12] and determination[632,633] of such compounds. The presence of two or three geminal halogen atoms seems to be a necessary, though not sufficient, condition for the reaction to take place.

V. FUNCTIONAL ANALYSIS BY PHYSICAL METHODS

A. Acid–Base Properties of Halogenated Carboxylic Acids and Amines

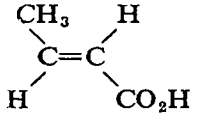
Experimentally it is easy to obtain good pK_a values of most organic acids or amines, and the difference defined according to equation (210)

$$\Delta pK_a = pK_a - pK_{a,ref} \tag{210}$$

(where $pK_{a,ref}$ is the value for a reference compound, usually the corresponding non-halogenated compound) is helpful in determining the substitution site in halo-derivatives.

In saturated carboxylic acids the absolute value of ΔpK_a increases with the degree of substitution in the order $H < I < Br \sim Cl < F$, and diminishes on increasing the distance between the carboxylic group and the substitution site (Table 20). When the chain between the carboxyl group and the halogen consists of conjugated double bonds, the effect of the halogen is transmitted better and the acidity increase is higher than with a corresponding saturated chain, (cf. entries 7 and 9 in Table 20).

TABLE 20. Effects of ω-halogenation on the acidity of straight-chain carboxylic acids[a]

No.	Reference compound	$pK_{a,ref}$	Number of ω halogen atoms	ΔpK_a[b]			
				F	Cl	Br	I
1	CH_3CO_2H	4·76	1	−2·19	−1·89	−1·87	−1·59
2			2	−3·52	−3·47		
3			3	−4·63	−4·11		
4	$CH_3CH_2CO_2H$	4·88	1		−0·85	−0·88	−0·79
5			3	−1·86			
6	$CH_3CH_2CH_2CO_2H$	4·82	1		−0·30	−0·23	−0·18
7			3	−0·66			
8	$CH_3CH_2CH_2CH_2CO_2H$	4·86	1		−0·16	−0·14	−0·09
9		4·69	3	−1·51			

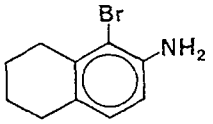
[a] From references 634 and 635.
[b] From equation (210).

TABLE 21. Effects of halogenation on the acidity of aromatic compounds[634]

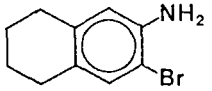
Substituent	ΔpK_a[a]		
	ortho	*meta*	*para*
A. Substitution in benzoic acid (pK_a 4·20)			
F	−0·93	−0·33	−0·06
Cl	−1·26	−0·37	−0·21
Br	−1·35	−0·39	−0·20
I	−1·34	−0·34	
CF_3		−0·41	
B. Substitution in phenol (pK_a 9·95)			
F	−1·14	−0·67	0·0
Cl	−1·47	−0·93	−0·57
Br	−1·53	−0·84	−0·61
I		−0·78	
C. Substitution in anilinium salts (pK_a 4·58)			
F	−1·62	−1·20	−0·06
Cl	−1·96	−1·26	−0·77
Br	−1·98	−1·07	−0·67
CF_3		−1·09	−2·01

[a] See equation (210).

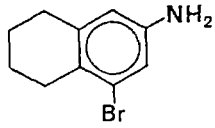
The effects of substituents in aromatic compounds were found to be additive in the pK_a scale. Halo substituents cause increase in acidity which are largest for *ortho* positions (Table 21). These values can be used for structural assignments, e.g. after bromination and hydrolysis of 6-acetylaminotetralin two monobrominated compounds of pK_a 3·05 were isolated; of the three possible isomers (**102–104**), the *meta*-brominated aniline (**104**) was discarded, as the pK_a value calculated for the analogous 3,4-dimethylaniline (5·15) becomes on bromination 3·18 for the two *ortho* and 4·09 for the *meta* product[636, 637].



(102)



(103)



(104)

B. Polarography

1. General considerations

The polarography of organic halides is an extension of the subject *reduction* treated in section IV. D, but now the reagent consists of the electrons present at the cathode. Indeed, polarographic processes find a rough parallel with formal mechanisms proposed for reactions in solution.

Three limiting mechanisms have been proposed resembling S_N2, S_N1 and free-radical chain reactions[638, 639] (reactions 211, 212 and 213, respectively). The nature of the cathode is also important in determining the mechanism, thus, for example, simple alkyl bromides and iodides undergo one-electron reduction at a stationary lead electrode[640], while at mercury electrodes the reductions are usually two-electron processes (see below).

$$R{-}X + 2e^- \longrightarrow X^- + R^- \qquad (211)$$

$$R{-}X \rightleftharpoons X^- + R^+ \xrightarrow{2e^-} R^- \qquad (212)$$

$$R{-}X + e^- \longrightarrow X^- + R^\bullet \longrightarrow \text{further reactions} \qquad (213)$$

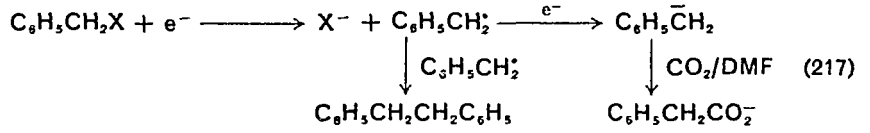
The most satisfactory mechanism seems to be a free radical one that incorporates some S_N-like features. Reactions (214–216) show the reduction of benzyl halides to toluene with concurrent formation of dibenzylmercury[641]. Benzyl chloride also yields bibenzyl from coupling of free

$$Hg + C_6H_5CH_2X \xrightarrow{e^-} X^- + C_6H_5CH_2Hg^\bullet \rightleftharpoons C_6H_5CH_2Hg^+ + e^- + X^- \qquad (214)$$

$$C_6H_5CH_2Hg^\bullet + e^- \longrightarrow C_6H_5CH_2^- + Hg \qquad (215)$$

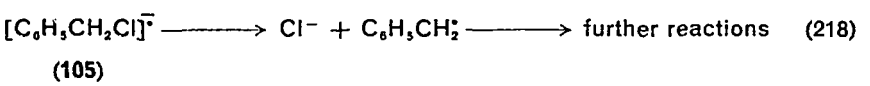
$$2\,C_6H_5CH_2Hg^\bullet \longrightarrow (C_6H_5CH_2)_2Hg + Hg \qquad (216)$$

radicals (reaction 217)[642]. At very negative potentials benzyl bromide in DMF in the presence of carbon dioxide produces small yields of phenylacetic acid from the benzyl anion (reaction 217)[643]. The fact that benzyl



(217)

chloride, reduced in aqueous lithium chloride solution at potentials more negative than $E_{\frac{1}{2}}$ (half-wave potential), shows only one electron transfer, is explained by the formation of intermediate **105** which is repelled by the cathode and proceeds to decompose far from it (reaction 218). Once bibenzyl is produced by dimerization it becomes adsorbed on the cathode,



(218)

(105)

gradually reducing the repulsion of **105** and thus allowing the benzyl cation to be reduced on the cathode to toluene in a two-electron overall process. Similarly, in the presence of surface-active tetramethylammonium salts the normal two-electron process is observed at all potentials[642].

Allyl and propargyl halides (but not benzhydryl bromide[646]) behave like benzyl halides[644, 645]. The polarography of organic halides has been reviewed[638, 647–650], and a compilation of literature from 1922 to 1955 has appeared[651].

2. Alkyl halides

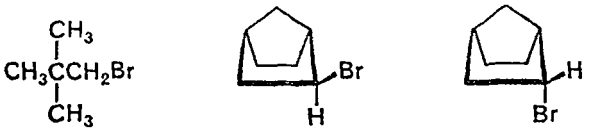
The ease of reduction of alkyl halides parallels the relative leaving-group ability of the anion in S_N2 reactions, namely I > Br > Cl. Also parallel to the S_N2 mechanism is the ease of displacement of simple alkyl bromides: ethyl > *n*-propyl > *i*-propyl. In *n*-alkyl bromides the ease of reduction decreases with chain length up to *n*-pentyl bromide, beyond which all bromides are reduced at nearly the same $E_{\frac{1}{2}}$[652]. The reduction of *t*-butyl bromide is easy (S_N1-like mechanism, see reaction 212)[653]. 1-Methyl-1-halocyclopropanes have been reduced with various extents of configuration retention[654].

Cyclopentyl bromide is easily reduced but not cyclohexyl bromide. Even more difficult to reduce are cyclopropyl, cyclobutyl and neopentyl (**106**) bromides[653]. Reduction of polyhalides where the halogen atoms are sited apart from each other seems to be stepwise, as was shown for 1,4-dibromoalkanes (reactions 219, 220)[655].

$$BrCH_2CH_2CH_2CH_2Br \xrightarrow{2e^-} BrCH_2CH_2CH_2CH_2:^- + Br^- \quad (219)$$

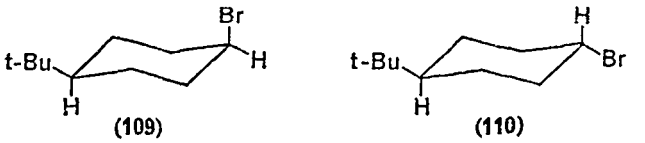
$$BrCH_2CH_2CH_2CH_2:^- + H^+ \longrightarrow BrCH_2CH_2CH_2CH_3 \quad (220)$$

The steric behaviour of polarographic reduction parallels in many cases the one observed for S_N1 and S_N2 reactions, in spite of their near equivalence in polarography[656]. Thus *exo*-norbornyl bromide (**107**) is reduced more readily than *endo*-norbornyl bromide (**108**).



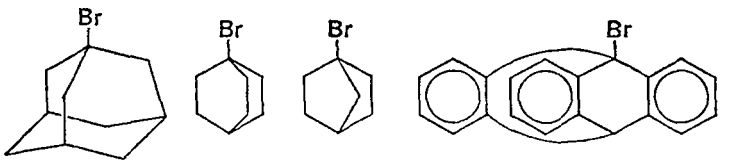
(106) (107) (108)

In *t*-butylcyclohexyl halides the *t*-butyl group holds the conformation fixed, and therefore **109** is reduced as readily as cyclohexyl bromide, while **110**, with the equatorial halogen, is reduced only with difficulty[656].



(109) (110)

Bridge-head halides such as **111–113** will undergo reduction with increasing difficulty in that order, as the carbonium ions obtainable by an S_N1-like mechanism become more and more strained. Compound **114**, on



(111) (112) (113) (114)

the other hand, is easily reduced, probably due to the inductive effect of the phenyl groups on the *t*-alkyl site[657]. It was concluded, however, from Hammett plots for benzyl bromides in dimethylformamide and acetonitrile, that their polarographic reduction is not an S_N1-like reaction[658]. Hammett plots in protic media were also studied[659].

The $E_{\frac{1}{2}}$ of alkyl halides is generally pH-independent, unless other functional groups are present too, as will be shown in section V. B. 7. In the presence of vitamin B_{12} the controlled potential reduction of alkyl halides is a two-electron process above $E_{\frac{1}{2}}$ and a one-electron process below $E_{\frac{1}{2}}$[660].

3. *gem*-Polyhalides

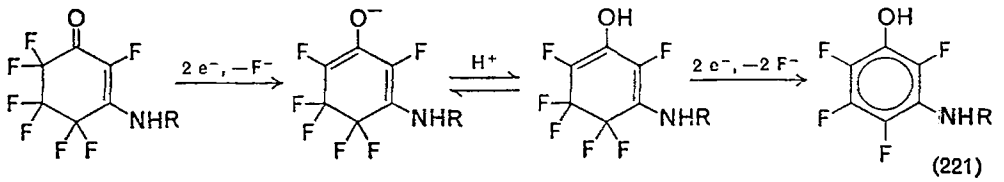
The presence of more than one halogen in the same carbon atom facilitates the reduction. Thus a *gem*-polyhalide gives a series of two-electron waves corresponding to stepwise, increasingly difficult replacement of halogen by hydrogen (Table 22).

TABLE 22. Polarographic reduction of some *gem*-polyhalides

Compound	Remarks	Reference
Carbon tetrachloride	Two two-electron waves. The $E_{\frac{1}{2}}$ of the second one is that of chloroform	661
Carbon tetrabromide	Analogous to carbon tetrachloride	661
Benzotrifluoride	Several electrons consumed. Nature of products not established	662
Trichloroacetic acid	One two-electron wave	663
Tribromoacetic acid	Three two-electron waves corresponding to a stepwise reduction to acetic acid	664
2,2,2-Trichloroethanol	One two-electron wave reduction to 2,2-dichloroethanol	665
Ring-alkylated trichloroacetanilides	One one-electron reduction to a dichloroacetanilide followed by two two-electron reductions to an acetanilide	666
Ring-alkylated dichloroacetanilides	Two two-electron reductions to an acetanilide	666
Pesticides derived from hexachlorocyclopentadiene	Several products may be obtained	667
Perfluorocyclohexenones	Four-electron reduction to the phenol (reaction 221)	668
7,7-Dihalo[4.1.0]bicycloheptanes	Non-stereospecific two-electron reduction	669
1,1,1,2-Tetrachloro-2,2-bis(*p*-chlorophenyl) ethane (**115**)	Two-electron reduction to DDD (**116**)	675

$(p\text{-}ClC_6H_4)_2ClCCl_3$ (**115**) $(p\text{-}ClC_6H_4)_2C{=}CCl_2$ (**116**)

The trifluoromethyl group does not ordinarily undergo reduction unless it is attached to a benzene ring, preferably substituted with electronegative groups[662]. Geminal difluoromethyl groups undergo reduction as shown in reaction (221) for polyfluorocyclohexenones[668].



(221)

4. *vic*- and *telo*-Dihalides

These compounds undergo a two-electron reduction which may be followed by elimination of halide forming an olefin, which may be further reduced as shown in reaction (222)[670].

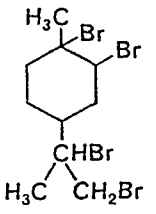
$$\begin{matrix} CH_2-CH_2 \\ | \quad | \\ Br \quad Br \end{matrix} \longrightarrow CH_2=CH_2 + CH_3CH_3 \qquad (222)$$

An axial halogen is more easily reduced in cyclohexane systems[671]. Among the isomers of hexachlorocyclohexane the most difficult one to reduce is the so-called β-isomer of benzene hexachloride, because of its all-equatorial conformation (**79**)[672], while an isomer containing a pair of geminal chlorine atoms is more readily reduced[671].

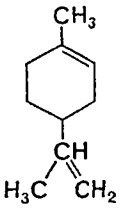
Some examples of polarographic reductions of *vic*-dihalides are shown in Table 23. The reductions are not stereospecific as shown in reaction (223), but *meso* isomers are more readily reduced than *dl* isomers.

TABLE 23. Polarographic reduction of some *vic*-dihalides

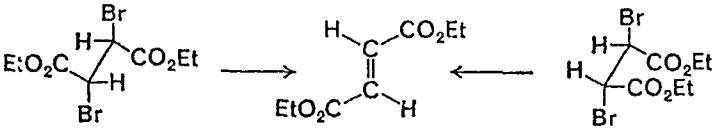
Compound	Remarks	Reference
Various hexachlorocyclohexanes	Six-electron reduction to benzene	671–673
Limonene tetrabromide (**117**)	Four-electron reduction to limonene (**118**)	674
Diethyl *meso*-2,3-dibromosuccinate (**119**)	Two-electron reduction to diethyl fumarate (**120**)	676
Diethyl *dl*-2,3-dibromosuccinate (**121**)	Two-electron reduction to diethyl fumarate (**120**)	676
2,3-Dibromobutane-1,4-diol	Two-electron reduction to 2-butene-1,4-diol	677
Pesticides derived from hexachlorocyclopentadiene	Several products are obtained	667
Perchloro-1,5-hexadiene	Two-electron reduction to perchloro-1,3,5-hexatriene	678



(**117**)

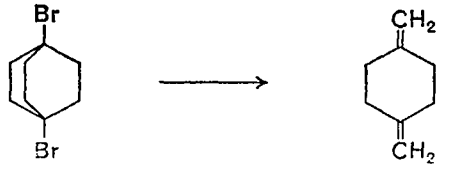


(**118**)



(119) (120) (121) (223)

The polarographic reduction of *telo*-dihalides has been explored. Under favourable steric conditions cyclic compounds are formed but reductions and rearrangements may also take place (reactions 224–226)[679].



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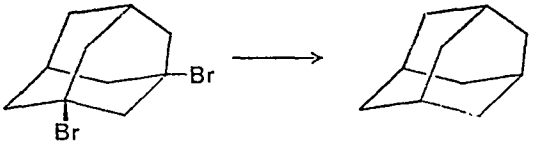

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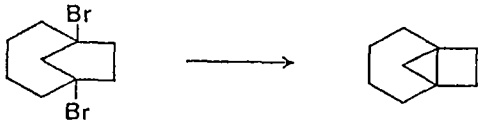


(226)

5. Aromatic halides

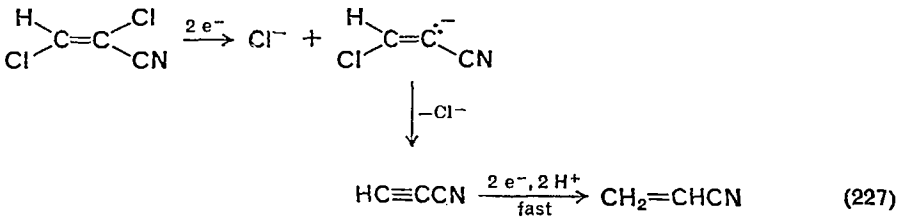
These compounds are more difficult to reduce than alkyl halides. The process is a two-electron reduction in which halide is expelled and a hydrogen atom takes its place. Polyhalogenated aromatic compounds undergo stepwise reduction[680]. Studies of several halonitrobenzenes in non-aqueous solvents show that the initial step is a one-electron wave yielding the anion radical which rapidly dissociates to halide and nitrophenyl radical[681, 682]. Some reduction processes are summarized in Table 24. Various Hammett plots for halobenzenes were studied[658, 683].

TABLE 24. Polarographic reduction of some aromatic halides

Compound	Remarks	Reference
Bromopyridines	Two-electron reduction	684
Chloropyridines	Two-electron reduction	684
Halopyrimidines	Complicated mechanisms conducent to dehalogenation and further reduction	685
Iodonitrobenzenes	Two one-electron waves in DMF	681, 682
m-Chloronitrobenzene	No halide loss	681
p-Fluoronitrobenzene	No halide loss	681
m-Dibromobenzene	Two two-electron waves corresponding to a stepwise reduction to benzene	686
o-Dibromobenzene	One four-electron reduction	686
Iodobenzenes	One-electron reduction, rate-determining	687, 688
o-Bromochlorobenzene	Benzyne formation	686
Iodobenzoic acids	pH-dependent reduction	689
Iodoanilines	pH-dependent reduction	689
p-Cl-, *m*-Br- and *p*-Bromobenzophenone	Three one-electron reduction steps to benzophenone in DMF	690

6. Vinyl halides

Similarly to aryl halides these compounds are more difficult to reduce than alkyl halides. *trans*-1,2-Dihaloethylenes may undergo acetylene-forming elimination, (reaction 227) while the *cis* isomer undergoes a



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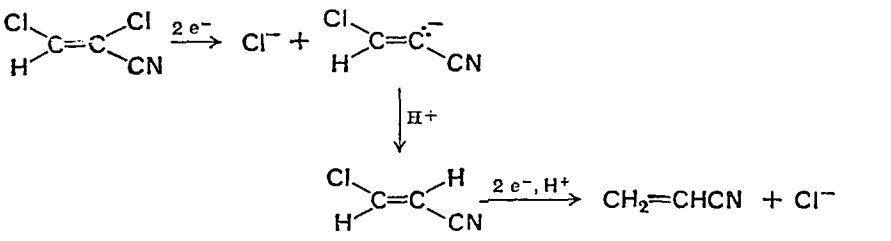


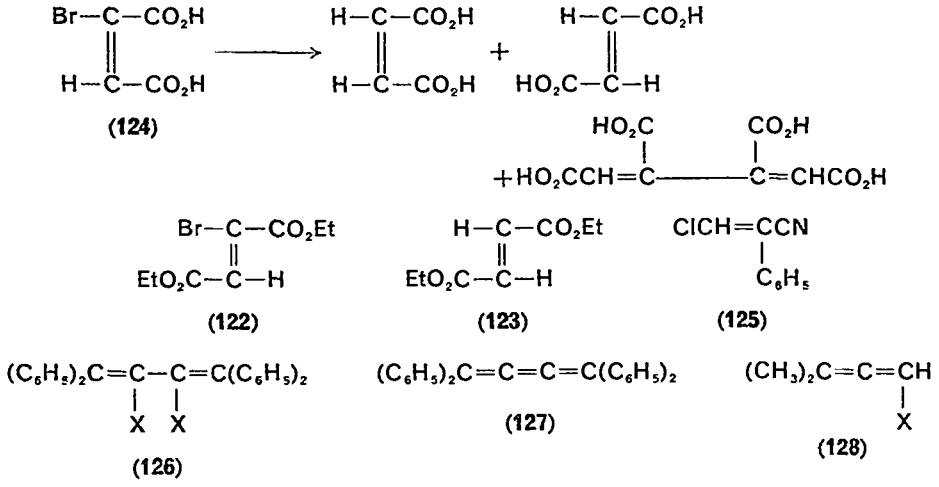
(228)

two-step halide reduction (reaction 228)[691]. Some examples are summarized in Table 25.

TABLE 25. Polarographic reduction of some vinyl halides

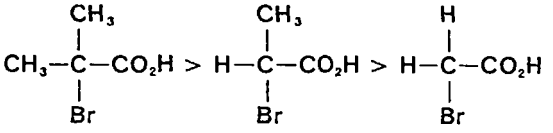
Compound	Remarks	Reference
Diethyl bromofumarate (122)	Two-electron reduction to diethyl fumarate (123)	692
Bromomaleic acid (124)[a]		692
Dihalo ethylenes	Two-electron reduction to an ethylene	693, 694
3-Chloro-2-phenylacrylonitrile (125)	Two two-electron steps reduction to 2-phenylpropionitrile	695
Dibromoolefins	Two-electron reduction to acetylenes (cf. reaction 227)	691
1,1,4,4-Tetraphenyl-2,3-dihalobutadienes (126)	Two-electron reduction to a cumulene (127)	696, 697
Triphenylbromoethylene	Two-electron reduction in dimethyl formamide. The resulting triphenylethylene may be reduced further to triphenylethane	698
1-Chloro- and 1-bromo-3-methyl-1,2-butadiene (128)	Various mechanisms, depending on the presence or absence of protonic donors	644, 699
Pesticides derived from hexachlorocyclopentadiene	Several products are obtained	667

[a] Bromomaleic acid and its esters lose configuration partially and undergo dimerization:



7. α-Halo acids

The ease of reduction of three α-bromo acids was found to be as shown in relation (229)[700, 701].



(229)

The $E_{\frac{1}{2}}$ value for organic halides is generally pH independent[702, 703]. However, compounds containing groups affected by pH near the halogen, such as α-bromoalkanoic acids[704], iodoacetic acid, iodobenzoic acids[705] and iodoanilines[689], show complications. At low pH values the protonated form is reduced in a pH-independent process, and the same occurs, at another $E_{\frac{1}{2}}$ value, for the deprotonated form at high pH values. At intermediate pH values, not much larger than the pK_a of the acid, the mechanism is such that the transition state seems to be that of the protonated form of the substrate, as shown in reaction (230).

(230)

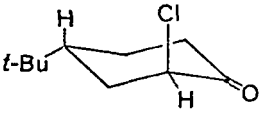
The reduction of optically active 2-phenyl-2-chloropropionic acid yielded an optically active product of inverted configuration[706].

8. Activated halides

Halogen atoms α to carbonyl, nitro or nitroso groups are very easily reduced in two-electron steps. The reduction of α-halo ketones is pH independent and resembles S_N2 displacements[649]. Some examples of reductions of these compounds are summarized in Table 26.

(129)

(130)



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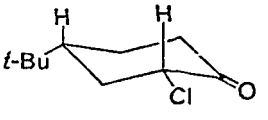

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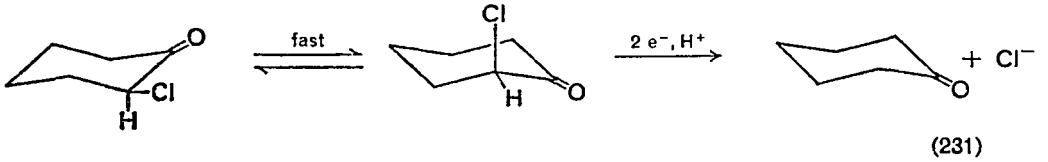

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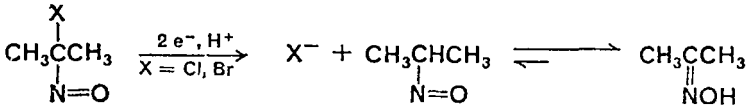

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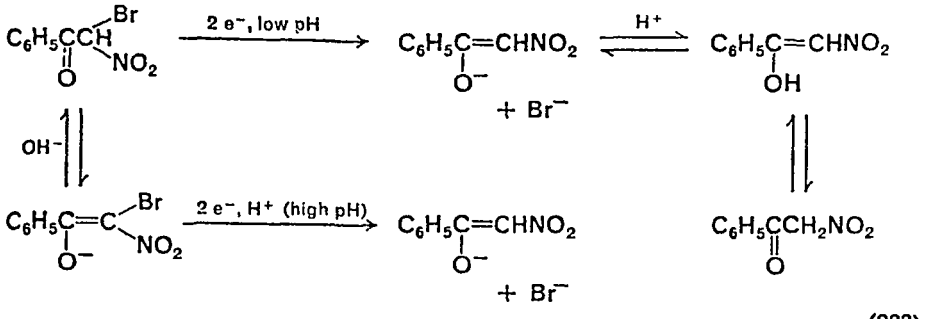


(233)

TABLE 26. Polarographic reduction of some activated organic halides

Compound	Remarks	Reference
Phenacyl bromide (**129**)	Two two-electron reduction steps, the second one corresponding to acetophenone reduction	709
α-Haloacetones	Some contradictory results were found on reducing di- and mono-haloacetones	707
α-Bromocamphor (**130**)	Two-electron reduction to camphor	674
2-Chlorocyclohexanone	Two-electron reduction (reaction 231)	708
Pentabromoacetone	Three two-electron waves, apparently due to reduction of dibromoacetic acid and bromoform (see Table 22) into which pentabromoacetone is hydrolysed	710
trans-4-*t*-Butyl-2-chlorocyclohexanone (**131**)	Two-electron reduction to the ketone. Reduction easier than that of **132** with $E_{\frac{1}{2}}$ equal to that of 2-chlorocyclohexanone (reaction 231)	711
cis-4-*t*-Butyl-2-chlorocyclohexanone (**132**)	Two-electron reduction to the ketone; more difficult than reduction of **131**	711
α-Halo aldehydes	Two reduction waves to the alcohol	712
2-Halo-2-nitropropanes	Two-electron reduction to 2-nitropropane	713
2-Halo-2-nitrosopropanes	Two-electron reduction according to reaction (232)	713
α-Bromo-α-nitroacetophenone	Two-electron reduction according to reaction (233)	714

C. Mass Spectrometry

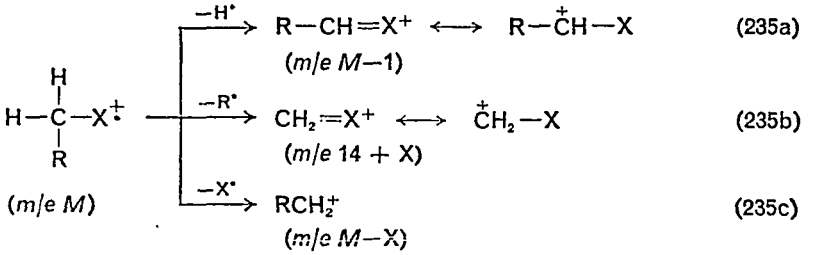
In section II. E the application of mass spectrometry to elementary analysis of halogen compounds was considered. In the following section some features of the degradation patterns of organic molecules will be correlated with their structure. The *molecular peak* is the most abundant peak corresponding to the radical ion obtained from a molecule M, according to reaction (234) and its *m/e* value is designated as *M*. The most abundant peak in a mass spectrum is called the *base peak*, and is given an arbitrary intensity of 100%.

$$M + e^- \longrightarrow M^{+\bullet} + 2\,e^- \qquad (234)$$

1. Alkyl halides

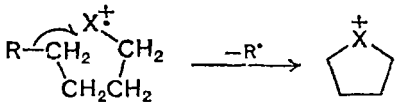
For terminal halides R—X the abundance of the molecular peak decreases in the order: R—H > R—I > R—Br > R—Cl > R—F, in accordance with the ionization potentials that decrease in the reverse order: R—I < ... < R—F[715]. The abundance of the X^+ ion decreasing in the order $I^+ > Br^+ > Cl^+ > F^+$, is in accord with the electron affinity of these elements[716]. When R increases the molecular ion $[R—X]^{+\bullet}$ tends to disappear[717].

The molecular ion of alkyl halides can undergo α-cleavage of two types (reactions 235a, b) and halogen radical loss (reaction 235c). α-Cleavages are most favoured with fluorides and their importance decreases in the order F > Cl > Br > I. On the other hand, halogen radical loss is usually preferred over α-cleavage and its importance increases with the atomic number of the halogen[717–719].



(235a) (235b) (235c)

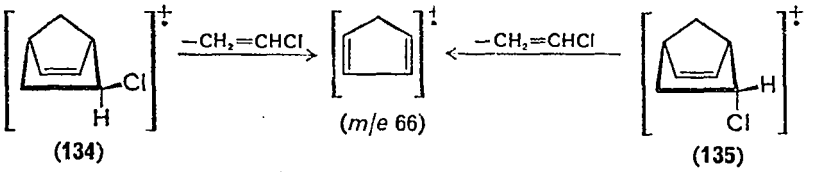
In *n*-alkyl chlorides and bromides (but not iodides) where the alkyl is sufficiently large (*n*-hexyl and upwards) one of the most prominent peaks (sometimes the base peak) corresponds to ion **133** arising as shown in reaction (236)[717,719]. Branching at the α-site drastically reduces the intensity of this peak and increases that of the *M*−HX peak[718].



(133, *m/e* 56 + X) (236)

Among the lower secondary alkyl chlorides the tendency to lose Cl• is nearly equal to that of losing HCl, while in similar tertiary alkyl chlorides the tendency to lose Cl• is prevalent. The general tendency in alkyl fluorides and chlorides is to lose hydrogen halide. This need not be, however, a 1,2-elimination[720]. The ions obtained from such eliminations show the homologous series of fractionations, similar to that of the corresponding alkanes[719].

The decomposition pattern of an alkyl halide depends on the rest of the molecule. For example, the molecular ions of both the *exo* (**134**) and *endo* (**135**) isomers of 5-chloronorbornene undergo a retro-Diels–Alder reaction (237)[721]. The *exo* (**136**) and *endo* (**137**) isomers of norbornyl bromide, on the other hand, undergo typical alkyl halide fragmentations (reaction 238)[722].



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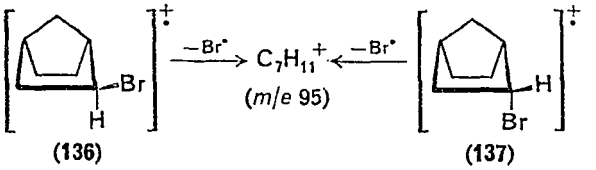

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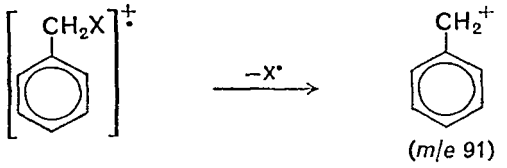

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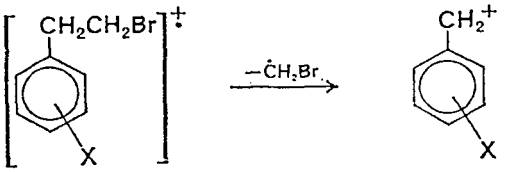
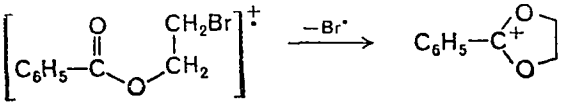


(240)

The benzyl cation (or an isomer) is produced from benzyl halides by halogen elimination (reaction 239)[723,724]. The analogous cation is also produced from side-chain halogenated alkyl benzenes as shown in reaction (240)[892].

The loss of bromine in 2-bromoethyl benzoates involves neighbouring group participation of the carboxylic carbonyl as was shown by scrambling of the labelled oxygen (reaction 241)[725].



(241)

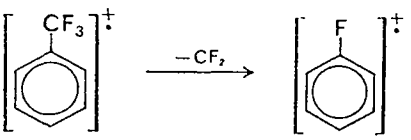
2. Aromatic halides

In aryl halides the molecular peak is more abundant than in alkyl halides. The loss of a halogen atom is an important process[723]. The C—F bond in aromatic fluorides is also more stable than in other types of fluorides[723,726].

Degradation patterns are usually complicated by rearrangements occurring in the aromatic ring prior to degradation. For example, halogenated phenylacetylenes undergo total randomization of the acetylenic and aromatic hydrogens prior to C_2H_2 elimination[727], and variously substituted chlorobenzenes undergo carbon scrambling before $Cl^{\bullet}$ loss[728].

3. Polyhalogenated compounds

Polyhalogenated, and in particular perhalogenated, compounds tend to undergo the so-called 'random rearrangements' during the degradation of the molecular ion, and this makes it difficult to correlate spectra with structure[729], e.g. in fluorine compounds CF_3^+ (*m/e* 69) is a very intense ion; however, the trifluoromethyl moiety need not be present in the original molecule; the ion $C_3Br_2F_3^+$ (*m/e* 232, 234, 236) appears in the spectrum of $BrF_2CCF{=}CFCF_2Br$; some fragmentations may cause confusion as to the structure of the parent molecule, as shown in reaction (242)[30,730] for α,α,α-trifluorotoluene, while fluorinated benzenes lose $\dot{C}F_3$ or $\dot{C}HF_2$[731].



(242)

The most abundant peak of perfluoroparaffins is CF_3^+ (*m/e* 69) which is also strong in other compounds containing the CF_3 group. The CF^+ ion

(*m/e* 31) is also prominent, especially in the case of unsaturated fluorocarbons. The molecular peak of fluorocarbons and other perhalogenated compounds is usually small; however, the $M-F$ ion is prominent in small fluorocarbon molecules[732]. The $M-CF_3$ peak is also important in compounds containing the CF_3 group[732]. The presence of unsaturations such as double or triple bonds in a fluorocarbon molecule tends to stabilize the molecular ion and to give stronger molecular peaks. The mass spectra of fluorocarbons, perfluoro fatty acids and fluorinated ketones have been reviewed[733].

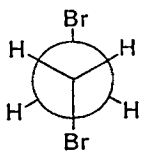
As with paraffins, in the case of fluorocarbons the series of ions of formula C_nF_{2n+1} is such that each of these ions is the most abundant among those containing n carbon atoms. The only exception is the $M-CF_3$ peak, of formula C_nF_{2n-1}. A common impurity accompanying perfluorocompounds is SiF_4 arising from traces of HF or F_2 that reacted with glass and this gives rise to the ion SiF_3^+ (*m/e* 85)[734]. Fluorocarbon compounds can be used for calibration of the mass scale of mass spectrometers[734].

The mass spectra of polychlorinated ferrocenes have been discussed[122].

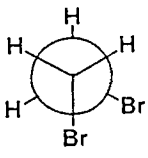
D. Dipole Moments

The negative bond moments of the C–halogen bonds (C—F 1·51, C—Cl 1·56, C—Br 1·48, C—I 1·29) and other groups can be used in estimating the dipole moment of a structure[735]. Such estimates may be helpful for verifying structural assignments after the dipole moment has been determined experimentally[3,4,735] and a few examples of such applications follow.

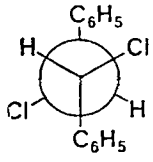
The dipole moment of 1,2-dibromoethane ($\sim$1D)[736] is indicative that this compound does not exist exclusively in the *anti* conformation (**138**) or in a state of free rotation. This, together with additional spectroscopic evidence, was proof of the existence of the *gauche* (**139**) conformation[3].



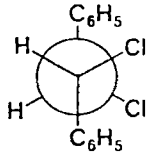
(138)



(139)



(140)



(141)

The most stable comformations of the two diasteroisomers of stilbene dichloride, namely those where the phenyl groups are *anti* to each other, should have dipole moments nil for the *meso* form (**140**) and a large one for

the *dl* form (**141**). The actual values found for two such components were 1·27 and 2·75D and could therefore be assigned the *meso* and *dl* configurations respectively[737].

Compounds of formula CX_4, where X is a non-linear, freely rotating substituent will have a dipole moment of $2\mu_1$ where μ_1 is the component of the dipole moment of the group in the direction of the rotation axis; for example, methyl orthocarbonate, $C(OCH_3)_4$, μ 0·8D, and pentaerythrityl nitrate, $C(CH_2ONO_2)_4$, μ 2·0D. Pentaerythrityl halides [$C(CH_2X)_4$, X = Cl, Br, I] have, on the other hand, a nil μ value, which was interpreted as the absence of free rotation in these compounds[738,739].

Vinylidene dihalides of *cis* configuration show high dipole moments while those of *trans* configuration are either nil or low, depending on the other substituents. For example for *cis*-CHX=CHX the dipole moments are: X = Cl, 1·89D; X = Br, 1·35D; X = I, 0·75D[735].

When estimating dipole moments of vinyl and aryl halides the mesomeric release of the halogen in the direction opposite to the C–halogen bond dipole has to be considered[735]. Correlations between dipole moments and properties of the OH groups were observed in halogenated phenols[740]. The conformations of 4-halocyclohexanones were studied in parallel by dipole moment measurements and n.m.r. spectroscopy[741].

E. Ultraviolet Spectra

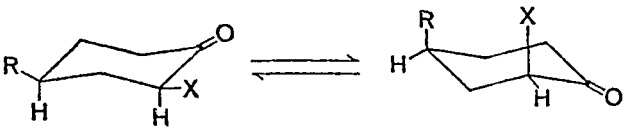
Introduction of an α-substituent in a cyclohexanone system causes a wavelength shift in the 280 nm absorption band of cyclohexanone, as shown in Table 27. By this method it was found that the equilibrium of

TABLE 27. Effects of α-substituents on the 280 nm absorption band of cyclohexanone[742, 743]

α-Substituent	$\Delta\lambda_{max}$(nm)	
	Axial	Equatorial
F[741]	~16	~0
Cl	22	−7
Br	28	−5
OH	17	−12
O_2CCH_3	10	−5

α-halocyclohexanone was displaced to the axial halogen conformation (**142b**, R = H) but the equatorial halogen conformation (**142a**, R = CH_3)

was preferred if a methyl group *cis* to the halogen was introduced in position 4 (reaction 243)[742].



(142a) (142b) (243)

F. Optical Properties of Asymmetric Compounds

1. Optical rotation

Measurements of optical rotations both at a fixed wavelength (given as specific rotations $[\alpha]_D$ or molecular rotations $[M]_D$)* or over a wavelength range (o.r.d. curves, $[M]$ vs. λ) have been applied in the elucidation of the absolute configuration of organic halides. Indeed, these compounds are especially amenable to successful predictions owing to the high atomic refractions of the halogens (see Table 28), a property on which optical

TABLE 28. Atomic refraction of substituents[745]

Substituent	Atomic refraction[a]	Substituent	Atomic refraction[a]
I	13·954	CO_2H	3·379 (4·680)
Br	8·741	CH_3	2·591
SH	7·729	NH_2	2·282
Cl	5·844	OH	1·518
C≡C	3·580 (7·159)	H	1·028
C≡N	3·580 (5·459)	D	1·004
C=C	3·379 (6·757)	F	0·81
C_6H_5	3·379		

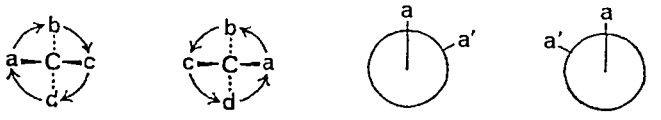
[a] The values for polyatomic groups are given as measured at their point of attachment. The refractions of a group as a whole are given in parentheses.

rotations are strongly dependent. It should be noticed in Table 28 that I, Br and Cl are among the strongest groups while F is the weakest.

Brewster developed a series of useful rules for correlating the absolute configuration of a compound with its optical rotation. A molecule with

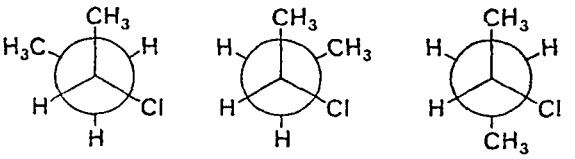
* The $[\alpha]_D$ values are optical rotations per unit concentration expressed in a g/l basis, under a certain experimental set up; $[M]_D$ values are defined as $[\alpha]_D \times$ molecular weight according to certain authors or $[\alpha]_D \times$ molecular weight/100 according to others[745]. The $[M]$ values of o.r.d. are calculated per mole/l unit.

one asymmetric centre, represented as Cabcd, where the atomic refractions of the substituents stand in the order a>b>c>d will be dextrorotatory or levorotatory, according to whether it can be superimposed on formula **143** or **144** respectively. This approach is valid when the groups attached to the asymmetric carbon do not impose a preferred conformation on the molecule, as was shown in a number of cases[746].



dextrorotation (143) levorotation (144) (+) (145) (−) (146)

When conformations are distinguishable the molecular rotation of a conformer is determined by the sum of partial terms over all the *gauche* pairs that can be defined. Each term has the form shown in the empirical equation (244), where R_a and $R_{a'}$ are the atomic refractions of groups a and a', and the sign is determined by whether the conformation in a Newman projection fits **145** or **146**. Brewster's rules also help to predict the most important conformation attained by a compound[747]. Thus, for example[748], 2-chlorobutane can be in three conformations (**147–149**), of



(147) (148) (149)

which **148**, with a methyl staggered between methyl and chlorine, should

$$\Delta[M] = \pm 160\sqrt{R_a R_{a'}} \tag{244}$$

be unimportant. The contributions of **147** and **149** are given in equations (245) and (246) respectively. The qualitative prediction of nearly equal importance for conformers **147** and **149** with $[M] = \frac{1}{2}(170-60°) = 55°$ is supported by the experimental value of 36°.

$$[M] = 160(\sqrt{R_{Me}}R_H - \sqrt{R_H}R_{Cl} + \sqrt{R_{Cl}}R_H - R_H + \sqrt{R_H}R_{Me} - R_{Me}) = -60 \tag{245}$$

$$[M] = 160(\sqrt{R_{Me}}R_H - \sqrt{R_H}R_{Cl} + \sqrt{R_{Cl}}R_{Me} - \sqrt{R_{Me}}R_H + R_H - \sqrt{R_H}R_{Me}) = 170 \tag{246}$$

The same principles can be applied to compounds with more than four atoms in a straight chain, to saturated cyclic compounds[749] and to endocyclic unsaturated compounds[750].

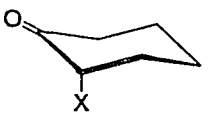
The optical rotation of a compound at the sodium D line is only one point of the dispersion curve, and it may be situated in a long-wave tail of rotation sign opposite to that of the peak rotations. In such cases Brewster's rules fail. For example[751], of the three isomers of α-(iodophenoxy)propionic acid of the same absolute configuration, the *meta* and *para* isomers have their optical rotation of sign opposite to that of the *ortho* isomer.

A different approach is now being developed in which the $[M]_D$ value is correlated empirically with the bond refractions of the groups surrounding the asymmetric carbon. Linear equations such as (247) are obtained in which a and b vary with the carbon skeleton of the compound[752].

$$[M]_D = a\sum R_D + b \tag{247}$$

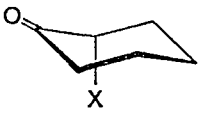
2. Optical rotatory dispersion

The shifts shown in Table 27 for the u.v. absorption peaks of cyclohexanones have a similar counterpart for the peaks and troughs of o.r.d. curves[753]. The amplitude of the peak is nearly doubled for an α-axial substituent and the sign of the Cotton effect can be inverted by introducing an α-halo group. The latter phenomenon depends on whether the α-axial haloketone attains one or other of the configurations **150** or **151**[754,755]. α-Fluoroketones do not exhibit this effect because of the low atomic refraction of fluorine. Deviations from these rules due to boat conformations are discussed elsewhere[4].



Positive
Cotton effect

(150)



Negative
Cotton effect

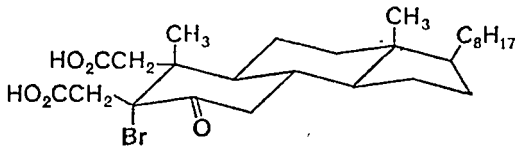
(151)

Various applications of the α-haloketone rules have been made:

(i) If on α-halogenation the Cotton effect is reversed the halogen is axial. If the sign is not reversed but the amplitude has increased and the peak maximum is bathochromically shifted the halogen is also axial[756].

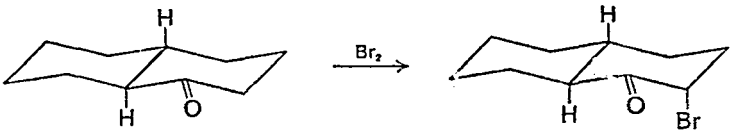
(ii) If an α-halogen is known to be axial and the configuration of the rest of the molecule is known, then the position at which the halogen is

inserted can be known from the sign of the Cotton effect. For example[756], the brominated product of 2,3-*seco*-6-ketocholestane-2,3-dioic acid has a negative Cotton effect and thus gives the structure **152** with the bromine at position 5 (compare with **151**) and not at the alternative position 7.



(152)

(iii) If both location and conformation of the halogen are known the absolute configuration of the haloketone and ketone may be deduced. For example[756,757], *trans*-decalone (**153**) yields 2-bromo-*trans*-decalone (**154**) with a strong positive Cotton effect, thus showing that the absolute configuration of **153** and **154** are as depicted in reaction (248) and not their enantiomorphs.



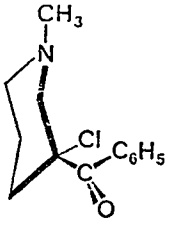
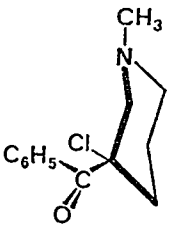
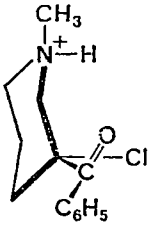
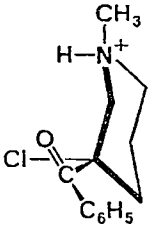
(248)

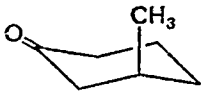
(153) **(154)**

The structure involving the keto group need not be a rigid one if further information or assumptions are introduced. Thus, for example[758], if it is assumed that the electron-rich centres N and O of an amino and a keto group in the same molecule will repel each other while the N^+ of an ammonium group will attract the ketonic O, then the Cotton effect of 3-benzoyl-3-chloro-1-methylpiperidine in octane and aqueous acid solvent can be correlated with the absolute configuration, as shown in Table 29.

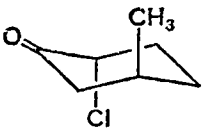
(iv) If the place of substitution and the configuration of an axial α-haloketone are known then the conformation may be deduced. For example[756,759], a 2-chloro-5-methyl-cyclohexanone was isolated from the chlorination of (+)-3-methylcyclohexanone (**155**⇌**156**). The product has one of two possible configurations, each of which may have two stable conformations, as depicted by the pairs **157**⇌**158** (*trans*) and **159**⇌**160** (*cis*). In octane solution the α-chloro is axial and the Cotton effect is negative, pointing to **157** as the preferred conformation with a *trans* configuration. In methanol the Cotton effect becomes positive, pointing to **158** as the preferred conformation. These solvent effects on the preferred conformation have been observed also in 2-bromocyclohexanone[760].

TABLE 29. Cotton effects for the two enantiomorphs of 3-benzoyl-3-chloro-1-methylpiperidine[758]

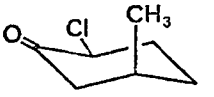
Solvent	N—O interaction	Conformations and sign of Cotton effect	
Octane	Repulsion		
		Negative (cf. **151**)	Positive (cf. **150**)
Aqueous acid	Attraction		
		Positive (cf. **150**)	Negative (cf. **151**)



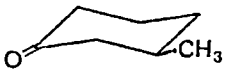
(155)



(157)

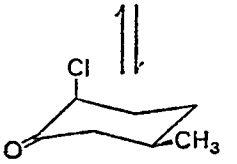


(159)



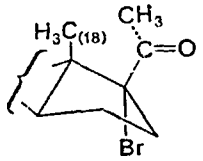
(156)

(158)

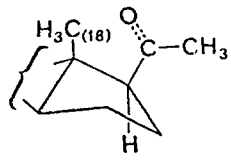


(160)

Also open-chain ketones can sometimes assume a preferred conformation. Thus for example[753], in 17α-bromo-3β-acetoxy-5α-pregnan-20-one the Cotton effect is negative pointing to **161a** with the carbonyl directed away from $C_{(18)}$ as the preferred conformation, while the non-halogenated steroid has a positive Cotton effect and conformation **161b**.



(161a)



(161b)

G. *Infrared Spectra*

A large number of works have appeared dealing with assignments and correlations of the various vibrational modes in organic halides, and these have been summarized to various extents[27, 29, 761–763]. Some of the correlations found are given in Table 30 and the sections below deal briefly with

TABLE 30. Examples of correlations found for the infrared spectrum of organic halides

Type of compound[a]	Correlation[b]	Reference
1 CH_3X	(a) ν(C—X) and force constant of H—X stretching	763
	(b) ν(C—X) and C—X distance	763
	(c) ν^2(C—X) and electronegativity of X	764
	(d) See items 4(b) and 6(a)	
2 $X—Hal_n$	(a) Vibrational frequencies of XBr_n to XCl_n and of XI_n to XBr_n, where X is a polyvalent element	765
3 $CH_2=CHX$	(a) $\nu(CH_2=$, wagging) and various σ substituent constants	766
	(b) $\nu(CH_2=$, wagging) and ν(CH, out of plane) of $XC\equiv CH$ compounds	767
4 $HC\equiv CX$[c]	(a) See item 3(b)	
	(b) ν(C≡C) and C—X force constant in $CH_3—X$	768
5 $N\equiv C—C_6H_4—X$	(a) C≡N stretching intensity and X Hammett σ constants	769, 770
6 $N\equiv C—X$[c]	(a) ν(C≡N) and C—X force constant in $CH_3—X$	768
7 $HO—C_6H_4—X$	(a) ν(OH) and X Hammett σ constants	771–776
	(b) ν(OH) and pK_a	771–776
	(c) OH stretching intensity and X Hammett σ constants	771–776
	(d) OH stretching intensity and pK_a	771–776

TABLE 30 (*cont.*)

Type of compound[a]	Correlation[b]	Reference
8 $HO_2C-C_6H_4-X$	(a) ν(OH, non-associated) in non-aqueous solvents and pK_a	777, 778
9 HO_2C-R_X	(a) ν(OH), non-associated) in non-aqueous solvents and pK_a	778, 779
10 XCH_2CH_2Y; X,Y = Br, Cl, F	(a) ν(C—X) and dielectric constant of solvent	780
11 XCH_2CH_2CN	(a) ν(C—X) and dielectric constant of solvent	780
12 $X_2C=CX_2$; X = F, Cl, Br, I	(a) ν(CX_2, bending) and changes in electronic and geometric structure of the molecule	781
13 $H_2C=CX_2$; X = F, Cl, Br	(a) As in item 12	

[a] X are various substituents, halogens included. R_X are halogenated aliphatic radicals.

[b] The correlations are usually linear, ν's are stretching frequencies, unless indicated otherwise.

[c] See Table 31.

the various types of compounds containing C–halogen groups. The C–halogen vibrations are rather unimportant but the group exerts a marked influence on nearly all the vibrational modes of other nearby features of the molecule.

I. C–halogen vibrations

The C—I bands occur at 500–600 cm^{-1}, those of C—Br in solution near 560 and 650 cm^{-1}, C—Cl at 600–800 cm^{-1} (usually in a more restricted region, say 700–750 cm^{-1}) and C—F in the 1000–1400 cm^{-1} region (in simple compounds a very strong band appears in the 1000–1100 cm^{-1} region)[29].

In cyclohexane systems axial halogen has lower frequency than equatorial halogen, e.g. axial Cl 688 cm^{-1}, equatorial Cl 742 cm^{-1}, axial Br 550–590 cm^{-1} and equatorial Br 700–750 cm^{-1} [29]. The C_2F_5 group presents bands at 1325–1365 and 730–745 cm^{-1} [29]. Halogenated aromatic compounds present characteristic substitution patterns in the 1100 cm^{-1} region[782]. Two rotamers of 4-halo-1-butenes were recognized from the analysis of C–halogen stretching frequencies[783].

2. Alkyl halides

The C—H stretching frequencies are raised by fluoro substituents[29], e.g. for R_FCHF_2 ν(C—H) 3000 cm^{-1} (R_F is a perfluoroalkyl group). The symmetrical deformation frequencies of CH_3—X are raised for F (1475 cm^{-1}) and lowered for Cl (1355 cm^{-1}), Br (1305 cm^{-1}) and I (1252 cm^{-1}) relative to a hydrocarbon (1370–1380 cm^{-1})[763].

3. Vinylic halides

Table 31 shows the stretching frequencies of the ethylenic double bond variously substituted with halogens. For all series of analogous compounds the frequencies are in the order F > Cl > Br > I, usually with F much higher than H and Cl approximately the same as H. The C=C twisting frequencies do not vary with the halogen but halogenated ethylenes differ from non-halogenated ones (Table 31). The CH_2=, wagging, on the contrary, shows no effect of halogen, except for fluorine (Table 31).

Perfluorination has a strong influence on the C=C stretching frequency, even when F is not directly attached to the double bond, affording frequency increases, as shown in Table 32.

4. Halogenated ketones and aldehydes

Two C=O stretching bands are observed on introducing one α-halogen into an open-chain ketone, one in the original frequency and one at a raised frequency. A second *gem*-halogen does not change frequencies but changes the intensity ratio of the bands while a third *gem*-halogen eliminates the lower frequency band. If halogen atoms are introduced in the α'-position a further raised frequency band appears. The higher frequency bands correspond to conformations where the halogen and the carbonyl are *eclipsed* while the lower bands correspond to *gauche* conformations. For example, in α-chlorocyclohexanones the equatorial form has a higher C=O frequency than the axial form, and a parallel effect is observed for the C—Cl stretching frequencies[785, 786].

Perfluorination of one or both alkyl radicals attached to a carbonyl group causes a substantial rise in the C=O stretching frequency, e.g.,

$$RC(=O)R' \text{ (1700–1725 cm}^{-1}\text{)}^{762} < R_FC(=O)R' \text{ (1770 cm}^{-1}\text{)}^{29}$$

$$< R_FC(=O)R'_F \text{ (1785 cm}^{-1}\text{)}^{29, 787, 788}$$

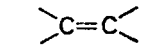
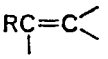
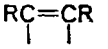
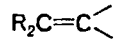
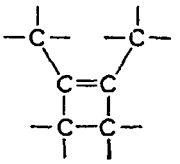
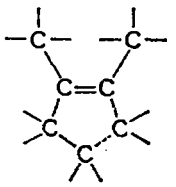
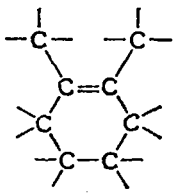
The carbonyl frequencies of pentane-2,4-dione (**162**) and 1,5-diphenylpentane-2,4-dione (**163**) do not change on halogenation of the central carbon, presumably because these compounds are both before and after

TABLE 31. Some characteristic vibration frequencies[a] of halogenated ethylenes (in cm^{-1})[763]

	$CH_2=CHX$			$CH_2=CX_2$	$CF_2=CHX$	$CF_2=CFX$	$CF_2=CX_2$
X	Stretching	Twisting	Wagging	Stretching	Stretching	Stretching	Stretching
F	1650	925	863	1728	1788	1872[b]	1872[b]
Cl	1610	938	894	1620	1750	1792	1747
Br	1605	936	898	1593	1742	1788	1718
I	1593	943	905				
H	1623[b]			1623[b]	1728	1788	1728
CH_3	1647	983	908				

[a] Stretching frequencies are those of C=C. ν(C=C) and ν(C—Hal) for many tetrahaloethylenes can be found in reference 784.
[b] Determined by Raman spectroscopy.

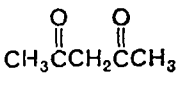
TABLE 32. C=C stretching frequencies (cm^{-1}) of olefins and their perfluoro analogues[29, 763]

Structure[a]	Perhydrogenated	Perfluorinated
	1623[b]	1872[b]
	1640–1645	1800
	1635–1675	1735
	1640–1660	1750
	1685	1789
	1686	1754
	1685	1740

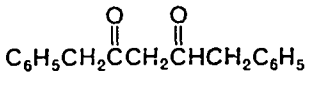
[a] The empty bonds are to be filled with H or F atoms and R represents accordingly an alkyl or a perfluoroalkyl radical.
[b] Determined by Raman spectroscopy.

halogenation in the enolic form (**164**), with the C=O and C–halogen bonds pointing away from each other[763].

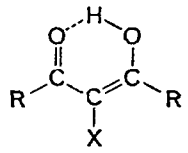
α-Halogenation of aldehydes raises the C=O stretching frequencies but no double bands appear due to rotational isomers[789], as was the case with α-haloketones. This may be due to free rotation in α-haloaldehydes which



(162)



(163)

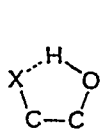


(164)

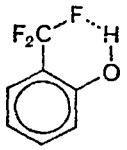
disappears in α-haloketones or α-haloacyl halides (e.g. $CF_3C(=O)F$)[790]. Evidence for rotational isomerism in dihaloacetaldehydes was found from i.r. and Raman spectra[791] and from n.m.r. spectra[792].

5. Halogenated alcohols and phenols

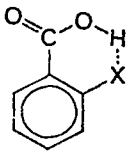
β-Halo alcohols and *o*-halophenols present two bands assigned to the O—H stretching vibration: the higher frequency one corresponds to the free OH and the one at lower frequency to the hydrogen-bonded OH, as depicted in **165**[763, 793–795]. The $\Delta\nu$ value observed for the two bands increases from nearly 0 for F to 95 cm^{-1} for I. Most studies with fluoro compounds involve a five-membered ring formation; however, if a six-membered ring is formed, as in *o*-trifluoromethylphenol (**166**), a displacement of 18 cm^{-1} is observed in isooctane[796]. The proportion of hydrogen-bonded OH is the largest for F and decreases gradually with the atomic number of the halogen. For example, 2-chloroethanol presents O—H stretching bands at 3365 cm^{-1} of the *gauche*, hydrogen-bonded rotamer and at 3500 cm^{-1} of the *trans*, free OH rotamer. The presence of a non-hydrogen-bonded *gauche* rotamer in relatively low concentrations could be also recognized[797]. Perfluoroalkyl carbinols (R_FCH_2OH) show the O—H stretching band at frequencies as low as 3300 cm^{-1} [29]. See also Table 30.



(165)



(166)



(167)

6. Halogenated carboxylic acids and derivatives

a. Free carboxyl groups. Under ordinary resolution, halogenated carboxylic acids show only one C=O stretching band for the monomeric form and one for the dimeric form, both of which increase in frequency with increasing halogenation. α-Chloro fatty acids have the C=O band at

1720–1740 cm^{-1} [798]. A study of fluoroacetic acid with high resolution showed five C=O stretching bands, two of monomeric rotamers and three of dimeric rotamers[799,800]. Apparently no hydrogen bonding of the type depicted in **167** occurs in *o*-halobenzoic acids[777,778]. Perfluoro carboxylic acids present their C=O stretching frequencies at 1775 cm^{-1} while the ordinary saturated fatty acids have this band at 1700–1725 cm^{-1} [29]. See also Table 30.

b. Carboxylates. The carboxylate anion has two stretching frequencies (ν_{sym}, ν_{as}) which do not vary much with unsubstituted radicals, be they alkyl, aryl or vinyl. However, with other substituents big variations are observed[801]. The ν_{as} frequencies follow the same order of increase as that occurring in the carbonyl stretching, although the displacement in carbonyl compounds is larger. The ν_{sym} frequencies are always lower than ν_{as} and their order does not parallel that of ν_{as}. The ν_{as} and ν_{sym} frequencies of $X—CO_2^-$ are ordered as shown in relations (249) and (250) respectively.

$$\left.\begin{aligned} t\text{-Bu}\,(1551\ cm^{-1}) < Et < Me\,(1583\ cm^{-1}) = CH_2I < CH_2Br < CH_2Cl \\ = CH_2CN < CHBr_2 < CH_2F < CHCl_2 \\ < CBr_3\,(1659\ cm^{-1}) < CCl_3 < CF_3\,(1689\ cm^{-1}) \end{aligned}\right\} \quad (249)$$

$$\left.\begin{aligned} CBr_3\,(1338, 1355\ cm^{-1}) < CCl_3 < CHBr_2 < CH_2CN < CH_2I < CHCl_2 \\ < CH_2Br < CH_2Cl < Me\,(1413\ cm^{-1}) < Et \\ < CF_3 \sim CH_2F\,(1448\ cm^{-1}) \end{aligned}\right\} \quad (250)$$

Again, as was the case with carbonyl compounds, the possibility of multiple bands arises when *cis* and *gauche* conformers exist, as is sometimes revealed in the Raman spectra of aqueous solutions[703].

c. Esters and thioesters. α-Halogenated esters behave similarly to α-halogenated ketones, with a high frequency C=O stretching band for the eclipsed C–halogen C=O bonds and a low frequency band for the *gauche* conformation. In α-fluoro esters the *cis* conformation is slightly more stable than the *gauche* form[802–805]. The *gauche* conformation of α-halo thioloesters ($XCH_2C(=O)SR$ or $X_2CHC(=O)SR$) has the highest C=O stretching frequencies[806].

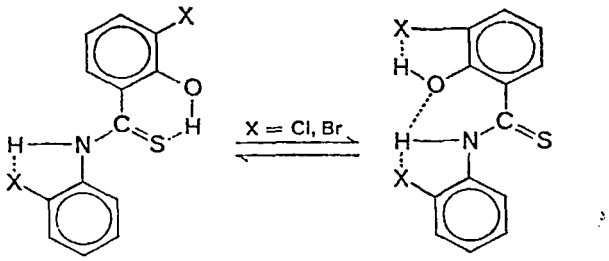
d. Acyl halides. α-Halogenation has the same effect in acyl chlorides as in ketones on the C=O stretching frequencies. The high frequency band moves to lower frequencies with increasing α-halogenation[789]. Mono- and dihaloacetyl chlorides were found to be in two rotational states in the vapour and liquid phases[807,808]. Further details on the i.r.

spectra of these compounds are treated elsewhere in the *Functional Groups* series[809].

e. Amides and thioamides. No change in the C=O stretching frequencies of an amide is observed on introducing one α-halogen. On second halogenation tertiary amides show two peaks corresponding to rotamers, whereas secondary amides show one peak only, at slightly raised frequencies, corresponding to an internally hydrogen-bonded species. In the series of halogenated acetamides α-chloroacetamide has the same C=O stretching frequency as acetamide, dichloroacetamide shows a frequency increase by 21 cm^{-1} and incipient doubling of band, and trichloroacetamide shows a further rising of 16 cm^{-1}[810].

The N—H stretching frequencies of fatty acid amides shift to lower frequencies and higher intensities on introduction of one α-halogen. On further halogenation the frequency rises although not to the original level and the intensity remains enhanced[811–813]. There is probably competition between intramolecular hydrogen bonding and the intermolecular type common in amides[814].

Two isomers can be isolated from the anilides of thiosalicylic acid when properly substituted by halogens, as shown in reaction (251). The influence of halogen on the various absorption bands is very strong (the *B*-band is typical of thioamides)[815].



(251)

ν(NH) 3325–3340 cm^{-1}	ν(NH) 3240–3300 cm^{-1}
ν(OH) 2600–2800 cm^{-1}	ν(OH) 3320–3430 cm^{-1}
ν(*B*) 1490–1536 cm^{-1}	ν(*B*) 1518–1555 cm^{-1}

7. Halogenated acetylenes and cyanogen halides

The C≡C and C≡N stretching frequencies in compounds X—C≡CH and X—C≡N (Table 33) undergo frequency shifts similar to those observed for vinyl halides, namely an increase for X=F and a gradual decrease for Cl to Br to I (see Table 31). The influence of CH_2–halogen groups is only slight (Table 33). See also Table 30.

TABLE 33. Stretching frequencies (cm^{-1}) of acetylenes and nitriles of formula X—C≡CH and X—C≡N[a]

X	≡C—H	C≡C	C≡N
F	3355[b]	2255[b]	2290
Cl	3340[b]	2110[b]	2214
Br	3325[b]	2085[b]	2200
I	3320[b]	2075[b]	2175
Me	3320	2130	2255
Et	3320	2121	
FCH_2	3322	2148	
$ClCH_2$	3315	2132	
$BrCH_2$	3315	2126	
ICH_2	3315	2128	

[a] From references 763, 768 and 816–818.
[b] In gaseous state.

8. Nitro-halo compounds

The N=O stretching frequencies (ν_{as}, ν_{sym}) in compounds of general formula $XCH_2—NO_2$ change according to the nature of X as shown in relation (252) for ν_{as} and relation (253) for ν_{sym}[819,820].

$$C \sim N < OR < Cl < F \quad (252)$$

$$N \sim OR < Cl < F < C \quad (253)$$

H. Nuclear Magnetic Resonance

This method is extremely useful for the structural elucidation of organic halides. The information available may be of various types:

(i) Variation of the chemical shift of protons in the neighbourhood of the halogen.

(ii) Splitting of bands due to asymmetry introduced on halogenation.

(iii) Spin–spin coupling of ^1H with nearby ^{19}F nuclei.

(iv) ^{19}F magnetic resonance spectra.

(v) Coupling constants of various magnetically active nuclei and satellite spectra.

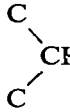
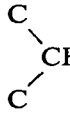
Many textbooks and reviews on this type of spectroscopy[27,821–825] and useful compilations of actual examples[826] have appeared.

1. Chemical shifts of ^1H

Table 34 summarizes the chemical shifts of alkyl protons with various types of halogen substitution. Geminal attachment of a proton and a

halogen atom causes a strong displacement to lower fields, which is weakened with distance.

TABLE 34. Typical chemical shifts (δ p.p.m.) of the protons in alkyl halides[a]

Proton types X =	F	Cl	Br	I
$CH_3—X$	4·25	3·05	2·70	2·15
$C—CH_2—X$	4·50	3·45	3·40	3·15
	4·80	4·05	4·10	4·25
$CH_3—C—X$	1·55	1·55	1·80	1·75
$C—CH_2—C—X$	1·85	1·80	1·85	1·80
	2·15	1·95	1·90	2·10

[a] From reference 27.

A useful method for estimating chemical shifts is the use of shielding constants. These are increments characteristic of each substituent group attached to a proton-bearing group to which a fixed chemical shift is empirically given. For example, the chemical shifts of $X—CH_2—Y$ can be calculated according to equation (254), where Z_X and Z_Y are the corresponding shielding constants taken from Table 35 [27,827]. The results are only a helpful approximation, correct to within ±0·5 p.p.m., and big deviations are sometimes obtained, as shown in the examples of Table 36.

TABLE 35. Shielding constants Z (p.p.m.) for various substituents in compounds of the type $X—CH_2—Y$ [27, 827]

Substituent	Z	Substituent	Z
$—C=C$	1·32	$—CF_2$	1·21
$—C\equiv C$	1·44	$—CF_3$	1·14
$—CH_3$	0·47	—Br	2·33
$—C_6H_5$	1·85	—Cl	2·53
		—I	1·82

TABLE 36. Examples of chemical shifts (δ p.p.m.) of methylene groups

Compound	Calculated[a]	Observed[b]
$CH_2=CHCH_2Cl$	4·08	4·08
$CH_2=CHCH_2Br$	3·88	3·93
$CH_2=CHCH_2I$	3·37	3·87
CH_3CH_2Cl	3·23	3·57
CH_3CH_2Br	3·03	3·43
$CH_3CF_2CH_2Cl$	3·97	3·63

[a] From data in Table 35, according to equation (254).
[b] In chloroform solution, from reference 826.

$$\delta(CH_2) = 0{\cdot}23 + Z_X + Z_Y \tag{254}$$

Many interesting applications of the chemical shifts and coupling constants to the study of comformations in halogen compounds have appeared with increasing frequency in recent times (see for example references 785, 792, 828–832).

Shielding constants have also been proposed for the substituents attached to an ethylene centre, so that the chemical shift of each of the olefinic protons can be calculated according to equation (255)[833]. The Z values for various substituents appear in Table 37. These calculations are only approximate as is shown in Table 38, with an estimated standard

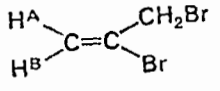
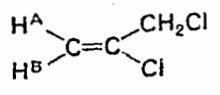
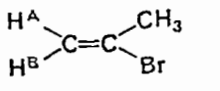
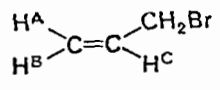
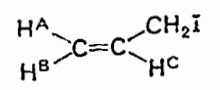
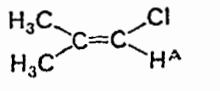
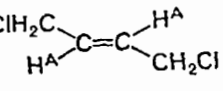
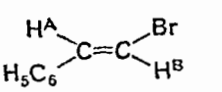
$$\delta(\text{olefinic H}) = 5{\cdot}28 + Z_{gem} + Z_{cis} + Z_{trans} \tag{255}$$

TABLE 37. Shielding constants (p.p.m.) for ethylene substituents, for the estimation of chemical shifts of ethylenic protons[833]

Substituent	Z_{gem}	Z_{cis}	Z_{trans}
—H	0	0	0
—alkyl	0·44	−0·26	−0·29
—alkyl (ring)[a]	0·71	−0·33	−0·30
—C=C	0·98	−0·04	−0·21
—C=C (conjugated further)	1·26	0·08	−0·01
—aryl	1·35	0·37	−0·10
—Cl	1·00	0·19	0·03
—Br	1·04	0·40	0·55
$-CH_2Cl$	0·72	0·12	0·07
$-CH_2Br$	0·72	0·12	0·07
$-CH_2I$	0·67	−0·02	−0·07

[a] The double bond is part of the ring.

TABLE 38. Examples of chemical shifts of olefinic protons (δ p.p.m.)

Compound	Proton	Calculated[a]	Observed[b]
	A	5·95	6·02[c]
	B	5·75	5·62[c]
	A	5·43	5·42
	B	5·54	5·59
	A	5·57	5·52[c]
	B	5·39	5·33[c]
	A	5·40	~5·32
	B	5·35	~5·12
	C	6·00	~6·05
	A	5·26	5·15
	B	5·21	5·05
	C	5·95	5·93
	A	5·73	5·77
	A	6·12	5·93
	A	7·03	7·10
	B	6·69	6·75

[a] From data in Table 37 according to equation (225).
[b] In chloroform solution, from reference 826.
[c] The assignments in reference 826 show proton B at a field lower than proton A, however, the assumptions underlying such assignments were probably erroneous (private communication by Dr. L. F. Johnson of Varian Associates).

deviation of ±0·15 p.p.m.[833]. Various effects observed in the n.m.r. spectra of halogenated olefins were reviewed elsewhere in this series[834]. Many studies have been concerned with the additivity correlations of substituent effects with chemical shifts and coupling constants in substituted aromatic compounds in general and halogenated aromatic compounds in particular[835–838].

2. Asymmetric halogenated centres

a. Small molecules. The introduction of halogen in aliphatic chains is frequently coincident with the formation of an asymmetric centre at the halogenated carbon. This makes the protons of an adjacent methylene group magnetically different, even in cases when free rotation is extant. If these methylene groups are not coupled with too many protons it is possible to assign with ease the various multiplets of the spectrum[822]. For example, (1,2-dibromoethyl)benzene (**168**), a molecule in which the α-carbon is asymmetric, shows in its spectrum a multiplet near δ 4 p.p.m., corresponding to the protons on the β-carbon, and a multiplet near δ 5 p.p.m., of the proton on the α-carbon. The schematic representation and assignments of these multiplets appear in Figure 12.

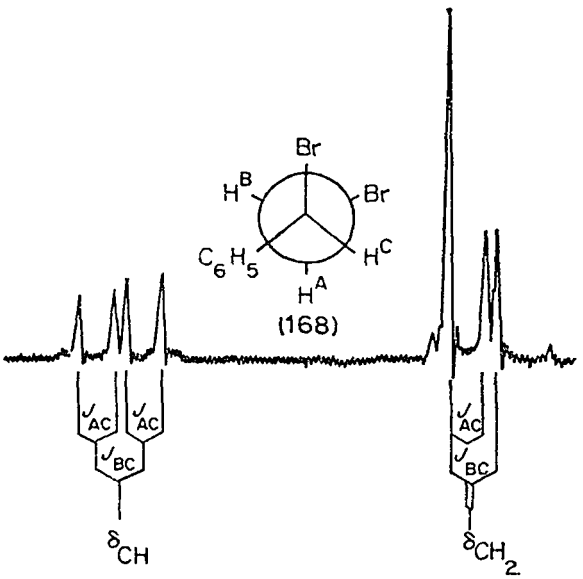
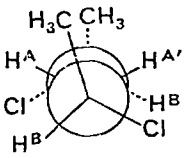


FIGURE 12. Splitting of the aliphatic proton signal of α,β-dibromoethylbenzene. Spectrum determined in chloroform-*d* solution with tetramethylsilane as internal reference[826]. Reproduced by permission of Varian Associates.

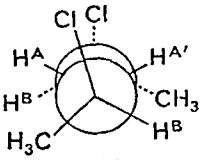
An important application of these spectral properties is the determination of the tacticity of vinyl polymers, among which polyvinylchloride is of special interest in the present chapter[839], and the principles on which such determinations are based will be outlined here.

Before dealing with the polymer it is convenient to consider a much simpler case, namely 2,4-dichloropentane[840-843], which exists in two configurations, *racemic* and *meso*.

Under the assumption that staggered conformations are to be preferred all along the molecular chain, then steric interaction among the groups present at two consecutive carbon atoms will cause that in the *racemic* form only two conformations become statistically important. These conformations are **169** and **170**. In both conformations the two methylene



(169)



(170)

protons are isosteric. If it is assumed that the J coupling between two vicinal protons depends on whether they are *trans* (J_t) or *gauche* (J_g) to each other, then the *racemic* forms will give rise to two coupling constants, one for protons A and B (equation 256) and one for protons A′ and B (equation 257), in which both forms **169** and **170** intervene, owing to their fast rate of interconversion. The coefficients x_1 and x_2 represent respectively the proportions of forms **169** and **170** in the mixture. On subtracting

$$J_{AB} = x_1 J_t + x_2 J_g \tag{256}$$

$$J_{AB'} = x_1 J_g + x_2 J_t \tag{257}$$

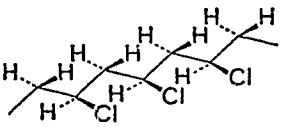
$$J_{AB} - J_{AB'} = (x_2 - x_1)(J_g - J_t) \tag{258}$$

equation (256) from (257), equation (258) entices, showing that one doublet should be obtained only in the case when $x_1 = x_2$, and two doublets otherwise. Experimentally it was found that the latter is the case.

The case of the *meso* configuration is more complicated as it corresponds to an AA′BC spectrum. It will not be discussed here but it may be pointed out that essentially the same principles intervene, although the expressions for the J couplings become more involved than equations (256) and (257). Similar studies have been carried out for 1,2,4,5-tetrachloro-perfluoropentane[844], 2,4-dibromopentane[842] and other non-halogen substituted pentanes[822].

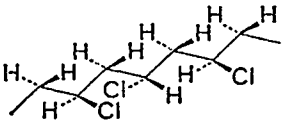
b. Macromolecules. The ideas developed above regarding the spectra of 2,4-dichloropentane can be extended to high polymers[822,839]. From the point of view of configurational regularity along a chain of polyvinylchloride three types of strands can be recognized: *isotactic* (**171**), *syndiotactic* (**172**) and *atactic* (**173**).

The methylene groups of an isotactic sequence have a structure resembling that of *meso*-2,4-dichloropentane, those of a syndiotactic sequence



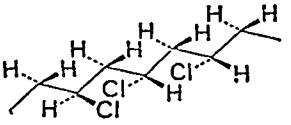
isotactic

(171)



syndiotactic

(172)



atactic

(173)

have the structure of one of the *racemic* forms and an atactic strand has some of its methylene groups resembling *meso* forms and some resembling *racemic* forms. The methylene groups of polyvinylchloride in chlorobenzene solution appear as a complex multiplet which can be resolved into two overlapping triplets. The first one centred at δ 2·04 p.p.m. attributed to the *racemic* methylenes and the second one centred at 2·22 p.p.m. for the *meso* methylenes[845] (the triplets arise from splitting by two adjacent CClH protons). Characteristic bands are also shown for the CClH protons, at δ4·29 p.p.m. for isotactic strands, 4·52 p.p.m. for syndiotactic strands and 4·41 p.p.m. for heterotactic regions (either atactic or transition between two regions of different tacticity). Each band is a quintet arising from splitting by two adjacent methylenes.

The considerations for the methylene groups in polyvinylchloride mentioned above were referred to one methylene group flanked by two chloromethine groups. However, frequency analyses of longer sequences have also been carried out[839,846]. The n.m.r. spectrum of polytrifluorochloroethylene has been studied[844].

3. ^{13}C magnetic resonance

Chemical shifts of ^{13}C have found limited application, but they may be of aid in structural analysis in the future, both because they become more accessible with the newer instrumentation and because of the wide range of values they cover (about 350 p.p.m.)[822,847]. Attachment of electronegative groups to ^{13}C causes deshielding, but iodine or more than one bromine on the same atom cause shielding, e.g. methyl iodide-^{13}C is more shielded than methane-^{13}C[848]. The ^{13}C magnetic resonance spectra of

chlorinated ethanes and ethylenes has been studied[849] and stereochemical assignments similar to those of section V. H. 2. a have been made, based on ^{13}C magnetic resonance spectra[850].

Of more immediate application are the satellite spectra arising from ^{13}C–^{1}H coupling, as they are superimposed on the ordinary proton spectra. Satellite spectra are closely related to the *s* character of the C—H bonding orbital, and the coupling constants J_{CH} are nearly proportional to this value, as shown in equation (259), where ρ_{CH} is the percentage of *s* character of the bond[851] (see, however, reference 852). For compounds of

$$\rho_{CH} = 0{\cdot}20 J_{CH} \tag{259}$$

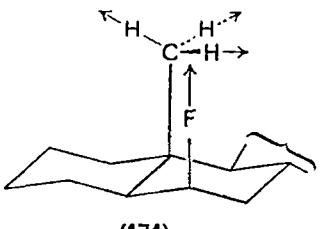
general formula CHXYZ the value of J_{CH} is an additive function of the substituents[853]. The sign of $J_{^{13}C^{1}H}$ is positive[854] and that of $J_{^{13}C^{19}F}$ is negative and its value is about 250 Hz[855]. Bilinear correlations between J_{CH} and $\delta(^{13}C)$ or $\delta(^{1}H)$ have been observed for methane derivatives CH_3—X, with the halides forming a separate class[852].

4. ^{1}H–^{19}F spin–spin coupling

Coupling between protons and fluorine nuclei can be observed in the ordinary proton spectra and are very useful in structural elucidation. Geminal couplings are of the order of 45–55 Hz but they may increase up to 75 Hz in compounds with the CHF_2Z structure with electronegative Z groups[856]. Vicinal couplings tend to follow a Karplus behaviour similar to that of ordinary ^{1}H–^{1}H couplings, but substituents may cause large variations in the J_{HF} values[785, 831, 856–858]. H–F couplings can be established through 3–4 carbon–carbon links and also through space as will be discussed below.

In a series of studies on fluorinated steroids[824, 859–862], it was found that H–F couplings are established if the vector anchored on C and directed along the C—F bond intersects the vector anchored on C and directed along the pertinent C—H bond. This has been called the *converging vector rule*[824, 860]. For example the 6β-fluoro steroid **174** shows splitting of the signal belonging to $C_{(19)}H_3$, as these protons fulfil the rule on freely rotating around the $C_{(10)}$–$C_{(19)}$ axis. In the 6α-fluoro isomer **175** the pertinent vectors are divergent and no coupling is observed. In the difluoromethylene derivative **176** of a steroid only one $C_{(19)}H_3$ splitting is observed, due to the coupling with F^A while F^B cannot afford such coupling[859]. Studies on the long range couplings of F–F and F–H are now in progress[863, 864].

N,*N*-Dimethyl-*o*-fluorobenzamide (**177**) shows H–F coupling with one of the methyl groups, as these are non-equivalent, due to restricted



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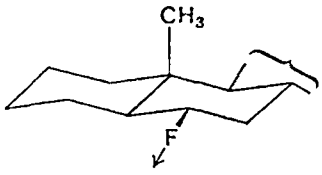

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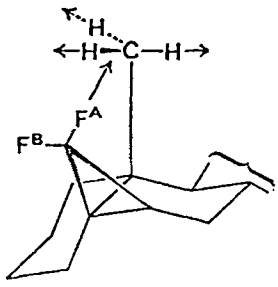
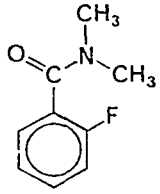


(176)

rotation around the amidic C—N bond[865]. *N,N*-Dimethyltrifluoroacetamide (**178**) shows at room temperature two quartets for the non-equivalent methyl groups, due to restricted rotation (**179**), which coalesce at higher temperatures where free rotation is prevalent[866].



(177)

(178) (179)

The H–F couplings in aromatic compounds are strongest for *ortho* protons (~6–10 Hz), somewhat weaker for *meta* protons (~6–8 Hz) and weakest for *para* protons (−2 to +2 Hz)[825].

5. ^{19}F Magnetic resonance

The n.m.r. spectra of fluorinated compounds have been reviewed[822,823]. Chemical shifts are usually measured in the δ scale, in p.p.m., with respect to trifluoroacetic acid used as an external reference. The Φ scale has been proposed, using CCl_3F both as reference and solvent, and it is designated as Φ^* after extrapolation to infinite dilution. For fluorocarbons and their halogen derivatives equation (260) holds[823].

$$\delta = \Phi^* - 76{\cdot}5 \qquad (260)$$

The δ values of organic fluoro compounds vary in the range of −150 to +150 p.p.m. with respect to CF_3CO_2H. The lower fields, from 100 to 150 p.p.m. correspond to fluorine-containing groups such as —C(=O)F, —C(=S)F and $-SO_2F$. However, nearly all other fluorinated groups appear upfield from 0 p.p.m.[867].

It is hard to correlate chemical shifts with the usual deshielding properties of substituents. For example, the chemical shifts of trifluoromethyl halides increase with the electronegativity of the halogen, from Φ^* 5 p.p.m. for CF_3—I to 69 p.p.m. for CF_3—F. In perfluoroisopropyl

halides, on the other hand, the deshielding of the secondary fluorine atom follows a reversed order, with Φ* 131·2 p.p.m. for >CF—F to 148·6 p.p.m. for >CF—I. At the same time the chemical shifts of the trifluoromethyl groups in these compounds follow the opposite order, from Φ* 75·7 p.p.m. for the 2-iodo derivative up to 82·8 p.p.m. for perfluoropropane[823].

The influence of dispersion forces arising from other groups within the molecule and from the solvent seems to be very important in determining chemical shifts of fluoro compounds[867]. The chemical shifts and coupling constants of some perfluorovinyl compounds have been studied[868].

^{19}F–^{19}F spin–spin couplings are important not only in vicinal nuclei but even at a distance with 3–4 intervening carbon atoms[822,823]. The coupling between geminal fluorine atoms has been measured in many compounds and was found to have very high J values, e.g. 284 Hz for perfluorocyclohexane[869]. It has been suggested that F–F coupling can take place through space, if the nuclei are at a distance shorter than 2·73 Å, and therefore certain conformations may contribute strongly to long-range coupling[870]. This statement has been criticized, however[871,872]. The sign of the through-space F–F couplings has been determined in various compounds[873].

^{19}F spectra are convenient for studies in conformational analysis as the large differences between the chemical shifts shown by the various conformers allow an easier 'freezing' of the conformations, as compared to ^{1}H spectra. Such studies have been reported for fluoroethanes[874] and fluorocyclohexanes[785,831].

Applications of ^{19}F magnetic resonance in the analysis of hydroxylic compounds have been reported: mixtures of *o*- and *p*-alkylphenols are placed in trifluoroacetic anhydride for 5–24 h and the ^{19}F spectrum in trifluoroacetic acid solution is determined. All esters present distinct δ values with the *ortho* isomer at ~5–17 Hz downfield from the *para* isomer. Quantitative determinations of such *ortho–para* mixtures can also be performed[875]. The optical purity of alkan-2-ols was similarly determined by first preparing the L-mandelate which was then trifluoroacetylated (reaction 261). The CF_3 peak of the L,L diasteroisomer appeared always at a field lower than that of the D,L diasteroisomer, by 1·5–2·5 Hz[876].

$$\mathrm{ROH} + \underset{\mathrm{OH}}{\mathrm{C_6H_5{-}CHCO_2H}} \longrightarrow \underset{\mathrm{OH}}{\mathrm{C_6H_5CHCO_2R}} \xrightarrow{(\mathrm{CF_3CO})_2\mathrm{O}} \underset{\mathrm{O_2CCF_3}}{\mathrm{C_6H_5CHCO_2R}} \qquad (261)$$

I. Nuclear Quadrupole Resonance

Of the 'organic' elements listed in Table 6, those with nuclear spin $I \geqslant 1$ possess a nuclear quadrupole moment. Nearly all these nuclides

show only one resonance frequency ν while ^{127}I and ^{17}O show two resonance frequencies.

As the theory of these spectra is too abstruse to be summarized in a few paragraphs, only some results will be mentioned to point out the importance of this analytical tool in the field of organic halogen compounds.

Pure nuclear quadrupole spectra are usually obtained for organic compounds in the form of a polycrystalline solid at low temperatures. The resonance frequencies ν are proportional to a quantity called the *molecular quadrupole coupling constant* and denoted as e^2Qq (some authors use eQq). The proportionality constant is a function of I. The resonance frequencies for halogen compounds are for the case $I = \frac{3}{2}$ as shown in equation (262) and the two frequencies for $I = \frac{5}{2}$ as shown in equations (263) and (264). The q factor is the electrical field gradient in the z direction of the *principal axis system* of the resonating nucleus, and it is produced by the electron

$$\nu = \frac{e^2Qq}{2h}\left(1+\frac{\eta^2}{3}\right)^{\frac{1}{2}} \tag{262}$$

$$\nu_1 = \frac{3e^2Qq}{10h}(1-\tfrac{11}{54}\eta^2) \tag{263}$$

$$\nu_2 = \frac{3e^2Qq}{20h}(1+\tfrac{5}{54}\eta^2) \tag{264}$$

cloud surrounding the nucleus. The *asymmetry parameter* η is a measure of the difference of the electrical field gradient in the x and y directions of that co-ordinate system, and it is usually of the order of 0·01–0·1 for organic halides.

The e^2Qq value is a measure of the ionic character of the C–halogen bond and is given usually as the resonance frequency ν. The η value, on the other hand, is a measure of the double-bond character of this bond. Only for ^{127}I can the values of both e^2Qq and η be found by simultaneously solving equations (263) and (264). For the chlorine and bromine nuclides additional information is needed to estimate η. This can be obtained from rotational spectra or molecular beam spectra.

The subject of nuclear quadrupole spectroscopy and its applications has been dealt with in detail elsewhere[877, 878].

It happens that the pure nuclear quadrupole spectra of organic halides, especially chlorides, have been extensively studied. The resonance frequencies of Cl, Br and I lie respectively in the 15–60, 150–350 and 150–700 MHz ranges. Table 39 summarizes some correlations that have been found for organic halides of various types.

TABLE 39. Some correlations involving the nuclear quadrupole spectra of organic halides

Type of compound	Correlation[a]	Reference
RCH_2Cl	$\nu(RCH_2{}^{35}Cl) - \nu(Et^{35}Cl)$ vs Taft's σ^* constants (see next entry)	878
$R^1R^2R^3CCl$	$\nu = 32{\cdot}5 + 1{\cdot}019(\sigma_1^* + \sigma_2^* + \sigma_3^*) \pm 0{\cdot}35$	879
Organic chlorides and bromides	$(\nu/\nu_0)_{Br}$ vs $(\nu/\nu_0)_{Cl}$	878
	$\frac{\nu(RBr) - \nu(MeBr)}{\nu(MeBr)}$ vs $\frac{\nu(RCl) - \nu(MeCl)}{\nu(MeCl)}$	
Organic chlorides and iodides	$(\nu/\nu_0)_I$ vs $(\nu/\nu_0)_{Cl}$	878
	$\frac{\nu(RI) - \nu(MeI)}{\nu(MeI)}$ vs $\frac{\nu(RCl) - \nu(MeCl)}{\nu(MeCl)}$	
$CH_{4-n}Cl_n$ (n = 1,2,3,4)	(ν/ν_0) vs n	880–883
$CHF_{3-n}Cl_n$ (n = 1,2,3)	(ν/ν_0) vs n	880–883
$CF_{4-n}Cl_n$ (n = 1,2,3,4)	(ν/ν_0) vs n	880–883
Chlorinated cyclopropanes	ν vs effective electronegativity at the halogenated carbon	884
Alkyl iodides	ν vs half-wave potentials in polarographic reduction	885
Aryl and alkenyl chlorides	ν and η values vs double-bond character of C—^{35}Cl	886
X—C≡N, X—C≡CCH$_3$, X—CH=CH$_2$ and X—CH$_2$CH$_3$	ν vs C—X bond length for X = ^{35}Cl, ^{81}Br, ^{127}I	886
Substituted chlorobenzenes	$\nu(Ar^{35}Cl) = 35{\cdot}826 + 1{\cdot}024\sigma$	887
Substituted bromobenzenes	$\nu(Ar^{81}Br) = 227{\cdot}19 + 8{\cdot}18\sigma$	888, 889
	$\nu(Ar^{81}Br) = 226{\cdot}932 + 7{\cdot}693\sigma \pm 2{\cdot}98$	
Substituted iodobenzenes	$\nu(Ar^{127}I) = 267{\cdot}0 + 1{\cdot}424\sigma$	889
	ν and η values vs double-bond character of C—^{127}I	889
	ν vs half-wave potentials in polarographic reduction	885
$C_6H_{6-n}Cl_n$ (n = 1, . . ,6)[b]	(ν/ν_0) vs n	890
	$(\nu/\nu_0) = (\nu/\nu_0)_{C_6H_5Cl} + 1{\cdot}30n_o + 0{\cdot}45n_m + 0{\cdot}25n_p$	891
$RSiCl_3$	$\nu = 18{\cdot}919 + 0{\cdot}457\sigma^* \pm 0{\cdot}099$	878
$R^1R^2R^3SiCl$	$\nu = 16{\cdot}649 + 0{\cdot}399(\sigma_1^* + \sigma_2^* + \sigma_3^*) \pm 0{\cdot}128$	878
$R^1R^2R^3GeCl$	$\nu = 17{\cdot}420 + 0{\cdot}937(\sigma_1^* + \sigma_2^* + \sigma_3^*)$	878

[a] ν values in MHz. ν_0 is the frequency of the element in its atomic form. σ and σ^* are Hammett and Taft substituent constants.

[b] n_o, n_m and n_p are the number of chlorine atoms at positions *ortho*, *meta* and *para* relative to the pertinent chlorine atom, and may have the values 0, 1 or 2.

VI. ACKNOWLEDGMENTS

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The Chemistry of The Carbon-Halogen Bond: Part 1
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CHAPTER 4

Mass spectrometry and the carbon-halogen bond

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INTRODUCTION

This chapter discusses the nature and fragmentation patterns of gaseous ions whose behaviour is influenced by the presence of a carbon–halogen bond. To help in this a brief discussion of some general, relevant points will first be presented.

The most frequently used method of producing ions is the bombardment of a gaseous substrate with a beam of electrons of known kinetic

energy. Collision between an electron and a gaseous molecule can result in one of several processes (1)–(3) of which (1) is normally the most important at electron energies much above the ionization potential. When a molecular ion is first formed fragmentation may occur with or without rearrangement. Rearrangement can also lead to radical ions, i.e. $[F_1]^{+\cdot}$ or $[F_1]^{-\cdot}$ and non-radical neutral fragments in processes (1) and (2).

$$M + e \longrightarrow \overset{M^{+\cdot} + 2e}{\nearrow \quad \searrow} \quad F_1^+ + F_2^{\cdot} + 2e \qquad (1)$$

$$M + e \longrightarrow \overset{M^{-\cdot}}{\nearrow \quad \searrow} \quad F_1^- + F_2^{\cdot} \qquad (2)$$

$$M + e \longrightarrow F_1^- + F_2^+ + e \qquad (3)$$

Ionization by light and subsequent study either of the ions produced (photoionization spectroscopy)[1] or of the energy of the electrons produced (photoelectron spectroscopy)[2] is also important. Processes similar, but not necessarily identical to (1) and (3) can occur. A mass spectrum then consists of the ions produced by any of these interactions or by the subsequent breakdown of these ions.

The most generally accepted theory of positive ion formation, the Quasi-Equilibrium Theory (QET)[3,4] proposes that upon electron impact molecular ions with a variable excess internal energy (E) are formed. Before fragmentation this energy reaches an internal dynamic equilibrium and the fragment ions are then formed by a series of competitive and consecutive unimolecular reactions. A much simplified form of the theory[4] gives equation (4) for the rate $[k(E)]$ of such a fragmentation. In this ν is a

$$k(E) = \nu(1 - E_0/E)^{N-1} \qquad (4)$$

frequency factor similar to the Arrhenius A-factor and E_0 is the minimum excess energy for the reaction to occur. N represents, in principle, the number of degrees of freedom in the ion, but in practice it often has to be reduced[5] or modified[6].

Since in a conventional electron impact mass spectrometer the spectrum is produced by expelling the ions from the ionizing region (source) about 10^{-6} s after formation and collecting them after about 10^{-5} s, observable fragmentation only occurs if $k(E) > 10^5\ s^{-1}$. This implies that for a given E_0 a minimum excess energy (E_s) is necessary for the ions to fragment in the source and a slightly lower energy (E_m) for the ions to fragment before collection. This approach is shown in the (arbitrary) graph of $N(E)$, the

number of molecular ions with an excess energy in the range E to $E+dE$ (Figure 1) against E. The area under this curve to the left of the line $E = E_m$ represents the intensity of the molecular ion, the area under the curve and between $E = E_m$ and $E = E_s$ represents the intensity of the so-called metastable ions breaking down in flight[7]. Extending McLafferty's approach[7] there is an energy E_d such that the intensity of the molecular and all the primary fragment ions is represented by the area under the

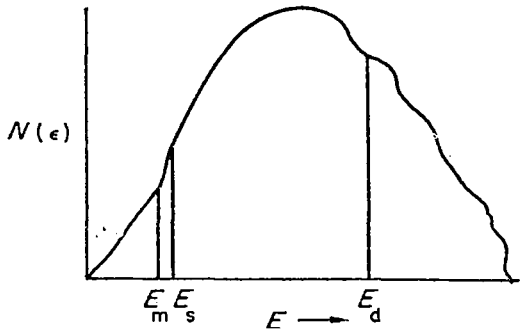


FIGURE 1. Arbitrary graph of $N(\varepsilon)\,\nu(\varepsilon)$.

curve bounded by $E < E_d$. The metastable ions can often be used to identify some of the precursors[8] of a particular ion. Unless there are only secondary fragment ions of weak intensity the relative abundances* of the primary fragment ions cannot be even taken as a semi-quantitative guide to the amounts of these ions originally formed.

If an ion fragments in two ways to give the ions a and b, then in those parent ions where $E_m^b > E > E_m^a$ fragmentation can only give a. Competition can occur only in those ions where $E > E_m^b$ and this requires that $\nu_b > \nu_a$ (see equation 4). In ions where $E \gg E_m^b$ frequency factors have more influence on the abundances of the two ions[9]. Thus at high electron energies reactions with high frequency factors will be relatively more important than those with low frequency factors and necessarily lower E_s. If the intensity ratio $(a)/(b)$ increases with decreasing electron voltage then $E_s^a < E_s^b$. This does not necessarily imply that, if b is formed by a direct cleavage reaction, then a must be formed by a rearrangement, since direct cleavage reactions could have quite different frequency factors. Experimentally, it is often, but not always, found[10,11] that a rearrangement process has a more intense metastable ion, and this is often taken as

* The intensities of metastable ions relative to normal ions are always low and unless specified abundances means of the ions formed in the source (normal ions).

evidence for an otherwise undetectable rearrangement, involving perhaps neighbouring group participation[12,13]. However, this criterion cannot be regarded as unequivocal.

In order to determine E_s and E_m the ionization potential of the molecule [I(M)] and the appearance potential (A[F_1^+]) of either the normal or metastable form of the ion $[F_1]^+$ must be determined[14]. These are the electron beam energies at which the ions are just detectable. The difference between the appropriate appearance potential and the ionization potential gives E_s or E_m[15].

Where an appropriate appearance potential has not or cannot be determined, a minimum estimate of E_s is given by $\Delta H_r - I(M)$. ΔH_r is the difference between the heats of formation of the products and the reactants. Since A[F^+] is positive then, if ΔH_r is positive, the appearance potential can be equated (equation 5) to ΔH_r and the excess energy (E_x), if any, imparted to the products.

$$A[F^+] = \Delta H_r + E_x = \Delta H_f[F^+] + \Delta H_f(\text{Neutral products}) + E_x - \Delta H_f(M) \quad (5)$$

Since I(M) is defined by equation (6) it can be seen why this minimum estimate of E_s is reasonable, if E_x is small. This will often be the case, if

$$I(M) = \Delta H_f[M^{+\bullet}] - \Delta H_f(M) \quad (6)$$

the reaction has a high frequency factor and low E_s. If the frequency factor is low, then for the reaction to occur in the source E_s must be somewhat larger than E_0. Thus E_x will be important and this effect is called the kinetic shift[7]. If the reaction is not the fastest, then for it to be observed E_s must be larger than E_0 and again E_x will be appreciable. This is known as a competitive shift[7]. However in these cases the minimum estimate of E_s may explain why an ion is not observed. Although the atomic composition of $[F_1]^+$ can be determined[8a,b], use of equation (5) implies an assumption of this ion's structure and those of the neutral fragment(s). If A[F^+] is known, then equation (5) can be used to check these assumptions, in particular ruling out combinations which make E_x negative.

II. DATA SELECTION, PRESENTATION AND ERRORS

The following section applies to data in the text and in the tables unless otherwise indicated.

A. Intensity Data

In this work X denotes a halogen, (Z) means the intensity of the $[Z]^+$ ion. In the case of the monohaloalkanes[16] and the monohalo-aromatics[17],

unless otherwise specified, the *m/e* values versus intensity data have been taken from the work of McLafferty. For the polyhaloalkanes the data of McCarthy[18] have been used, supplemented where necessary by data from compilations which give the eight[19] or ten[20] most intense peaks. Where more than one spectrum of a compound was available, the results were averaged in terms of the total ion current carried by each ion, but spectra containing spurious peaks were first rejected. In the case where the only spectrum available contained spurious peaks the obviously spurious peaks were rejected. In all cases the intensities of the ions containing the heavier isotopes of chlorine and/or bromine were added to that of the ion containing only the lighter isotopes. Intensities are given as a percentage of the total ion current unless otherwise stated. Variations of $\pm 5\%$ occur in spectra of the same compound run under different conditions and will not be considered significant, if observed between the spectra of two compounds, unless the spectra were run under the same conditions. Where the intensity of a particular ion is not recorded in the compilations[19,20] a maximum estimate was made by taking its intensity as equal to that of the least intense ion recorded. In intensity ratios this is denoted by the symbols $<$ or $>$ as appropriate.

B. Energetic Data

Ionization and appearance potential data were taken from the compilation of Franklin and coworkers[21] unless otherwise indicated by references. When several reasonably similar values for these (or for ΔH_f's for ions) were recorded, these were averaged, otherwise an attempt was made to decide on a 'best' value. Ionization potentials determined by electron impact on the same machine for a series of related compounds are probably accurate, relative to each other, to $\pm 0{\cdot}05$ eV (eV = electron volts) and appearance potentials to $\pm 0{\cdot}2$ eV and differences less than this will be neglected. In some cases larger differences are recorded in values observed by different research groups (see Tables 5 and 20). More accurate values can be determined by photoionization and photoelectron methods, but these may not involve the same excitations as electron impact. Generally in comparing these with electron impact values the vertical ionization potentials are used. Thermodynamic data for the neutral species were taken from the book of Stull, Westrum and Sinke[22].

III. THE MASS SPECTRA OF THE HALOALKANES

A. Nature of the Ground State of the Molecular Ions

The electron impact ionization potentials of the normal primary monohaloalkanes and the corresponding alkanes are given in Table 1.

By examination of the photoionization curves of alkyl bromides and alkyl iodides Hashmall and Heilbronner[23] and Cocksey and coworkers[24], respectively, showed that in the ground state of the molecular ion the charge is essentially located on the halogen. This can also be deduced from the comparison with the ionization potentials of the corresponding

TABLE 1. The ionization potentials of some *n*-alkanes and *n*-haloalkanes (R—Y)[d]

R	Y				
	Cl[a]	Br[a]	I[a]	H	F[c]
Me	11·2	10·5	9·55	12·9	12·8
Et	11·0	10·3	9·35	11·6	12·7
Pr	10·8	10·2	9·20	11·1	12·2
Bu	10·6	10·1	9·20	10·6[b]	11·7
Am	10·8[b]	10·1	9·20	10·45[b]	—

[a] These agree well with the photoionization data of Hashmall and Heilbronner[23] (Y = Br), Cocksey and coworkers[24] (Y = I) and Watanabe and coworkers[25] (Y = Cl) except for *n*-butyl chloride (10·8 eV).

[b] These are photoionization values; they are in good agreement with the electron impact values in the other cases.

[c] Calculated, as described in the text, except for methyl fluoride, whose photoionization ionization potential is 12·50 eV[26].

[d] All values in electron volts (eV).

hydrocarbons. In the alkanes the charge is assumed to be delocalized over the whole of the molecule and in the chlorides a similar situation, judging by the electron impact ionization potentials, seems to exist when the alkyl group is larger than ethyl. In the case of methyl chloride Cocksey and coworkers[24] imply that the lone-pair ionization potential is the lowest, but Krauss and coworkers[26] consider that the matter is not as clear as that. However, Cocksey and coworkers have analysed the ionization potentials of all the alkyl halides except fluorides[24] and found that they can be represented by equation (7) where $\chi_{(R-X)}$ depends only on the

$$I(R-X) = I(M-X) + \chi_{(R-X)} \mid \mu_R \qquad (7)$$

halide and μ_R only on the alkyl group. This would imply a similar charge localization in each case. In contrast to this in the methyl compounds a plot of the ionization potentials against Taft's inductive constant (σ_i)[27] gives a straight line except for methyl iodide. This would suggest a different charge location in the iodides. Linear extrapolation against σ_i of the

ionization potentials of the chloride and the bromide give the calculated ionization potentials of the fluorides recorded in Table 1; the corresponding iodide does not fall on this line.

The photoionization data[23–25] show that the ionization potentials of the secondary and tertiary halides are a little lower (ca. 0·1 eV) than those of their primary isomers. This is possibly due to stabilization of the small induced positive charge on the carbon carrying the halogen, but a similar effect is also noticeable in the corresponding hydrocarbons. In the latter this is presumably due to overall changes in the orbitals which are delocalized over the molecule and a similar process could occur in the halides.

The effect of polyhalogenation is shown by the data in Table 2. There is no change in the ionization potentials on substituting the hydrogens in methyl bromide by bromine. However, the substitution of fluorine or

TABLE 2. Ionization potentials (in eV) of molecules of the type CX_nY_{4-n}

n	CF_nCl_{4-n}[a]	CF_nBr_{4-n}[b]	CF_nH_{4-n}[a]	CCl_nH_{4-n}[c]	CBr_nH_{4-n}[d]
0	11·47	10·50	12·90	12·90	12·90
1	11·77	10·70	13·07	11·28	10·53
2	12·31	10·90	13·29	11·35	10·49
3	12·91	11·85	14·77	11·42	10·51
4	15·00[d]	15·00[d]	15·00[d]	11·50[e]	10·50

[a] Photoionization data.
[b] Photoionization data, reference 28.
[c] Photoionization data, reference 29.
[d] For CF_4 this is the spectroscopic value, reference 30.
[e] Electron impact value, reference 31.

chlorine for hydrogen results in an increase in the ionization potential relative to the monohalomethane containing the least electronegative halogen. This can be explained in the case of CF_nCl_{4-n} and CF_nBr_{4-n} by assuming that the location of the charge in the least electronegative halogen destroys the stabilization in the neutral molecule due to partial back-bonding between this element and the carbon.

B. Fragmentation Processes in the Haloalkanes

Three primary fragmentation processes (8), (9) and (10) are observed. The relative intensity of the ions depends on the nature and number of

$$R^1R^2R^3C{-}X^{1+\bullet} \longrightarrow R^1R^2R^3C^+ + X^\bullet \quad (8a)$$

$$R^1R^2R^3C{-}X^{1+\bullet} \longrightarrow X^+ + R^1R^2R^3C^\bullet \quad (8b)$$

$$R^1R^2R^3C{-}X^{1+\bullet} \longrightarrow [M{-}XY]^{+\bullet} + XY \quad (9)$$

$$R^1R^2R^3C{-}X^{1+\bullet} \longrightarrow R^{1+} + R^2R^3C{=}X^\bullet \quad (10a)$$

$$R^1R^2R^3C{-}X^{1+\bullet} \longrightarrow R^2R^3C{=}X^{1+} + R^{1\bullet} \quad (10b)$$

the halogens, the chain length and its branching, if any. The intensities for all these cations and for the molecular ions in the case of the straight-chain primary alkyl halides are given in Table 3. A fairly detailed study by thermodynamic and other techniques has been made of the ions corresponding to (8a) and (9) and the energetic data for these two reactions

TABLE 3. Intensities of the molecular ions and the ions formed by fragmentations (8)–(10) in some normal primary alkyl halides ($R^1R^2R^3C{-}X$)

Ion or Fragmentation	X = F[a]				X = Cl[a]			
	R				R			
	Me	Et	Pr	Bu	Me	Et	Pr	Bu
(M)	47	5	1	v.s.	74	42	3	0·2
(8a)	6	1	1	1	12	16	4	1
(9)	—	4	10	17	—	16	40	38
(10a)	—	—	38	21	—	1	16	12
(10b) ($R^1 \neq H$)	—	15	3	2	—	8	3	1
(10b) ($R^1 = H$)	41	54	0·1	—	7	2	—	—
Total	94	79	53	41	93	85	66	52
	X = Br				X = I			
(M)	63	60	19	7	60	56	26	18
(8a)	15	16	40	26	7	20	38	33
(8b)	4	4	1		22	8	5	2
(9)	—	—	3	3	—	—	1	1
(10a)	—	—	2	1	—	—	—	—
(10b) ($R^1 \neq H$)	—	—	1	1	—	—	1	1
(10b) ($R^1 = H$)	13	—	—	—	8	—	—	—
Total	95	80	66	38	97	84	71	55

[a] Process (8b) is effectively absent. v.s. = very small.

are summarized in Table 4. In principle (8a) is a direct cleavage reaction. However, in the case of *n*-propyl and *n*-butyl chloride the observed values[32] are too low to fit direct cleavage according to equation (5) and have been interpreted by Baldwin and coworkers[32] as evidence for rearrangement. These low values seem to be due to an experimental artifact since 50% of the ion current at *m/e* 43 and 60% of the ion current at *m/e* 57, respectively,

TABLE 4. Energetic data for processes (8a) and (9) (eV) in normal primary alkyl halides ($R^1R^2R^3C—X$)[f]

R	X = F[a]		X = Cl[e]		X = Br[e]		X = I[e]	
	A (8a)	A (9)[b]	(8a)	(9)	(8a)	(9)[d]	(8a)	(9)[d]
Me	14·5 (1·6)	—	2·3	—	2·2	—	2·8	—
Et	13·3	10·7	1·3	0·35	1·2	1·0	1·7	1·8
Pr	13·2	10·8	1·3[c]	0·30	1·1	1·0	1·2	2·0
Bu	13·4	11·2	1·4[c]	0·40	1·1	0·6	1·2	1·8

[a] Calculated appearance potentials except for methyl fluoride where the value in the brackets is the E_s.

[b] Calculated on the assumption that the hydrogen lost is on the carbon remotest from the carbon carrying the fluorine, assuming Green's arguments are correct[33] (see section III. B).

[c] Calculated (see section III. B).

[d] Calculated assuming 1,3-elimination; see section III. B.

[e] E_s values.

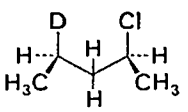
[f] For process (8b) in the methyl halides the E_s values are X = Cl, 5·3, Br, 4·2 and I, 3·8 eV[34].

are due to the $^{13}C_1$ isotope of the ion at *m/e* 42 and 56. In both cases this has a lower appearance potential[32] and, as shown by Baldwin and coworkers in a similar case[32], this will lower the observed appearance potential for the alkyl ions. In some long-chain alkyl bromides and iodides evidence has been produced for the isomerization of the $[M\text{-}X]^+$ ions before subsequent fragmentation[35]. This suggests but does not require isomerization before or during the formation of these ions.

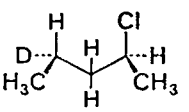
In the case of process (9), Duffield and coworkers[36] have shown by labelling that mainly 1,3-elimination occurs in the case of *n*-butyl chloride and that in the case of 1-chloropentane about 85% of the elimination is 1,3 and the rest is 1,4. For *n*-butyl fluoride, 1,3-elimination accounts for 40% and 1,4 for 50%; in 1-hexyl fluoride 1,4-elimination accounts for 22% at 70 eV and 31% at 12 eV, whereas 1,5-elimination accounts for 76% at 70 eV and 63% at 12 eV[37]. In the case of *n*-propyl chloride $\Delta H_f[C_3H_6]^{+\bullet}$ is 244 kcal/mole which agrees well with the ΔH_f of the cyclopropane cation (245 kcal/mole), but is about 15 kcal/mole higher than that for the

molecular ion of propene. In the case of *n*-butyl chloride $\Delta H_f[C_4H_6]^{+\bullet}$ observed is 234 kcal/mole, about 13 kcal/mole higher than for the molecular ion of 1-butene. For the methylcyclopropyl cation ΔH_f is 231 kcal/mole[38] which is in reasonable agreement with this value. In this case and the others discussed below an alternative explanation would be that the olefin was formed with excess energy. In view of the labelling evidence this seems unlikely, the main significance of the thermodynamic evidence being that it agrees with the labelling evidence. For *n*-pentyl-1-X, ΔH_f values of 222 (X = Cl) and 227 (X = F) kcal/mole are obtained from the appearance potentials. These are a little high, particularly in the case of X = F, for the formation of the molecular ion of 1-pentene (ΔH_f = 214 kcal/mole) but are in good agreement with the value for the cyclic cation (ΔH_f = 225 kcal/mole). The ΔH_f values for the ethylcyclopropyl and methylcyclobutyl cations are not available for comparison.

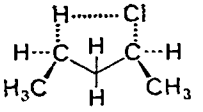
The work of Green and coworkers[33] gives further insight into the factors controlling this elimination reaction. In the case of 2-*n*-pentyl chloride, analysis of the spectra of compounds **1** and **2** not only showed that about 90% of the elimination was 1,3 but that at electron voltages near the appearance potential the preferred conformation for elimination corresponds to the more stable *cis*-isomer of 1,3-dimethylcyclopentane, which molecule the transition state **3** presumably resembles. The preference probably represents a difference in frequency factors due to the



(1)



(2)



(3)

greater population of the more stable conformation. The difference between the two conformers can only be a few hundred cal/mole and the difference in populations would become smaller at higher electron volts. The preference for elimination via this conformation drops at higher electron volts in keeping with these ideas. That such a small difference shows up lends support to the suggestion[36] of Duffield and coworkers that the absence of 1,4-elimination in the case of *n*-butyl chloride is due to the higher bond energy of a primary carbon–hydrogen bond, whereas in the case of *n*-pentyl-1-chloride, the observed 1,4-elimination involves a secondary hydrogen. The frequency factor will of course be lower for a 1,4-elimination but the E_s value may also be lower for a reason pointed out by Green and coworkers[33]. They point out that in the transition state for this elimination in these compounds the hydrogen and halogen come

closer together as the number of intervening carbons increases. For chlorine the distance apart is less than the sum of the bonding radii when the number of intervening carbons is three or four; for fluorine, due to its smaller bonding radius, this requires four or five carbons. When the two atoms can get within the sum of their bonding radii, the E_s value will be a minimum due to maximum bonding in the transition state. Thus a compromise between these two factors will determine which elimination (1,3, 1,4 or 1,5) predominates. Thus the slight change in bond energy between the two hydrogens involved in the case of 1,3 and 1,4 in *n*-butyl chloride may explain the absence of 1,4-elimination here. Although the larger transition states observed for fluorides (cf. chlorides) are in keeping with this argument, yet the decrease in relative importance of the 1,5-elimination in the case of 1-*n*-hexyl fluoride with decreasing electron voltage is peculiar. This would suggest a relatively higher E_s but in the absence of complete spectra easier subsequent decomposition of the $[M\text{-}HX]^{+\bullet}$ ion so formed cannot be ruled out. Finally, this argument is the reason for using, where possible, 1,3-elimination to calculate E_s values for (9) in the case of the alkyl bromides and iodides (Table 4).

Green and coworkers[33] also showed that in cyclohexyl chloride 1,4-elimination is about twice as favourable as 1,3-elimination and that both processes are probably 100% *cis*-eliminations.

It is interesting to note that in the corresponding unimolecular gas-phase elimination from alkyl chlorides there is no evidence for anything other than 1,2-elimination[39]. In the thermal case energetic factors would be expected to be more important and this result is surprising in view of the above argument.

The energetic data for fragmentations (10a) and (10b) are summarized in Table 5 and vary considerably from source to source[21].

Consideration of the E_s or appearance potential values in Tables 4 and 5 and the lower frequency factors for (9) shows that there is a good correlation between these factors and the intensity data in Table 3. For example, in the fluorides the decline of process (8a) with increasing size of the alkyl group is in agreement with the decrease in the calculated appearance potential for process (10a) and the low appearance potential for process (9). The relative importance of the $[M\text{-}H]^+$ ion in the case of ethyl fluoride may be due to the extra stabilization due to the presence of a methyl group in this ion. This is not present either in the $[M\text{-}H]^+$ ion in methyl fluoride nor in the $[M\text{-}Me]^+$ ion in the case of ethyl fluoride. Presumably this effect will be most marked in the fluorides since fluorine is the most electron-demanding of the halogens. In the propyl compound the stabilizing methyl group is replaced by an ethyl group which will not be much

better than a methyl group as far as stabilization is concerned. However, the heat of formation of an ethyl cation is considerably less than a methyl and so process (10a) becomes important here and for similar reasons in the butyl compound. Similarly in the chlorides the increase in importance of process (10a) presumably is related to the fact that in this reaction alone

TABLE 5. E_s or appearance potentials (eV) for fragmentations (10a) and (10b) for primary alkyl halides (R—X)[f]

R	X = F[a]		X = Cl[b]		X = Br[b]		X = I[b]	
	(10a)[c]	(10b)[c]	(10a)[c]	(10b)[c]	(10a)[c]	(10b)[c]	(10a)[c]	(10b)[c]
Me[d,e]	—	0·6	—	2·1	—	2·5	—	3·55
Et	12·6	12·2	4·9	2·4	6·6	3·8	6·95	4·45
Pr	11·35	12·05	1·6	2·5	4·1	3·2	2·2	2·7
Bu	10·9	12·1	1·1	2·5	2·1	2·1	2·2	2·3

[a] Except for MeF these are calculated appearance potentials; for MeF this is an E_s value.
[b] For the propyl and butyl compounds these are calculated E_s values.
[c] This is for the loss of an alkyl group when R > Me.
[d] For the methyl halides the data of Hamill and coworkers[34,40] agree reasonably well with the above values for E_s.
[e] No intensities for the $[H]^+$ ion are available, therefore the corresponding E_s values were not calculated.
[f] All values are E_s values unless otherwise mentioned.

the E_s value drops on increasing the size of the alkyl group. This drop is presumably for similar reasons as outlined for the fluorides. The lower molecular ion intensities in the chlorides and fluorides compared with the corresponding bromides and iodides when R > Me are easily related to the low energy demands of process (9) in the former compounds. Except for methyl iodide, in the bromides and iodides the major fragmentation is (8a) and this is in keeping with the fact that E_s for this reaction is the lowest.

Examination of the spectra of the *n*- and *iso*-propyl bromides and iodides shows that the intensities of the molecular ions in each pair are very similar (Table 6). Here the increase in stability of the secondary carbonium ion which lowers E_s for the most facile process (8a) slightly does not affect the intensity of the corresponding ion. This may reflect a deep valley in the $N(E)$ versus E curves for the molecular ions at this point ($E = E_s$). Such minima have been reported by McLafferty and coworkers[7] from photoionization data in other cases. In the case of isopropyl fluoride the only important reaction is (10b). This gives the same ion as ethyl fluoride, but the ejection of a methyl group in this case

rather than a hydrogen should lower the appearance potential by about 1 eV. A similar depression compared to the ethyl compound is calculated for process (8a).

In the case of isopropyl chloride the E_s value for process (8a) is apparently only 0·3 eV although this value may be a little low[32]. However, the lowering of this E_s coupled with a higher frequency factor compared

TABLE 6. Intensities of molecular and principal fragment ions in the mass spectra of propyl and butyl halides[a]

R	X = Cl[b]					X = Br[c]			X = I[d]		
	Process					Process			Process		
	(M)	(8a)	(9)	(10a)[e]	(10b)[e]	(M)	(8a)	(10b)[e]	(M)	(8a)	(8b)
n-Pr	3	4	40	16	3	19	40	1	26	38	5
i-Pr	14	42	2	0·5	16	20	44	2·5	17	37	6
n-Bu	0·2	1	38	12	0·4	7	26	0·5	18	33	2
s-Bu	0·1	20	23	1·5	16	0·1	40	1·5	16	41	2
i-Bu	0·2	1·5	3	3·6	4	3	33	2	15	38	2
t-Bu	0·0	35	2	0·7	22	0·1	48	5	2	42	5

[a] Data are available only for *n*-butyl fluoride and *n*-propyl and isopropyl fluoride. For the former two see Table 3, for the latter the only primary fragmentations are (10b), 68 and (10a), 1·5; the molecular ion intensity is 0·6.)

[b] Process (8b) is negligible.

[c] Process (9) varies from 1 to 3, (10a) is negligible except in the case of *i*-butyl bromide (12) and *s*-butyl bromide (19); however, in the latter case the ion at *m/e* 29 corresponding to (10a) could be formed from *m/e* 57 (8a) by the loss of ethylene.

[d] Process (9)'s intensity varies between 0·3 and 2, (10a) is only important in the isopropyl compound (1).

[e] Intensities for processes (10a) and (10b) include all the ions corresponding to those processes (i.e. a loss of different R^1s).

with process (9) would account for the increase in the ratio (8a)/(9) by a factor of 200 compared with *n*-propyl chloride.

The spectra of the butyl iodides except for the tertiary compound, in which the molecular ion intensity drops by a factor of 10, are very similar. Although the latter could be related to the decrease in E_s for the most facile process (8a) to about half the value in the normal compound a similar drop would be expected in the secondary compound, but this is not reflected in the intensity of the molecular ion of the latter. This may be a pyrolysis effect. In the corresponding bromides a similar drop in E_s would be expected and here the molecular ion intensity in both compounds is effectively zero. The calculated appearance potential for the $[M\text{-}Br]^+$

ion in the case of *t*-butyl bromide and the threshold voltage for photoionization to occur[23] are the same. In the case of *iso*-butyl bromide E_s for process (10a) is 1·4 eV (calc.) which compared with E_s for process (8a), 1·2 eV (calc.), is in keeping with the observation that this reaction is important here.

In the chlorides the variations in the fragmentation patterns can be rationalized using the same arguments as in the case of the propyl fluorides. Thus in the secondary and tertiary compounds the processes (8a) and (10b) ($[M\text{-}C_2H_5]^+$, $[M\text{-}Me]^+$, respectively) become important. In the case of isobutyl chloride the calculated E_s for (10a) is about 0·1 eV whereas for (8a) it is about 0·6 eV and for (9) effectively zero. Allowing for the lower frequency factor for process (9) it is not surprising that the fragmentation (10a) predominates and that (8a) and (9) are still observable, nor that the molecular ion intensity is very low. The observed appearance potential for process (9)[32] gives the same ΔH_f for $[C_4H_8]^{+\cdot}$ as in the *n*-butyl compound, suggesting 1,3-elimination.

In the polyhalomethanes somewhat different factors may be at work. In the case of compounds of the type CY_nF_{4-n} the variations in the intensity ratio (M-Y)/(M-F) and in ΔE_s, the difference E_s(M-F)$-E_s$(M-Y), are given in Table 7. In the case of $n = 1$, in comparison with the monohaloalkanes, this ratio is very small considering the ΔE_s values. There are

TABLE 7. E_s(M-F)$-E_s$(M-Y) (ΔE_s eV) and (M-Y)/(M-F) ratios for CY_nF_{4-n} compounds

$n/(4-n)$	Y = Cl		Y = Br		Y = H	
	E_s	(M-Cl)/(M-F)	E_s	(M-Br)/(M-F)	E_s	(M-H)/(M-F)
0·33	2·3	2·7[a]	2·8[a]	4·0[a]	1·8	0·5[a]
1·0	0·3[c]	10·0	—	16·0	—	0·9
3·0	0·8–1·5	39·0[b]	—	25·0	1·0[c]	2–7[d,a]

[a] Reference 41.
[b] Reference 42.
[c] See Tables 4 and 5.
[d] Reference 18.
[e] Calculated.

two possible explanations for this. The first is that these reactions occur from isolated states, i.e. that interconversion of all the electronic states initially formed is not possible. This is against the principles of QET (see Introduction). The second is that frequency statistical control is important in the 70 eV spectra. The observation that ΔE_s decreases with increasing *n*, but that the intensity ratio increases approximately linearly with

$n/(4-n)$ also seems to rule out energetic control of these fragmentations. This approximately linear increase does suggest statistical control rather than isolated electronic states.

Similar effects are seen in the case of the compounds CF_2BrH and $CFBr_2H$ as well as in the corresponding chlorine compounds. In the monochloro compound the intensity ratio (M-Cl)/(M-F) is 6, but E_s is 2·4 eV[43]. In all these compounds the $[M\text{-}X]^+$ and $[M\text{-}Y]^+$ ions carry a large portion of the total ion current so their recorded intensities are a semi-quantitative guide to the relative amounts of these ions formed.

The polyhaloethanes behave in a similar way both to the monohaloethanes and the polyhalomethanes. Not surprisingly the $[M\text{-}HX]^{+\bullet}$ ions are gradually replaced by $[M\text{-}XY]^{+\bullet}$ ions (Y = X or another halogen) as the number of hydrogens decreases. In contrast to the monohaloethanes the competing direct cleavage reactions (8a) and (10a)+(10b) [= (10)] seem to be controlled by the same factors as in the polyhalomethanes since the ratio (8a)/(10) remains virtually constant in the perfluorochloroethanes (Table 8). In the case of perfluoroethane if the intensity ratio were to be explained in terms of the ΔE_s then a smaller difference between $A[M\text{-}F]^+$ and $A[CF_3^+]$ than that recorded (1·75–1·3 eV)[44,45] would be expected. With the exception of $(CHCl_2)_2$ and $CHCl_2CH_3$ the same ratio in the

TABLE 8. Some intensity data for the perfluorochloroethanes[a]

Compound:	C_2F_6	CF_2ClCF_3[b,c]	$(CF_2Cl)_2$	CCl_2FCF_3[c]	CF_3CCl_3[c]
(8a)/(10)	2·2	33·0	1·8	1·3	1·0
$\frac{(CF_nCl_{3-n})^d}{(CF_mCl_{3-m})}$		26·6		2·2	7·0[e]
Compound:	CCl_2FCF_2Cl[c]	$(CCl_2F)_2$	CCl_3CF_2Cl	C_2Cl_6	
(8a)/(10)	2·0	2·0	1·1	0·7	
$\frac{(CF_nCl_{3-n})^d}{(CF_mCl_{3-m})}$	3·0		5·5		

[a] For $(CCl_2F)_2$ the percentage of these ions is 60, in all other cases > 70.
[b] This molecule seems to fragment in an unexpected fashion, only one spectrum is available[18].
[c] Data from reference 18.
[d] $n<m$.
[e] For values of $A[CF_3^+]-A[CCl_3^+]$ see text.

polychloroethanes is also reasonably constant (Table 9). In the isomeric pairs containing the same number of chlorines it is noticeable that the ratio (8a)/(10) is lower in the isomer in which the chlorines are more evenly distributed between the two carbon atoms. Further, except in the dichloro compounds, the sum of the intensities of (8a) and (10) in each

TABLE 9. Some intensity[a] and E_8 (eV) data for the polychloroethanes

Compound	(8a)/(10)	(8a) (M-Cl)	(10)	$(CH_mCl_{3-m})/(CH_nCl_{3-n})$[b]	ΔE_8[f]
C_2Cl_6	0·7	32	44	—	—
C_2Cl_5H	0·8	36	46	0·3	0·6[g]
$(CHCl_2)_2$	0·1	8	68	—	—
CCl_3CH_2Cl	1·3	38	29	0·1	0·6[d]
$CHCl_2CH_2Cl$	1·0	29	29	0·08	0·0[d]
CCl_3CH_3	4·0	52	13	0·2	1·0[d]
$(CH_2Cl)_2$	·0·5	7	14	—	—
$CHCl_2CH_3$	6·9	48	7	0·3	0·6
C_2H_5Cl[c]	1·6	16	10	0·05	0·6[d] (1·7)[e]

[a] In all cases except $(CH_2Cl)_2$ the sum of the intensities of (8a), (10) and the molecular ion is 65 or greater.
[b] $n < m$.
[c] Reference 16.
[d] ΔE_8 calculated from data in reference 46.
[e] Obs., reference 47.
[f] $\Delta E_8 = A[CH_nCl_{3-n}^+] - A[CH_mCl_{3-m}^+]$.
[g] $A[CCl_3^+]$, reference 21; $A[CHCl_2^+]$ calculated from data in reference 46.

pair is reasonably constant, which would be expected if these two were the main, competing primary fragmentations. In the case of 1,2-dichloroethane the $[M\text{-}Cl]^+$ ion in the 1,1-isomer is replaced by the $[M\text{-}HCl]^+$ ion (intensity 35).

In the monohaloalkanes the more intense of the ions formed by processes (10a) and (10b) when R^1 was an alkyl group was shown to be the one for which the appearance potential was lower (Tables 3 and 5). This also seems to be the case in 1,1,1-trifluoroethane where $A[CH_3^+] - A[CF_3^+] = 1{\cdot}1$ eV and $(CF_3)/(CH_3) = 9$. In the perfluorochloroethanes no experimental appearance potential data are available but, depending on the value chosen[46] for $\Delta H_f[CF_3]^+$, $A[CF_3^+] - A[CCl_3^+]$ lies between 0·3 and 1·3 eV, for CF_3CCl_3. Judging by other thermodynamic data when X = F in an ion of the type $[CX_nZ_{3-n}]^+$ the difference between the heats of formation of this ion and the corresponding radical is greater than in the case where X = Cl. Hence from equation (5) the appearance potential of

this type of ion with more fluorines in will be higher. This is in keeping with the intensity ratios in Table 8. In the case of the polychloroethanes complete thermodynamic data are available although ΔH_f values for $[CH_2Cl]^+$ and $[CHCl_2]^+$ are not very reliable[46]. Here the calculated appearance potential differences and the intensity ratios (Table 9) fit the general picture.

In polyhaloethanes containing bromine among the other halogens the intensity ratio (M-Br)/(10) is larger than the ratio (M-X)/(10) in the compounds where the bromine(s) are replaced by chlorine(s) or fluorine(s) (Table 10). This is not surprising since $E_s[M\text{-}Br]^+$ might be expected to be lower (see Tables 4 and 7) than that for the loss of chlorine or fluorine. Also, as far as can be seen from the data for the monohaloalkanes (Table 5) the substitution of bromine for chlorine increases E_s for process (10), perhaps due to a competitive shift effect[7] rather than an appreciable change in bond energy.

TABLE 10. Effects of substitution of chlorine or fluorine by bromine on the ratio (8a)/(10) in polyhaloethanes

Molecule		CF_2XCF_2Y	$CFClXCFClY$	CH_2ClCH_2X
X	Y			
Br	Br	0·20	4	18
Cl	Cl	0·55[a]	0·5	0·5
F	F	0·45	0·55[a, b]	—
Cl	F	0·03[a, b]	0·5	0·5

[a] Data from reference 18.
[b] This compound seems to fragment in an unusual way, see footnote *b*, Table 8.

The formation of ions of the type $[CXYZ']^+$ in which a substituent from one of the carbons (see equation 11) has interchanged with one on

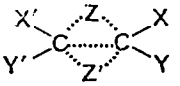
$$CXYZ\text{—}CX'Y'Z'^{+\bullet} \longrightarrow CXYZ'^{+} \qquad (11)$$

the other carbon atom is also noticeable[18]. Thus in 1,1-dichlorotetrafluoroethane the intensity of the ion CF_2Cl ($Z' = Cl$) is 16 and in general this rearrangement seems most marked in those molecules containing fluorine and/or chlorine and less than three hydrogens. These reactions presumably occur since the activation energy for the rearrangement is lower than for the direct cleavage reaction. Thus although this rearrangement (equation 11) must have a lower frequency factor than the direct

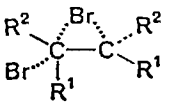
cleavage reaction, there will be a certain portion of the molecular ions in which the rate constant for the rearrangement will be faster than for cleavage and the rearranged molecular ions will then have enough energy to fragment.

Where appearance potential data have been determined these ions produced by rearrangement have higher E_s values. These values are of course the sum of the energies required for rearrangement and fragmentation if these two processes are separate. Thus the higher E_s values such as those recorded by Steele and Stone[48] do not necessarily invalidate the preceding argument. Steele and Stone found in the case of 1,1,1-trifluoroethane[48] that $A[CF_3^+] = 13{\cdot}9$ eV, $A[CH_3^+] = 15{\cdot}0$ eV, but $A[CH_2F^+] = 15{\cdot}9$ eV. In the case of trifluoromethylethane[48] $A[C_2H_5^+] = 12{\cdot}8$ eV and $A[CH_3^+] = 14{\cdot}8$ eV whereas for the rearrangement ions $[CF_2H]^+$ and $[CH_2F]^+$ the appearance potentials are 15·9 and 15·7 eV respectively. Calculation of $\Delta H_f[CF_3]^+$ from its appearance potential in the case of 1,1,1-trifluoroethane gives a value of 108 kcal/mole which lies between the high and low values for this ion[46]. This indicates that the ion is formed with excess energy. This could be either due to a competitive shift[7] (see Introduction) caused by the rearrangement reaction or due* to the fact that the $[CF_3]^+$ ion is planar whereas in the paraffin the fluorines of the CF_3 radical are not. Similarly $\Delta H_f[CH_3]^+$ is high in this case but this could be caused by a competitive shift[7] (see Introduction) due to the easier formation (lower E_s) of the $[CF_3]^+$ cation without the need to invoke the rearrangement as a competitor.

This rearrangement could proceed via the intermediate shown below and a similar bridged ion has been postulated by Pechine[49] to explain his



observations in some vicinal dibromoalkanes. Thus in the case of racemic (*r*) and *meso* (*m*) 2,3-dibromobutanes Pechine found that[49] $(M)_m/(M)_r$ was 0·61 and virtually independent of electron voltage. If at low excess energies backside attack by one bromine to displace the other occurred (see below)



consideration of steric crowding in the transition state suggests that E_s for the loss of bromine would be higher for the racemic mixture than the

* Suggested by a referee.

meso compound, since the transition state in the latter would have a lower $\Delta H_f^{\ddagger}$ and there is no difference in the heats of formation of the molecules. This essential invariance of the relative molecular ion intensities is more characteristic of a frequency factor effect. However, examination of Pechine's data shows that the intensity ratios $(M\text{-}Br)_m/(M\text{-}Br)_r$ and $(M\text{-}Br)_m+(M\text{-}HBr_2)_m/(M\text{-}Br)_r+(M\text{-}HBr_2)_r$ increase with decreasing electron voltage which is consistent with his proposal[9]. In these and the cyclic compounds discussed below the presence of metastables shows that the $[M\text{-}HBr_2]^+$ ion is formed from the $[M\text{-}Br]^+$ ion (see Introduction). Pechine also showed that, in the *cis*- and *trans*-1,2-dibromocyclopentanes and the corresponding cyclohexanes, $(M)_c/(M)_t$ are 5 and 23 respectively and independent of electron voltage. More convincingly, the similar intensity ratios as described above for the butanes, where now the denominator consists of the intensities of the ions in the *trans* compounds, decrease slightly with decreasing electron voltage. This would be consistent with some anchimeric assistance by backside attack of the second bromine in the *trans* compounds, where the stereochemistry is correct. Here and elsewhere the low frequency factor for the anchimerically assisted reaction will probably rule it out except in those ions whose excess energy is just above E_s.

These ideas can be used to try to rationalize some of the observations in the case of the ethanes. Mention has already been made of the difference in behaviour of 1,1- and 1,2-dichloroethane. In the case of the corresponding bromine compounds, although the intensities of the $[M\text{-}Br]^+$ ions are similar, the molecular ion intensity in the 1,1-compound is 17, but in the 1,2-compound only 1·5. This can be correlated with a much larger $[M\text{-}HBr_2]^+$ ion in the spectrum of the latter. This would very tentatively suggest that anchimeric assistance could be occurring in the 1,2-compound. In the dichloro compounds the intensities of the molecular ions are very similar but in the 1,2-compound, the intense $[M\text{-}Cl]^+$ ion observed for the 1,1- compound is replaced by an $[M\text{-}HCl]^{+\bullet}$ ion. Now this cannot be explained by anchimeric assistance and the mass spectra of the 1,2-dichlorocyclopentanes and hexanes[50] show no evidence for the occurrence of anchimeric assistance. Any slight differences in the cyclohexane spectra have been attributed to neutral molecule enthalpy differences[51]. This difference in the behaviour of the chlorine substituent compared with bromine may be due to one or both of the following factors. (i) Chlorine is less able to donate electrons to the reaction site on the neighbouring carbon due to their being more tightly bound and closer to the nucleus[33]. (ii) However, as in aromatic substitution, when an electron deficiency develops on the carbon to which it is attached it may

be able to donate electrons to it. The latter would assist the formation of the $[M\text{-}Cl]^+$ ion in the 1,1-dichloro compound and in its isomer it would help the stretching of the hydrogen bond necessary for the formation of the $[M\text{-}HCl]^{+\bullet}$ ion.

C. Intensities of the Molecular Ions

In the monohaloalkanes the intensities of the molecular ions were correlated (see section III. B) with the magnitude of the lowest estimated or observed E_s. A similar correlation can be made in the polyhalomethanes where the intensity of the molecular ion (Table 11) decreases with increasing halogenation. Thus in the case of carbon tetrachloride and bromide

TABLE 11. Intensities of the molecular ions of polyhalomethanes (CX_nH_{4-n})

	$n=4$	$n=3$	$n=2$	$n=1$
X	—	1·0	—	—
F	0·00	1·0	5	50
Cl	0·00	1·0	38	63
Br	0·00	1·3	48	59
I	–	–	42	55

– spectra not available in compilations[18-20]. The molecular ion of methane has an intensity of 47.

the calculated appearance potential for the $[M\text{-}X]^+$ ion is below the probable electron impact ionization potential. In the case of the tetrafluoride the observed appearance potential for the $[M\text{-}F]^+$ ion is about 0·3 eV above the apparent spectroscopic ionization potential[31]; the latter are, however, often a little lower than the electron impact ionization potentials. Walter and coworkers suggest[52], from examination of the $[M\text{-}F]^+$ ionization efficiency curve, that this ion is formed by direct dissociation. In the trihalo compounds $A[CF_3^+] = 14{\cdot}7$ eV[43] and is the same as the lowest ionization process detected in the photoionization experiments[28]. A similar situation exists for $A[CCl_3^+]$ in the case of chloroform[41] and for $A[CBr_3^+]$ (calculated) in the case of bromoform.

In the dihalo compounds $A[CHF_2^+]$ is essentially the same[46] as the ionization potential (see Table 2). In the dichloro and dibromo compounds $E_s(M\text{-}X)$ is 0·9 and 0·7 eV respectively[53]. The calculated value in the case of the di-iodo compound, estimating the heat of formation of this compound, is about 0·6 eV.

Since all these are direct cleavage reactions with high frequency factors the correlation is obvious. This result is rather odd in view of the bond energies in the ground state of the neutral molecules which increase in the order I < Br < Cl < F. In qualitative terms, due to the electron-attracting ability of the halogens, the environment becomes increasingly more electron-demanding as more halogens are added to the same carbon. Thus the tendency increases to fragment to give a cation where the charge is located partially on a trivalent carbon, as opposed to being delocalized over the halogens in the molecular ion. This is naturally more marked with fluorine than with the other halogens. A similar explanation was used in the case of the monohaloalkanes.

IV. THE HALOETHYLENES

A. The Nature of the Molecular Ions

From the ionization potentials (Table 12) it can be seen that the replacement of hydrogen by halogen lowers the ionization potential from that of ethylene (10·6 eV). From this and the fact that the ionization potentials

TABLE 12. The electron impact ionization potentials of haloolefins ($C_2X_nH_{4-n}$)

X[a]	$n = 4$	$n = 3$	$n = 2(1,1\text{-})$	$n = 2(cis)$	$n = 2(trans)$	$n = 1$
F[b]	10·10	10·30	10·45	—	—	10·45
Cl	9·50	9·45	9·80	9·65	9·65	10·00
Br	—	9·30	—	9·45	9·45	9·80

[a] No data are available for the iodoethylenes.
[b] Data from reference 54.

for the corresponding alkyl halides are also higher it seems that the molecular ion is best represented as having the charge delocalized over the carbons and halogen(s)[54,55]. Lake and coworkers[56] have determined the vertical ionization potentials of CF_2CHCl (10·00 eV), CF_2CFCl (10·14 eV) and CF_2CCl_2 (9·84 eV) and reached a similar conclusion.

B. Fragmentation Patterns

In general the E_s values for these compounds are higher than in the corresponding ethanes and this is consistent with the much higher intensities (20–50) observed for the molecular ions.

The simple cleavage reactions resulting in the formation of the $[M\text{-}F]^+$ and $[M\text{-}H]^+$ ions in the fluoroethylenes have been investigated in detail by

Lifshitz and Long[54,57] and by Jennings[58]. The E_s values for these and other haloethylenes are given in Table 13.

TABLE 13. E_s values (eV) for the $[M\text{-}X]^+$ and $[M\text{-}H]^+$ ions formed from some haloethylenes[a]

Compound:	C_2F_4	C_2F_3H	CH_2CF_2		C_2H_3F	
Radical[b]	F	F	F	H	F	H
E_s	5·9	5·8	4·4	6·2	3·9	3·6

Compound:	*cis*-$(CHCl)_2$	*trans*-$(CHCl)_2$	*cis*-$(CHBr)_2$	*trans*-$(CHBr)_2$
Radical[b]	Cl	Cl	Br	Br
E_s	2·65	2·8	1·95	2·2

[a] For the fluorine compounds the values are from reference 54.
[b] I.e. radical lost.

The E_s data in the 1,1-difluoroethylene combined with the ratio (M-F)/(M-H) = 0·5 suggests that here frequency factor control is operating. In the mixed chlorofluoro compounds (Table 14) the intensity ratios are also consistent with statistical frequency factor control. The situation

TABLE 14. (M-Cl)/(M-F) intensity ratios in some chlorofluoroethylenes

Compound:	C_2F_3Cl	$CHClCF_2$	CFHCFCl	CFHCHCl	CHClCFCl
Ratio	0·5	1	5	2·6	>6

Compound:	$CFHCCl_2$	C_2Cl_3F
Ratio	>6	>10

is not so clear with some of the bromine-containing ethylenes. Only an $[M\text{-}Br]^+$ ion is observed in the spectra of CF_2CClBr, CF_2CBr_2, CFClCFBr, $CClBrCCl_2$ and CFHCFBr but in CFHCFBr the intensity ratio (M-Br)/(M-F) is 2 and in $CHBrCCl_2$ the (M-Br)/(M-Cl) ratio is 5.

These compounds also fragment by the expulsion of hydrogen halides. The E_s values for the monofluoro-, 1,1-difluoro- and trifluoro-ethylenes are 3·2, 4·0 and 4·5 eV respectively and these are considerably above the calculated values[54,57,58]. About half of this is due to the ion being formed with release of kinetic energy[58], presumably generated due to the low bonding radius of fluorine not allowing complete hydrogen–fluorine bond formation in the transition state[33]. The possibility of the rest being due to a kinetic shift[7] has been ruled out in the case of monofluoroethylene by

Jennings[58]. The explanation could lie in a competitive shift[7] since these E_s values are near those observed for the direct cleavage reactions. Also some of the excess energy could be carried away by the neutral fragment. In the two 1,2-dichloroethylenes $E_s[M\text{-}HCl]^{+\bullet}$ is the same (3·6 eV) being about 0·8 eV higher than the calculated value, presumably for one or more of the reasons suggested for the fluorine compounds. The fact that this ion occurs in the *trans* compound and that the E_s values are the same for both suggests that free rotation around the carbon–carbon bond can occur in the molecular ion, in agreement with its proposed structure. Although the energetic data are not available in the corresponding fluorine compounds, the similarity of the spectra, particularly the metastable ion intensities[58], suggests the same situation in these compounds*.

Direct cleavage of the carbon–carbon bond to give ions of the type $[CXY]^{+\bullet}$ often occurs. Thus the ion $[CF_2]^{+\bullet}$ comes from all the polyfluoroethylene molecular ions as shown by the presence of metastable ions[58], although its intensity is very small in some cases. In the tetrafluoro compound it comes also from the $[M\text{-}F]^+$ ion and in the trifluoro compound from the rearrangement ion $[CHF_2]^+$. The latter ion and its counterpart $[CX]^+$ come not only from the molecular ion but other ions as well in the case of the fluoroethylenes[58]. These rearrangement ions are mainly noticeable in the fluorine-containing compounds and as far as the data are available and reliable, their absence or presence seems to be governed by energetic factors. Thus in 1,1-difluoroethylene $E_s[CH_2F]^+$ is 0·3 eV higher than $E_s[M\text{-}F]^+$ and the former ion is observed. However, the calculated E_s for the $[CHF_2]^+$ ion in this compound is 0·8 eV higher than for the $[M\text{-}F]^+$ ion and this ion is not observed. The combination of higher E_s and lower frequency factor is presumably responsible for this. In the case of 1,1-dichloroethylene the corresponding difference in E_s values for the formation of the $[CH_2Cl]^+$ ion would be about 3·5 eV and it is not surprising that this ion is not observed. Thus where the data are known the spectra of these compounds can be rationalized.

V. INFLUENCE OF REMOTE π-ELECTRONS ON THE FRAGMENTATION OF CARBON–HALOGEN BONDS

Remote in this context means that the halogen is not attached to a carbon of the π-electron system in the neutral molecules. The case of the benzyl halides is more conveniently discussed elsewhere (section VI. C).

* The basis of this and other statements about the 1,2-difluoro-compounds rests on Jenning's comments that the spectra of these molecules and the metastables are very similar to the 1,1-compound[58]. The author gives no details.

In the case where the π-electrons are associated with a simple double bond in the neutral molecule the phenomenon of double-bond migration under electron impact complicates the issue[59]. In the case of propene this has been shown to involve 1,2- and 1,3-hydrogen shifts, but not to demand the equivalence of the three carbons[60]. The similarity of the spectra of the 1-, 2- and 3-monohalopropenes (Table 15) suggests considerable substituent migration such as occurs in the haloethanes and haloethylenes.

TABLE 15. The intensities of some selected ions in the mass spectra of the monohalopropenes[a]

Position of halogen	2-F	3-F	1-Cl	2-Cl	3-Cl	1-Br	2-Br	3-Br
(M)	20	23	23	26	19	22	27	16
(M-X)	4	3	38	39	42	45	37	48
(M-H_2X)	17	11	23	21	23	23	22	24

[a] When allowance is made for the intensity of the $[M-H]^+$ ion in the 2-fluoro compound (36) and the 3-fluoro (40) it can be seen that in all cases these ions constitute more than 75% of the total.

The absence of energetic data precludes any more detailed discussion but the problem of double-bond migration and/or substituent migration makes the interpretation of the results in the other cases more difficult.

Tomer and coworkers[12] have examined the possibility of anchimeric assistance by π-electrons in the case of 4-bromo-1-butene and 5-bromo-1-pentene. In these compounds $E_s[M-Br]^+$ is 0·7 and 0·6 eV respectively, which although apparently lower than the values in Table 4, for the loss of bromine from alkyl bromides, is in fact probably the same within experimental error. The magnitude of error in determination of E_s values by different groups in the case of alkyl bromides is typified by a recent value for $E_s[M-Br]^+$ for ethyl bromide of 0·6 eV [61] compared with the value given in Table 4. Thus it does not seem necessary to invoke anchimeric assistance in this case. Tomer and coworkers[12] have also examined the spectra of some ring-substituted 5-bromo-2-phenyl-2-pentenes in which the major primary fragment ions are $[M-Br]^+$ and $[M-CH_2Br]^+$. In all cases the ratio (M-Br)/(M-Br)+(M-CH_2Br) increases with decreasing electron voltage, showing that $E_s[M-Br]^+$ is the lower. This is not unexpected since this is the case in most of the alkyl bromides (Tables 4 and 5) and a similar observation has been made in the case of the bromo butene and pentene mentioned above, where $E_s[M-CH_2Br]^+$ is about 2·6 eV. In these compounds the metastable intensity for the $[M-Br]^+$ ion, except

in the *p*-methoxy compound, is always larger than that for the $[M\text{-}CH_2Br]^+$ ion. This can be taken as indication, but is not proof (see Introduction), of the fact that rearrangement occurs in the formation of the $[M\text{-}Br]^+$ ion. Finally, where observed, the loss of C_4H_8 from the $[M\text{-}Br]^+$ ion must involve a rearrangement, requiring complete hydrogen scrambling[12] in the case of the parent compound. Whether this occurs before or after the expulsion of bromine is not known. As the authors conclude, the possibility of anchimeric assistance cannot be ruled out, but the evidence is not conclusive.

In the *endo* and *exo*-5-X-2-norbornenes (X = Cl or Br) $E_s[M\text{-}X]^+$ is the same for both isomers (X = Cl, 1·9 eV [62]; X = Br, 0·95 eV [12]). Thus any anchimeric assistance cannot amount to more than a few kcal/mole. For X = Br in both isomers the intensity of the $[M\text{-}Br]^+$ ion increases relative to that of the other primary fragmentation, the retro-Diels–Alder reaction[59], on decreasing the electron voltage. The measured appearance potentials for these reactions are the same within experimental error. Tomer and coworkers[12] conclude on the basis of the E_s values that anchimeric assistance occurs here in both isomers but the fact that the (M-Br)/(retro-Diels–Alder ion) intensity is lower in the *endo* compound is due to a lower frequency factor in this case. This they consider to be due to a twisting of the double bond necessary in the *endo* compound to permit anchimeric assistance. This conclusion seems open to three criticisms: the first is that the E_s values for $[M\text{-}Br]^+$ are no lower than in the alkyl bromides (Table 4). It could be argued, following a suggestion of Cooks and coworkers[63], that this comparison may not be valid here since in the norbornenes the charge is not located on the bromine in the ground state as it is in the alkyl bromides. However, if the ionization potential of the lone pair of the bromine atom in the norbornenes is the same as in the alkyl bromides then the comparable E_s would be nearly zero since $A([M\text{-}Br]^+)$ is 10·1 eV (Table 1).

Secondly, if the double bond has to be twisted in the *endo* compound this should result in an increase in E_s for the loss of bromine compared with the *exo* compound. This is not observed.

Thirdly, by analogy with the gas-phase retro-Diels–Alder reactions of cyclohexene, 4-methyl- and 4-vinyl-cyclohexene[64], this reaction of the molecular ions should have a very high frequency factor. That the $[M\text{-}Br]^+$ ion, with a similar appearance potential, competes with this reaction implies that it must have a high frequency factor. The only explanation for the difference in intensities seems that in the *exo* compound the product is stabilized by bond formation after loss of bromine. The absence of a complete spectrum makes this point difficult to check. In the chlorine

compounds the intensities of the $[M\text{-}Cl]^+$ ions are smaller and probably no anchimeric assistance occurs here since the (M-Cl)/(M) ratios are similar in both compounds.

A similar observation, although its precise significance is not clear, is that of De Jongh and coworkers[65]. They find that the ratio (M-Br)/(M) in *exo*-norbornyl bromide is ten times that in the *endo* compound when 70 eV electrons are used. From photoionization studies the same ratio is 13·6 times higher in the *exo* compound. The authors suggest that, in the latter case, the exciting line corresponds to 10·2 eV but this seems too low. Bunton and Pesco[66] have examined the spectra of some methylated norbornyl chlorides. In the case of *iso* (*exo*) bornyl chloride the (M-Cl)/(M) ratio is about twice as large as that in the *endo* isomer (bornyl chloride), but in the case of α-fenchyl chloride this ratio is about half that in the *endo* isomer (β-fenchyl chloride). Thus a similarity in behaviour between the saturated and unsaturated anologues is observed.

Shapiro and Jenkins[13] have examined the possibility of participation of the benzene ring in the loss of bromine from 2-phenylethyl bromide and ring-substituted analogues. This was prompted by the observation of McLafferty that the intensity of the $[M\text{-}Br]^+$ ion was larger in this compound than in the case of 3-phenylpropyl bromide[17]. In all the compounds studied[13] it was found that the intensity of the $[M\text{-}Br]^+$ ion relative to the other primary fragment ion $[M\text{-}CH_2Br]^+$ increased by a factor of between 2 and 16, depending on the substituent, when the electron voltage was dropped from 22 to 10 or 11 eV. This shows, as expected from the $E_s[M\text{-}Br]^+$ and $E_s[M\text{-}CH_2Br]^+$ values in Tables 4 and 5, that $E_s[M\text{-}CH_2Br]^+ > E_s[M\text{-}Br]^+$. This is also in keeping with the results for 4-bromo-1-butene and 5-bromo-1-pentene discussed above. Further, Grützmacher[61] has shown that $E_s[M\text{-}Br]^+$ is the same for the 3-phenylpropyl and 2-phenylethyl compounds (1·1 eV) and higher than the value he determined (0·6 eV) for $E_s[M\text{-}Br]^+$ in ethyl bromide. In the case of some of the substituted compounds Grützmacher has shown that, whereas the ionization potential depends on the substituent, the appearance potential for the $[M\text{-}Br]^+$ ion is almost independent of it (Table 16). This

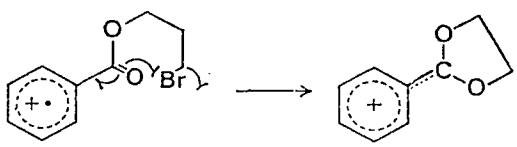
TABLE 16. Ionization potentials of and A($[M\text{-}Br]^+$) for some ring-substituted 2-phenylethyl bromides

Substituent	*p*-NO_2	*p*-Cl	*m*-Cl	H	*p*-MeO	*m*-MeO	*p*-NH_2
I(M) (eV)	9·6	8·8	9·1	9·0	8·2	8·5	7·8
A($[M\text{-}Br]^+$) (eV)	10·3	10·1	10·3	10·1	10·1	9·9	10·1

he interprets as showing that in the $[M\text{-}Br]^+$ ion the charge is isolated from the phenyl ring, whereas in the molecular ion the ionization potentials correspond to the charge being located on the phenyl residue. The suggestion of Cooks and coworkers[63] that the reactive state of the molecule is that in which the charge in the molecular ion is located on the bromine, runs into the same objections as in the case of the norbornenyl bromides. It also does not explain why, if the phenyl ring is involved, it does not change the appearance potentials more dramatically.

Grützmacher[61] also points out that at all electron voltages the ratio (M-Br)/(M) is the same for any pair of *meta* and *para* isomers, which is consistent with non-involvement of the phenyl residue. The observation by Grützmacher[61] and Nibbering and de Boer[67] that the hydrogens in the $[M\text{-}Br]^+$ ion are completely randomized before expulsion of acetylene does not tell us whether this occurs before or after the formation of the $[M\text{-}Br]^+$ ion. Although the metastable intensity for the $[M\text{-}Br]^+$ ion is always larger than that for the $[M\text{-}CH_2Br]^+$ ion this is also not conclusive evidence for phenyl participation. Grützmacher rationalizes the original observation of the relatively low intensity of the $[M\text{-}Br]^+$ ion in the 3-phenylpropyl bromide by pointing out that, unlike the case of the 2-phenylethyl compound, cleavage of the $[M\text{-}Br]^+$ ion to give *m/e* 91 is favourable. A metastable confirms this reaction in the 3-propyl compound only and the intensity of this ion is much higher in this compound compared with the 2-ethyl compound. The intensities of the molecular ions in the two compounds are similar, which again argues against a difference in behaviour. Finally in the 3-phenylpropyl bromide the formation of an $[M\text{-}C_2H_4]^{+\bullet}$ ion[68] shows phenyl participation in this case and generally (see section VI. D) five-membered ring ion formation[70] seems more important than four-membered ring ion formation in this type of compound.

Two cases of neighbouring-group participation involving the expulsion of a halogen seem to have been proven and one is discussed in section VI. D. Shapiro and Tomer[11] have shown that in the case of β-bromoethyl benzoate the $[M\text{-}Br]^+$ ion probably has a cyclic structure. Labelling the carbonyl group with ^{18}O and measuring the metastable intensity for the



(12)

transition $[M\text{-}Br]^+$ to *m/e* 107 ($C_7H_5{}^{18}O$) and to *m/e* 105 ($C_7H_5{}^{16}O$) gave the result that these two intensities were equal. This implies that the two

oxygens have become equivalent, which is most easily explained by the formation of the $[M\text{-}Br]^+$ ion according to (12). In this case there seems no reason for bond formation to occur after the loss of bromine since the bond would have to be broken again before further fragmentation and this mechanism would have a lower frequency factor and probably a higher E_s. Other data and deductions similar to those in the case of 2-phenylethyl bromide were also presented. For the same reasons these in themselves are not convincing, but since they occur in this well-documented case, they support the arguments of Shapiro and coworkers in the other cases[12,13].

VI. AROMATIC AND BENZYLIC HALIDES

A. Nature of Molecular Ions of Halobenzenes and Benzyl Halides

The ionization potentials for benzene and the monohalo compounds are given in Table 17. Both the electron impact and photoionization data show the same trend. A graph of the electron impact ionization

TABLE 17. Ionization potentials (eV) of benzene and the monohalobenzenes

Substituent	F	Cl	Br	I	H
I(M) Electron impact[a]	9·75	9·55	9·45	9·05	9·70
I(M) Photoionization[b]	9·18	9·03	8·95	8·68	9·25

[a] Taken from reference 69 these agree well with the data in reference 70.
[b] Reference 71.

potentials against Taft's inductive constant (σ_i)[27] gives a straight line in agreement with the idea of charge localization on the benzene ring in the ground state of the molecular ion. Further, the lone pair ionization potentials have also been detected[71]. A similar situation presumably exists in the benzyl halides where the ionization potentials are X = Cl, 9·2 eV; X = Br, 8·9 eV and X = I, 8·8 eV, very similar to the halotoluenes[70].

B. Primary Fragmentations of Aromatic Halides

Apart from fluorobenzene, which also loses hydrogen, the major primary fragmentation in these compounds is the loss of the halogen and the E_s values for this are given in Table 18. With the exception of the E_s value for bromine these values agree well with the bond energies in the neutral molecule. In these compounds, since the charge is not located near the carbon–halogen bond, its bond energy is likely to be similar in

TABLE 18. E_s Values[a] for the $[M\text{-}Y]^+$ ion formed from, and (C-Y) bond energies in, compounds of the structure C_6H_5Y in eV

	Y = H	Y = F	Y = Cl	Y = Br	Y = I
E_s	4·4	4·75	3·6	2·5	2·4
Bond energy (C-Y)[b]	4·4	4·5[c]	3·7	3·1	2·5

[a] These are the minimum E_s values reported[21, 70]; for higher values see reference 21.
[b] Reference 72.
[c] Reference 73.

the molecular ion and molecule. This agreement would suggest that the loss of hydrogen and halogen was a direct cleavage reaction. The E_s value of 2·5 eV [70] for bromobenzene may be a little low in view of the good agreement observed between bond energies and E_s values in other cases. A direct cleavage reaction would also be in keeping with the similarity in the ratio (M-X)/(M) in various aromatic halides. Thus for the four aromatic residues phenyl, 1- and 2-naphthyl and 2-biphenyl, for a given halogen, a maximum variation by a factor of 2 is observed[17].

Brown[74] has determined E_s values for the loss of chlorine from a series of *meta*- and *para*-substituted chlorobenzenes. The differences between isomers in each isomeric pair range between 0·05 and 0·15 eV. These differences are hardly experimentally significant, and Brown suggests that this is consistent with rearrangement involving the loss of positional identity. However, as Brown himself points out, it is not clear what difference would be expected if direct cleavage occurred. On the basis of Brown's evidence, with one exception, there is no definite conclusion to be drawn.

Brown also remarked[74] on the very low E_s values for the loss of chlorine from *meta*- and *para*-chlorotoluene and suggested that this was probably due to ring-expansion to the cycloheptatriene ring system before fragmentation. Yeo and Williams[70] have studied all the halotoluenes except the fluoro compounds and determined E_s values for the $[M\text{-}X]^+$ ions. These values (X = Cl, 2·8 eV; X = Br, 2·4 eV and X = I, 2·4 eV) are independent of the position of substitution. Comparison of the values for the chlorotoluenes with that for chlorobenzene suggests that in the toluenes ring-expansion to the cycloheptatriene ring system occurs before or during the loss of chlorine. In the case of bromine and iodine these values agree well with the values determined by the authors[70] for the loss of halogen in the monohalobenzenes (Table 18) and they conclude that in this case direct cleavage occurs. Analysis of the peak intensities in the halotoluenes

compared with the halobenzenes and the benzyl halides shows that the chlorotoluenes resemble benzyl chloride, but that in the other cases they resemble the halobenzenes. The authors consider that these figures imply that E_s for this ring isomerization lies between 2·4 and 2·8 eV. This would imply an E_s of 0·4 eV for the loss of chlorine from the cycloheptatriene, which seems rather low and suggests that this may be a concerted elimination and expansion. An alternative explanation will be discussed below.

One other curious point which may be related to this is the observation that for the halobenzenes the intensities of the molecular ions decrease in the order F > Cl > Br > I, whereas a different order is observed (Table 19) in the alkyl-substituted halobenzenes. If ring-expansion occurs only in

TABLE 19. Intensities of the molecular ions of compounds of the type p-RC_6H_4Y

R	Y = F	Y = Cl	Y = Br	Y = I	Y = H
H	75	61	55	50	50
Me	28	25	42	50	31
Et	18	10	25	—	15

the fluoro and chloro compounds this would lower the E_s values in these compounds for the loss of hydrogen (R = Me)* and methyl (R = Et)*. This is based on the figures for $E_s[M\text{-}H]^+$ in toluene† (ca. 1·5 eV) and for $E_s[M\text{-}Me]^+$ in ethylbenzene† (ca. 2·4 eV). Both these reactions are energetically at least as favourable as the loss of bromine and iodine from the corresponding halotoluenes. The lower frequency factor in the case of the ring-expansion reaction may well be why it does not occur in these compounds. However, in the case of the fluoro and chloro compounds the higher E_s values for the loss of the halogen and for the loss of a methyl group from the aromatic ring without ring-expansion allow this ring-expansion to occur. Thus more of the molecular ions will have enough energy to fragment in the fluoro and chloro compounds. The low E_s value for the loss of hydrogen from toluene implies that the lower limit of 2·4 eV for the ring-expansion reaction suggested by Yeo and Williams[70] is too high, essentially due to a kinetic shift effect[7] due to the low frequency

* There is a marked increase in the intensity of the $[M\text{-}H]^+$ ions in the chloro and fluoro toluenes and the $[M\text{-}CH_3]^+$ ions in the chloro and fluoro ethylbenzenes compared with these ions in the corresponding bromine and iodine compounds.

† Ring-expansion is known to occur in toluene and ethylbenzene.

factor, combined with a competitive shift[7] because of the relatively easy loss of the bromine or iodine atom. This would result in a somewhat higher value for the energy required for the loss of chlorine from the rearranged chlorotoluenes than that of 0·4 eV deduced from the work of Yeo and Williams[70].

C. Fragmentation of Benzyl Halides

The major fragmentation in these compounds is the loss of the halogen atom but it is not clear whether this occurs before, during or after ring-expansion. Using the data considered by Lossing[75] to be the most reliable for the heats of formation of the tropylium and benzyl cations, the appearance potentials for the loss of the halogen by direct cleavage and for rearrangement before or during loss can be calculated. These are compared with the observed values in Table 20. In the case of the iodine

TABLE 20. Comparison of observed and calculated A([M-X]$^+$) values in benzyl halides

X	A([C_7H_7]$^+$)[a]	A([$C_6H_5CH_2$]$^+$)[b]	Photo-ionization[c]	Obs.[d]	Obs.[e]
Cl	11·20	11·75	11·60	10·6	10·4
Br	9·15	9·55	9·40	9·1	9·7
I	8·80	9·15	9·20	9·2	9·3

[a] Calculated on the basis of formation of tropylium ion before or on fragmentation.
[b] Calculated on the basis of direct cleavage.
[c] Calculated using the result of Lossing[75], determined by photoionization, that ΔH_f is the same for the tropylium and benzyl cation. Lossing[75] considers that this result may not be correct.
[d] Reference 70.
[e] Reference 76.

compounds, since the observed values are in reasonable agreement with that calculated for the formation of the benzyl cation and since this reaction would have a higher frequency factor, direct cleavage seems the most likely route. In the case of the bromide the values suggest a preference at excess energies just above E_s[M-Br]$^+$ for ring-expansion. The observed results in the chloro compound are most puzzling, being lower than those calculated either for direct cleavage or ring-expansion. Meyerson and coworkers[76] have shown that in benzyl chloride the loss of acetylene from the [M-Cl]$^+$ ion occurs after hydrogen randomization in the [M-Cl]$^+$ ion. This is consistent with, but not proof of, ring-expansion before or during chlorine loss.

Tait and coworkers[77] have determined the differences in A([M-X]$^+$) for the *meta* and *para* isomers of the type $RC_6H_4CH_2X$ in order to investigate this problem. It has been shown experimentally that the carbon–halogen bond energy in such pairs does not differ by more than 2 kcal/mole and so equation (13) is a good approximation to the difference in appearance potentials for the [M-X]$^+$ ion, if the benzyl radicals are formed[77]. The ionization potentials of the substituted benzyl radicals have been determined or estimated[78] and thus the validity or otherwise of equation (13) can be determined. For X = F and R = Me or F the observed difference in

$$A([M\text{-}X]^+)_m - A([M\text{-}X]^+)_p = I(RC_6H_4CH_2^\cdot)_m - I(RC_6H_4CH_2^\cdot)_p \qquad (13)$$

appearance potentials was zero, within experimental error, whereas the difference in the ionization potentials of the corresponding radicals was $0{\cdot}2 \pm 0{\cdot}06$ and $0{\cdot}4 \pm 0{\cdot}16$ respectively. While the value for R = F may be just experimentally significant and suggests ring-expansion, the value for R = Me allows no decision to be made. In the case where R = MeO and X = Cl the observed difference in appearance potentials of $1{\cdot}15 \pm 0{\cdot}1$ eV is in good agreement with the estimated difference in ionization potentials of $1{\cdot}00 \pm 0{\cdot}1$ eV and thus suggests direct cleavage. In general, if ring-expansion occurred, loss of positional identity is imagined to occur due to rapid hydrogen shifts and hence the difference in appearance potentials should be zero. Thus the result for R = Me does not rule out ring-expansion, whereas it is definitely ruled out for R = MeO.

Nibbering and coworkers[67,79] have examined the structure of the decomposing [M-Br]$^+$ ion in the case of 1-phenylethyl bromide. By the use of deuterium labelling it has been shown that the loss of acetylene from this ion to give *m/e* 79 occurs after all the hydrogens have become scrambled[67]. However, the ^{13}C results[79] although complex show that simple C_6 to C_7 ring-expansion does not occur. A partial analysis of their results is given in Table 21. The $[C_6H_7]^+$ ion comes from the [M-Br]$^+$ ion as shown by the

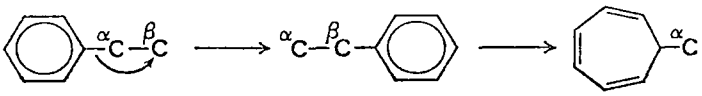
TABLE 21. Partial analysis of the ^{13}C labelling results for $\alpha^{13}C_1$, $\beta^{13}C_1$ and $\alpha,\beta^{13}C_2$ 1-phenylethyl bromide

Ion formulae	C_6H_5		C_6H_6		C_6H_7		
Position of label	α	β	α	β	α	β	$\alpha\beta$
% Total retention[a] of label	73	51	100	63	33	32	23

[a] For the $^{13}C_2$ no figures can be calculated for complete retention in the $[C_6H_6]^{2+\cdot}$ and $[C_6H_5]^+$ ions.

presence of a metastable. The 70 eV data for this ion fit a combination of two mechanisms, one being direct loss of the side-chain carbons and one in which all the carbon atoms become equivalent, perhaps involving the formation of an eight-membered ring. The $\alpha^{13}C_1$, $\beta^{13}C_1$ and $\alpha,\beta^{13}C_2$ compounds labelling results give the same fraction (0·43) for the complete carbon randomization reaction. The 15 eV spectra are not reliable, since the unlabelled compound shows that 6% of the total ion current in the C_6 region is due to the $[C_6H_5]^+$ ion but there is no trace of this ion nor its $^{13}C_1$ analogue in the spectra of the singly labelled compounds. This suggests that the voltage scale has not been calibrated correctly. In the metastable spectra the fraction of complete randomization rises, as expected, to 0·60 in the singly labelled compounds and 0·65 in the doubly labelled compound. This variation is probably within the experimental error in measuring metastable intensities.

There is no metastable evidence as to the origin of the $[C_6H_6]^{+\bullet}$ ion but the observation of 100% label retention in the case of the $\alpha^{13}C_1$ compound rules out direct loss of the side-chain carbons in its formation. The observation of approximately two-thirds label retention only in the $\beta^{13}C_1$ compound rules out an expansion to a C-7 ring followed by the loss of a C_2 unit involving only the carbon atoms of the original phenyl group. The only simple mechanism which may explain the results is shown below and would result in a 70% label retention in the $\beta^{13}C_1$ compound if the carbon atoms are completely randomized in the seven-membered ring, i.e. the (α)C—(β)C bond being broken.



The labelling results for the $[C_6H_5]^+$ ion, whose origin is unknown, can be explained on the basis of two mechanisms: (i) direct cleavage, and (ii) a similar rearrangement to that postulated for the $[C_6H_6]^{+\bullet}$ ion. The percentage loss of label in the $\alpha^{13}C_1$ and $\beta^{13}C_1$ compounds gives values of 27 and 33% respectively for the direct cleavage reaction. On this combination of mechanisms the loss of label in the $\alpha,\beta^{13}C_2$ compound should be ca. 30%. The experimental results are such that all that can be said is that this value lies between 20–27%, which makes the hypothesis just acceptable.

The purpose of this detailed analysis is to show that in no case is the structure of the decomposing $[M\text{-}Br]^+$ ion one which involves the incorporation of the α carbon in a seven-membered ring, and hence by analogy that this does not occur in the case of benzyl bromide. This has already

been ruled out in the case of the formation of the $[C_6H_6]^{+\bullet}$ ions. In the case of the $[C_6H_5]^+$ ions partial involvement of this mechanism would require equal or greater retention of the label in the $\beta^{13}C_1$ compound than in the $\alpha^{13}C_1$ compound, assuming the other mechanism was direct cleavage or expansion to a C-8 ring. In the case of the $[C_6H_7]^+$ ion the similarity of retention of label in the monolabelled compounds could be explained by a mixture of a direct cleavage reaction and expansion to a C-7 ring involving the α carbon. This would require that the $(\alpha)C—(\beta)C$ bond was not broken, i.e. no expulsion of the side-chain atoms as part of an acetylene unit. This would require that the percentage total label retention in the $\alpha,\beta^{13}C_2$ was the same as in the monolabelled compounds, which is not the case, and therefore this mechanism can be ruled out.

D. Neighbouring Group Participation in Expulsion of Aromatic Halogens

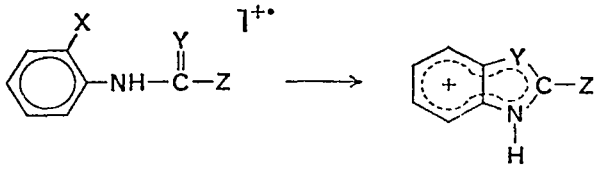
Baldwin and coworkers[69,80] have examined the spectra of some ring-substituted halophenyl-ureas, thioureas, acetanilides and thioacetanilides. On the basis of the much higher intensities of the $[M\text{-}X]^+$ ions in the *ortho* compounds compared with the *meta* and *para* compounds and the lower E_s values (Table 22) compared with the halobenzenes (Table 18), the

TABLE 22. $E_s[M\text{-}X]^+$ in compounds of the type $o\text{-}XC_6H_4NHC(Y)Z$

Compound	X = F	X = Cl	X = Br	X = I
Acetanilide (Y = O, Z = CH_3)[a]	[b]	0·85	0·85	0·85
Halophenylurea (Y = O, Z = HN_2)	[b]	0·90	0·90	0·85
Thioacetanilide (Y = S, Z = CH_3)	1·20	0·60	0·45	0·40
Halophenylthiourea (Y = S, Z = NH_2)	1·40	0·45	0·30	0·20

[a] These values agree with those determined by Benezra and Bursey[81] except for X = I where they find E_s = 0·60 eV.
[b] Ion intensity too small to be measured.

authors concluded that a five-membered ring ion is formed during the expulsion of the halogen. The absence of any noticeable difference in the behaviour of the monohaloanilines rules out a three-membered ring and a more detailed analysis suggests the most likely structure in all cases



involves the ion above. Similar ions are formed in the halophenyl guanidines[82] and in other aromatic compounds[83]. The formation of a six-membered ring ion in the case of *o*-chlorobenzylthiourea[69] has also been demonstrated and the absence of any difference between the spectra of *o*- and *p*-chlorobenzylamines[84] shows in this case the lack of formation of a four-membered ring ion.

VII. NEGATIVE ION FORMATION (PROCESS 2)

Since in this case the formation of negative ions often does not involve a metastable molecular ion, rearrangement processes are not so often observed and ions corresponding to simple bond cleavage on electron impact are mainly formed in the primary process. The thermodynamic relationship (14), in which $E_a[R^-]$ is the electron affinity of $[R^-]$ and E_x

$$A[R^{1-}] = E(R^1-R^2) - E_a[R^{1-}] + E_x \qquad (14)$$

any excess energy, governs fragmentation according to equation (2) of a molecule R^1-R^2. $E_a[R^{1-}]$ is defined by equation (15) and the bond energy

$$E_a[R^{1-}] = \Delta H_f(R^1) - \Delta H_f(R^{1-}) \qquad (15)$$

of the neutral molecule is $E(R^1-R^2)$. Although relatively few electron affinities are known those for the halogens are F, 3·50 eV; Cl, 3·61 eV; Br, 3·44 eV and I, 3·07 eV [85]. As pointed out by Blaunstein and Christophorou[86], except for X = F E(R-X) < $E_a[X]^-$ and hence if E_x is small $A[X^-] = 0$. This indeed seems to be the case in the chloromethanes where $A[Cl^-] = 0{\cdot}038$ eV and similar results have been found for other halomethanes not containing fluorine[85]. For compounds of the type $C_nH_{2n+1}Br$ [87] for $n = 1$, 10 $A[Br^-] = 0{\cdot}0$ and when $2 \leqslant n \leqslant 6$ it is 0·1 eV. It was suggested that the formation of the $[Br]^-$ ion proceeds from a short-lived (10^{-13} s) molecular ion.

A variety of fluorine-containing compounds have been examined and the appearance potential data for some alkyl fluorides are summarized in Table 23. Similar values for $A[F^-]$ have been observed for larger molecules[45].

As can be seen, these ions are formed in many cases with excess energy. In the case of carbon tetrafluoride this seems to be associated with the CF_3 moiety[89]. However, the semi-quantitative prediction obtained by using equation (14), i.e. that only in the case of $[F]^-$ or $[CF_3]^-$ formation should the appearance potentials be much above zero, is confirmed ($E_a[CF_3^-] = 1{\cdot}8$). This has also been confirmed in the case of trifluorochloromethane and dichlorodifluoromethane[86] where $A[F^-] = 3{\cdot}8$ and 1·5 eV respectively, but $A[Cl^-]$ is effectively zero. Many other processes

producing $[F]^-$ have been detected in the case of fluoroform, 1,1,1-trifluoroethane[88] and carbon tetrafluoride[89] and for the formation of $[CF_3]^-$ from perfluoroethane[88]. These could correspond to the molecules disintegrating into two or more neutral fragments as well as the ion, perhaps by a multi-step process.

TABLE 23. Lowest $A[F^-]$ and $A[CF_3^-]$ values (eV) for some fluorocarbons

Compound	$A[F^-]$	E(C—F)[f]	E_x[j]	$A[CF_3^-]$	E(C—Y)[h]	E_x[j]
CHF_3[a]	2·00	5·45[g]	0·7	—	—	—
CF_4[b, c]	4·70	8·15	2·50	5·40	7·2	1·65
CF_3CH_3[a]	1·50	4·95	–	—	—	—
CF_3CF_3[a, e]	1·70	5·15	–	1·60	3·4	−0·8
$CF_3C_2F_5$[d, e]	1·35	4·8	–	2·00	3·8	–

[a] Reference 88.
[b] Reference 89.
[c] Reference 86 gives $A[F^-] = 0·3$ eV which seems too low.
[d] Reference 90.
[e] Higher values are given in reference 45.
[f] Calculated using equation (14) and electron affinity values from reference 89.
[g] E(C—F) calculated.
[h] Y = F or C as appropriate.
[j] Calculated from thermal bond energies.
– means no independent values for E(C—F) available.

In the case of some other perfluoro compounds Naff and coworkers[91] have found that the maximum cross-section for the attachment of an electron is at 0·05 eV. These authors suggest that there are two states of the molecular ions with half-lives of about 10^{-13} and $10^{-4·5}$ s. This cross-section with a maximum at 0·05 eV must correspond to the long-lived ion since Bibby and Carter[92] have shown in the case of some of these compounds that $A[F^-] = 1·7$ eV. On the time scale of a normal mass spectrometer decompositions after 10^{-5} s are not detected.

Naff and coworkers find that the eV for maximum electron attachment in benzene is 1·55 and on fluorination it decreases until reaching 0·00 for 1,2,3,4-tetrafluorobenzene and pentafluorobenzene[91]. For substituted chlorobenzenes and chlorobenzene the calculated value of $A[Cl^-]$ using 14 is 0·1 eV, if E(C—Cl) (3·7 eV) for chlorobenzene is used. The observed values for chlorobenzene and *o*-chlorotoluene are 0·30 and 0·35 eV, suggesting a reaction with a small E_x whereas for all the dichloro compounds and monobromo- and monoiodo-benzene $A[X^-] = 0·00$ eV[92]. This is the result to be expected for the last two compounds on the basis of equation (14). The behaviour of chlorobenzene under these circumstances has been discussed theoretically by Clarke and Coulson[94].

VIII. ION PAIR FORMATION (PROCESS 3)

The major study in the case of the alkyl halides in this field is that of Hamill and coworkers[34,40]. They used a specially designed source which removes much of the effect of the energy spread in a beam of electrons produced by heating a metal filament. A more detailed discussion of this source is given in Field and Franklin's book[14]. The effect of this source is to make any breaks in the curve of ion current against electron voltage more distinct. The authors then[34,40] assign the breaks in these curves (ionization efficiency curves) to one of the three processes (1), (2) or (3) by comparing the eVs at which these breaks occur with appearance potentials calculated by using equations (5), (14) and (16) and assuming

$$A[F_1^-] = \Delta H_f(F^-) + \Delta H_f(F_2)^+ - \Delta H_f(M) + E_x \qquad (16)$$

that $E_x = 0$ in all cases. Apart from observing ground-state processes, breaks in the curves due to the formation of excited alkyl or halide ions were also observed. The data for the ground-state processes are given in Table 24. As can be seen in the case of *n*-propyl bromide and iodide the

TABLE 24. Ground-state appearance potentials[34,40] for $[R^+]$ formation from R—X by an ion pair mechanism (equation 3)

X	$R = CH_3$		$R = C_2H_5$		$R = n$-Pr		$R = i$-Pr	
	Obs.	Calc.	Obs.	Calc.	Obs.	Calc.	Obs.	Calc.
Cl	9·8	9·8	8·5	8·6	—	—	7·7	7·6
Br	10·7[a]	9·5	8·2	8·3	7·8	8·3	—	7·3
I	9·1	9·2	8·8	7·8	7·2	7·9	—	6·9

[a] See text.

observed appearance potentials suggest a partial isomerization to the isopropyl cation.

Within experimental error the difference between the observed value for $A[Me^+]$ from methyl bromide and the calculated value corresponds to the energy required to excite $[Me]^+$ to its first excited state. This value is determined by observing the breaks in the ionization efficiency curves for the other methyl halides at higher eV. In the case of methyl fluoride the observed $A[CH_3^+]$ is 10·8 eV whereas the calculated value is 11·24 eV.

The data[34,40] for the ionization potentials of these molecules are either in good agreement with the data in Table 1 or they quote previous values which are in good agreement with their values. Likewise except for

process (10b) in methyl iodide the E_s values calculated from their data are in good agreement with those quoted in Tables 4 and 5.

These authors have also established the operation of the ion-pair process corresponding to (10b), i.e. the formation of $[H]^-$ and $[CH_2X]^+$ in the methyl halides. In all cases the observed values are in good agreement with the calculated values and are between 0·6 and 0·7 eV lower than those for (10b), this difference being in good agreement with the electron affinity of hydrogen (0·77 eV).

IX. CONCLUSION

In general the formation of positive ion and neutral fragments, i.e. process (1), is to some extent understood and as far as processes (2) and (3) are concerned few theoretical problems have yet arisen. However, much more work remains to be done.

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The Chemistry of The Carbon-Halogen Bond: Part 1
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CHAPTER 5

Hydrogen-bonding and complex-forming properties

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I. INTRODUCTION

Halogen atoms linked to carbon atoms formally have three sets of lone-pair electrons. Further, particularly with fluorine, there is a large electronegativity difference between the two atoms and therefore carbon–halogen bonds are highly polar, the halogen atom being at the negative end of the dipole. Hence there should be the possibility of hydrogen bond formation with, for instance, hydroxyl or imino groups, the halogen atom acting as the electron donor (proton acceptor). In certain cases there is well-established evidence that this definitely occurs, but in other instances opinion is by no means unanimous, and both the evidence and its interpretation seem to be quite conflicting. This is especially true with regard to the relative behaviour of different halogen atoms under otherwise comparable circumstances.

There is little doubt that a halogen atom bonded to a carbon atom will exert an attraction upon a hydrogen atom linked to a strongly electronegative atom, but whether this attraction is strong enough in any particular instance to lead to hydrogen-bonding in which electron exchange occurs seems to be a matter for some speculation. In any case the evidence is that the bonds formed are very weak and therefore readily broken on the introduction of compounds with groups containing electron-donor atoms other than halogens and hence capable of yielding more stable hydrogen bonds. In favourable circumstances, however, the bonding, weak as it must be, is capable of having a profound effect on the properties of a molecule. In no case, though, has it been suggested that a halogen atom linked to a carbon atom is sufficiently basic as to lead to cation or zwitterion formation such as encountered, say, with an amino nitrogen atom.

In a similar way the halogen atoms concerned in carbon–halogen bonds should be capable of forming complexes with other electron-acceptor atoms, that is with Lewis acids. It was suggested some years ago that such compounds may be formed as intermediates in the Friedel–Crafts reaction. The present evidence is that such complexes are actually formed, but that they are extremely unstable at room temperature. A form of this behaviour which might be expected to occur under favourable circumstances is the formation of chelate compounds between *o*-halophenols or *o*-halobenzoic acids and metal ions, but no complexes of this type seem to have been reported.

In addition, the carbon–halogen bond is highly polarizable and so association should be possible between perhalogenated hydrocarbons and other polar or polarizable molecules. This has possibly not been taken into account sufficiently when many workers have regarded carbon tetrachloride, for instance, as an ideal solvent for dipole moment determinations, i.r. spectroscopic measurements, etc.

Finally, the presence of carbon–halogen bonds has a pronounced electron-withdrawing effect upon other bonds associated with the same carbon atom. Hence in polyhalogenated hydrocarbons the hydrogen atoms may become sufficiently acidic as to act as electron-acceptor atoms in hydrogen bonds, that is to form C—H···O or C—H···N bridges which would be quite impossible in the absence of vicinal carbon–halogen bonds.

There are therefore ample opportunities for various types of hydrogen bond and other complex formation to arise from the presence of carbon–halogen bonds, and the evidence for these will be reviewed successively.

II. HYDROGEN BONDING

A. Factors Influencing the Formation of Hydrogen Bonds by the Halogen Atom of a Carbon–Halogen System

The possibility of the formation of a hydrogen bond between the halogen atom of a carbon–halogen bond and a proton-donor group depends on a number of properties of the particular system concerned. These features also tend to determine the relative strengths of the bonds when they are formed. Hydrogen-bonding can occur intermolecularly or, if the halogen atom and the proton-donor group occupy suitable positions relative to one another, intramolecularly. Some of the factors considered here apply equally to the two types, while others apply mainly or exclusively to one type only. They may be summarized briefly as follows:

(i) Bond formation should be favoured by high basicity of the halogen atom. This is normally greatest for the fluorine atom, as exhibited by the hydrogen bonding which effects the formation of the bifluoride ion. Hence, in the absence of other factors, bonding would be expected to occur most frequently with the fluorine members of a series of halogen compounds. This basicity is reduced when the halogen atom is linked to an aromatic ring or other system to which electron density is donated by the halogen atom through a mesomeric effect. Such mesomerism is increased when an electron-withdrawing group, such as a nitro- or cyano-group occupies a position in the aromatic ring *o*- or *p*- to the halogen atom.

(ii) Bond formation should also be favoured by high acidity of the proton-donating group. Therefore the hydrogen atom of a hydroxyl group should hydrogen-bond most readily, this being followed by those of the imino- and amino-groups, as usually observed in hydrogen-bonding. Such acidity is favoured by the same factors as tend to decrease the basicity of the halogen atom. When a hydroxyl group, say, is linked to a conjugated system, as in phenol, it is a much stronger proton donor than it is in an alcohol. This effect would be intensified by the presence of electron-withdrawing groups *o*- or *p*- to it in the same ring, but such groups themselves tend to hydrogen-bond with the hydroxyl group.

(iii) Bonding is strongly influenced by an entropy effect in that the proton must have a reasonable chance of approaching the halogen atom. It is therefore favoured by donor and acceptor atoms being in close proximity in the same molecule so that intramolecular hydrogen bonds can be formed. Also there should be as few axes of internal rotation as possible between the two groups. Five- or six-membered rings might be expected to be the most easily formed. The hydroxyl hydrogen atom of a long-chain α-hydroxy-ω-halohydrocarbon would have only a very small chance of approaching the halogen atom.

(iv) Steric effects may be important in preventing the proton-donor group from approaching the halogen atom. Thus in the case of aromatic compounds the size and nature of groups occupying positions *o*- to the proton-donor group or the halogen atom will have an obvious effect. With intramolecular hydrogen-bonding steric effects may also arise from constraints, e.g. double bonds, within the molecule.

(v) It must be borne in mind that the most stable forms of hydrogen bond occur when the proton-donor, hydrogen and proton-acceptor atoms are colinear. 'Bent' hydrogen bonds can occur but become progressively weaker as the angle of 'bend' decreases. Hence an 'atomic size' factor may enter into questions of intramolecular bonding.

B. Evidence from Simple Physical Properties

In cases of known intermolecular hydrogen-bonding between molecules of the same species it is found that such bonding tends to lead to an increase in the boiling and melting points[1]. This is only to be expected, since such bonding, though forming and breaking rapidly, leads to an increased average molecular weight. A familiar example is provided by the higher boiling and melting points of water in comparison with its analogue hydrogen sulphide. Therefore when groups *p*- or *m*- to a proton-donor group in an aromatic compound can hydrogen-bond with the proton-acceptor group of another molecule of the same kind the compound is relatively involatile. On the other hand, when the groups are in *o*-positions the formation of intramolecular hydrogen bonds becomes possible. Bonding of this type maintains the compound in the monomeric state and so tends to keep the volatility of a liquid 'normal', resulting in a lower boiling point than for the other positional isomers. A classical example of this is provided by the nitrophenols, where the *o*-compound is appreciably steam-volatile. Also the *o*-compounds, having their affinities more fully satisfied internally, are less readily stabilized by falling into an ordered crystal lattice and thus often have lower melting points than their isomers.

Indeed, the possession of lower boiling and melting points by the *o*-isomer has often been taken as a criterion of intramolecular hydrogen-bonding in the latter, but in the absence of other evidence it should be taken, rather, as an indication of the presence of intermolecular bonding in the other isomers but of its relative absence in the *o*-isomer. This may conceivably be due either to preferential intramolecular bonding or to steric inhibition of intermolecular bonding.

In considering this test as applied to compounds containing a carbon–halogen bond the examples which come most obviously to mind are the various series of halophenols. As shown by the figures in Table 1 the

TABLE 1. Boiling and melting points of positional isomers

	Boiling points (°C)			Melting points (°C)		
	ortho-	*meta-*	*para-*	*ortho-*	*meta-*	*para-*
Fluorophenols	151·2	174	186	16·1	—	48
Chlorophenols	175·6	214	217	7	32·8	43
Bromophenols	194	236·5	238	5·6	33	63·5
Iodophenols	187	dec.	dec.	43	40	94
Fluoroanilines	175	186·1	187·6	−29		−0·82
Chloroanilines	208·8	229·8	231	−3·5	−10·4	70·2
Bromoanilines	229	251	dec.	32	18·5	66·4
Iodoanilines	dec.	dec.	dec.	56·5	33	68
Chlorobenzaldehydes	208	214	214	11	18	47·5
Xylenes	144·7	139·1	138·6	−29·1	−47·4	13·2
Cresols	191·5	202·8	203·5	30	12	36
Chlorotoluenes	159	162	162	−34	−47·8	7·5
Bromotoluenes	181·7	183·7	183·7	−27	−39·8	28
Dichlorobenzenes	183	172	173·4	−17·5	−24·8	53
Dibromobenzenes	224	219·5	219	5·6	−6·9	86·9
Toluidines	199·8	203·3	200·3	−16·3	−31·5	45
Tolualdehydes	194·5	199	204	—	—	—

boiling and melting points of the *o*-isomers are in each case appreciably lower than those of the corresponding *m*- and *p*-isomers. It is difficult to find complete analogies among compounds in which this type of hydrogen-bonding cannot occur but for which the physical measurements are about the same, but it may be noted that for the xylenes, dichlorobenzenes and dibromobenzenes the *o*-compounds have slightly the highest boiling points, whereas the *p*-compounds with their greater symmetry have in each case much the highest melting points. The latter property, therefore, should be discounted somewhat as evidence of hydrogen-bonding, as it appears to be primarily a reflexion of the ease of fit into a stable crystal lattice.

With regard to the boiling points it is noticeable that that of *o*-chlorophenol is lower than that of either *o*-cresol or of *o*-dichlorobenzene, whereas the boiling points of the other chlorophenols are appreciably greater than those of the corresponding cresols and dichlorobenzenes. On this evidence, therefore, there is probably hydrogen-bonding in the halophenols, occurring intermolecularly with the *m*- and *p*-compounds and intramolecularly in the case of the *o*-isomers. It is noticeable, however, that the effects upon which this conclusion is based are less pronounced

in the fluorophenols than in the other members of the series. The data presented in Table 2 support the conclusion regarding bonding in chlorophenols, since the dichlorophenols in which the hydroxyl group is *o*- to a chlorine atom have lower boiling points than those of the other isomers.

TABLE 2. Boiling points (°C) of dichlorophenols, dichloroanilines and related compounds

	2,3-	2,4-	2,5-	2,6-	3,4-	3,5-
Dichlorophenols	—	210	211	219	253·5	233
Dichloroanilines	252	245	251	—	272	260
Trichlorobenzenes	219	213	—	219	—	208·5
Diaminotoluenes	255	280	274	—	265	285
Trimethylbenzenes	176·1	169·4	—	176·1	—	164·7

Amongst the other series of compounds included in Table 1 the greatest suggestion of a lower boiling point for the *o*-isomer is observed in the case of the various haloanilines, but the effects are only about half of those for the corresponding halophenols. However, the toluidines have almost equal boiling points. Again the effect for the fluoroanilines is less than for the chloro- and bromoanilines; the iodoanilines cannot be included in this comparison as they decompose below their boiling points. The analogy between the boiling points of the hydroxy- and amino-compounds, but with smaller differences between the *o*-compounds and their isomers occurring in the latter case, extends to the dichloroanilines, where the isomers with a chlorine atom *o*- to the amino group are appreciably the more volatile.

The boiling points of *o*-chlorobenzaldehyde and of *o*-chloro- and *o*-bromotoluene are all slightly lower than for the respective *m*- and *p*-compounds. These differences, however, are hardly greater than those observed in the tolualdehydes. In the cresols hydrogen-bonding must occur primarily between the hydroxyl groups of different molecules, and this may well be sterically slightly hindered in the *o*-compound. The same may therefore be true also of *o*-chlorobenzaldehyde.

It was suggested by Friend[2] that hydrogen-bonding has a profound effect upon the viscosities of certain groups of compounds. Following up this point, Kendall[3] pointed out that *o*-chlorophenol has a much lower viscosity than its *m*- and *p*-isomers. This he took as evidence that intramolecular hydrogen-bonding occurred in the former but intermolecular bonding in the other two isomers.

The viscosity values shown in Table 3 show that similar arguments may be used with regard to the bromoanilines. The effect is less than for the chlorophenols but the viscosities of *o*-toluidine and *o*-xylene are actually greater than for the respective *m*-isomers. In support of the view that intermolecular hydrogen-bonding occurs in the *m*- and *p*-chlorophenols

TABLE 3. Viscosities (in centipoises) of compounds which contain aromatic carbon–halogen bonds, in comparison with those of analogous compounds

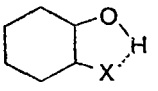
		Temperature (°C)				
		20	25	40	50	80
Chlorophenols	*ortho-*	4·20	4·11	—	2·015	—
	meta-	16·7	11·55	—	—	—
	para-	23·0	—	—	4·99	—
Bromoanilines	*ortho-*	—	—	3·19	—	—
	meta-	6·81	—	3·70	—	1·70
	para-	—	—	—	—	1·81
Xylenes	*ortho-*	0·810	—	0·627	—	—
	meta-	0·620	—	0·497	—	—
	para-	0·648	—	0·513	—	—
Cresols	*ortho-*	—	—	4·49	—	—
	meta-	20·8	—	6·18	—	—
	para-	—	—	7·00	—	—
Toluidines	*ortho-*	4·39	—	—	—	—
	meta-	3·81	—	—	—	—
	para-	—	—	—	1·80	—

and bromoanilines, as well as in *m*-cresol, the viscosities of these compounds show a relatively rapid decrease with rise of temperature. With *o*-chlorophenol the relative decrease with rise of temperature is little greater than that of the xylenes.

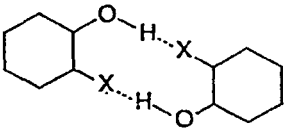
Summing up, therefore, the evidence obtained from boiling points and viscosities is that *m*- and *p*-compounds containing an aromatic carbon–halogen bond and a proton donor group undergo intermolecular hydrogen-bonding. This association does not necessarily involve the carbon–halogen group, but more probably occurs between two proton-donor groups. On the other hand, intermolecular bonding does not take place to the same extent with the *o*-compounds, being most reduced for the *o*-halophenols and less so for the *o*-haloanilines. That this is not due entirely to steric inhibition is evidenced by the fact that the boiling point and viscosity of *o*-cresol, where similar steric forces come into play, are only slightly lower than for the *m*- and *p*-isomers, and the boiling point of

o-toluidine is only very slightly lower but its viscosity is actually greater than for the *m*-isomer.

The indication is, therefore, that in the *o*-halophenols and *o*-haloanilines intramolecular hydrogen bonds are formed. These presumably occur as in **1**, although the formation of bimeric molecules as in **2**, though improbable, is not to be excluded entirely.



(1)



(2)

It would appear at first sight that the problems of molecular association might be resolved by cryoscopic means, but the low stabilities of the hydrogen bonds, if formed, preclude their persistence at the low concentrations required for meaningful studies by this method.

C. o-Halophenols

Boiling point and viscosity data suggest that a series of compounds in which direct evidence of hydrogen-bonding interaction by the halogen atom bonded to carbon might be most fruitfully sought would be the *o*-halophenols. The formation of an intramolecular bond in these compounds, however, involves the formation of a five-membered ring, so the atoms cannot possibly approach the linear O—H···X disposition which is the optimum for the formation of a strong hydrogen bond. On the other hand, the presence of an *o*-halogen atom increases the acidity of the phenolic group and hence should favour its ability to interact.

The first positive evidence of hydrogen-bonding in *o*-halophenols came from the results of i.r. spectroscopy. During a comprehensive study of the first overtone of the hydroxyl stretching band, Wulf and Liddel[4] observed that in most phenols this normally occurred at a characteristic frequency. For phenol itself it was at 7050 cm^{-1}, but for 2,4,6-trichlorophenol it occurred at 6890 cm^{-1}. With *o*-chlorophenol, however, there were two peaks, a weaker one at 7050 cm^{-1} and one about ten times as intense at 6910 cm^{-1}. Pauling[5] immediately suggested that in phenols the C—O bond has some double-bond character arising from resonance. Hence the hydrogen atom tends to lie in the plane of the rest of the molecule. For phenol itself and for 2,4,6-trichlorophenol the two coplanar positions of the molecule are equivalent, but the two compounds differ since in trichlorophenol the hydrogen atom is in each case in proximity to a chlorine atom. For *o*-chlorophenol, however, the positions differ; in a

trans form the phenolic hydrogen atom is in surroundings similar to those in a phenol, whereas in the *cis* form it comes near to the chlorine atom as in trichlorophenol and, according to Pauling's view, tends to interact with it. Pauling did not specifically mention hydrogen-bonding but this was undoubtedly implied. Such interaction tends to make the *cis* form the more stable and this form should therefore tend to predominate. This is supported by the fact that Wulf and Liddel's results indicate that the weaker band has the same frequency as that of phenol and therefore is due to the *trans* form. The relative intensities of the two bands indicated the presence of about 91% of *cis* and 9% of *trans*. Such a concentration ratio corresponds with a free energy difference of about 1·4 kcal between the *trans* form, which can only have weak bonds to solvent molecules, and the *cis* form with its intramolecular hydrogen bond. As the two peaks observed with *o*-chlorophenol correspond closely with the single peaks for phenol and 2,4,6-trichlorophenol, respectively, this may be taken as the energy difference arising from the interaction of the hydrogen and chlorine atoms. Pauling suggested that his interpretations could be tested by studying the effect of temperature on the relative areas of the two peaks.

While Wulf and Liddel's observations had been made upon carbon tetrachloride solutions, Badger and Bauer[6] found that the spectrum of *o*-chlorophenol in the vapour state has also two unequal peaks, and they supported Pauling's suggestion of the existence of two forms.

It was found by Wulf, Liddel and Hendricks[7] that *o*-bromo- and *o*-iodophenols, as well as *o*-chlorophenol, each show two distinct peaks in the first harmonic of hydroxyl stretching bands. The departure from the usual phenol frequency in their 'anomalous' peaks was found to increase in the order Cl < Br < I, suggesting a progressive increase in proton attraction in this order. This was attributed to the increasing polarizability of the halogen atoms, while the dipole moments of the carbon–halogen bonds, which are in the reverse order, were considered by them as relatively unimportant. Such a view was regarded as quite reasonable, since the directional axis of the moment of the C—X bond is almost at right angles to the direction of the H···X bond. For *o*-fluorophenol they could detect a single peak only. This was rather broad and had a maximum at about 7015 cm^{-1}, apparently somewhat lower in frequency than the *trans* peaks for the other *o*-halophenols. This behaviour was accounted for on the supposition that the absorption is really composed of two peaks, as in the other cases, but that one occurred at about 7050 cm^{-1} and the other at 7015 cm^{-1}, so that these overlapped considerably.

It was observed by Wulf and Jones[8] that in carbon tetrachloride solution *o*-halo- and symmetrical trihalophenols showed behaviour in the second

overtone region of the hydroxyl stretching absorption resembling that in the first overtone region. However, there was an increased displacement of the component absorptions relative to one another, while subsidiary peaks also occurred, and these appeared to stand in ordered relation to the principal peaks. Their relative intensities confirmed that the degree of intermolecular association in the *o*-halophenols is only about one-tenth that in phenol itself. The combination frequencies were studied in detail by Wulf and Deming[9].

Pauling's suggestion that his interpretations could be tested by studying the effect of temperature on the relative intensities of the two peaks was first followed up by Davies[10]. Working again on the first overtone of the hydroxyl stretching band of *o*-chlorophenol he found that the ratio of the intensities of the two peaks was 1 : 7·98 at 73°C. From this result he deduced that the free energy difference between the two forms was 14·20 cal/gram (i.e. 1·84 kcal/mole) at this temperature. He accepted the existence of *cis* and *trans* forms postulated by Pauling.

Later, Davies[11] showed that in the fundamental hydroxyl vibration region of *o*-bromophenol, absorptions occur at 2·84 and 2·785 μ (3521 and 3591 cm^{-1}) and that their relative intensities are 4·31 : 1 at 17°C and 2·95 : 1 at 75°C, corresponding with an energy difference of 0·850 kcal/mole. On comparing these results with the energy values calulated on the basis of electrostatic interactions, however, he concluded that it is not necessary to invoke hydrogen-bonding to account for the observations.

From a comprehensive study of the absorption peaks of the two forms of *o*-chlorophenol in the vapour phase, Zumwalt and Badger[12] found that over the temperature range of about 450–540K the enthalpy of the *trans* form exceeded that of the *cis* form by $3{\cdot}9 \pm 0{\cdot}7$ kcal/mole. The free energy change accompanying the interconversion of the two forms was $2{\cdot}8 \pm 0{\cdot}5$ kcal/mole and the entropy change 2·4 cal/degree at 180°C. They accounted for the fact that this free energy change was higher than that deduced by Pauling from data on solutions by the suggestion that the solvent tends to stabilize the *trans* form. To explain the large change in entropy, a change much greater than would be expected from the loss of only one degree of freedom, they suggested that the higher frequency band is due in part to molecules which perform complete rotations and the circumstance that, in the *cis* form at least, two bending vibrations have much higher frequencies than in the *trans* form owing to the contribution of the hydrogen bond to the rigidity of the chelated state.

On the other hand, Rossmy, Luttke and Mecke[13] expressed doubts regarding the validity of some of the quantitative inferences drawn by previous authors regarding intramolecular hydrogen-bonding in the

o-halophenols. This doubt arose from the large discrepancies in the *cis* : *trans* ratios which had been derived from the relative intensities of the two peaks, especially when different harmonics had been studied. This they attributed to the presence of phenol in the specimens of *o*-chlorophenol used. They also cast doubt on the inferences drawn from studies of the effect of temperature. Using specimens which had been carefully freed from phenol, they studied again the i.r. spectra of carbon tetrachloride solutions of *o*-chloro-, *o*-bromo- and *o*-iodophenols from the fundamental to the third overtone, together with the spectra of the vapours for the fundamental only. As a result of the purification many of the peaks attributed to the *trans* form were greatly reduced in intensity, while combination frequencies involving the *cis* form were detected. The frequency differences which they observed for the bands of the *cis* and *trans* forms and the ratios of their intensities are shown in Table 4.

TABLE 4. Frequency differences and *cis* : *trans* ratios for the *o*-halophenols in the vapour state and in carbon tetrachloride solution

	o-Chloro-		*o*-Bromo-		*o*-Iodo-	
	Frequency difference (cm^{-1})	Intensity ratio	Frequency difference (cm^{-1})	Intensity ratio	Frequency difference (cm^{-1})	Intensity ratio
Vapour						
Fundamental	83 (174°C)	70 : 1	93 (174°C)	—	115	16 : 1 (125°C) 19 : 1 (200°C)
Solution						
Fundamental	55	44 : 1	75	37 : 1	93	12 : 1
First harmonic	260	50 : 1	192–207	14 : 1	201	6 : 1
Second harmonic	234	215 : 1	320	40 : 1	384	7·5 : 1
Third harmonic	242	10 : 1	110	—	610	6 : 1

These results were in agreement with the values found from a study of the Raman spectra. From the effect of temperature on the relative proportions of the two forms of iodophenol in the gaseous state they deduced that the enthalpy difference between the two forms is 3·2 kcal/mole, whilst the free energy difference deduced from the proportions themselves was 2·8 kcal/mole. On the other hand, for dilute solutions in carbon tetrachloride the free energy difference calculated was only 1·4 kcal/mole,

so they inferred that the *trans* form seemed to be stabilized to the extent of 1·4 kcal/mole relative to the *cis* form through interaction with the solvent. For *o*-bromophenol in carbon tetrachloride the free energy difference was found to be about 2·1 kcal/mole, whilst the values for the vapour state and for *o*-chlorophenol were greater still.

The entropy difference between the two forms suggested by the results for *o*-iodophenol vapour (not more than 1 cal/degree) is much more reasonable than that found previously for *o*-chlorophenol, but at the same time the differences in *cis* : *trans* ratio found for the fundamental and the various harmonics suggest that these results must still be regarded as qualitative rather than sufficiently quantitative to permit the accurate calculation of entropy changes.

Rossmy, Luttke and Mecke pointed out that, when these results are taken into account, calculations based on simple electrostatic interaction[11] lose their good agreement with experimental data, so the conclusion of Davies regarding the predominantly electrostatic character of the hydrogen bonds in these compounds is diminished in force.

The difficulty in separating the *o*-halophenols from phenol was also stressed by Baker[14], but he confirmed that even after careful purification the spectra of all these compounds except *o*-fluorophenol still showed the hydroxyl group doublet. Further, the *cis* : *trans* ratios deduced from the relative intensities were not changed after further chemical purification. He suggested that the results, shown in Table 5, were much higher than

TABLE 5. Frequencies (cm^{-1}) attributed to the *trans* and *cis* dispositions of the hydroxyl group in *o*-halophenols and the *cis* : *trans* ratios indicated

	Frequencies		Difference in frequency	*cis* : *trans* Ratio
	trans	*cis*		
o-Fluorophenol	—	3584	—	—
o-Chlorophenol	3600	3582	18	56 : 1
o-Bromophenol	3598	3524	74	38 : 1
o-Iodophenol	3593	3500	93	13·5 : 1

those previously reported, but comparison with the figures in Table 4 reveals a good degree of agreement with the results of Rossmy and coworkers as far as the vexed question of the ratios of the intensities is concerned. The frequencies recorded, however, especially for the *cis* form of *o*-chlorophenol, differ considerably from those reported for the fundamental by these workers.

Baker pointed out that both the *trans* : *cis* ratio and the frequency difference between the bands attributed to the two forms follow the order F < Cl < Br < I. As this is the same as the order of the atomic diameters, he suggested that increased overlap between the hydrogen and halogen orbitals may occur, leading to increase in bond strength in this order in spite of decreasing electronegativity. He also suggested that Badger's Rule[15] may hold, i.e. that the change in frequency attributed to the formation of a hydrogen bond is a valid measure of the strength of the bond formed. He suggested that the *trans* isomers may be destabilized with respect to the *cis* forms in the order F < Cl < Br < I through (i) rehybridization of the oxygen orbitals, a resulting non-bonding sp^2 orbital overlapping and repelling a similar orbital of the halogen atom, and (ii) the ability of the halogens to participate in such an effect decreasing in the order F > Cl > Br > I.

An ingenious means of checking the order of the halogens in hydrogen-bonding with the hydroxyl group of the halophenols was employed by Baker and Kaeding[16]. Studying the absorption peaks and their relative intensities for a series of 2,4,6-trisubstituted phenols, they were able to identify the fundamental frequencies associated with the structures in which the phenolic hydrogen atom was hydrogen-bonded to each of the two different halogen atoms occupying the positions *ortho* to the phenolic group. From the relative intensities of the two bands they deduced the proportions in which the two forms were present. Their results are summarized in Table 6.

TABLE 6. Absorption frequencies (cm^{-1}) observed for the 2,4,6-trihalophenols and relative intensities of the bands

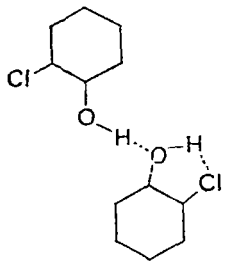
Substituent			Frequency when bonded to		Intensity ratio bonded to 2- : bonded to 6-
2-	4-	6-	2-	6-	
F	I	I	3568	3504	1·96
F	Br	Br	3574	3522	0·72
F	Cl	Cl	3580	3541	0·66
Cl	Cl	I	3535	3502	3·25
Cl	Cl	Br	3535	3515	1·6
Br	Br	I	3515	3496	2·2

On this evidence they inferred that the order of the hydrogen bond strengths in these compounds is Cl > Br > F > I, and that in this case Badger's Rule breaks down. The anomalous order was ascribed to a combination of the varying size of the halogen with an effect due to an

orbital–orbital repulsive interaction which would increase in the order Cl < Br < I. As this interaction was postulated to occur between the O—H bonding orbital and the electron-donating lone-pair orbital of the halogen atom, it would be affected by the small amount of directional character in the lone-pair orbitals and by interaction with lower-lying completed shells. For this reason they regarded the decrease in frequency as a measure of the interaction energy of the hydroxyl group with the halogen rather than that of the net energy of the resultant bonds.

In another attempt to determine the enthalpy changes associated with hydrogen and deuterium bonding in the *o*-halophenols and the corresponding deuterated compounds, Tien-sung Lin and Fishman[17] recorded their i.r. spectra in the vapour state at temperatures from their boiling points to 290°C. From the changes in relative peak heights with temperature they calculated ΔH values for the formation of intramolecular hydrogen bridges. Fluoro compounds did not yield clearly defined *cis* and *trans* peaks, but for *o*-chloro-, *o*-bromo- and *o*-iodophenol ΔH was 3·41, 3·13 and 2·75 kcal/mole, respectively, whilst for the three deuterium compounds it was 2·81, 2·65 and 2·65 kcal/mole, respectively, but the reason for the equality of the values for the bromo- and iodo-compounds is not clear. The effect of deuteration was attributed to partial excitation of the out-of-plane O—H and O—D bending modes of vibration of the *cis* isomers.

There is some evidence that the strengths of these bonds may be affected by quite other factors. Thus the observation of Errera and Mollet[18] of a maximum at 6620 cm^{-1} in the first overtone spectrum of *o*-chlorophenol was attributed by Pauling[19] to the formation of double molecules of the type shown in 3. These would be stabilized by the energy of the strong intermolecular O—H···O bond, which would increase the electronegativity of the proton-donor oxygen atom and increase the positive charge on the hydrogen atom linked to it, thus leading to the formation of a stronger intramolecular O—H···Cl bond, with resultant decrease in the hydroxyl group stretching frequency.



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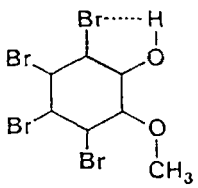

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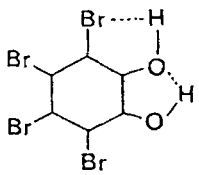


(5)

Similarly, a broad peak in the first overtone of the hydroxyl stretching band of tetrabromoguiacol (**4**) was found[7] to have a maximum at about 6816 cm^{-1}. This is lower than the frequency observed for monohalophenols and it appeared to be characteristic of phenols with both *ortho* positions occupied by a group exercising proton attraction, but it can be equally well explained by the presence of other halogen atoms as substituents in the ring increasing the electron density at the bromine. However, Pauling[19] inferred that under the particular steric conditions prevailing in this compound the proton attachment of the O—H···Br bond seems to be greater than that of the O—H···O bond. He also inferred that the two equal peaks reported[7] for tetrabromocatechol at 6820 and 6920 cm^{-1} arise from the structure **5**.

Very similar results have been reached as a result of the careful analysis of dipole moment measurements. In 1943 Anzilotti and Curran[20] observed that the moments of *o*-fluoro-, *o*-chloro- and *o*-bromophenols as measured in carbon tetrachloride solution were much lower than the values to be expected for equimolar amounts of the *cis* and *trans* forms or for free rotation of the hydroxyl group about the C—O bond. Instead they were such as to suggest that about 86% of the *o*-chlorophenol, for instance, had the hydroxyl group in the *cis* conformation. The similarity of the results for all three compounds suggested that the proportion of the *cis* form was about the same in each. In benzene solution the results suggested that in this solvent about 82% was *cis*. Considering the possible errors of this method, which involves *inter alia* an assumption regarding the orientation of the dipole axis in phenol itself, the agreement with the deductions of Wulf and Liddel, at that time the most modern, was remarkably good. The preference for the *cis* form was again attributed to intramolecular hydrogen-bonding by the molecule whilst in this conformation.

The apparent dipole moment of phenol itself is higher when measured in dioxan solution than in carbon tetrachloride or in benzene (Table 7), due to hydrogen-bonding of the phenolic hydrogen atom to the dioxan molecule. The fact that the moments of the *o*-halophenols were also higher in dioxan than in the other solvents was attributed partly to the circumstance that dioxan forms hydrogen bonds with the *trans* molecules and thus upsets the *cis* : *trans* equilibrium. Their evidence indicated that the increase in dipole moment produced in dioxan solution was greatest for *o*-bromophenol and least for *o*-fluorophenol, indicating, according to their interpretation, that the H···Br hydrogen bonds are more easily broken than H···Cl or H···F bonds. They were therefore forced to conclude that the strengths of the intramolecular bonds followed the order F > Cl > Br, and this in spite of the fact that the electrons of the bromine

TABLE 7. Dipole moments of phenol and of *o*-halophenols in various solvents

	Phenol	*o*-Fluoro-	*o*-Chloro-	*o*-Bromo-	*o*-Iodo-
μ_{calc} *cis*	—	0·42[b]	0·44[b]	0·43[b]	0·43[b]
μ_{calc} *trans*	—	2·79[b]	2·89[b]	2·87[b]	2·72[b]
μ_{calc} free rotn.	—	1·95[b]	2·07[b]	2·05[b]	1·94[b]
μ_{CCl_4}	1·46[a]	1·16[c]	1·15[c]	1·15[c]	
$\mu_{benzene}$	1·53[a]	1·32[b]	1·33[c]	1·39[b]	1·54[b]
$\mu_{cyclohexane}$	1·33[a]		1·10[b]	1·05[b]	1·25[b]
μ_{dioxan}	1·86[a]	1·84[c]	2·11[c]	2·36[c]	2·70[b]
		1·87[b]			

[a] Reference 21.
[b] Reference 22.
[c] Reference 20.

atom can approach the hydroxyl hydrogen more closely than can those of the other atoms.

This series of measurements was extended by Richards and Walker[22] who found the increases in moment in dioxan solution to be greater still for *o*-iodophenol. They also observed that the difference between the moments in dioxan and carbon tetrachloride solutions was about the same for *p*-chloro- and *p*-bromophenols as were those of 2,4,6-trichloro- and 2,4,6-tribromophenols in dioxan and cyclohexane. Hence they supposed that without hydrogen-bonding the effects would be about the same in *o*-chloro- and *o*-bromophenols. From their results, however, they inferred that the increase in the proportion of the *trans* form on hydrogen-bonding with dioxan was greatest with *o*-iodophenol and decreased with decreasing size of the halogen atom to become least in *o*-fluorophenol.

Interesting as these results are, they must be taken with a certain amount of reserve. In any case conclusions drawn from dipole moments should be regarded as indicative rather than quantitative, especially when the measurements are made on solutions. In the present instance, as has been mentioned, the calculation of the theoretical moments involves an assumption regarding the orientation of the dipolar axis in phenol. Further, even if this were known with certainty, it has always proved impossible to predict accurately the moments of *ortho* compounds from a knowledge of group moments. Also, in interpreting the results obtained in dioxan solution it has to be borne in mind that the difference between the moments in dioxan solution and those in a non-hydrogen-bonding solvent may depend in some way upon the inductive and mesomeric effects in the molecules as well as on the extent of hydrogen-bonding, since these

differences are about 0·57 D and 0·60 D for *p*-chloro- and *p*-bromophenols, respectively, as against about 0·40 D for phenol itself.

A technique which might be expected to give more direct evidence regarding the intramolecular hydrogen-bonding in the *o*-halophenols is that of nuclear magnetic resonance, as this method gives information regarding the environment of the proton. However, relatively few investigations by this method seem to have been attempted.

The first study using this technique was by Huggins, Pimental and Shoolery[23], who measured the proton magnetic chemical shifts of phenol, *o*-, *m*- and *p*-chlorophenols and *o*-cresol over the maximum concentration ranges which were permitted by their solubilities in carbon tetrachloride. Each solution showed one shift which was attributable to the hydroxylic proton, the results being summarized in Table 8. These reveal a distinctive

TABLE 8. Extrapolated values of the chemical shifts, attributable to the hydroxylic proton, in the n.m.r. spectra of phenols, at zero concentration (δ_0) and for the pure state (δ_1) and the variation of the chemical shifts with molar fraction at zero concentration [$(d\delta/dx)_0$]

	δ_0	δ_1	$(d\delta/dx)_0$
Phenol	2·8	−5·6	42
o-Cresol	3·1	−5·15	16
p-Chlorophenol	3·3	−5·6	20
m-Chlorophenol	3·1	−5·6	22
o-Chlorophenol	4·1	4·87	~0

pattern for *o*-chlorophenol. The fact that $(d\delta/dx)_0$ has almost zero slope is in accord with the view that intramolecular hydrogen-bonding keeps this isomer essentially monomeric, as against intermolecular bonding, probably not involving the chlorine atom, occurring in the other cases. Evidence for hydrogen-bonding is also provided by the fact that δ_0 is significantly greater than for the other phenols. The observation that δ_1 is lower than for the other compounds was attributed alternatively to the inductive effect of the substituent or to reduced intermolecular hydrogen-bonding. As the steric effects in *o*-cresol and *o*-chlorophenol should be about the same, the difference in δ_1 suggests that some contribution from the monomeric form of the latter exists even at $x = 1$.

The dilution chemical shifts in the proton resonance spectra of the hydroxyl group have been studied by Allen and Reeves[24] for all the

o-halophenols in carbon disulphide solution at $-53°C$ and at concentrations of 1–5 mole%. It was observed that the slope of the shift was finite and constant from 3 or 4 mole% concentration to 1 mole% for *o*-chloro-, *o*-bromo- and *o*-iodophenol, but that the results for *o*-fluorophenol were anomalous. From the chemical shifts at infinite dilution they were able to calculate the equilibrium constants between the two forms and their energy differences. Their results, shown in Table 9, indicate very good

TABLE 9. *trans* : *cis* Ratios for the *o*-halophenols and the enthalpy differences (ΔH) at 272·38K as determined by n.m.r.

	Ratio *trans* : *cis*	ΔH (kcal/mole)
o-Chlorophenol	1 : 56	2·356
o-Bromophenol	1 : 38	2·141
o-Iodophenol	1 : 19	1·651

agreement with the best results obtained from i.r. spectroscopy. For *o*-fluorophenol, on the other hand, they found that the internal energy change was so low that its presence could only be inferred from a slight temperature dependence of the shift at infinite dilution in carbon disulphide. Hence they concluded that there was no evidence of hydrogen bond formation in this compound, presumably owing to the large H···F distance.

In a very different method of attacking the problem by proton magnetic resonance, Krakova and Reeves[25] studied the temperature variation of the rate of the first-order reaction and thence the heat of activation for proton transfer between dry methanol and *o*-chlorophenol. The latter property would be expected to be increased if intramolecular hydrogen-bonding occurs, but it was found to be only 4·58 kcal/mole, so it was inferred that the hydrogen-bond can play only a minor role in impeding proton transfer.

One would anticipate that another valuable method of investigating the intramolecular hydrogen-bonding in the *o*-halophenols should be the study of their dielectric relaxation times, but work in this field seems again to be very limited. Fischer[26] studied in particular the ratio of relaxation time to viscosity at various concentrations. With *o*-chlorophenol this ratio showed a particularly large increase with increasing concentration, and this was taken as clear evidence of interaction between the hydroxyl group and the chlorine atom.

Yet another technique that has been suggested for the detection of intramolecular hydrogen bonds is that of paper chromatography[27], the R_f values from which were generally found to be related to the dipole moment. The difference between the experimental R_f values and those calculated from the moments, as deduced from the bond moments, were found to be proportional to the hydrogen-bonding energy. *o*-Chlorophenol gave reasonable results for this energy when studied in this manner.

One would scarcely expect intramolecular hydrogen bonds in *o*-halophenols to persist in aqueous solution, where their formation would be in competition with the strong tendency towards intermolecular bonding of the phenolic group with water molecules. Such is evinced by the strongly hygroscopic character of phenol itself. In line with this view Jenkins[28] showed that the dissociation constants of various isomeric substituted phenols and benzoic acids could be explained on purely inductive grounds. They were related to the dissociation constants of phenol or benzoic acid itself by the relation $\ln K_s = \ln K_u - \beta F$, where K_s and K_u are the dissociation constants of the substituted acid and of benzoic acid itself, respectively, and F is the electrical intensity at the carbon atom to which the hydroxyl group is attached and β is a constant for any substituent, but varies with its nature. As the *o*-halophenols were found to conform regularly with this rule he suggested that they should be regarded as 'regular' and not anomalous.

On the contrary, McDaniel and Brown[29] considered that the acid strengths of the *o*-halophenols were readily explainable by hydrogen-bonding, which, they considered, would tend to stabilize the undissociated phenols and reduce their acid strengths in the manner they observed. In support of this view they pointed out that the order of the effects of the various halogens was F > Cl > Br, I, corresponding with the order to be expected for the relative importance of hydrogen-bonding.

Finally, while discussing the intramolecular hydrogen bonds of *o*-halophenols, it may be pointed out that Simard and coworkers[30] have utilized the circumstance that the hydroxyl group stretching frequency of brominated phenols, which is at 2·84 μ (3520 cm^{-1}) as against 2·7 μ (3700 cm^{-1}) for unbrominated ones, remains constant so long as there is a bromine atom *ortho* to a hydroxyl group. They suggest the use of the intensity of this absorption in fully brominated commercial samples as an index of their content of phenols.

D. o-Haloanilines

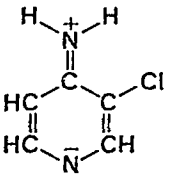
The evidence of boiling point and viscosity determinations appears to suggest that, after *o*-halophenols, the most likely compounds in which

intramolecular hydrogen bonds might be present should be the *o*-haloanilines, but relatively little attention seems to have been directed at their study from this point of view. In 1962 Krueger[31] carried out systematic investigations of the symmetrical and unsymmetrical stretching frequencies of the amino groups of various amines in carbon tetrachloride solution. By applying Linnett's valency force field equations[32] to his results he inferred that the apparent H—N—H angles in the *o*-haloanilines increased in the order F < Cl < Br < I. He suggested that $NH_2 \cdots F$ interactions may be very weak because of the extremely small size of the fluorine atom, preventing the hydrogen atom getting near its lone-pair orbitals. The increasing sizes of the atoms, however, seemed to more than offset the corresponding decreases in electronegativity. The increases in the integrated absolute intensities often observed for the fundamental hydroxyl stretching frequencies on intramolecular hydrogen-bonding were not observed for the *o*-haloanilines, probably because in these strained hydrogen bonds charge–transfer effects are not as important as electrostatic interaction. On the other hand, the narrow band widths accord with the concept of intramolecular hydrogen-bonding as this implies a restriction of the configuration such as is brought about by bonding.

Hambly and O'Grady[33] pointed out that the fact that the substitution of a halogen atom *ortho* to an amino group causes deviations from the equation of Bellamy and Williams[34] for the frequency of the hydroxyl stretching bond supports the view that some hydrogen-bonding occurs. They found that non-deuterated *o*-bromo- and *o*-iodoanilines gave evidence of extremely weak hydrogen bonds whereas in monodeuterated *o*-fluoroaniline hydrogen-bonding was negligible.

Hydrogen-bonding interaction between the amino group and the chlorine atom was also postulated by Cumper and Singleton[35] to account for the dipole moment of *o*-chloroaniline being anomalous in that the interaction moment calculated from it is apparently too small. They also obtained evidence of an even stronger interaction between the amino group and the chlorine atom in 4-amino-3-chloropyridine. This they considered to arise from the more nearly planar configuration of the amino group in the pyridine compound and the greater stability of the structure **6**. The effect of the hydrogen-bonding was interpreted as rendering the second hydrogen atom of the amino group more acidic, as indicated by its association with dioxan, than it is in 4-aminopyridine itself. Similar conclusions were drawn from measurements on 3-amino-2-chloropyridine.

In spite of the fact that, as in the case of the *o*-halophenols, any intramolecular hydrogen-bonding in the *o*-haloanilines would not be expected



(6)

to persist in aqueous solution, the pK_a values of these compounds were interpreted by McDaniel and Brown[36] as indicating some evidence of such interaction. In this series of compounds they suggested that the observed values could be best explained by a combination of hydrogen-bonding and so-called F strain, i.e. steric inhibition of the stability of the protonated cationic state. They inferred that the latter is the dominating factor in *o*-iodoaniline, being sufficient to counterbalance any effect of hydrogen-bonding.

On the other hand, Jenkins had concluded in 1939[28] that the *o*-haloanilines conformed to a linear relationship similar to that holding for acids and phenols, relating in this case the dissociation constants of the substituted anilinium ions with that of the anilinium ion and with the electrostatic potential at the carbon atom carrying the amino group. Whilst this is by no means the same thing as the acidity of the neutral amine, which is the property actually involved in the hydrogen-bonding, it is evidence that the basic properties of the *o*-haloanilines are not anomalous, as they should be if one of the amino hydrogen atoms were engaged in intramolecular hydrogen-bonding.

E. Other Aromatic Compounds

As the effect of the introduction of an *o*-halogen atom upon the acid strength of thiophenol was found to be nearly twice as great as for phenol, McDaniel and Brown[29] made the rather surprising suggestion that hydrogen-bonding must be more important in *o*-halothiophenols than in *o*-halophenols. This effect being the reverse of that usually postulated, it was suggested that it may arise because the C—S—H group has a smaller bond angle than the C—O—H group and from the fact that sulphur is a larger atom than oxygen. Both these factors would place the hydrogen atom in a better position to approach the halogen atom and so favour hydrogen-bonding. They considered that the size of the sulphur atom should cause it to have some repulsive effect on the halogen atom, this repulsion being diminished by the formation of the intramolecular hydrogen bond. Such behaviour on the part of the *o*-halothiophenols seems so unlikely, however, that this observation seems, rather, to cast even more

doubt on pK_a values giving a valid indication of the persistence of intramolecular hydrogen bonds in aqueous solution.

Other compounds in which a five-membered ring might conceivably be formed by hydrogen-bonding are the *o*-halobenzaldehydes. Although the data in Table 1 indicate that *o*-chlorobenzaldehyde does not have a very anomalous boiling point as compared with its positional isomers, some anomalies of behaviour have been observed. As a result of studies of the i.r. spectra over the range 33–400 cm^{-1}, Miller, Fateley and Wilkowski[37] found that with *m*-halobenzaldehydes the *O-cis* rotamer is the more stable, whereas in the *o*-substituted compounds the *O-trans* form is the more stable. Thus in *o*-chlorobenzaldehyde at ordinary temperature about 70% exists in the latter form. It is tempting to attribute this to hydrogen-bonding to the halogen atom in the *o*-isomer but not in the *m*-compound, but it is more probable that the dominant factor is the greater steric requirements of the oxygen atom and that the effect is to be attributed rather to repulsion between the halogen and oxygen atoms than to attraction between the halogens and hydrogen.

One of the most favourable conditions for intramolecular hydrogen-bonding might at first sight appear to arise in the *o*-halobenzoic acids. Such bonding would lead to the formation of a six-membered ring in which the hydrogen atom is more favourably disposed to form a nearly linear O—H···X bond than is possible with the *o*-halophenols. This six-membered ring formation, in which the groups concerned have one more degree of rotational freedom than for five-membered ring formation, has therefore a less favourable entropy effect. More important, however, is that in the condensed phase or in non-hydroxylic solvents this intramolecular hydrogen-bonding would have to compete with the very strong tendency for intermolecular bonding between the two carboxyl groups, with the formation of acid dimers or more complex entities involving the carboxyl groups only.

Through ionization and by hydrogen-bonding of the carboxyl group to solvent molecules, the conditions become less favourable still in hydroxylic solvents. However, Dippy and coworkers[38], finding the strengths of the *o*-halobenzoic acids to be greater than those of their *m*- and *p*-isomers, suggested rather tentatively that in all cases except that of *o*-fluorobenzoic acid an oxygen atom of the carboxylate ion may act as an electron donor to the halogen atom, which expands its octet: such chelate formation would tend to stabilize the ion. On the contrary, Jenkins[39] showed that the *o*-halobenzoic acids conformed to his law[28], as discussed under *o*-halophenols, removing the necessity of invoking intramolecular chelation to explain acid strength. Here McDaniel and Brown[29] agreed with Jenkins'

view on the grounds that the order of the so-called *ortho* effect decreased from iodine to fluorine, the reverse of that which would be expected if hydrogen-bonding were important.

There is, therefore, at present no concrete evidence of intramolecular hydrogen-bonding in any series of aromatic *o*-halocompounds other than *o*-halophenols and *o*-haloanilines.

F. Halohydrins and Related Compounds

The aliphatic compound which most simply meets the requirement of having a halogen atom and a hydroxyl group linked to adjacent carbon atoms is ethylene chlorohydrin. Here, however, there should be obvious competition between potential intramolecular hydrogen-bonding, with the production of a five-membered ring, and intermolecular hydrogen bond formation between the hydroxyl groups of different molecules, like that present in alcohols. While analogous to the position with the *o*-halophenols the acidity of the hydroxyl group should be less, and the basicity of the halogen greater than in the aromatic compounds, though the former must be affected by the electron-withdrawing effect of the halogen atom. Other conflicting factors are that the entropy effect should be less favourable for ring formation, as there is an additional possibility of rotation about the C—C bond, whereas the C—C—X and C—C—O angles, being determined by the sp^3 hybridization of the carbon atom, will be less than in the *o*-halophenols, thus permitting closer approach of the hydrogen and halogen atoms.

As early as 1937 it was observed[40] that the hydroxyl group frequency near 3660 cm^{-1} is replaced by two bands when chlorine, bromine or iodine atoms occupy positions α to the hydroxyl group, and it was suggested that this effect was connected with the free rotation of the hydroxyl group. The third harmonic of the hydroxyl stretching bands of a number of halohydrins and related compounds was studied by Zumwalt and Badger[12]. The frequencies of the maxima of these various bands are best compared as illustrated in Table 10. Zumwalt and Badger observed that the third harmonic band of a primary alcohol is a doublet with components at 10,510 and 10,460 cm^{-1}, the former being considerably the stronger. In ethylene chlorohydrin and bromohydrin, however, a strong new component appeared. The primary alcohol doublet persisted but was shifted slightly to higher frequencies while the lower frequency component had increased in strength. With rise of temperature, however, the primary doublet increased in intensity at the expense of the strong lower frequency band. This is in accord with the behaviour to be expected if the latter were due to intramolecular hydrogen-bonding. In 3-chloro-1-propanol

and the analogous bromine compound the spectrum appeared to be similar to that of a primary alcohol, any new band being very weak, whereas in 1-chloro-2-propanol the new lower frequency band appeared in addition to the ordinary secondary alcohol band at 10,460 cm^{-1}. By comparison with the result for 2-methoxyethanol (glycol monomethyl

TABLE 10. Maxima (cm^{-1}) of the third harmonics of the hydroxyl bands in halohydrins and related compounds

Primary alcohols	—	10,460	10,510
2-Chloroethanol	10,367	10,484	10,526
2-Bromoethanol	10,318	10,470	10,527
2-Methoxymethanol	10,394	10,472	10,538
3-Chloro-1-propanol	—	10,467	10,525
3-Bromo-1-propanol	—	10,470	10,529
1-Chloro-2-propanol	10,326	10,460	—
1,3-Dichloro-2-propanol	10,243 10,325	—	—

ether) they inferred that hydrogen-bonding ring formation leads to shifts of the low frequency band to longer wavelength in the order O > Cl > Br as electron-donor atom. In symmetrical glycerin dichlorohydrin (1,3-dichloro-2-propanol) two intense bands appeared, whilst the band due to a secondary alcohol had disappeared or was very weak. They therefore made the suggestion that the 10,326 cm^{-1} band as in propylene chlorohydrin corresponds to the interaction of the hydroxyl group hydrogen atom with one chlorine atom, whilst the 10,243 cm^{-1} band of 1,3-dichloro-2-propanol results from this hydrogen atom reacting with both chlorine atoms, with consequent double-ring formation. From the integrated intensities of the bands the *trans* (non-hydrogen-bonded) form was judged to have a total energy $2{\cdot}0 \pm 0{\cdot}5$ kcal/mole higher than that of the hydrogen-bonded form, assumed to be *cis*.

At the time the last assumption seemed quite reasonable in view of the fact that measurements of the Raman effect, taken in conjunction with i.r. and polarization data, had led Kohlrausch and Ypsilanti[41] to the conclusion that molecules of the type $CH_2X—CH_2Y$ existed in the liquid state as an equilibrium mixture of two forms which they regarded as *cis* and *trans* respectively. As they had worked mainly with compounds where no intramolecular hydrogen bonds could be formed they concluded that the *trans* form seemed generally to predominate at room temperature, indicating its lower energy, but that the time of sojourn in either form, whilst long as compared to the time of molecular vibration, was so short as to prohibit chemical separation.

On the other hand, Mizushima and coworkers[42], as a result of both Raman and i.r. spectral investigations, whilst confirming that the chlorohydrins exist in two forms, not only in the vapour state but also in the pure liquids and in carbon tetrachloride solution, considered these to be the *trans* and *gauche* (not *cis*) forms. The energy difference between them they found to be $0{\cdot}95 \pm 0{\cdot}02$ kcal/mole, a value about equal to that found by Zumwalt and Badger. They suggested that there should be three possible stable positions of the hydrogen atom in the *gauche* form, one being much more stable than the other two owing to the internal hydrogen bond, without which the *gauche* forms would be less stable than the *trans*. The difference between their numerical result and that of Zumwalt and Badger was therefore attributable to the circumstance that their value applied to the weighted mean energy of the *trans* and non-hydrogen-bonded *gauche* forms above that of the hydrogen-bonded *gauche* form.

The observation by Zumwalt and Badger that hydrogen-bonding was almost completely absent in the β-halopropanols was in line with the later observation by Baker and Shulgin[43] that the frequency shifts of the infrared hydroxyl bands in phenol due to the presence of *ortho* halogen atoms were 18, 61, 78 and 105 cm^{-1}, for fluorine, chlorine, bromine and iodine, respectively. When, however, the halogen atom was in a side-chain as in α-chloro-*o*-cresol, the frequency is about equal to or slightly greater than when the halogen is attached directly to the ring, but the proportion bonded was found to change from 98% to 30% or less. The near-parallelism in bond strength was attributed to three factors, (i) the reduced acidity of the hydroxyl hydrogen atom, (ii) the increased basicity of the halogen and (iii) a smaller possible oxygen–halogen distance. To account for the results there may be added the less favourable entropy effect for closure of the six-membered ring, causing a decrease in the proportion bonded. On the other hand, the bond strength is favoured by the smaller strain involved when the bond is formed and by the possibility that the oxygen, hydrogen and halogen atoms can become more nearly colinear, though good overlap can be attained as long as the hydrogen atom lies on or near the axis of any hybrid orbital which can be regarded as occupied by one of the lone pairs of the halogen atom.

Further evidence of intramolecular hydrogen-bonding in ethylene chlorohydrin was obtained by Bastienson[44] as a result of electron-diffraction measurements. He found a peak corresponding to an interatomic distance of 3·17 Å, which he attributed to the Cl—O distance, as this value was reasonable for a hydrogen-bonded form.

In a study of the i.r. spectra of chloral hydrate and related compounds in the region 2·61–3 μ, Davies[11] found chloral hydrate and bromal hydrate

to have hydroxyl bands at 2·82 and 2·81 μ (about 3546 and 3559 cm^{-1}), respectively, while the latter gave indications of a subsidiary maximum at 2·76 μ (3623 cm^{-1}). He interpreted this as indicating that in the molecules giving rise to the main bands free rotation of the hydrogen atoms about the C—O linkages is inhibited by interaction with the halogen atom, whereas the subsidiary band arises from molecules in which there are free hydroxyl groups. This assignment accords with a higher stability in the hydrogen-bonded form. Evidence for the effect of the hydrogen–halogen interaction on the vibrations of the chloromethyl group was obtained from comparison of the spectra of chloral hydrate and trichloroacetic acid in the regions 7·5–8·5 μ and 12–15 μ. As a result of discussion of the relationship between the energy differences and frequency changes it was shown that the observed behaviour can often be accounted for by the energies of interaction as calculated electrostatically. Davies concluded, therefore, that the resonance contribution is often quite small. It will be recalled, however, that calculations on this basis for the *o*-halophenols have been called into question[13].

The fact that the effects of the formation of intramolecular hydrogen bonds go further than to the atoms concerned was also shown by Nickson[45]. As a result of a study of the i.r. spectra of a large number of compounds, e.g. halogenated sterols, containing both hydroxyl groups and halogen atoms, he concluded that in dilute solution in carbon disulphide the degree of perturbation of the O—H and C—OH stretching frequencies by halogen atoms depends upon their steric arrangements. If intramolecular hydrogen bond formation is geometrically feasible the hydroxyl group frequency is lowered by 25–48 cm^{-1} and that of the carbon–oxygen frequency is increased by 13–25 cm^{-1}. When internal chelation is impossible the change in the latter frequency difference is much reduced and is sometimes negligible. Halogen atoms were found to follow the sequence I > Br > Cl in their abilities to decrease the frequency of hydroxyl stretching vibrations but to adopt the reverse order with respect to the increase in the C—OH stretching frequency.

G. *Intermolecular Hydrogen-bonding*

It has been pointed out that the relatively low boiling points of, e.g. the *o*-halophenols as compared with their isomers have been used as evidence for their intramolecular hydrogen-bonding, but that it should rather be interpreted as a tendency not to undergo intermolecular bonding. In the *m*- and *p*-compounds, where this apparently occurs, the bonding probably involves the halogen atoms little if at all, the predominant feature being bonding between the phenolic groups of different molecules. Similarly

with the amines it is probable that bonding occurs between the amino groups of different molecules.

However, some indication that fluorine atoms in organic compounds have electron-donor properties such as to permit them to engage in intermolecular hydrogen bonds has been claimed. Zellhoefer, Copley and Marvel[46] had noted that the substitution of fluorine for chlorine in chloroform and methylene dichloride decreased the ratio of their observed solubilities in electron-donor solvents at 3°C to the values deduced from Raoult's Law. The fact that the solubilities of the fluorine compounds were actually less than the Raoult's Law values was explained by Marvell, Copley and Ginsberg[47] on the suggestion that anomalies arise through the existence of weak C—H···F bonds between the fluorinated hydrocarbon molecules.

In support of their view they found that the heats of mixing benzotrifluoride with *N*,*N*-dimethylacetamide and dimethylcyclohexylamine were less than half those of benzotrichloride. This was taken as evidence that molecular association involving C—F bonds occurs also in benzotrifluoride, since this result would be expected only if C—H···F bonds had to be broken. The heats of mixing observed with triethylphosphate, ethyl ether and acetone, however, were about the same for benzotrifluoride as for benzotrichloride, a phenomenon explained by the suggestion that in these cases the *p*-hydrogen atoms of the ring are not sufficiently activated to form C—H···O bonds of strengths greater than those of the C—H···F bonds. This explanation, though, seems rather unconvincing.

H. Conclusions

The inference to be drawn, especially from the results of i.r. and p.m.r. investigations, is that there is little or no evidence for the formation of O—H···F intramolecular hydrogen bonds in *o*-fluorophenol, but that otherwise the *o*-halophenols provide the best substantiated examples of hydrogen-bonding by halogen atoms linked to carbon. The strengths of the bonds formed seem to follow the order Cl > Br > I, as is to be expected from their relative electronegativities. The evidence for similar behaviour by the *o*-haloanilines is not so convincing, but weaker bonding is only to be expected in view of the lower acidity of the hydrogen atoms in the amino group, as reflected in the relative behaviours of phenol and aniline in intermolecular hydrogen-bonding to, e.g. dioxan. Bonding very similar to that in the *o*-halophenols is also observed in ethylene chlorohydrin and its derivatives, including particularly chloral hydrate. In all of these cases five-membered rings are formed by the bonding and the hydrogen bonds

formed must be very 'bent', i.e. the O—H···X system is far from colinear. Consequently even in the most favourable cases the orbital overlap in these bonds is probably somewhat restricted, and this is reflected in the fact that the enthalpy changes occurring are relatively small for hydrogen-bonding.

Doubtless the small size of the fluorine atom completely precludes the overlap of the hydrogen and fluorine orbitals. Such observations as its anomalous dipole moment may well be accounted for by the purely electrostatic attraction between the proton and the fluorine atom. Similar attraction must contribute strongly to the bonding in the other cases also, and it is really in the relative extents to which orbital overlap and electrostatic attraction contribute to the effects observed that the interpretations of different authors are at variance. In the optimum case the contribution of the former is probably relatively small.

There is no definite evidence of hydrogen-bonding by the halogen atom in any other series of *o*-haloaromatic compounds.

Intramolecular hydrogen-bonding is obviously impossible when there is a constraint such as that present in the *m*-halophenols, but in other cases when six-membered rings can be formed by O—H···X intramolecular bonds such bonding does occur, though not so readily as when five-membered rings result. When formed, however, the bonds are associated with a higher energy of formation. This illustrates the essentially dynamic nature of hydrogen-bonding, the rate of formation of the bonds depending considerably upon an entropy factor, i.e. the probability of the hydrogen atom approaching a suitable proton-acceptor atom, whilst the energy change on bonding depends on the overlap of suitable orbitals of the two atoms. The former is decreased when six-membered rings are to be formed instead of five-membered ones, but the latter is favoured by the groups being able to adopt a less strained configuration relative to one another. In view of the extra degree of freedom it is hardly surprising that no intramolecular bonds between halogen atoms and hydroxyl groups more widely separated than the α,γ-positions seem to have been suspected.

Evidence for the formation of intermolecular hydrogen bonds involving halogen atoms seems to be very slight indeed.

III. COMPLEX FORMATION WITH LEWIS ACIDS

The study of the formation of complexes between compounds containing carbon–halogen bonds and Lewis acids, such as the halides of Group III elements, is closely linked with the study of the mechanism of the Friedel–Crafts reaction[47a]. As a result of a thorough investigation by Werty-poroch[48] on the conductivities of solutions of aluminium tribromide in

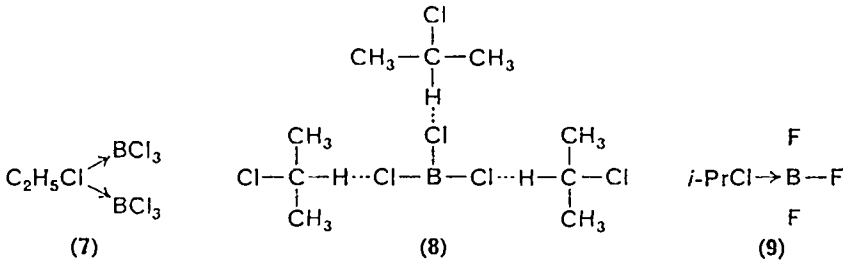
ethyl bromide and the effect of subsequent addition of benzene, Wohl and Wertyporoch[49] came to the conclusion that the first stage in the Friedel–Crafts reaction was association of the aluminium and alkyl halides to give a product which was converted gradually into a strongly conducting compound on the addition of an unsaturated or aromatic hydrocarbon. The rise in conductivity observed was considered not to be caused by the hydrogen halide formed.

Similarly Ulich and Heyne[50] decided from a study of the rate of hydrogen chloride evolution from a mixture of benzoyl chloride and benzene in carbon disulphide solution, in the presence of aluminium trichloride or gallium trichloride, that the reaction was unimolecular and proceeded by way of complexes of the type $MCl_3—C_6H_5COCl$. These complexes they considered to be very unstable, as the resulting benzophenone was found to form more stable complexes with aluminium chloride than did the benzoyl chloride, with consequent deactivation of the catalyst. Analogous complexes were apparently formed between the trihalides and *n*-propyl chloride, which, it was assumed, were in equilibrium with complexes formed by benzene and the reaction products. The changes in the equilibrium concentration of the complex caused by the reaction resulted in the dissolution of aluminium chloride in the early stages of the reaction, with consequent increase in the reaction velocity. Gallium chloride, on the other hand, was dissolved from the start and thus was a better catalyst than aluminium chloride.

The relative readiness of formation of an intermediate addition compound also seemed to account for the observation[51] that boron trifluoride catalysed the condensation of benzene with cyclohexyl fluoride but not with the bromide, whilst Brown and coworkers[52] obtained strong kinetic evidence that, for primary alkyl halides at any rate, aluminium chloride and bromide form complexes with the alkyl halide through the initial formation of a complex with the solvent.

In a direct attempt to detect the formation of complexes between alkyl chlorides and boron trichloride, Martin and coworkers[53, 54] studied the cryoscopic behaviour of mixtures of methyl, ethyl, *n*-propyl and isopropyl chlorides with boron trichloride over the temperature range from $-100°C$ to $-150°C$: From the fact that only ethyl and isopropyl chlorides appeared to form complexes they inferred that the ability to form such complexes and the thermal stability of the product increased with increasing dipole moment of the alkyl chloride. From the phase diagrams obtained they inferred that the compounds formed were $EtCl(BCl_3)_2$ and $(i\text{-}PrCl)_3BCl_3$ and to these most improbable looking products they assigned the even more improbable looking formulae **7** and **8**. Subsequent cryoscopic

studies[55], however, have indicated the existence of the more probable 1 : 1 addition complexes, which may be formulated as in **9**.



(7) (8) (9)

Some 1:1 complexes of alkyl fluorides with boron trifluoride had already been isolated at $-50°C$ to $-110°C$ during studies of the alkylation of aromatic compounds with alkyl fluorides[56]. Conductivity measurements suggested that the complexes of methyl and ethyl fluoride contained a polarized covalent bond, whilst those of propyl and *t*-butyl fluorides were of a much more dissociated type. This was in general agreement with the views of Brown[52].

Whilst studying the alkylation of toluene with alkyl chlorides in the presence of boron trifluoride, Nakane, Kurihara and Matsubori[55] were actually able to measure equilibrium constants for boron isotope exchange between boron trifluoride vapour and the complexes of this compound with *t*-butyl, *i*-propyl and methyl chlorides at $-95°C$ to $-112°C$. They interpreted their results as indicating that the polarities of the complexes studied by them decrease in the order: $Me_3CCl—BF_3 > MeF—BF_3 > Me_2CHCl—BF_3 > MeCl—BF_3$, and that the complexes are coordination compounds of type **9** and not carbonium ion complexes. They inferred that as *t*-butyl chloride acts as an alkylating agent in the presence of boron trichloride it also forms an addition complex with it.

As a result of a detailed spectroscopic study of the methyl fluoride–boron trifluoride complex at $-105°C$ in the region 400–4000 cm^{-1}, it was found[57] that the B—F antisymmetrical stretching frequency remained unchanged during the formation of the complex. Further, no symmetrical stretching frequency was observed, so these observations accord with the conclusion that the planarity of the boron trifluoride molecule is maintained in the complex.

Goldstein and Hemmings[58] have found that the kinetics of halogen interchange between alkyl halides and boron trihalides are also best explained by the intermediate formation of complexes of the type $RX—BY_3$. They were, however, unable to detect these at ordinary temperature by n.m.r. or i.r. spectroscopic techniques. Hence they

inferred that they were present in only very small quantity at any one time. It is evident, therefore, that the further study of these complexes will be fraught with considerable difficulty.

IV. COMPLEX FORMATION ARISING FROM THE POLARIZABILITY OF CARBON–HALOGEN BONDS

One of the first indications that the carbon–halogen bonds in fully halogenated hydrocarbons may not be so inert as had been commonly supposed came as a result of studies by Bellamy, Hallam and Williams[59] on the frequency of X—H stretching vibrations as a function of solvent. They found that the N—H and O—H frequencies of such compounds as aniline and phenol suffered a displacement to lower frequencies and an increase in half-band width which increased progressively with the proton-acceptor strength of the solvent. They concluded that these shifts are determined by both the proton-donating powers of the solutes and the accepting powers of the solvents. Even with carbon tetrachloride as solvent they found the frequency to be slightly lower than with hexane. They inferred, therefore, that in most solvents the X—H dipole seeks out an appreciably charged polar group of the solvent with which to associate, even the polar $\overset{+}{C}—\overset{-}{Cl}$ bond of a carbon tetrachloride molecule. This observation also supports the view that there is a continuous progression between pure electrostatic attraction and 'pure' hydrogen-bonding, which probably reaches its limit in the bifluoride ion F—H···F, and that it is quite arbitrary where a line should be drawn separating the two phenomena.

Earp and Glasstone[60] had previously provided evidence by dielectric polarization measurements that carbon tetrachloride and hexachloroethane form 1:1 complexes with ethers, acetone and quinoline, but that the bonding was much weaker than that with chloroform or pentachloroethane, where bonding does not occur directly through the halogen atoms but through an activated C—H bond. It must be noted, however, that the quantitative conclusions of Earp and Glasstone were called into question by Hammick, Norris and Sutton[61] on the grounds of the misapplication of the law of mass action.

Partington and Middleton[62] also found that the dipole moment of pyridine seemed to be abnormally high in carbon tetrachloride, ascribing this to the presence of interaction between the solvent and solute, and subsequent studies on various compounds have shown similar anomalies. For instance, in determining the dipole moments of diethyl ketone and of benzophenone in various solvents, Granier[63] excluded carbon

tetrachloride on the unequivocally stated grounds that it undergoes molecular association with ketones.

On the other hand, in observing that the dipole moment of pyridine was 0·12 D higher in carbon tetrachloride than in benzene, whilst quinoline and isoquinoline showed similar but rather smaller differences, LeFèvre and coworkers[64] attributed such behaviour to an increase in atom polarization in this solvent rather than to the formation of a polar adduct. The origin of such a large change in atom polarization is, however, difficult to envisage.

Other evidence has not assisted in solving this problem. Raman spectra indicate[65] that the doublet of carbon tetrachloride at 790 cm^{-1} changes both in frequency and intensity when ammonia is added, but the relaxation time of aniline in carbon tetrachloride solution is such as to suggest that any association occurring can be, at most, very slight[66].

Sharpe and Walker[67] found, however, that whereas the dipole moments of aniline and of some pyridine derivatives are slightly greater in benzene than in carbon tetrachloride, the moments of aliphatic amines, pyridine itself and some other pyridine derivatives are greater in the latter solvent, the difference varying from low values up to 0·17 D for butylamine and 0·47 for 4-methylpyridine-1-oxide. They suggested that since these correspond with differences in total polarization of up to 17·1 cm^3 for the amines and no less than 91·8 cm^3 for 4-methylpyridine-1-oxide they were unlikely to be due solely to increases in atom polarization.

Sharpe and Walker's arguments would have been strengthened if they had chosen cyclohexane rather than benzene as comparison solvent. Aniline doubtless forms hydrogen bonds with the π-electron system, thus accounting for its high apparent dipole moment in this solvent. Actually aniline has been reported[68] as having a moment 0·08 D higher in carbon tetrachloride than in cyclohexane.

It was suggested, however, by Sharpe and Walker that the differences in apparent moments which they observed in carbon tetrachloride and benzene solutions can best be explained by a donor–acceptor type of interaction, a transient increase in polarization occurring as carbon tetrachloride molecules approach the vicinity of the lone-pair electrons of the nitrogen atom. Such interaction would, they suggested, increase the total polarization of the interacting system partly by increasing the atom polarization of the interacting molecules and partly by a change in the dipole moment. If this explanation were true the increase should depend on the stability of the adduct formed, and hence the changes in total polarization and in dipole moment might be expected to increase with the basicity of the amine. In accord with this prediction, they found that if the difference in moment

or in polarization were plotted against the pK_a value of the bases an approximately straight line was obtained, as long as the steric effects by the 2- and 6-positions were small. With large groups in these positions, however, the effects were less than might be expected, this being attributed to the reduction in the volume in the neighbourhood of the nitrogen atom and hence to the reduction in the number of carbon tetrachloride molecules passing near to it. Other instances in which no effect was observed were explained on special grounds, e.g. the intramolecular hydrogen-bonding in 8-hydroxyquinoline.

Later[69] such interaction was also shown to occur with ethers, organic sulphides and phosphines, all of which can act as electron-donors to polyhalogenated hydrocarbons. Walker and coworkers[70] have regarded the fact that the dipole moment of pyridine derived from microwave measurements agrees with that obtained by the conventional method as strong evidence in favour of the explanation of the difference of moment in carbon tetrachloride being due to an interaction leading to a real change in dipole moment and not to an increase in atom polarization.

V. HYDROGEN-BONDING BY POLYHALOGENATED HYDROCARBONS

The presence of a carbon–halogen linkage is associated with a powerful electron-withdrawal from the carbon atom. Hence it increases the acidity of any hydrogen atoms linked to the same carbon atom. This effect is inappreciable in compounds such as methyl chloride, but in the case of polyhalogenated compounds it can have the effect of rendering the residual hydrogen atoms sufficiently acidic to make them potential proton-donors in hydrogen bond formation. The complexes formed in this way are only indirectly the result of the presence of carbon–halogen bonds and therefore will have only brief mention here.

It has been known for a long time that the mixture of chloroform with ether or acetone is associated with considerable evolution of heat, and it has gradually become appreciated that this is due to the formation of hydrogen-bonded complexes in which the chloroform is the proton-donor molecule. Similar behaviour occurs with bromoform and, to a lesser extent, with methylene dichloride, and a great many investigations have been directed towards the comparison of the various halogen atoms and the number of them present in the molecule in producing these effects.

Thus Earp and Glasstone[60] used dielectric polarization methods to study the interaction of chloroform and pentachloroethane with ethers, acetone and quinoline. Similarly in a series of papers[71], Marvell, Copley

and coworkers reported that electron-donor solutes are more soluble in partially halogenated hydrocarbons than in completely halogenated ones. For instance, they found that polymeric esters and ketones are more soluble in chloroform and tetrachloroethane than they are in carbon tetrachloride or tetrachloroethylene. Also, from measurements of the heats of mixing chloroform and its analogues with solvents of electron-donor properties, they concluded that bromine is slightly less efficient than chlorine in promoting acidic properties in the neighbouring hydrogen atoms, whilst iodine was found to be relatively ineffective. Further, whilst tetrachloroethane was found to be a very good proton-donor, trichloroethylene was found to be a much weaker one.

The effect of fluorine atoms is so great, apparently, as to cause molecular association in fluoroform[47], with the formation of C—H···F bonds. Even more surprising is the suggestion that the fluorine atoms in benzotrifluoride have an effect sufficient to activate a hydrogen atom linked to the aromatic ring, presumably that in the *para* position, so as to produce similar bonds[47].

In recent years other and more sophisticated methods of studying these properties have been used. For instance, Gent and Martin[72] have compared the association complexes of the various haloforms with anions of quaternary ammonium salts, using p.m.r. methods. From the concentration and temperature dependences of the proton-shieldings in the haloforms they deduced the shieldings in the complexes and the equilibrium constants for complex formation, as well as the thermodynamic parameters. The values obtained for the enthalpy changes occurring during association led them to suggest that the primary factor involved for fluoroform, chloroform and bromoform is hydrogen-bonding to the ion, but that for iodoform the complexes are predominantly of a charge–transfer type.

Other aspects of this effect of carbon–halogen bonds in promoting acidity in neighbouring hydrogen atoms, especially evidence from i.r. spectroscopy, have been reviewed thoroughly elsewhere[73].

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CHAPTER 6

Directing, activating and deactivating effects

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I. INTRODUCTION

Halogen derivatives constitute a very large class of organic compounds. Some of them are found in nature and many more have been synthesized for various purposes.

The halogens (F, Cl, Br and I) also constitute a series of substituents with gradually changing properties which make them of particular interest in studying structure–reactivity correlations.

We shall try in this chapter to discuss the ways of action of halogens on the organic moiety and how chemical properties are modified by halogen substitution. The literature has been covered up to the middle of 1971. References to some later published papers have been also made.

A. General Properties[1]

The halogens are strongly electronegative atoms as shown by the values of electronegativity reported in Table 1 together with ionization potentials and electron-affinities.

TABLE 1. Electronegativities, ionization potentials and electron-affinities of the halogens

	F	Cl	Br	I	Reference
Electronegativities	4·0	3·0	2·8	2·5	2
Ionization potentials (volts)	17·34	12·95	11·80	10·6	3
Electron-affinities (kcal/gm ion)	79·5	83·3	77·5	70·6	3

The first two properties decrease monotonically from fluorine to iodine as the central charge is more and more screened by closed electron shells. The electron-affinities have a less regular trend.

Qualitatively, the substitution of one or more hydrogens with one or more halogens in a molecule increases the electrophilic character of appropriate functions or atoms, because of their electronegativity. The effect is stronger for fluorine than for chlorine, bromine or iodine in the series and decreases with the distance of the halogen from the reacting centre. This way of interaction, usually classified as inductive effect (*I*), is the most general one. It is observed, uncomplicated by other kinds of interaction, when the halogens are neither linked to the reacting centre nor connected with it by a conjugate system. However, other complications may arise from anchimeric assistance phenomena (see below).

A typical case is the effect of halogens on the dissociation constants of aliphatic carboxylic acids (Table 2).

The electronegativity of halogens induces a partial positive charge on the carbon atom at which they are linked. This, in turn, causes an increase

TABLE 2. pK_a values at 25°C in water for some halogen-substituted aliphatic acids (RCOOH)[4]

R =	CH_3	CH_2F	CH_2Cl	CH_2Br	CH_2I	
pK_a	4·76	2·58	2·86	2·90	3·18	
R =	—	CHF_2	$CHCl_2$	CF_3	CCl_3	CBr_3
pK_a	—	1·24	1·29	0·23	0·63	0·66
R =	$CH(Cl)-CH_3$	$CH(Br)-CH_3$	$CH_2-CH_2(Cl)$	$CH_2-CH_2(Br)$		
pK_a	2·88	2·97 (18°C)	3·99	3·99 (18°C)		

of the bond strength between the 'central atom' and the other substituents. This would cause decreasing carbon hydrogen bond lengths and increasing ^{13}C coupling constants with halogen substitution. Although the differences are sometimes small and the experimental errors, at least in some cases[5], fairly large the data reported in Table 3 show the expected trends[5, 6, 7].

TABLE 3. Carbon hydrogen bond distances (C—H) and ^{13}C coupling constants ($J_{^{13}CH}$) in halogenomethanes (RR_1R_2C-H)[5, 6, 7]

R	R_1	R_2	C—H	$J_{^{13}CH}$
H	H	H	1·11	125
H	H	F	1·097	149
H	H	Cl	1·0959	150
H	H	Br	1·0954	152
H	H	I	1·0958	151
H	F	F	1·092	—
H	Cl	Cl	1·082	178
H	I	I	—	173
F	F	F	1·098	—
Cl	Cl	Cl	1·073	209
Br	Br	Br	1·068	206

This effect causes a ground-state stabilization which can modify rates and equilibrium constants (see section III).

Halogens have three unshared electron pairs. One of them may interact with an adjacent π-system and with an electron-accepting group (Y), if present, to give resonance structures **1a** and **1b**.

(1a) **(1b)**

The ability of the halogen to share the electron pair (to donate one electron) would be correlated with the electron potential and therefore would increase from fluorine to iodine. However, the strength of the new π-bond with the adjacent carbon is a function of the size of the *p*-orbital involved and decreases from fluorine to iodine.

The two conflicting effects overlap each other and the result is that the donor ability by resonance ($+T$ effect) of the halogens follows the series F > Cl > Br > I, as is shown by the effects of halogens on the acidity of benzoic acids, phenols, anilines, etc. (see Table 4).

TABLE 4. pK_a values of substituted benzoic acids, phenols and anilines in water[8]

	Benzoic acids			Phenols			Anilines		
	o-	*m-*	*p-*	*o-*	*m-*	*p-*	*o-*	*m-*	*p-*
H	4·20	—	—	9·95	—	—	4·62	—	—
F	3·27	3·87	4·14	8·81	9·28	9·95	2·96	3·38	4·52
Cl	2·94	3·83	3·99	8·48	9·02	9·38	2·62	3·32	3·81
Br	2·85	3·81	4·00	8·42	9·11	9·34	2·60	3·51	3·91
I	2·86	3·86	—	—	9·17	—	—	—	—

Another factor which affects the chemistry of the halogen compounds is the repulsion among the unshared electrons on the halogens and an unshared electron pair on an adjacent atom. The smaller the size of the halogen and the shorter the bond, the greater is the repulsive interaction.

Evidence of this kind of interaction is given by the energy of the halogen–halogen bonds which are reported in Table 5.

TABLE 5. Bond dissociation energies (kcal/mole)[2]

F—F	37
Cl—Cl	58
Br—Br	46
I—I	36

It has been suggested that the heavier halogens as well as other second or higher row elements may interact with an adjacent lone pair as electron-acceptor atoms by using *d*-orbitals[9]. This stabilizing effect may, in principle, overcome the destabilizing lone pair–lone pair interaction.

Finally the strength of the carbon–halogen bond, which again depends on the halogen, has a large effect on reactions which involve the breaking (and the formation) of such bonds.

B. *Quantitative Evaluation of the Effects of Halogens*[10]

The classical way to express the polar effects is by the use of the 'sigma' (σ) substituent constants. Because of the multiplicities of the effects there is a multiplicity of constants. They depend, empirically, on the method of evaluation and, theoretically, on the kind of interaction with the molecule of which the substituent is part.

The most common and frequently used constants of halogens are collected in Table 6.

TABLE 6. Substituent constants for halogens

		F	Cl	Br	I	CF_3	Comments
σ	*m*	0·337	0·373	0·391	0·352	0·42[a]	From ionization of benzoic acids[11]
	p	0·062	0·227	0·232	0·18	0·53[a]	
σ^n	*m*	0·337	0·373	0·391	0·352	—	Based on acidity of *m*-substituted benzoic acids. Values for *para* substituents evaluated through the Hammett equation by using an average ρ value[12]
	p	0·056	0·238	0·265	0·299	—	
σ^0	*m*	0·35	0·37	0·38	0·35	—	From ionization of $ArCH_2COOH$ [13]
	p	0·17	0·27	0·26	0·27	—	
σ^+	*m*	0·352	0·399	0·405	0·359	—	From solvolysis of *t*-cumyl chlorides[14]
	p	−0·073	0·114	0·150	0·135	[b]	
σ_I		0·52	0·47	0·45	0·38	0·33[a]	From ionization of XCH_2COOH [15]
σ_R^0	*m*	−0·17	−0·10	−0·07	−0·03	—	Resonance polar effects ($\sigma^0 - \sigma_I$).
	p	−0·35	−0·20	−0·19	−0·11	—	

[a] Taken from reference 16.

[b] Values of σ_p^- ranging from 0·6 to 0·7 have been reported[17–19].

The σ_I parameter represents the polar interaction of the halogen through the bonds (inductive effect) and through space (field effect). As expected by the qualitative analysis above, the series of decreasing electron-withdrawing effect is F > Cl > Br > I.

In first approximation the σ_m parameters would give a similar sequence. However, the resonance interaction of the halogen with the π-electrons of the benzene ring causes deviations from the expected series although the carbon atom at which the side-chain is linked is not formally modified. This effect, albeit small, is indicative of the weight of resonance interactions of the halogens, in particular fluorine.

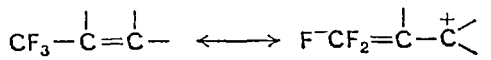
The σ_p parameters begin to give a clearer indication of how much the inductive effect of fluorine may be overweighted by the resonance effect. The σ_p of fluorine is very near to zero: a *para*-fluorine behaves almost like hydrogen. The different magnitude of resonance effects of the various halogens is given, even if in an approximate way, by the $\sigma_m - \sigma_p$ difference. As expected by the argument presented above, it decreases from fluorine to iodine, being very large with fluorine and smaller and smaller with the heavier halogens.

A more rigorous evaluation of the resonance effect is given by the σ_R^0 values ($\sigma_R^0 = \sigma^0 - \sigma_I$). The magnitude of the resonance effect is greater in the σ_p^+ constants, and again the behaviour of fluorine is striking. The σ_p^+ value is in fact negative, i.e. fluorine becomes a better electron donor than hydrogen. For the other halogens the resonance effect is always quite large but the σ_p^+ values never become negative.

Because of the large resonance effect of fluorine the statement found in many organic chemistry textbooks, 'halogens are deactivating, *ortho–para*-directing substituents in electrophilic aromatic substitution' is, in the case of fluorine, not correct since fluorine is often in fact an *activating* substituent.

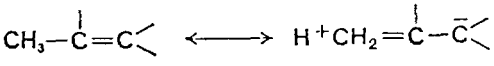
On the other hand, the great electronegativity of fluorine manifests itself in full in the strong electron-withdrawing effect of the CF_3 group. As reported in Table 6, the σ parameters of this group are very large and positive, greater than those of halogens.

Furthermore, the $\sigma_p - \sigma_m$ difference and the increased value of σ_p^- suggested a hyperconjugative mechanism of interaction for this group, which may be represented by the structures **2**.



(2)

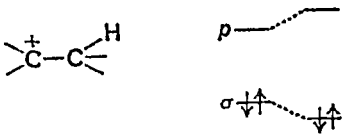
The hyperconjugation of CF_3 is formally the counterpart of the methyl hyperconjugation:



(3)

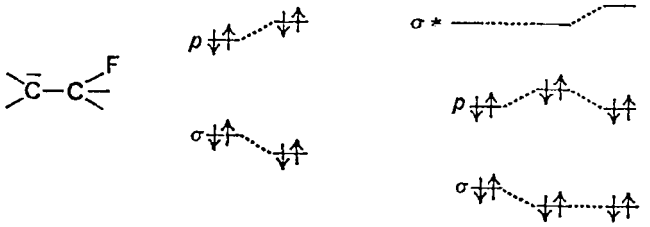
However, there are fundamental differences between the two 'hyperconjugative mechanisms' which make the hydrogen hyperconjugation more feasible than that of fluorine.

Simple MO considerations suggest that interaction of an occupied σ-orbital, if properly oriented, with an empty p-orbital causes a lowering of the energy (Scheme 1) whereas the interaction of a σ-orbital with a



SCHEME 1. Hydrogen hyperconjugation in a carbonium ion.

p-orbital both doubly occupied in first approximation is zero or slightly energy increasing because of electron repulsion. Gain in energy may be



SCHEME 2. Fluorine hyperconjugation.

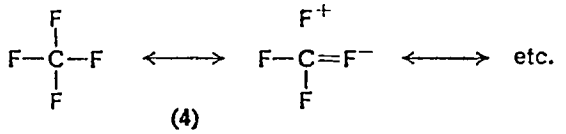
obtained if interaction with the σ^* orbital is taken into consideration. However, it is difficult to assess how effective this interaction may be.

The progressive shortening of the C—F bond with fluorine substitution (see Table 7) was tentatively explained in terms of increasing double-bond

TABLE 7. Carbon-halogen bond distances in halogen-substituted methanes[6]

X	CH_3—X	CH_2X_2	CHX_3	CX_4
F	1·391 1·385	1·358	1·332 1·326	1·323
Cl	1·784 1·781	1·772	1·767 1·761	1·766
Br	1·939	1·930		

character of the C—F bond (see **4**). This is not fully satisfactory since for one fluorine doubly bonded, there is another not bonded (i.e. one bond is

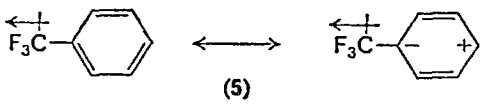


(4)

shorter but another longer) and it may be more simply accounted for by the increased positive charge on carbon, induced by fluorine substitutions, which increases the bond strength and hence shortens the bond length.

One of the main arguments advanced in favour of fluorine hyperconjugation was based on the values of σ constants (Table 6). However, a more close scrutiny of these data may allow an alternative explanation. The $\sigma_p - \sigma_m$ differences, even when the exalted σ_p^- is considered, are not very large and moreover the σ_p/σ_m ratio is between 1·28–1·43, to be compared with the values of $1{\cdot}14 \pm 0{\cdot}05$, taken by Exner[20] as typical when only inductive effects are operative, and 1·75–1·84 or even larger ratios (up to $\sim$2·6) when conjugation makes a contribution. The values for the CF_3 group are therefore in between the two limiting values, and by themselves do not rule out hyperconjugation, nor do they prove it.

The alternative explanation offered (which can also be valid for hydrogen hyperconjugation) is that the presence of a strong dipole outside the ring causes an induced polarization of the π-system which becomes more and more important when there is an electron-releasing group at the *para* position.



(5)

In conclusion, although fluorine hyperconjugation cannot be ruled out, theoretical and experimental arguments suggest that at least it has much less importance than once thought.

Since alternative, simpler, explanations may be given to phenomena once attributed to hyperconjugation, it is probably better to rely on the latter and wait for more accurate and reliable theoretical calculations before taking fluorine hyperconjugation for granted.

C. Anchimeric Effects[21]

Halogens may increase their covalence from one to two by formation of a π-bond (conjugative effect, see above) or of a second σ-bond. This ability is shown by the formation of hydrogen bonds[22], complexes with

Lewis acids[23], dialkyl halonium salts[24], and also by the formation of cyclic halonium ions[25] among which the three-membered rings have great importance on the reactivity and stereochemistry of halogen-substituted compounds.

The factors affecting the formation of the new bonds are not fully understood. Beside the complex formation with Lewis acids, where the nature of the central atom may play a fundamental role, the series of hydrogen-bonding ability is F > Cl > Br > I (see Table 8) whereas the series for three-membered ring formation is I > Br > Cl > F (see section II. A).

TABLE 8. Thermodynamic properties[22] of hydrogen bonds of phenol to cyclohexyl halides (RX) in CCl_4 solutions[a]

X	$-\Delta H_0$ (kcal/mole)	$-\Delta F_0$[b] (kcal/mole)	$-\Delta S^0$[b] (cal/deg mole)
F	3·13	1·31	6·1
Cl	2·21	0·87	4·5
Br	2·05	0·85	4·0
I	1·72	0·82	3·0

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

The charge density around the halogen may be important, particularly when weak bonds are formed, and this may be the reason why fluorine gives better hydrogen bonds than chlorine, bromine and iodine derivatives.

On the other hand, different factors such as ionization potentials and strength of the bond should be more important when true bonds are formed. The two factors change in opposite ways from fluorine to iodine and the prevalence of either one may explain the different series observed in conjugative effect (π-bond formation) and three-membered ring formation (σ-bond formation).

Although the different nature of the bond in the two cases may be sufficient to explain the change in the series, it seems probable that other factors, such as the size of the halogens and their polarizability, cooperate in making the iodine a much better bridging atom than fluorine.

It emerges from this general discussion that the ways in which halogens may affect the reactivity of the molecule of which they are part are varied and depend on a number of factors. Some typical, albeit not necessarily the most usual, reactions are discussed below. The aim was not to cover all possible reactions but to discuss at some length the most interesting cases.

II. EFFECTS ON CARBONIUM IONS

A. Effects on Stability

Taft and coworkers[26,27] measured the appearance potential (A) of a series of substituted methyl cations, by studying the system:

$$CH_3X + e \longrightarrow {}^+CH_2X + 2e + H \quad (1)$$

The difference between the appearance potentials relative to CH_4 and $X—CH_3$ (see equation 2) could be a measure of the effect of the substituent X on the stabilization energy (S.E.) of the cation. Relevant data are collected in Table 9.

$$S.E. = -(A_{CH_3X} - A_{CH_4}) \quad (2)$$

TABLE 9. Stabilization energy (S.E.), relative to CH_3^+, of substituted methyl cations[27]

Cation	S.E. (kcal/mole)
$CH_3CH_2^+$	37 ± 3
$F—CH_2^+$	27 ± 3
$Cl—CH_2^+$	30 ± 4
$Br—CH_2^+$	37 ± 5
$F_2—CH^+$	26
$F_3—C^+$	14

The stability of a carbonium ion is increased by substituting a halogen atom for the hydrogen. The order of stabilization is Br > Cl > F, which is in some way surprising since it is generally accepted that fluorine has a greater conjugative effect (+*T*) than chlorine and bromine. However, the data reported above refer to the gas phase and it may not be correct to apply them to solution chemistry. Cases of structural effects in the gas phase which are different from the liquid phase are now well documented[28]. For instance, the gas-phase acidities of some alcohols are[29] in the order *t*-Bu > *i*-Pr > Et > Me, exactly the reverse of what is found in solution. It may well be that in the gas phase the size of the halogen atom, which takes over much of the positive charge of the carbonium ion, plays a major role.

From the data of Table 9 it appears that multiple fluorine substitution leads to no further stabilization of the carbonium ion: in fact, CF_3^+ appears to be destabilized relative to FCH_2^+ and F_2CH^+ [27]. However, a recent *ab initio* molecular orbital study of fluorocarbonium ions[30] indicates that although the energy gain is not quite as large as that obtained upon

introduction of the first fluorine, a second fluorine atom increases the stability of a methyl carbonium ion. The calculated total energies of the carbonium ions (in atomic units, a.u.) are reported in Table 10 together with their heat of formation.

TABLE 10. *Ab initio* calculations of total energies of fluorocarbonium ions and their heat of formation[30]

	E (a.u.)	ΔE (a.u.)	ΔH_f (kcal/mole)	$\Delta\Delta H_f$ (kcal/mole)
CH_3^+	−38·7917	—	+261	—
	—	−97·5117	—	64
FCH_2^+	−136·3034	—	+197	—
	—	−97·4899	—	53
F_2CH^+	−233·7933	—	+144	—

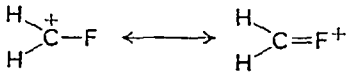
The decrease in ΔE by difluoro substitution compared to monofluoro substitution of 0·0218 a.u. (or 13·7 kcal/mole) is in good agreement with the corresponding decrease in the experimental heat of formation change of 11 kcal/mole.

The discrepancy between the results of Baird and Datta[30] and of Taft and coworkers[27] has been attributed[30] to neglect of the effect of substituents on the neutral molecule. In fact Taft and coworkers[27] compared the energy changes in the hydride abstraction reaction (equation 3) which

$$CH_{4-n}F_n \longrightarrow (CH_{3-n}F_n)^+ + H^- \qquad (3)$$

may not reflect the energy properties of the ion. As a matter of fact the *ab initio* calculations by Baird and Datta[30] indicate that the bonding energy of the molecules increases with fluorine substitution. The increased strength of the C—H bond with α-fluorine substitution is also indicated by the shortening of this bond in passing from methane to trifluoromethane (see Table 3).

In the same calculation[30] the C—F bond length in CH_2F^+ was evaluated as 1·26 Å: this is very short for a linkage of this type (the average value in neutral fluoroethylenes and fluorobenzenes is[31] 1·33 Å) which is indicative of relatively strong dative π-bonding from F to C:



(6)

Recent calculations on fluoroethyl cations[32] showed that the 1-fluoroethyl cation is 39·36 kcal/mole lower in energy than the 2-fluoroethyl cation. Moreover, the comparison of the relative energies for the process $RH \rightarrow R^+ + H^-$, taking this reaction with ethane as standard, gives relative energies for the production of CH_3CH^+F (−29·5 kcal/mole) and of $CH_2F—CH_2^+$ (+9·9 kcal/mole), and therefore fluorine in α position stabilizes and in β position destabilizes the carbonium ion in respect to unsubstituted ethyl cation. The above data are in good agreement with those of Taft[27].

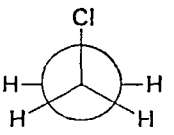
Calculations of barriers to internal rotations in ethyl cations are quite interesting (see Table 11). The data show that the effect of the substituent

TABLE 11. Calculated barriers to rotation in carbonium ions $XCH_2—C^+H_2$

X	Barriers to rotation (kcal/mole)	Reference
H	0·00	33
F	10·53	32
Cl	1·40	34
CH_3	2·52	35
CH_2F	2·11	35
CH_2OH	0·91	35

on rotational barriers is quite important. Rotation is hindered even in the unsubstituted propyl cation which is in contrast to what was calculated for substituted propanes, where the barrier is independent from the substituent[35].

The 2-fluoroethyl cation has a much higher barrier to rotation (10·53 kcal/mole) than the chloro derivative (1·4 kcal/mole). Moreover, whereas the more stable rotamer of the 2-chloroethyl cation has the staggered conformation (7), the most stable structure of the 2-fluoroethyl cation has hydrogen eclipsing fluorine (8). The least stable conformation is the staggered one (9).



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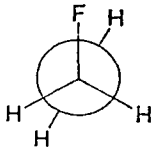

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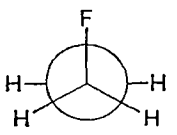
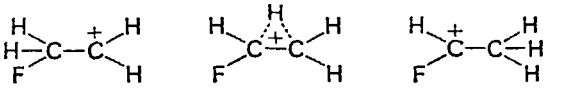


(9)

The staggered conformation, however, is the preferred one for the 1-fluoroethyl cation where a very low barrier to rotation was computed (0·62 kcal/mole)[32]. Dissection of the total energies into attractive and repulsive terms indicates that the barrier to rotation is dominantly attractive in the fluoro cation and dominantly repulsive in the chloro cation.

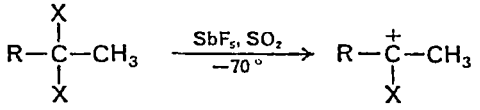
It has also been calculated[36] that the potential surface connecting the 2-fluoroethyl cation (**10**) with the 1-fluoroethyl cation (**12**) through the hydrogen-bridged protonated fluoroethylene (**11**) does not present any



(**10**) (**11**) (**12**)

local minimum and hence the bridged ion is not an intermediate. The bridged ion is calculated to be 12·1 kcal/mole more stable than the classical 2-fluoroethyl cation. Moreover, the energy for production of bridged protonated fluoroethylene is 7·8 kcal/mole lower than that required for the production of protonated ethylene[37].

Other information on the relative stabilities and geometries of halocarbonium ions comes from n.m.r. studies. Olah and Comisarow[38] observed that by treating dimethyl or methylphenyl dihalomethanes with SbF_5 in SO_2 at $-70°$ the corresponding halocarbonium ions are formed.



(**13**) (**14**)

X = F, Cl, Br
(**13a**) and (**14a**): R = CH_3
(**13b**) and (**14b**): R = C_6H_5

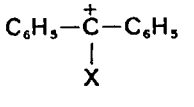
The proton resonances in **14** (see Table 12) are considerably deshielded from those of precursors **13** and the deshielding depends on the halogen

TABLE 12. Chemical shifts of methylhalocarbonium ions **14** and precursors **13**

	X		
	F	Cl	Br
13a	1·30[a]	1·89	2·38
14a	3·83[a]	4·06	3·82
13b	1·62[a]	2·30	2·71
14b	3·46[a]	3·72	3·82

[a] J_{CH_3-F} (Hz): (**13a**) 17·6; (**14a**) 25·4; (**13b**) 17·8; (**14b**) 22·8.

(F > Cl > Br) and on the ability of R to stabilize the carbonium ion. Similarly, diphenyl chloro and fluorocarbonium ions (**15**) were obtained from diphenyldihalomethanes.

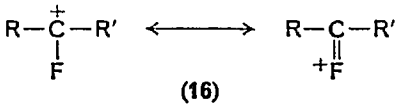


(15)

X = F, Cl

It is interesting that dimethylfluoro and chlorocarbonium ions (**14a**; X = F, Cl) were stable even at −30°, whereas the bromo-derivative (**14a**; X = Br) is only stable below −70°; above this temperature bromine–fluorine exchange is observed. It is not known whether this ion is inherently unstable because of a lesser amount of charge delocalization onto bromine or because of low C—Br bond strength compared to that of C—F and C—Cl. The methylphenylhalocarbonium ions (**14b**) were also stable at −30°.

The study of fluorine resonance gives further information: by changing the groups at the sp^2 carbon from dimethyl to diphenyl (**16**) the fluorine



(16)

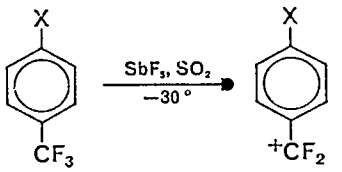
resonance moves progressively to higher fields as the delocalizing ability of the remaining groups on the central carbon atom increases (see Table 13).

TABLE 13. ^{19}F resonance of fluorocarbonium ions (**16**)

R	R′	ϕ	Δ^a
C_6H_5	C_6H_5	−11·26	−100·87
C_6H_5	CH_3	−51·48	−140·17
CH_3	CH_3	−181·91	−266·84

[a] Δ is the difference between the fluorine shift of the ion and its precursor (in p.p.m.).

Reaction of SbF_5 in SO_2 with *para*-substituted benzotrifluorides (**17**) yields the corresponding cations **18**. The resonances of the $^+CF_2$ groups for **18** are reported in Table 14 together with CF_3 resonances of benzotrifluorides **17**.



(17) (18)

X = H, F, Cl, Br

TABLE 14. Chemical shifts of substituted benzotrifluoride (p-$XC_6H_4CF_3$, **17**) and the corresponding aryldifluorocarbonium ions (**18**)

X	$\phi(CF_3)$	$\phi'(CF_2^+)$	$\Delta\ (=\phi'-\phi)$
H	63·63	−11·99	−75·62
F	62·92	−6·77	−69·69
Cl	63·49	−8·61	−72·10
Br	63·54	−8·78	−72·32

The differences in chemical shifts of fluorine resonance in **17** and **18** (see last column of Table 14) decrease following the series: X = F < Cl ≃ Br < H. This would mean that in this system all three halogens are electron donors with respect to hydrogen.

The study of equilibrium (4) shows that the p-F group does, in fact, stabilize the resulting carbonium ion[39,40], (see Table 15), since the pK_{R+} of

$$Ar_3C{-}OH + H_3O^+ \rightleftharpoons Ar_3C^+ + 2\,H_2O \qquad (4)$$

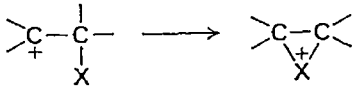
triphenylcarbonium ion (−6·44)[41] is slightly increased to −6 for the tris-(p-fluorophenyl)carbonium ion[39,40]. The m-fluoro substitution is destabilizing[39]. The tris-(p-chlorophenyl)carbonium ion on the contrary is less stable than the triphenyl carbonium ion[42]. This is at variance with

TABLE 15. pK_{R+} values for phenylcarbonium ions

	pK_{R+}	Reference
$(m\text{-}FC_6H_4)_3C^+$	−10·71	39
$(p\text{-}FC_6H_4)_3C^+$	−5·96	39
	−6·05	40
$(C_6H_5)_3C^+$	−6·44	41
$(p\text{-}ClC_6H_4)_3C^+$	−7·74	42

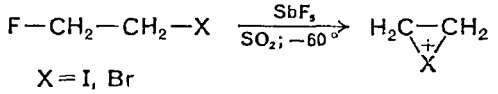
what is found for deshielding of CF_2^+ resonance in *para*-substituted phenyl difluorocarbonium ions. It once again emphasizes the point[10,43] that the resonance effect of substituents (quantified generally as σ^+ or σ^- constants) changes with the electronic requirement of the reaction centre which in turn also depends on the reaction media.

On the basis of the inductive effect, a β-halo carbonium ion should be destabilized in respect to the unsubstituted term. The results of calculations on the relative stabilities of fluoroethyl cations confirm this hypothesis[32]. However, kinetic and stereochemical studies suggest that a β-halogen substituent may stabilize a carbonium ion by bridging and forming a cyclohalonium ion:



The relative stabilities of bridged ions compared to the corresponding open ions seem to vary with the halogen, whose bridging ability follows the series I > Br > Cl > F, and with the ability of the α-groups to disperse the positive charge. Direct evidence of bridged ions has been presented by Olah and coworkers[44-46].

Treatment of 1-fluoro-2-iodo (**19**, X = I) or 1-fluoro-2-bromo ethane (**19**, X = Br) with antimony pentafluoride in sulphur dioxide at −60° results in the formation of the corresponding ethylene iodonium (**20**,

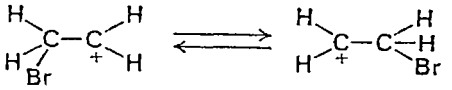


X = I, Br

(19) (20)

X = I) or bromonium (**20**, X = Br) ions[46]. This conclusion was based on (i) a sharp singlet in the ^1H n.m.r. spectrum, indicating loss of fluoride and production of equivalent methylene groups; (ii) downfield shifts of the methylene protons; (iii) isolation of 1-methoxy-2-halo-ethane on solvolysis of **20** in methanol.

More recently[47] the ^{13}C shift of the ethylene bromonium ion has been measured in SbF_5–SO_2 solution: the value obtained (120·8 p.p.m. from $^{13}CS_2$) differs greatly from the calculated value (13 p.p.m.) for an open, rapidly equilibrating, pair of primary carbonium ions (**21**) whereas it is in



(21)

reasonable agreement with the predicted chemical shift of 125 p.p.m. for a cyclic ethylene bromonium ion (**20**, X = Br)[47].

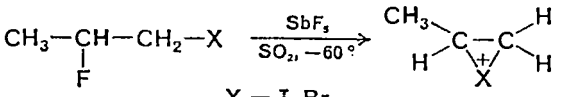
1-Chloro-2-fluoroethane does not give in SbF_5—SO_2 solution at −60° the ethylene chloronium ion, but shows a ^1H n.m.r. spectrum attributed to a complex (**22**). Heating of the solution results in the formation of an

$$SbF_5 \leftarrow FCH_2CH_2Cl$$

(**22**)

unknown substance and of protonated acetaldehyde in nearly equal amounts. Protonated acetaldehyde is also formed on treating with SbF_5–SO_2 1,1-dichloro and 1,1-dibromoethane[46].

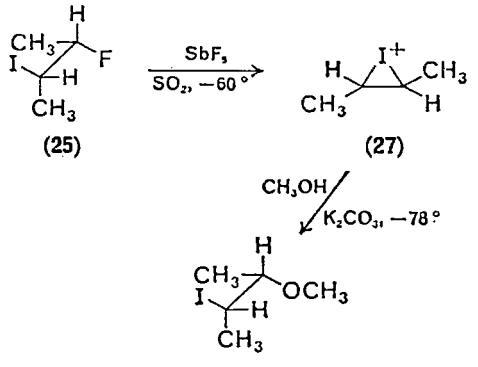
Similarly, 2-fluoro-1-iodo (**23**, X = I) and 2-fluoro-1-bromopropane (**23**, X = Br) form stable cations in SO_2–SbF_5 at −60°, whereas 1,2-dichloropropane gives polymerization[46].



(**23**) (**24**)

Since primary or secondary alkylcarbonium ions are not stable in these conditions and it is apparent that alkylcarbonium ions bearing a β-halogen atom should be even less stable, the formation of the cations is in itself evidence for the cyclic nature of propylene iodonium and bromonium ions (**24**, X = I, Br).

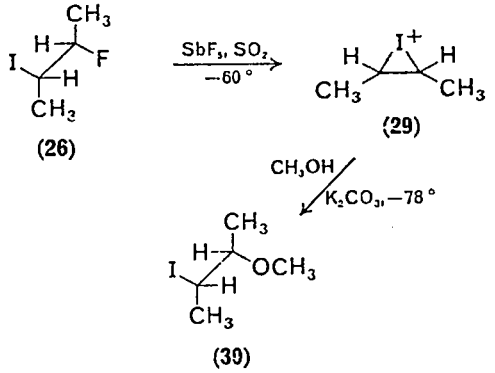
Evidence for a cyclic iodonium ion is also provided by the ionization of *erythro-dl-* (**25**) or *threo-dl*-2-iodo-3-fluorobutane (**26**). This reaction is at least 95% stereospecific. Thus **25** produces an ion **27**, to which the *trans* configuration could be assigned, which on reaction with methanol in the presence of solid potassium carbonate produces *erythro-dl*-2-iodo-3-methoxybutane (**28**), almost without contamination with the other



(**25**) (**27**) (**28**) (5)

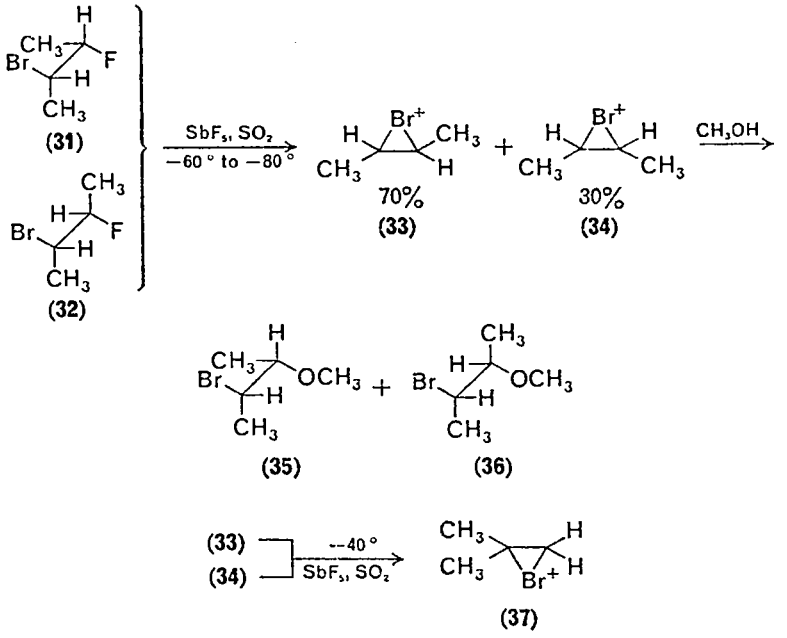
stereoisomer (see equation 5; in this and following equations only one stereoisomer of the *dl* pair is shown for sake of simplicity).

Similarly, **26** gives the *cis* dimethylethylene iodonium ion (**29**), which on reaction with methanol affords *threo-dl*-2-iodo-3-methoxy butane (**30**) (equation 6).



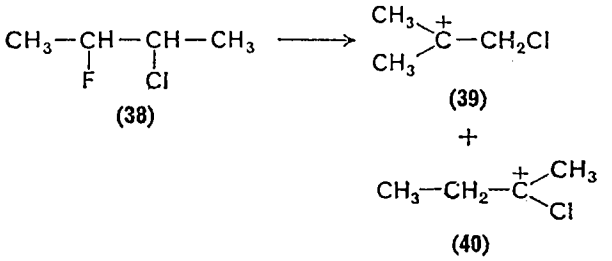
(6)

Different results are obtained with bromo and chloro fluorobutanes. Starting from either *erythro-dl*- (**31**) or *threo-dl*-2-bromo-3-fluorobutane (**32**), the same mixture of *trans* (**33**) and *cis* (**34**) bromonium ions (70 : 30) is obtained. The methanolysis product is again a mixture of 70% *erythro-dl* and 30% *threo-dl*-2-bromo-3-methoxybutane (**35** and **36**, respectively).



It was not stated whether equilibration occurs during ionization or after the formation of the bridged ion. Warming **33** and **34** at −40° for 5 min causes 1,2-methyl shift to give the 1,1-dimethylethylene bromonium ion (**37**).

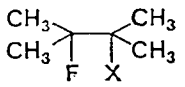
Ionization of *erythro-dl-* and *threo-dl-*2-fluoro-3-chlorobutane (**38**) results in immediate rearrangement to a 40 : 60 mixture of ions **39** and **40**. It is not known whether a chloronium ion is involved in the rearrangement[46].



(**38**) (**39**) + (**40**)

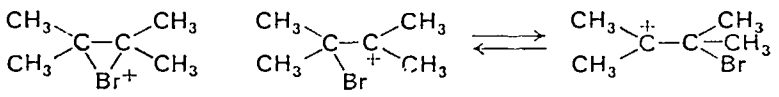
The results reported above for halobutanes may be explained assuming that the iodonium ions (**27** and **29**) are stable. The bromonium ions (**33** and **34**) are in equilibrium with the corresponding open ion, although cyclic structures are favoured; whereas the chloronium ion is, possibly, only an intermediate along the path leading to the rearrangement products **39** and **40**.

By treating 2-fluoro-3-bromo-2,3-dimethylbutane (**41**) with SbF_5 in SO_2, the corresponding bromocation is obtained. ^1H n.m.r. spectrum shows that the methyl groups are all equivalent. However, the ^{13}C chemical shift of the tetramethylethylene bromonium ion is +55·2 (from $^{13}CS_2$) [47],



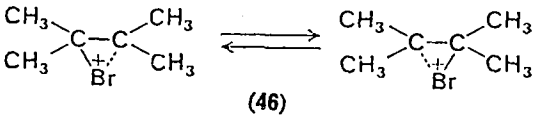
(**41**) X = Br
(**42**) X = Cl
(**43**) X = I

that is 65·6 p.p.m. to low field of the ethylenebromonium ion. For comparison, the ^{13}C shift of tetramethylethylene oxide is 21·2 p.p.m. to low field of ethylene oxide[47]. An open equilibrating ion is expected to give a shift of about −10 p.p.m. The observed chemical shift was explained by



(**44**) (**45a**) (**45b**)

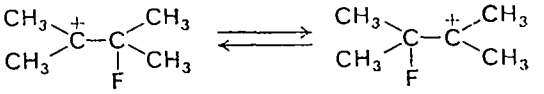
assuming that the ion exists as a 1 : 1 mixture of **44** and **45** or that the ion is present in a rapidly equilibrating pair of partially bridged ions.



(46)

It is interesting to observe how the increased stability of the open carbonium ion (passing from a secondary to a tertiary) favours the open structure.

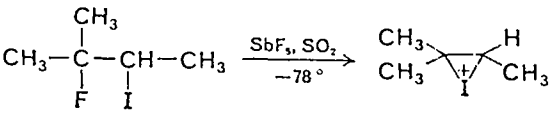
The ions obtained from 2,3-difluoro, 2-fluoro-3-chloro (**42**) and 2-fluoro-3-iodo-2,3-dimethylbutane (**43**) have again ^1H n.m.r. spectra in which the four methyls are equivalent. However, the chemical shift in the case of fluoro compound rather suggests that the ion may be represented as a pair of rapidly equilibrating open ions.



(47a) (47b)

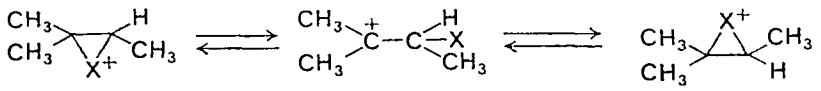
The bridged fluoronium ion may, in principle, take part in the equilibrium, but it may also be a representation of the transition state of the transformation of **47a** into **47b**.

Simple considerations based on the ^1H n.m.r. shifts indicate that the chloro and iodo cations may have the bridged structure. However the ^{13}C n.m.r. spectrum discussed above for the bromine derivative suggests that conclusions based only on ^1H n.m.r. data are not always unambiguous. Possibly the tetramethylethylene iodonium ion has a bridged structure, as it is also suggested by the results obtained with 2-fluoro-3-iodo-2-methylbutane (**48**). It gives an ion (**49**) in which the geminal methyls have different resonance (−3·23 and −3·42δ) as required by a cyclic structure.



(48) (49)

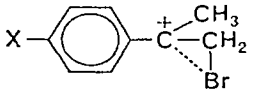
The corresponding chloro and bromo derivatives show only one resonance absorption for the geminal methyls. Either they are made equivalent by a fast equilibration (equation 7) or they happen to have the same chemical shift. In this case also a ^{13}C study would be desirable.



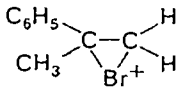
(7)

Another example of the importance of the inherent stability of the open structure in affecting the balance between open and bridged structures is given below.

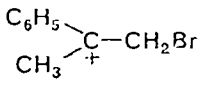
It has been shown[48] that the β-bromocumyl cation (**49a**) cannot have a symmetrical bridged structure (**49b**), since the methylene protons are equivalent and the ^{13}C shift (**49a**; X = H = −37·9, *p*-CH_3 = −28·0, *p*-CF_3 = −44·4 p.p.m. from $^{13}CS_2$) of the sp^2 carbon is distinctly different from that of the bridged ethylene bromonium ion (120·8 p.p.m.)[47].



(49a)



(49b)



(50)

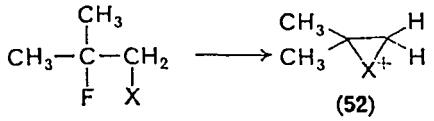
Moreover, in the series **49a** from X = *p*-CH_3 to X = *p*-CF_3 the bridging becomes most important for the *p*-CF_3 derivative for which stabilization from the phenyl ring is least. However, equilibration between an open (**50**) and bridged ions (**49a** or **49b**) could probably also explain the reported ^{13}C shift[48].

From what is reported above it emerges that bromine and iodine easily give three-membered cyclic bromonium and iodonium cations whereas chlorine and particularly fluorine are reluctant to behave in the same way. This general trend is supported also by the observation that 1-halo-2-fluoro-2-methylpropanes (**51**) with SbF_5 in SO_2 give cations which in the case of iodo and bromo derivatives appear to be cyclic halonium ions (**52**, X = Br, I). In the case of the chlorine derivative the cation is certainly open (**53**). Finally, the corresponding fluoro cation, obtained by another route (**54** → **55**), undergoes a rearrangement to the more stable methyl-ethyl fluorocarbonium ion (**56**), possibly because of the combined factors of inability of fluorine to give a three-membered cyclic fluoronium ion and the destabilization of the carbonium ion by β-fluorine substitution.

An indirect evaluation of the relative stability of β-halogenocarbonium ions was obtained[45] by following the fate of 1-halogeno-2-methyl-2-methoxypropanes (**57**) when treated with FSO_3H–SbF_5 in SO_2 at −60°.

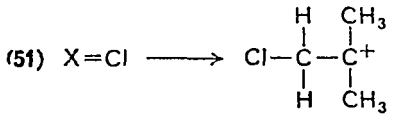
For **57**, X = Cl, the protonated ether (**58**) slowly undergoes loss of methanol to give the open cation (**53**); for **57**, X = Br the loss of methanol is faster and the cyclic ion **59** is formed. Finally in the case of the iodo compound (**57**, X = I) the protonated ether cannot be observed because of very fast formation of the cyclic iodonium ion **60**.

The examples reported above stress the different abilities of the halogens to give bridged ions. It is also shown that the importance of cyclic structures increases with decreasing stability of the open carbonium ion. A

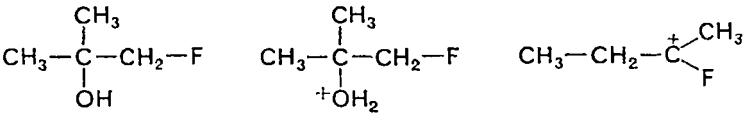


(51)

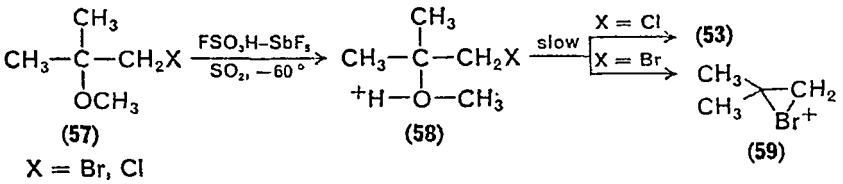
X = Br, I



(53)



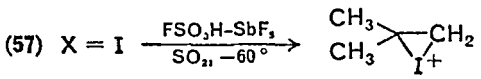
(54) (55) (56)



(57)

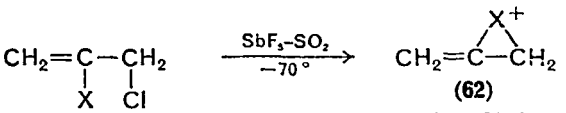
X = Br, Cl

(58) (59)



(60)

further example is offered by the observation[49] that the cations obtained from compounds **61** and **63** have the bridged structures **62** and **64**. In this case, possibly because of the great instability of the open ion, even chlorine gives a stable cyclic ion.

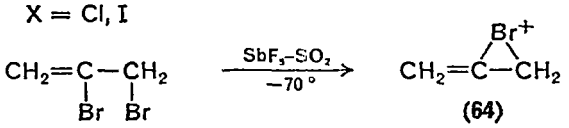


(61)

X = Cl, I

(62)

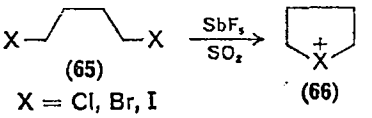
X = Cl, I



(63) (64)

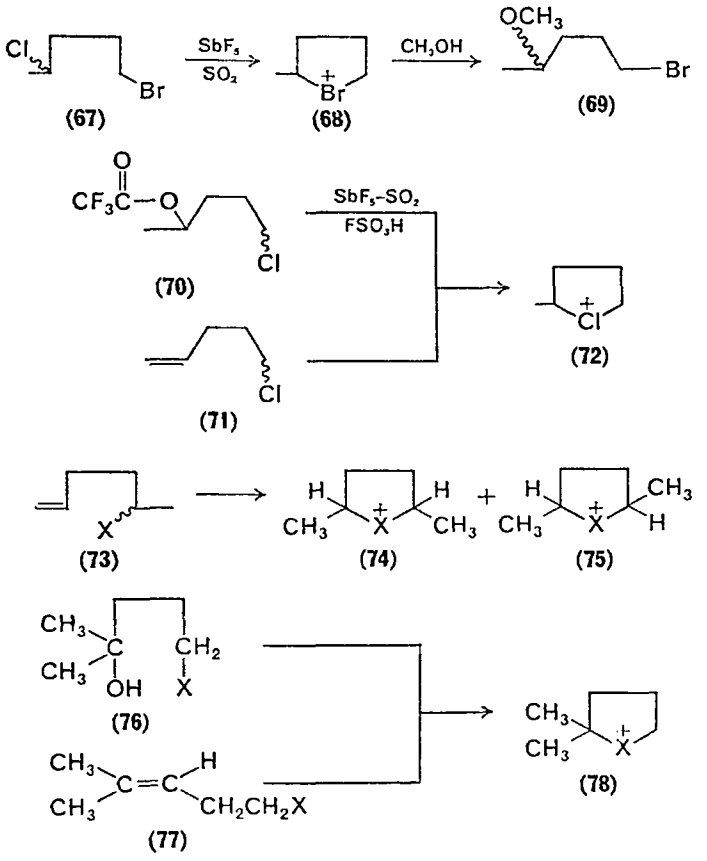
When the halogens are further removed from the cationic centre, they may still give cyclic ions, particularly when medium size rings are formed.

By the action of SbF_5 in SO_2 on 1,4-dichloro-, 1,4-dibromo- and 1,4-diiodo-butanes (**65**) the corresponding tetramethylene halonium ions (**66**) were obtained[50,51].

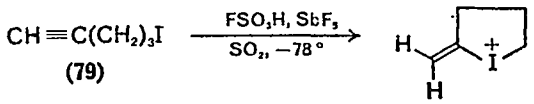


(65)
X = Cl, Br, I
(66)

Also in this case[50], reaction of 1,4-difluorobutane gives only unidentifiable species, with no absorption interpretable as arising from the tetramethylene-fluoronium ion. 2-Methyl[50], 2,2-dimethyl[51] and 2,5-dimethyl-[50]tetramethylene-halonium (X = Cl, Br, I) ions have been prepared according to the reactions shown below:



Protonation of 5-iodo-1-pentyne (79) in 'Magic Acid' gives an n.m.r. spectrum indicating the formation of a five-membered ring iodonium ion (80)[51].

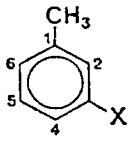


(79) (80)

Reaction of 5-chloro and 5-fluoro-1-pentyne in the same solutions gave uninterpretable spectra[51].

Another aspect of how the halogens may affect the stability of a positive centre is offered by studies of halobenzenonium ions which have been obtained by protonation of halobenzenes in SbF_5–FSO_3H [52] or HF–SbF_5 [53,54] solutions. Since the properties of arenonium ions have been recently reviewed[55] we will deal only with some peculiar behaviour of halotoluenes and haloxylenes.

Protonation of halotoluenes affords a mixture of three isomers in ratios depending on the nature of the halogen (see Table 16).

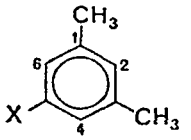


(81)

TABLE 16. Percentage of protonation occurring at the various positions of 3-halotoluenes (81)[54]

X	2	4	6
Br	3	41	56
Cl	2	40	58
F	—	11·5	88·5

The preference for protonation *para* to one of the substituents was also observed in other systems[55]. It is obvious, from inspection of Table 16, that the directing power of the fluorine is greater than that of CH_3, whereas that of Cl and Br is of the same order of magnitude. In the 5-halo-*m*-xylenes (82) a similar behaviour was found (see Table 17)[53].



(82)

TABLE 17. Percentage of protonation occurring at the various positions of 5-halo-*m*-xylenes (82)[53]

X	4 or 6	2
Br	66·6	33·5
Cl	64·0	36·0
F	16·5	83·5

The basicities of the three positions are almost equivalent for the chloro- and bromo-derivatives. In the fluoro compound, however, the 2-position, *para* to the halogen, is about ten times more basic than the other two points of possible attack.

B. *Effects on Reactivity*

1. Electrophilic additions to halogenoethylenes

The ionic addition of acids to alkenes is initiated by the attack of a proton on a double bond with the subsequent formation of the more stable carbonium ion[56]. It is expected, in the light of the above discussion, that proton addition to haloolefins would give the α-halogeno carbonium ion.

Between 1928 and 1940, Kharasch and coworkers[57] conducted a long series of comparative experiments on the mechanism of the addition reactions of HCl, HBr and HI on CH_2=CHCl. They concluded that the additions of HCl and HI, although at somewhat different rates, occur by similar mechanisms which do not involve radical chain reactions. On the other hand, the addition of HBr may involve chains, in which Br is the chain carrier. The effect of peroxides on the mechanism and rates was explained and it was found that the ionic addition of the three halogeno acids to vinyl chloride gave 1,1-dihaloethane as the only product, provided the HBr addition was run in the presence of added salts such as $FeCl_3$.

The addition of HCl to vinyl chloride in the gas phase has been recently checked and found by v.p.c. to give only 1,1-dichloroethane without a trace of the 1,2-isomer[58]. Similarly, ionic addition of HBr and HI to 1,1-difluoroethylene gives 1,1,1-trihaloethane[59].

$$CH_2{=}CF_2 \xrightarrow{HBr} CH_3{-}CF_2{-}Br \quad (84)$$
$$CH_2{=}CF_2 \xrightarrow{HI} CH_3{-}CF_2{-}I \quad (85)$$
(83)

The 1-chloro-2,2-difluorethylene adds HI to give as the only product 1-chloro-2-iodo-2,2-difluoroethane: qualitatively, the reaction occurs at a rate much slower than addition to **83**. HF addition to haloalkenes follows the same general features, giving products derived from proton addition to the carbon bearing less halogens[60, 61].

It is interesting to compare the addition of hydrogen halides to 1-halopropenes. The HF addition to 1-chloropropene (**86**)[61] gives a mixture of **87** and **88**.

$$HF + CH_3{-}CH{=}CHCl \longrightarrow CH_3{-}\underset{H}{CH}{-}\underset{F}{CH}{-}Cl \quad (87)$$
(86)
$$CH_3{-}\underset{F}{CH}{-}\underset{H}{CH}{-}Cl \quad (88)$$

The yield of **88** is about twice that of **87**. Similarly[57], the addition of HBr, HCl or HI to 1-bromopropene (**89**) gives **90** and **91** in a ratio of about 1 : 2. This means that chlorine and bromine have a directing effect similar to that of methyl.

The addition to 3,3,3-trifluoropropene of HCl[62] gives as the only product the compound **92**.

$$CH_3{-}CH{=}CHBr + HX \longrightarrow CH_3{-}CH_2{-}CHBr{-}X \quad (90)$$
(89)
X = Cl, Br, I
$$CH_3{-}\underset{X}{CH}{-}CH_2Br \quad (91)$$
$$CF_3{-}\underset{H}{CH}{-}\underset{Cl}{CH_2} \quad (92)$$

It is evident that the strong electron-withdrawing effect of the CF_3 group directs the formation of the cation at the atom away from the carbon bearing the substituent. When the substituents are halogens, the conjugative effect overcomes the inductive electron-withdrawing effect and favours the formation of the carbonium ion at the α-carbon.

As far as reactivity is concerned, qualitative evidence suggests[59-61] that halogen substitution decreases the reactivity of a carbon–carbon double bond towards electrophiles. For instance, perfluorobut-2-ene is unreactive towards hydrogen halide additions[59]. On the other hand, the

gas-phase addition of HI to vinyl chloride was estimated[63] to be faster than to ethylene although ten times slower than to propene.

More recently Peterson and Bopp[64] measured the rates of CF_3COOH addition to 2-halopropenes and the data are given in Table 18. The rates

(93)

TABLE 18. Rates of addition to 2-substituted propenes (93) of CF_3COOH at 60° [64]

X	$k \times 10^5$ (s^{-1})	k_X/k_H
H	4·81	1
F	340·0	71
Cl	1·70	0·35
Br	0·395	0·082

decrease in the order F > H > Cl > Br, showing that fluorine is actually an activating group in electrophilic additions.

2. Effect of α-halogeno substitution on solvolysis

Solvolytic reactions are affected by α-halogeno substitution[1,43,65] and it was predicted[66] that α-chlorine substitution would decrease the activation energy of formation of carbonium ions.

The rates of the hydrolysis of benzylic halides in 50% aqueous acetone are collected in Table 19. The rates of hydrolysis were assumed to refer to S_N1 reactions although a contribution to the rates by S_N2 displacement was not ruled out with certainty. This could be responsible for some irregular trends which arise when the behaviour of trihalo and dihalo compounds is compared.

The replacement of an α-hydrogen by chlorine causes increased reactivity. This is also generally true for bromine. However, the effect of an α-fluorine atom is very much smaller than that of α-chlorine and α-bromine and it may even be of a deactivating nature. The fluorine behaviour is not fully understood; perhaps ground-state stabilization (see section I. B) might be responsible for the low reactivity.

The accelerating effect of the α-halogen is attributed to the resonance stabilization of the carbonium ion, which is expected to be greater for

TABLE 19. Rates of hydrolysis of α-halogeno benzyl halides ($C_6H_5—CR^1R^2—X$) in 50% aqueous acetone at 30°

R^1	R^2	X	$k \times 10^4$ (min^{-1})	E_a	Reference
H	H	Cl	0·223	21·2	67
H	Cl	Cl	2·3	23·3	67, 68
Cl	Cl	Cl	110·0	20·5	67, 68
F	F	Cl	0·0419	21·2	69
H	H	Br	5·68	19·1	67
H	Cl	Br	31·1	21·9	67
H	Br	Br	6·85	24·6	67
Cl	Cl	Br	2120·0	19·2	67
Cl	Br	Br	1800·0	18·2	67
Br	Br	Br	1130·0	20·1	67

chlorine than for bromine due to the greater ease of double-bond formation with the former halogen.

The stabilization effect of chlorine was found to depend on the solvent[70], being less important in 80% ethanol than in 50% acetone, and on the nature of substrates, being less in benzhydryl chloride than in benzyl chloride. This is not surprising, since other factors, such as solvation and aryl substitution, may help to disperse the positive charge on carbon and therefore less participation by chlorine will be required.

Inspection of Table 19 shows that the replacement of the α-hydrogen by chlorine in $C_6H_5CHBr_2$ increases the solvolysis rate 263-fold whereas the replacement of α-hydrogen by chlorine in $C_6H_5CHBrCl$ increases it by only 68-fold.

Apparently, the magnitude of increase in reactivity upon introduction of a second halogen atom depends on the nature of the groups already linked to the reacting centre: i.e. with a better resonance electron-donor group (Cl) present the substitution of hydrogen by halogen will produce a smaller increase in reactivity. This point has been tested in other systems[71], and even retarding effects were observed, as shown for example in the rates of solvolysis of chloro-substituted dimethyl ethers (Table 20).

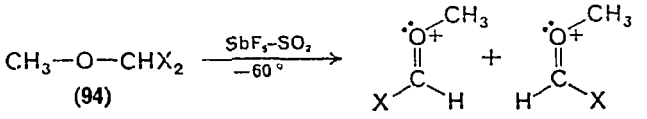
TABLE 20. Rates of solvolysis of chloro-substituted dimethyl ethers in Et_2O/EtOH (1 : 1) at 0° [71]

Substrate	$k \times 10^6$ (s^{-1})
$CH_3—O—CH_2—Cl$	1210
$CH_3—O—CHCl_2$	30
$CH_3—O—CCl_3$	0·46

A similar behaviour was qualitatively found for methyl fluoromethyl ether, which hydrolyses within minutes in aqueous methanol at room temperature[72], and for methyl difluoromethyl ether which does not solvolyse in CH_3OH at 35° over a day[73].

This behaviour was explained[71] by invoking ground-state stabilization. A second explanation, or rather a second factor which comes into play, is that the OCH_3, being a very good electron-donor group, will take most of the positive charge. Therefore the conjugative interaction of the halogen will be decreased.

That this could be the case is suggested also by results of Olah and coworkers[74]. They observed *cis–trans* isomerism in halogeno-methoxy carbonium ions. In fact, when α,α-dichloro- or α,α-difluoro-methyl methyl ether are dissolved in SbF_5–SO_2, solutions at low temperature give ^1H p.m.r. spectra indicating the formation of the methoxyhalo-carbonium ions (**95**) and (**96**) and showing that in these ions most of the positive charge is on oxygen.



(a) X = F	70%	30%
(b) X = Cl	80%	20%
	(95)	(96)

3. Effect of β-halogeno substitution on solvolysis

The solvolysis of 2-X-cyclohexyl aryl sulphonates in CH_3COOH was studied by Winstein, Grunwald and coworkers[75] and the effect of β-halogens discussed in a series of classical papers on neighbouring-group participation.

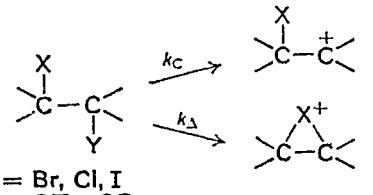
In Table 21 some data are reported showing the effect of β-halogens on solvolysis.

TABLE 21. Effect of *trans*-β-halogens on the reactivity of cyclohexyl aryl sulphonates in CH_3COOH at 25° [75]

X	k/k_H	k_Δ/k_C	k_C/k_H
Cl	$0{\cdot}94 \times 10^{-4}$	—	$0{\cdot}94 \times 10^{-4}$
Br	$7{\cdot}12 \times 10^{-2}$	383	$1{\cdot}87 \times 10^{-4}$
I	1120	$1{\cdot}7 \times 10^{6}$	$6{\cdot}7 \times 10^{-6}$

The overall rate coefficient (k) was dissected in direct (k_C) and assisted (k_Δ) ionization steps (see equation 8).

The ratios k_C/k_H show that halogeno substitution decreases the rates of unassisted reactions following the series Cl > Br > I as expected from their



(8)

electron-withdrawing power. On the other hand, the assisted route makes the overall rate for iodo compounds greater than that for the unsubstituted ones and that for the bromo derivative not as low as could be expected on the basis of the inductive effect alone. The entity of neighbouring-group participation is better shown by the ratios k_Δ/k_C which indicate that β-chlorine is not able to participate contrary to α-bromine and in particular to α-iodine.

The participation of β-halogens in the above reaction has also been studied by Streitwieser[76]. He found that the reactivities of secondary alkyl and *cis*-2-substituted cyclohexyl systems define a straight line when plotted against the appropriate Taft σ^* [15]. The points related to a participating neighbouring group fall above the line and their distances are a measure of anchimeric assistance (see Table 22). The values obtained in this way

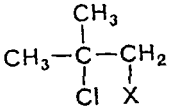
TABLE 22. Acetolysis of 2-substituted cyclohexyl-brosylates at 75°

Substituent (X)	k_X/k_H	k_{obs}/k_{calc}
cis-2-Cl	$1{\cdot}27\times10^{-4}$	—
cis-2-Br	$1{\cdot}24\times10^{-4}$	—
trans-2-Cl	$4{\cdot}80\times10^{-4}$	—
trans-2-Br	0·101	450
trans-2-I	1170·0[a]	1,500,000

[a] 2-Iodocyclohexyltosylates at 23·6°C.

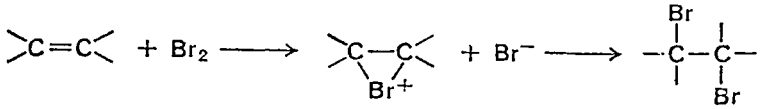
for the anchimeric effect of *trans*-2-Br and *trans*-2-I groups are somewhat different in absolute magnitude from those reported by Winstein and Grunwald[75] but the trend is very much the same, indicating that the iodine is more effective than bromine as a neighbouring group.

It should also be pointed out that in this case the assistance by β-halogens depends on the requirements of the reacting centre. For instance, solvolysis of tertiary chlorides shows a smaller participation by β-halogens: in particular, the increase in rates due to a β-iodine is only 740-fold[76].



4. β-Halogenocarbonium ions via halogen addition

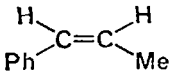
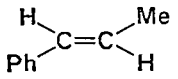
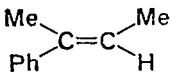
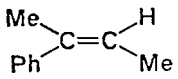
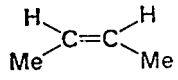
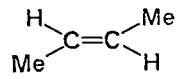
To explain the fact[77] that bromination of maleic and fumaric acid occurs in a stereospecific *anti* fashion, Roberts and Kimball[78] proposed that the bromine addition involves the formation of a cyclic bromonium ion. This



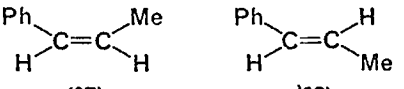
conclusion has been extended to other alkenes and halogens, generalizing the formation of cyclic halonium ions in the additions of halogens to alkenes. Recent studies, however, clearly show that electrophilic additions to double bonds are not typically stereospecific and *anti*.

Elegant work by Yates and coworkers[79–82] showed that whereas in all the solvents studied bromine additions to *cis*- and *trans*-2-butenes are completely stereospecific and *anti*, the additions to ring- and side-chain-substituted styrenes are non-stereospecific (see Table 23). Moreover, the

TABLE 23. Stereochemistry of bromine addition to alkenes in CH_3COOH [80]

Alkenes	% *anti* addition
	73
	83
	68
	63
	100
	100

stereochemisty of bromine addition to *cis* (**97**) and *trans* (**98**) 1-phenylpropene was found[81] to depend on the solvent (see Table 24).



(**97**) (**98**)

TABLE 24. Solvent dependence of stereochemistry of bromine addition to *cis* (**97**) and *trans* (**98**) 1-phenylpropene[81]

Solvent	% *anti* addition to		Dielectric constant
	97	**98**	
CH_3COOH	73	83	6·2
$HCCl_2—CHCl_2$	66	85	8·2
CH_2Cl_2	70	87	9·1
$(CH_3CO)_2O$	49	83	21·0
$C_6H_5NO_2$	45	82	35·0
CCl_4[a]	83	88	2·2
$CDCl_3$[a]	78	84	4·8
CH_2Cl_2[a]	74	—	9·1

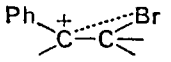
[a] From reference 83.

A marked decrease of *anti* addition to the *cis* compound (**97**) was observed in the solvents of highest polarity, the additions in acetic anhydride and nitrobenzene being virtually non-stereoselective. The results for the *trans*-1-phenyl propene (**98**) show, on the other hand, a much smaller dependence on the nature of the solvent. Similar results were found for bromine addition to *cis* and *trans* stilbenes[84].

The stereochemical results clearly show that whereas the bromination intermediate from *cis*- and *trans*-2-butenes has the bridged bromonium ion structure proposed by Roberts and Kimball[78], that formed by addition to phenyl-substituted olefins, such as styrenes or stilbenes, cannot be of the same nature. However, also in these cases, some bridging interaction must be present in the intermediates, since open and freely rotating carbonium ion intermediates would be expected to give rise to the same product distribution from either a *cis* or *trans* starting material.

The above results are consistent with an unsymmetrical bridged intermediate (**99**) in which there is a weak interaction between the carbonium

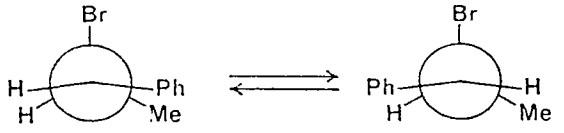
ion and the β-bromine, which is, however, strong enough to prevent free rotation. Since the interaction is weak, the barrier to rotation may be



(99)

easily overcome, particularly in the more polar solvents where open-charged species such as benzylic carbonium ions can be more effectively stabilized.

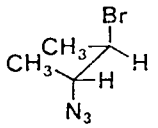
The fact that the stereochemistry of the addition to the *cis* olefin is more sensitive to solvent polarity than that to the *trans* olefin may reflect a greater driving force for rotation around the C—C bond in the intermediate (**100**) from the *cis* olefin due to partial eclipsing of the adjacent methyl and phenyl groups.



(100)

Kinetic evidence for an unsymmetrical charge distribution at the transition state for bromine additions to styrene systems has also been reported[82].

Substantially similar results were reported by Hassner and coworkers[85] for the addition of BrN_3 to alkenes in methylene chloride-nitromethane. The addition to *cis*- and *trans*-2-butenes gives respectively the *threo* and *erythro* adducts **101** and **102**. On the contrary, the addition to *cis*-β-deuteriostyrene (**103**), followed by reaction of the adduct **104** with



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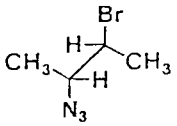
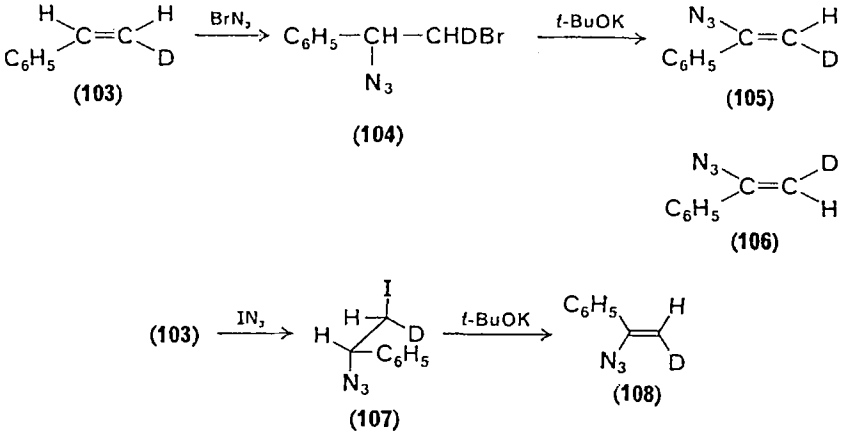


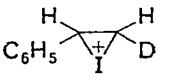
(102)

potassium-*t*-butoxide in ether, affords a 1 : 1 mixture of *cis*- and *trans*-deuterated vinyl azides (**105** and **106**). This implies the formation of an open, or partially bridged, β-bromo cation.

In agreement with the different ability of bromine and iodine to give bridged ions, the addition of IN_3 to **103**, after reaction with *t*-BuOK, afforded the α-azido-*trans*-β-deuterio styrene (**108**) in 96% yield[85].



These results suggest the formation of a cyclic iodonium intermediate (**109**), which does not equilibrate readily to an open carbonium ion, as



does the analogous bromonium ion, despite the presence of a phenyl group.

The addition of chlorine to *cis*- and *trans*-2-butene has been found to occur exclusively *anti* in non-polar[86,87] as well as in acetic acid[88] solutions. This was taken as an indication of chloronium ion formation (**110** from *trans*-2-butene). However, the data to hand do not rule out an intermediate of the kind proposed by de la Mare[89] (**111**), provided the interaction indicated by the dotted line is strong enough to preclude rotation around the C—C bond before the attack of the nucleophile.

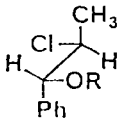
The addition of chlorine to 1-phenylpropene occurs in a different way (see Table 25)[88]. The products obtained are those expected for carbonium ion reactions as shown by the formation of solvent-incorporated adducts (**112** and **113**) in CH_3OH and CH_3COOH. The lack of stereospecificity indicates an open, rather than a bridged, ion intermediate.

Moreover, the dichloride formed in largest quantity is usually the *syn* addition product. Preferential *syn* collapse is not unreasonable if ion pairs

TABLE 25. Stereochemistry of chlorine addition to *cis* (97) and *trans* (98) -1-phenylpropene[88]

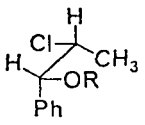
Solvent	% *anti* addition to	
	98	97
CCl_4	46	31
CH_2Cl_2	66	26
AcOH	41[a]	25[b]
CH_3OH	55[c]	47[d]

[a] Solvent incorporated products 29%; **112a** : **113a** = 2·6 : 1.
[b] Solvent incorporated products 32%; **112a** : **113a** = 1·13 : 1.
[c] Solvent incorporated products 83%; **112b** : **113b** = 3·6 : 1.
[d] Solvent incorporated products 83%; **112b** : **113b** = 1 : 2·6.



(112)

(a) R = $COCH_3$
(b) R = CH_3



(113)

(a) R = $COCH_3$
(b) R = CH_3

are involved: different ion pairs are produced starting from *cis*- or *trans*-1-phenylpropene and this would explain why, even if the reaction goes through an open carbonium ion, a different isomer ratio is found in the two cases. It may also be possible that the rate for rotation around a carbon–carbon single bond is comparable to the rate of the ion pair collapse[90].

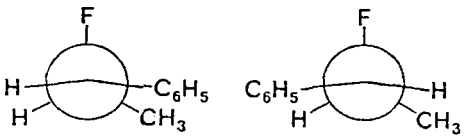
Addition of fluorine to *cis*- and *trans*-1-phenylpropene has been carried out in polar and non-polar solvents to give a mixture of *erythro* and *threo* 1,2-difluoro-1-phenyl propane[91]. The stereochemical results are collected in Table 26.

TABLE 26. Product composition in the fluorination of *cis*- (97) and *trans*- (98) 1-phenylpropene[91]

Solvent	T (°C)	98		97	
		erythro	*threo*	*erythro*	*threo*
CCl_3F	−78	31	69	78	22
	−126	27	73	—	—
CCl_2F_2	−145	29	71	79	21
CH_3OH[a]	−78	7	44	38	12

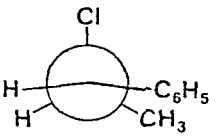
[a] The material balance is completed by a mixture of *dl-erythro* and *dl-threo*-1-methoxy-1-phenyl-2-fluoropropane.

The fluorination is more stereospecific than chlorination, and, again, *syn* addition is the preferred path. Possibly this results from a decreased rate of rotation of β-fluoro cations **114** and **115** compared to the β-chloro cations **116** and **117** and from an increased rate of collapse.



(114)

(115)



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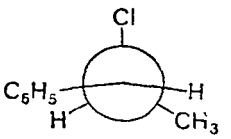


(117)

In fact, as already discussed in section II. A, the barrier to rotation was calculated as 10·5 kcal/mole for the β-fluoroethyl cation and 1·4 kcal/mole for the β-chloroethyl cation[32,34]. The low temperature at which the fluorination was carried out may exaggerate this difference. On the other hand, carbonium ions are strongly destabilized by β-fluorine substitution and hence the rate of ion pair collapse should increase.

Stereochemical results for the addition of halogens to 1-phenylpropene are summarized in Table 27.

TABLE 27. Stereochemistry of halogen addition to *cis*- (**97**) and *trans*- (**98**) 1-phenylpropenes

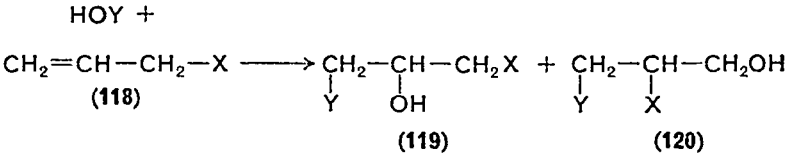
Reagent	Solvent	T (°C)	% *anti* addition to		Reference
			97	**98**	
IN_3[a]	CH_2Cl_2—CH_3NO_2	RT[b]	100	—	85
Br_2	CCl_4	2–5	83	88	83
	$C_6H_5NO_2$	RT[b]	45	82	81
Cl_2	CCl_4	0	31	46	88
F_2	CCl_3F	−78	22	31	91

[a] The addition was run on β-deuteriostyrene.
[b] Room temperature.

The stereochemistry of the addition to *cis*- and *trans*-1-phenylpropene changes with the electrophilic reagent. Chlorine and fluorine, which have poor bridging ability, form open carbonium ions and give non-stereospecific additions. Iodine, a very good neighbouring group, gives addition through a bridged iodonium ion. The bromine behaves in an intermediate way giving a partially bridged bromonium ion in solvents of low polarity (preferential but non-stereospecific *anti* addition) which changes to an open carbonium ion in solvents with higher dielectric constants.

Another fact emerges from the data reported above: it seems that when an open cation is formed, the initial ion pair is *syn* oriented and if rotation is slow in respect to the rate of collapse *syn* addition becomes preferred over the *anti* addition. The latter orientation appears, therefore, to be linked either to a bridged ion or to a termolecular process[79] in which the nucleophilic attack at the β-carbon is concerted with the attack of the electrophile at the α-carbon.

A particular case of halogen participation was found in the addition of hypohalites to allyl halides **118**, where together with the expected **119** some rearranged product **120** is formed[92-94].

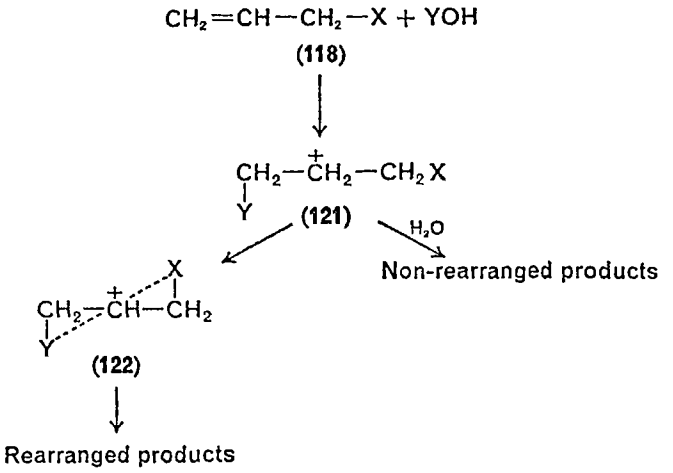


The amount of rearrangement is a function of X and Y as can be seen from Table 28.

TABLE 28. Percentage of rearranged product **120** in the addition of HOY to allyl halides **118**[92-94]

Y	X		
	Cl	Br	I
Cl	4	28	48
Br	0·8	23	
I	ca. 0		

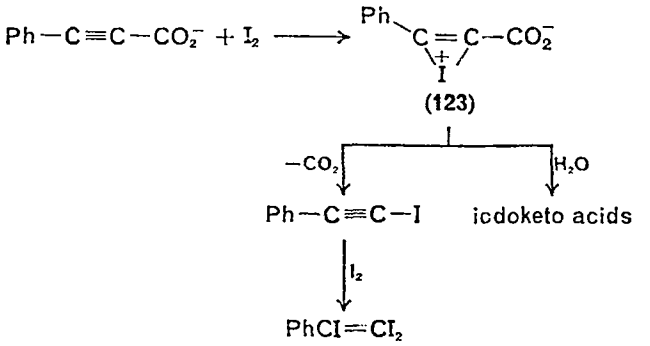
The results have been explained (see the following scheme) by intervention of bridged structures such as **122**. The importance of **122** will increase with the ability of X to bridge, that is in the order I > Br > Cl. Moreover, a decrease in yield of rearranged product is expected if Y is able to compete with X in forming bridged structures.



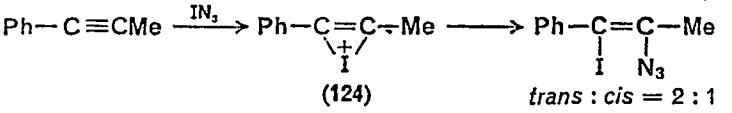
5. β-Halogenovinyl cations

The influence of halogen substituents on vinylic carbonium ions[95] has not yet been studied in detail. It seems, however, that in this case also iodine, and to a lesser degree bromine, are able to stabilize a β-carbonium ion through a bridged structure.

Wilson and Berliner[96] suggested that one of the mechanisms of addition of I_2 to phenylpropiolic acid involves the formation of a cyclic iodonium ion (**123**).



Similarly, Hassner and coworkers[97] suggested the formation of a cyclic iodonium ion (**124**) in the IN_3 addition to 1-phenylpropyne. However, the



complex stereochemistry of the reaction may suggest a more complicated mechanism.

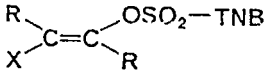
The bromine addition, on the other hand, has been shown to occur via a cyclic bromonium ion to alkylacetylenes and via an open vinyl cation to arylacetylenes[98]: the stereochemical data are collected in Table 29.

TABLE 29. Stereochemistry of bromine addition to acetylenes in CH_3COOH

Acetylene	% *trans*-dibromo[a]
Ph—C≡CH	42
p-$CH_3C_6H_4$—C≡CH	69[b]
Et—C≡C—Et	100
n-Bu—C≡C—H	100

[a] Based on dibromo adducts.
[b] Solvent-incorporated products (14%) and 1-bromophenyl acetylene (25%) also formed.

Very recently[99] the solvolysis of vinyl esters **125** has been studied in nitromethane/methanol. The data collected in Table 30 allow a comparison of the effect of β-halogeno substitution.



(125)

TNB = 2,4,6-trinitrophenyl

TABLE 30. Relative rates of solvolysis of vinyl sulphonates **125** in nitromethane–methanol at 25° [99]

X	Relative rates	X	Relative rates
	R = Ph[a]		R = Me[b]
Br	0·0076	Br	0·025
Ph	1·0	Me	1·0
I	9·2	I	400·0
Ph—S	20·0	Ph—S	4700·0

[a] In nitromethane : methanol (19 : 1).
[b] In nitromethane : methanol (9 : 1).

The β-iodovinyl sulphonates react faster than β-phenyl and β-methyl derivatives: the larger reactivity observed when X = I, in particular for R = Me (see **125**), must be attributed to the anchimeric effect of the β-iodine which overcomes the electron-withdrawing inductive effect of the halogen which should destabilize the intermediate cation.

It is noteworthy that the effect of β-iodine compares favourably with that of β-sulphur for which compelling evidence of formation of a cyclic ion has been presented[95,100].

More significant results, albeit preliminary ones, were obtained[99] studying the acetolysis of *cis*- and *trans*-2-halogeno-1,2-di-*p*-tolylvinyl trinitrobenzene sulphonates at 80°. The following approximate relative rates were found: *cis*-Cl = 1; *trans*-Cl = 1; *cis*-Br = 2–3; *trans*-Br = 20–30; *trans*-I = 8–9000[99]. These data confirm the ability of iodine to assist the vinyl cation and are quite clear evidence that bromine but not chlorine may exert a definite anchimeric assistance effect, when appropriately located.

Acid-catalysed additions to halogenoacetylenes should form halogenovinyl cations. Apparently, these reactions have not been studied in detail[101]. Some data are available for acid-catalysed addition of water to phenyl and alkyl haloacetylenes (**126**). For X = Br, Cl, I and R = C_6H_5 or alkyl the only product observed is **127**.

$$R-C\equiv C-X$$

(126)

$$R-\underset{\underset{O}{\|}}{C}-CH_2X$$

(127)

The orientation appears to be governed by the R group. Probably, by analogy with electrophilic additions to halogenoethylenes (see above), suitable choice of R would allow observation of products derived from both α- and β-halogeno vinyl carbonium ions.

6. ω-Halogenocarbonium ions

The influence of a halogen substituent in a position farther away than β has been studied[102] in bromination (in methanol) and iodination (in water) of **128**. By using an attenuation plot (n = 1–4) it was shown that for

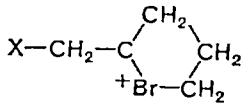
$$CH_2=CH-(CH_2)_n-Br$$

(128)

the bromination there is no rate enhancement over that expected on polar grounds. For iodination of the same series in water, the rate coefficients show no abnormally large values although there is a small rate maximum

at $n = 3$. A ratio of about unity was estimated for assisted and unassisted reaction to be compared with a value of 60 obtained for iodination of the corresponding alcohols.

It was concluded that no bridged ions of the type **129** are formed by halogenation of **128** in hydroxylic solvents. In trifluoroacetic acid, how-



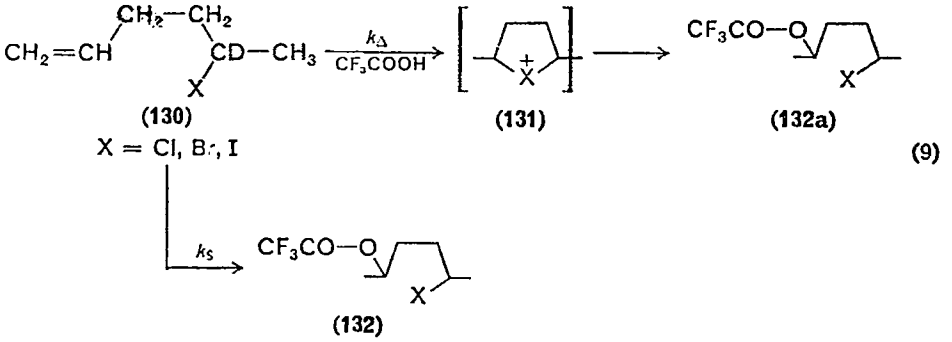
(129)

ever, Peterson and coworkers[103] observed participation via five- and six-membered rings, in the addition of trifluoroacetic acid to olefins, in the order Cl ~ Br ~ I ~ OR. First evidence was given by the observation[104] that the rates of trifluoroacetic acid addition to 5-substituted-1-hexenes were retarded by halogens to a lesser extent than expected on the basis of the inductive effect of substituents (see Table 31).

TABLE 31. Relative rates of addition of trifluoro acetic acid to 5-X-1-hexenes (**130**)[104]

X	k_H/k_X
H	1·0
Cl	4·13
Br	33·35
I	3·50
CH_3COO	32·6

The hypothesis was further substantiated by direct observation of ions **131** by ^1H n.m.r. spectra (see section II. A) and by experiments on **130** labelled with deuterium on the carbon bearing the halogen (X = Cl) which gives 60% of unrearranged and 40% of halogen-shifted products (see equation 9).



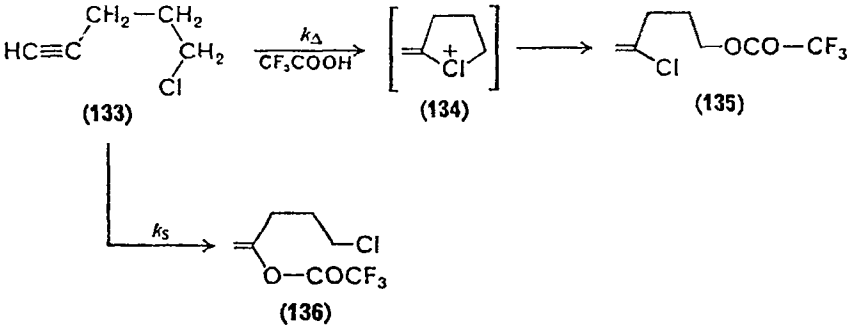
(130) **(131)** **(132a)**

X = Cl, Br, I

(132)

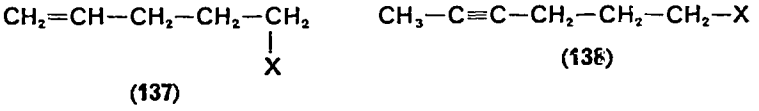
(9)

A similar 1,4-chlorine shift was observed in the trifluoroacetic acid addition to 5-chloro-1-pentyne (see equation 10).



(133) (134) (135) (136) (10)

Among other systems, the trifluoroacetic acid addition to 5-halogeno-pentenes (**137**) and 6-halogeno-2-hexynes (**138**) have also been studied.



(137) (138)

Quantitative evaluations of halogen participation (k_Δ/k_s) in trifluoroacetic acid addition to alkenes and alkynes are reported in Table 32.

TABLE 32. Halogen participation (k_Δ/k_s) in the addition of CF_3COOH to alkenes (**130** and **137**) and alkynes (**133** and **138**)

X	130	137	133	138
Cl	14	7·5	3·4[a]	5·8
Br	14	7·0	4·3[a]	14·0
I	8·1	—	6·1[a]	—

[a] Higher values were evaluated based on the percentage of halogen shift.

Halogen participation was also observed in the solvolysis of tosylates (*p*-toluenesulphonates) and nosylates (*p*-nitrophenylsulphonates) (see Table 33)[105].

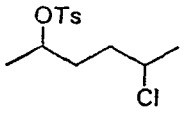
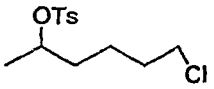
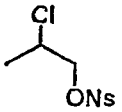
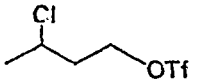
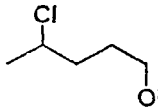
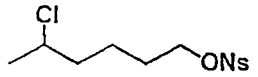
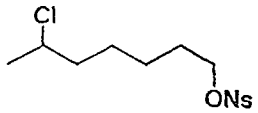
The effect of chlorine on the solvolysis of several nosylates and tosylates was studied in more detail (see Table 34)[106].

TABLE 33. Halogen participation (k_Δ/k_s) in the acetolysis of 4-X-1-butyl tosylates and nosylates

	Tosylates			Nosylates	
	X = Cl	X = Br	X = I	X = Cl	X = Br
k_Δ/k_s	0·22	0·70	3·09	0·37[a]	0·79

[a] In trifluoroacetic acid a ratio $k_\Delta/k_s = 170$ was found.

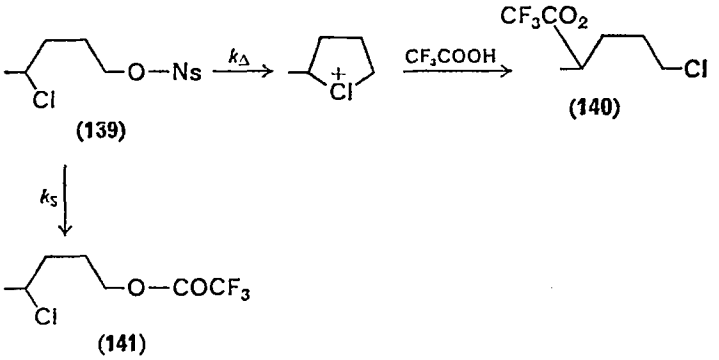
TABLE 34. Chlorine participation in trifluoroacetolysis[106]

Compound[a]		k_Δ/k_s
	*erythro*	99
	threo	65
		33
		2000
		<7·1
		760
		7·1
		0·20

[a] OTs = p-$CH_3C_6H_4SO_2O$; ONs = p-$NO_2C_6H_4SO_2O$; OTf = CF_3COO.

The effect of chlorine is also evident when the halogen is six carbon atoms away from the reacting centre (e.g. 6-chloro-1-phenyl nosylate). The data of Table 34 were also confirmed by product studies. Large amounts (99·5%) of chlorine rearranged product **140** were observed (see equation 11) in the trifluoroacetolysis of 4-chloro-1-pentyl nosylate (**139**)[106].

It would be interesting to know whether fluorine could be a 1,4-participating substituent. Earlier data on trifluoroacetic acid addition to alkenes and alkynes suggested a weak participation. Recently, however, it was shown that 4-fluorobutyl *p*-nitrobenzene sulphonate solvolyses without rate enhancement[106] and 4-fluoro-4,4-dideutero butyl trifluoromethane sulphonate without fluorine shift[107]. Further work appears necessary to resolve these contradictory results.

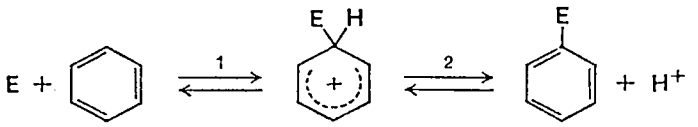


(11)

Apart from the as yet undefined behaviour of fluorine, it is remarkable that the ability of the halogens to give bridged ions depends so much on the size of the ring to be formed, although the fundamental process is apparently the same: i.e. increasing the covalency from one to two via sigma-bond formation. Possibly, the size of the halogen, and hence the strain in the smaller rings, plays a role as well as the different polarizabilities of the halogens. Factors such as the degree of bonding in the transition state leading to the bridged ions might also be important, but their relevance is difficult to assess because of the paucity of the data so far available.

7. Electrophilic aromatic substitution

The electrophilic aromatic substitution has been studied in great detail[1,108–111] and in this context the effect of halogens on rates and on orientation has been investigated. The reaction is usually represented as in equation (12).



(12)

(142)

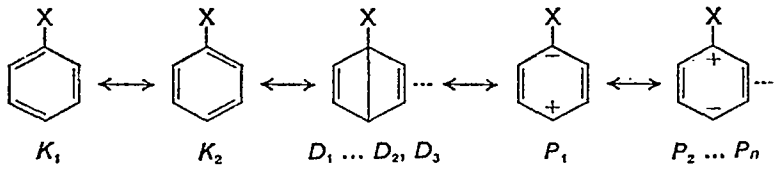
For many, but not all, cases the first step is rate-determining. When the substituent effects are examined, the formation of the Wheland intermediate (**142**) is taken as the stage in which the substituent has the greatest effect. This assumption usually does not lead to great errors even in the cases where the expulsion of the proton is relatively slow.

However, the very important point that the transition state leading to **142** may vary with the electrophile and the substrate must be carefully considered. If the transition state is very much on the reagent side, say the bonding between *E* and carbon is almost negligible, the effect of substituents reflects mainly the modification of charge distribution in the initial state, whereas if the transition state is very similar to the Wheland intermediate the effect of substituents has to be evaluated on this model.

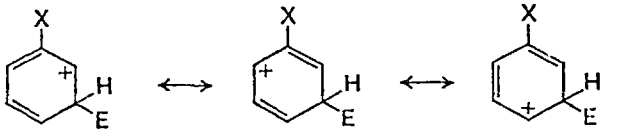
Moreover, it must be remembered that the former situation is associated with low energy of activation and hence low selectivity, contrary to the situation of the latter case.

These points are of particular relevance in discussing the directing and activating effects of halogens because they act inductively as electron-attractors ($-I$) and by resonance as electron-donors ($+T$). The magnitude of the two effects, particularly the latter, is expected to be different in the ground state and in the Wheland intermediate.

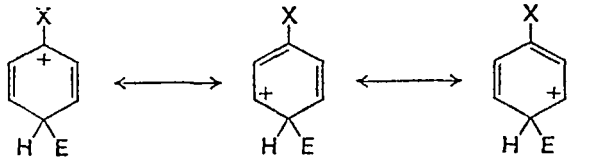
Because of the $-I$ effect, the halogens should make the aromatic ring less reactive and deactivate the *ortho* and *para* more than the *meta* positions. It may be explained by assuming that the electronic distribution in a substituted benzene derivative is no longer symmetric and that forms P_1 make greater contributions than P_2 because of unfavourable charge repulsions.



Investigation of the Wheland intermediate derived from *meta* and *para* (or *ortho*) attack of an electrophile would lead to similar conclusions, since the former (**143**) appears to be less destabilized than the latter (**144**).



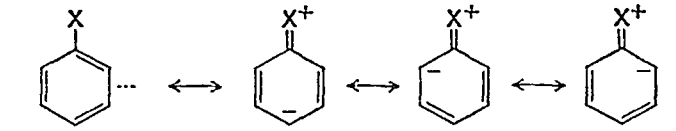
(143a) (143b) (143c)



(144a) (144b) (144c)

The selectivity, however, would be considered to be low, i.e. the reactivity at the *meta* position is expected to be greater but not very much greater than that at the *ortho* or *para* position.

On the contrary a $+T$ substituent increases, with high selectivity, the electron density on the *ortho* and *para* positions by participation of structures $R_1 \ldots R_3$ to the resonant system.



K_1, K_2, D, D_2, D_3 R_1 R_2 R_3

Inspection of the Wheland intermediate suggests that $+T$ substituents should have a selective effect greater than that in the ground state because of the positive charge in the ring, as shown by formulae **145**, **146**, **147**.

The combination of the two mechanisms of interaction is such that in the ground state the *ortho* and *para* positions have greater electron-density than the *meta* position. Theoretical calculations cannot show, at the present level of sophistication, if the overall effect is activating or deactivating in respect to the unsubstituted benzene.

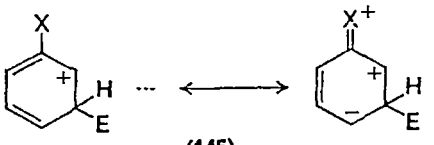
On the other hand, it must be expected that, if the transition state resembles the reagent and hence the substituent affects the reactivity in much the same way as it affects the initial state, the contribution of the inductive effect should be relatively more important than in the case in which the transition state resembles the Wheland intermediate.

In Table 35 the relative rates for *para* substitution in a number of electrophilic reactions are reported.

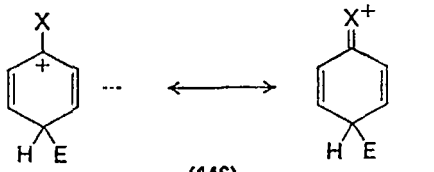
TABLE 35. Partial rate factors of electrophilic aromatic substitutions at the *para* position of benzene derivatives (ArX)

Reaction	Conditions	X						Reference
		Me	H	F	Cl	Br	I	
Nitration	$AcONO_2$	60·0	1	0·77	0·137	0·112	0·78	112, 113
Hydroxylation	CF_3CO_3H	13·7	1	1·34	—	—	—	114
Alkylation	$EtBr/GaBr_3$	5·70	1	0·738	0·538	0·433	—	115
Acetylation	$AcCl/AlCl_3$	749·0	1	1·51	0·125	0·084	—	116
Mercuration	$(CH_3COO)_2Hg$	23·2	1	2·98	0·36	0·27	—	117
Detritiation	$CF_3COOH/H_2SO_4/H_2O$	313[a]	1	1·73	0·127	0·072	0·086	118
Bromination	$Br_2/AcOH$ or $MeNO_2$	534·0	1	4·62	0·145	0·062	0·080	119
Chlorination	$Cl_2/AcOH$ aq.	705·0	1	3·93	0·406	0·31	—	120
Protodetrimethylsilylation	$AcOH/H_2SO_4$ aq.	18·0	1	0·95	0·19	0·104	0·101	121
Bromodetrimethylsilylation	$Br_2/AcOH$ aq.	48·8	1	0·68	0·092	0·071	0·088	122

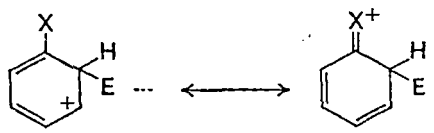
[a] In $CF_3COOH/H_2O/HClO_4$; in the same conditions the f_pF is 1·7.



(145)



(146)



(147)

The data show that the series F > Cl > Br ~ I holds in all the reactions. The critical and interesting point is that fluorine may behave as activating or deactivating in respect to hydrogen. It is clear from the relative rates with a methyl substituent, which can be taken as a measure of the selectivity of the reaction, that, in general, the fluorine is activating when the selectivity of the reagent is high and vice versa. It corresponds to the transition state on the product side and on the reagent side respectively.

In terms of σ constants it means that $\sigma^+_{p\text{-}F}$ may have positive or negative values depending on the reaction. This variability of σ^+ values is not surprising in itself as it is now generally accepted that the values of σ^+ and σ^- parameters depend on the reaction.

The ambiguity of the position in the series of iodine and bromine is less important. First in some cases the data of iodo compounds may be in error because of side reactions at the halogen, secondly the effects of bromine and iodine are very similar and the differences in relative rates are always small. Therefore an inversion in the series may easily occur.

As expected, the halogens are deactivating for substitution at the *meta* position (see Table 36).

The partial rate factors for *meta* positions cannot be evaluated by the product ratios because the amount of *meta*-substituted product is often very small. They are therefore evaluated by the rate of substitution of poly-substituted compounds, assuming the additivity principle. The data reported in Table 36 show that the effects of the four halogens are similar

TABLE 36. Partial rate factors for *meta* position in bromination (A) and chlorination (B) of substituted benzenes (ArX)

	X						Reference
	CH_3	H	F	Cl	Br	I	
A	472	100	0·104	0·057	0·053	0·22	119
B	560	100	0·56	0·23	0·32	—	120

and that the reactivity sequence is I > F > Cl > Br, which is not the one expected on the basis of inductive effects.

The observed order was explained by assuming that the resonance interaction of the substituent with the π-system increases the electron density in the ring, and hence the reactivity, although the positions formally involved in the conjugation are not those undergoing substitution. Finally, the product ratios obtained in electrophilic substitutions of halogenobenzenes must be considered and some data are reported in Table 37.

TABLE 37. Isomer proportions of products of electrophilic substitutions on halogenobenzenes (ArX)

	ortho (%)	*meta* (%)	*para* (%)
Nitration with $AcONO_2$ [112, 113]			
X = F	8·7	0	91·3
Cl	29·6	0·9	69·5
Br	36·5	1·2	62·3
I	38·3	1·8	59·7
Positive chlorination[123]			
X = Cl	36·4	1·3	62·3
Br	39·7	3·4	56·9
Ethylation[115]			
X = F	43	14	43
Cl	42	16	42
Br	24	22	54
Benzylation[124]			
X = F	14·7	0·2	85·1
Cl	33·0	0·6	66·4
Br	32·5	0·7	66·8
I	30·6	0·7	68·7

The sulphonation and molecular bromination of halogenobenzenes give almost exclusively *para* isomers.

The results on orientation suggest that on increasing the selectivity of the reagent the *para* substitution prevails over the *ortho*. This fact cannot be explained by the intervention of steric effects since it appears to be independent of the size of the reagent. This, of course, does not mean that steric effects cannot play a role in electrophilic aromatic substitution but simply that the preferred *para* orientation sometimes observed does not depend only on steric effects.

What appears to be the dominant factor is that the *para*-like Wheland intermediate is inherently more stable than the *ortho*-like analogue. Theoretical calculations as well as the relative stabilities of stable model compounds support this hypothesis. From this point of view, the slower and more selective the reaction the more the transition state resembles the Wheland intermediate and therefore the factors affecting its stability play a greater role in the orientation of the reaction.

III. EFFECTS ON CARBANIONS

A. *Effects on Stability*

Carbanions would be stabilized by the presence at the α-carbon of an electron-withdrawing group[125]. In the case of halogen substitution, however, the inductive effect may be counterbalanced by the lone-pair repulsion[5], which intervenes when two pairs of non-bonding electrons are present on adjacent atoms. Furthermore, other effects could, perhaps, intervene, such as ground-state stabilization (see section I. A and below) and *d*-orbital participation.

Therefore the influence of halogens on carbanion stabilization will mainly result from a balance of the two opposite effects: inductive effect and lone pair–lone pair repulsion, both decreasing in the series F > Cl > Br > I. The prevalence of one effect over the other will determine whether the fluorine is better or worse than iodine in stabilizing α-carbanions. Examples of both cases will be found below.

The rates of base-catalysed deuterium exchange of deuterohaloforms were measured in ordinary water solutions[126,127] (see Table 38).

From Table 38 it may be seen that in haloforms the various halogens increase the reactivity in carbanion formation in the order I > Br > Cl > F.

It has to be noted that even though the replacement of a fluorine atom by chlorine or a chlorine by bromine increases the rate constants for carbanion formation, it does not do so by a constant factor. The effect produced by such substitutions becomes less important as the reactivity

TABLE 38. Rates of deuterium exchange of polyhalogenomethanes in water at 0° [126, 127]

	Substrate					
	CDI_3	$CDBr_3$	$CDCl_3$	CDI_2F	$CDBr_2F$	$CDCl_2F$
$k \times 10^2$ (s^{-1})	60·1	57·9	0·47	5·07	2·07	0·00893

	Substrate			
	$CDBr_2Cl$	$CDCl_2Br$	$CDCl_2I$	CDBrClF
$k \times 10^2$ (s^{-1})	14·3	2·9	2·75	0·21

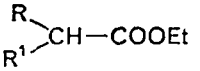
of the substrate increases, showing the presence of saturation effects. However, the fluorine is found to increase by a factor of 10^6 the acidity of polyhalogenomethanes with respect to hydrogen[128] (see Table 39).

TABLE 39. Rates of hydrogen exchange in various polyhalogenomethanes in CH_3OD at 35° [128]

	Substrate			
	CBr_2H_2	CBr_2FH	CI_2H_2	CI_2FH
k ($M^{-1}\,s^{-1}$)	$3{\cdot}1 \times 10^{-6}$	0·67[a]	18×10^{-6}	1·4[a]

[a] Estimated.

By comparison of the data in Table 39 with the results[128] on hydrogen exchange in ethyl acetate derivatives **148** (see Table 40) it is possible to show the importance of the lone-pair repulsion effect.



(148)

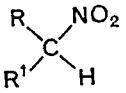
In the ethyl acetate series, the first fluorine substitution slightly increases the acidity of the hydrogen, whereas the second fluorine actually decreases it by a factor of 10^3. Obviously, the relative importance of inductive effect and lone-pair repulsion is different, as far as the fluorine atom is concerned,

TABLE 40. Hydrogen exchange in ethyl acetate derivatives (**148**) in CH_3O^-/CH_3OD at 35° [128]

R	R^1	k ($M^{-1}\,s^{-1}$)
H	H	$1{\cdot}26\times10^{-3}$
H	Et	$1{\cdot}29\times10^{-4}$
H	F	$2{\cdot}28\times10^{-3}$
F	F	$7{\cdot}55\times10^{-6}$

in the polyhalogenomethanes and in the ethyl acetates. This is not surprising if the geometries of the two resulting anions are taken into consideration. The trihalogenomethane anions have a pyramidal structure with a significant inversion barrier[129] and in effect the hydrolysis of optically active 1,1,1-bromochlorofluoroacetone with aqueous potassium hydroxide gives optically active CClBrFH [130]. On the other hand, the anions derived from the esters are, because of conjugation with the carbonyl group, sp^2 hybridized. Therefore, the lone-pair repulsion will be very effective due to the favourable geometry of the interacting orbitals.

Another example of this phenomenon is found in Table 41, where the acidities of several halogenonitroalkanes (**149**) are compared[131,132].



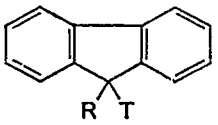
(**149**)

TABLE 41. pK_a Values of halogenonitroalkanes (**149**) in water at 25° [131,132]

R^1	R			
	COOEt	$CONH_2$	Cl	NO_2
Cl	4·16	3·50	5·99	3·80
H	5·75	5·18	7·20	3·57
F	6·28	5·89	10·14	7·70

In all the compounds, substitution of H by fluorine diminishes the acidity of the resulting nitroalkane. Even for chlorine the lone-pair repulsion appears to play a role, although to a lesser degree, since the pK_a

enhancement is less than would be expected for the normal inductive effect and, actually, dinitromethane has a lower pK_a value than dinitrochloromethane. An estimation of the magnitude of the lone-pair repulsion has been reported[133] for the 9-tritio-9-fluorofluorene (**150**, R = F).



(150)

It was found (see Table 42) that the rates of hydrogen exchange in several 9-substituted fluorenes **150** are correlated with the acidity of the corresponding carboxylic acid (RCOOH)[134]. This was taken as evidence that the inductive effects of the R groups were the most important factors in determining the acidity of the 9-hydrogen.

TABLE 42. Relative rates of tritium exchange of 9-fluorene derivatives **150** in CH_3O^-/CH_3OD at 45° [133, 134]

	R					
	H	CH_3	C_2H_5	$CH_2—C_6H_5$	CH_2OCH_3	CF_3
$(k/k_0)_{exch}$	1	0·26	0·18	0·72	12·9	2×10^4

	R		
	Br	Cl	F
$(k/k_0)_{exch}$	7×10^2	4×10^2	0·14

On the basis of the σ_I constants one would have predicted the exchange rate for 9-fluorofluorene to be 10^5 times greater than for the unsubstituted compound. Therefore, the lone-pair repulsion effect is responsible for a million-fold decrease in rate. Of particular interest is the comparison with the 9-CF_3 derivative. The CF_3 and F groups have almost the same inductive effect but the rates of exchange are very different with the CF_3 derivative reacting about 10^5 times faster. In this compound, however, the lone-pair repulsion effect cannot be of importance, since the fluorine is remote from the carbanionic centre, and therefore the inductive effect will be able to stabilize the α-carbanion.

By contrast, two α-fluorines increase the lithium cyclohexylamine-catalysed exchange of a methyl hydrogen in toluene by a factor of 10^4 [133].

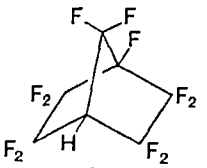
To explain these results Streitwieser and Mares suggested that the 9-fluorofluorenyl anion is planar whereas the α,α'-difluorobenzyl anion is pyramidal. For the benzal fluoride the increased conjugation of a planar benzyl anion is counteracted by the corresponding increase in repulsions between fluorine lone pairs and π-electrons on carbon. This second effect prevails and the carbanion is forced to be pyramidal. Estimates of the magnitude of the inductive stabilization of a non-conjugative pyramidal phenyldifluoromethyl anion are consistent with the observed reactivity of benzal fluoride[133].

The stability associated with a planar fluorenyl anion, however, is much greater than for a phenyl anion and overcomes the destabilizing effect due to lone-pair repulsion of a single fluorine. The great effect of CF_3 in enhancing the rate of formation of α-carbanions was also observed in other systems (see Table 43).

TABLE 43. Hydrogen exchange in CH_3O/CH_3OD of some polyfluoroalkanes[135, 136]

	Relative rates
$CF_3—H$	1
$CF_3(CF_2)_6—H$	6
$(CF_3)_2CF—H$	2×10^5
$(CF_3)_3CH$	10^9
151	5×10^9

The substitution of CF_3 for F in trifluoromethane causes a 10^9 increase in rates of hydrogen exchange[135]. This was taken as evidence[135] of carbanion stabilization through bond–no-bond resonance[137]. However, this kind of resonance has been criticized[5, 138] and actually experiments with compound **151**, where there is a steric hindrance to such a resonance



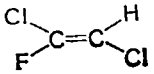
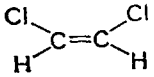
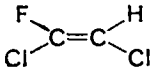
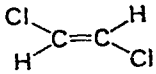
(151)

showed (see Table 42) a rate of exchange of the same order of magnitude as $(CF_3)_3CH$ [136]. This is further evidence that the CF_3 effect on rates of exchange is that normally expected from its electron-withdrawing power,

whereas in the fluorine case the inductive effect is counterbalanced by the lone-pair repulsion.

Recently quantitative results on halogen stabilization of vinyl carbanions have become available. Viehe and coworkers[139] reported the rates of base-catalysed hydrogen–deuterium exchange of several di- and trihalogenoethylenes in CH_3ONa–CH_3OD solutions. Pertinent data are collected in Table 44.

TABLE 44. Rates of hydrogen exchange of halogenoethylenes in CH_3O^-/CH_3OD at 33°C [139]

No.	Substrate	$k \times 10^3$ (1 mole^{-1} s^{-1})	No.	Substrate	$k \times 10^3$ (1 mole^{-1} s^{-1})
1	$CHCl_3$	102	6		6·33
2	$CCl_2{=}CHBr$	68	7	$CF_2{=}CHCl$	9·8[a]
3	$CCl_2{=}CHCl$	24·1	8	$CF_2{=}CHF$	0·05
4	$CCl_2{=}CHF$	0·57	9		0·16
5		31·2	10		0·114

[a] Upper limit, due to competing methanol addition.

Many factors influence the hydrogen acidity in halogenoethylenes. Some generalizations, however, can be made from the above data: α-halogen substituents facilitate vinyl carbanion formation in the same order Br > Cl > F observed for haloforms (see compounds 2, 3, 4 and 7, 8); two fluorine atoms on the β-carbon are less effective than two chlorine atoms (see 3 and 7, 4 and 8). On the other hand, one fluorine lowers the acidity of a β-*trans*-hydrogen but increases that of a β-*cis*-hydrogen, when compared with chlorine (compare 6 and 3, and 5 and 3 respectively). A similar effect is also observed for *cis*- and *trans*-chlorine (9 and 10).

However, the substantial difference of steric requirements between chlorine and fluorine (compounds 3, 5 and 6) and between chlorine and hydrogen (compounds 9 and 10) may be, at least in part, responsible for the difference observed.

It is interesting to compare the above results with those obtained with halogenobenzenes. In a classical paper Roberts and coworkers[140] reported

the rates of exchange of deuterated benzene derivatives with potassium amide in liquid ammonia. The data, collected in Table 45, show that the rates are greatest for the *ortho* and smallest for the *para* compounds, the reactivity of the *meta* compound being intermediate.

TABLE 45. Rate coefficients for deuterium exchange of deuterobenzenes (C_6H_4DX) in liquid ammonia in the presence of 0·6M KNH_2 [140]

X	k (s^{-1})	X	k (s^{-1})	X	k (s^{-1})
2-F	4×10^{-1}	3-F	4×10^{-4}	4-F	2×10^{-5}
2-CF_3	6×10^{-2}	3-CF_3	1×10^{-3}	4-CF_3	1×10^{-3}
2-OCH_3	6×10^{-4}	3-OCH_3	1×10^{-7}	4-OCH_3	$\sim 10^{-8}$
2-CH_3	Very slow				
H	$\sim 10^{-7}$				

This suggests that the attack of the base is actually occurring on the hydrogen, and not on the benzene nucleus, without involving the π-electron system in an important way. Therefore, the combined inductive and field effects of substituents appear to play a major role. In fact, electronegative substituents, F, CF_3, OCH_3, increase the rates and the only evidence of a resonance effect is that anisole-4-*d* seems to exchange more slowly than benzene-*d*. However, owing to the low reactivity of the two substrates, an accurate comparison was not possible. The ratio k_m/k_p is smaller than k_o/k_m: this is expected since the combined field and inductive effects should decrease with increasing distance from the substituents. The rate of fall-off of log k seems to be a function of the number of carbon atoms between the deuterium and the electronegative group.

More recently Streitwieser and Mares[141] measured the rates of deuterium exchange in the lithium cyclohexylamide–cyclohexylamine system with fluorobenzene. They found partial rate factors of $6{\cdot}3 \times 10^5$, $1{\cdot}1 \times 10^2$ and $1{\cdot}1 \times 10$ for the *ortho*, *meta* and *para* positions, respectively. These factors are to be compared with the above data of Roberts[140] which were transformed to partial rate factors by Shatenshtein[142]: *ortho* = 10^6, *meta* = 10^3, *para* = 10^2. Roberts' data[140] for *meta* and *para* positions were not as accurate as Streitwieser's[141], due to the slowness of the exchange in liquid ammonia.

Shatenshtein[142] correlated the rates of hydrogen exchange with σ_I constants, showing that the inductive effect of the substituent is responsible for the reactivity of the *ortho* hydrogens. Streitwieser and Mares[141] calculated the charge-dipole electrostatic energies for *ortho*-, *meta*- and *para*-fluorophenyl anions. A plot of $\log k_{rel}$ for the exchange reaction

versus the calculated electrostatic energies for the said positions is reasonably linear, thus showing that ordinary inductive field effects can account for the positional effects of a substituent in stabilizing a phenyl anion.

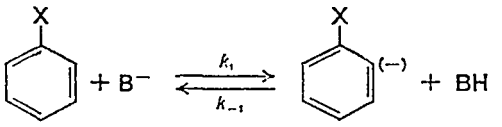
Semiquantitative data of Wittig's group[143] showed that fluorine should be a better stabilizing substituent for the *ortho* aryl anion than the other halogens. They examined, under standardized conditions, the reactions of aryl halides with phenyl lithium in ether at 20°. Their results are collected in Table 46.

TABLE 46. Relative yields in reactions of aryl halides ($Y-C_6H_4-X$) with phenyl lithium in ether at 20° [143]

X	Y = H	Y = *m*-OCH_3	Y = *p*-OCH_3
F	8·75	3·6	15
Cl	1	2	1
Br	1·25	2	1·4
I	1[a]	1[b]	1[c]

[a] 8% Yield of biphenyl after 20 h.
[b] 25% Yield of lithium halide after 5 h.
[c] 5% Yield of lithium halide after 20 h.

Quantitative data were obtained by Huisgen and Sauer[144] for reactions of aryl halides with phenyl lithium and lithium piperidide in ether. They found that the reactions follow the scheme:



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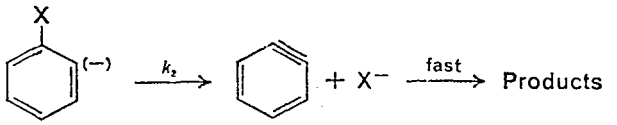


(14)

The rate of benzyne formation, as evaluated by halide ion titration, can be derived from the expression:

$$\frac{d[X^-]}{dt} = \frac{k_1 k_2 [ArX][B^-]}{k_2 + k_{-1}[BH]} \tag{15}$$

Therefore, when BH is a very weak acid or its concentration is zero, k_1 becomes rate-limiting and the values obtained represent the rates of metalation of halogenobenzenes, which should be a function of the α-halogeno

aryl anion stability (see Table 47, columns A and B). When free acid (BH) is added, however, the k_{-1}[BH] term cannot be neglected and the rate of halide ion production will depend on the ability of halogen as leaving group (I > Br > Cl > F) as well as on the effect of halogen on hydrogen abstraction (F > Br > Cl > I). By varying the nature and the amount of BH almost any reactivity scale can be obtained. An example is given in Table 47.

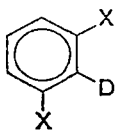
TABLE 47. Relative rates of the reactions of halogenobenzenes (C_6H_5—X) with C_6H_5—Li (A), and lithium piperidide (B and C) in ether at 20° [144]

X	A	B	C[a]
F	15	6·5	0·008
Cl	1·5	1·6	0·42
Br	1·7	2·6	2·9
I	1·0	1·0	1·0

[a] [Piperidine]/[piperidide] = 1·5.

The same process may explain the order of reactivity found in the amination with KNH_2 in liquid ammonia which is Br : I : Cl = 20 : 8 : 1 and 13·5 : 5 : 1 for halogenobenzenes[145] and 3-halogenotoluenes[146], respectively. In both cases the fluorine derivative remained unchanged.

Further substitution of halogenobenzenes with electron-withdrawing groups increases, as expected, the reactivity towards strong bases[147]. Hine and Langford[148] measured the rates of hydrogen exchange of 1-deutero-2,6-dihalobenzenes in the CH_3O^-/CH_3OH system. Their data are shown in Table 48. Replacement of chlorine by fluorine enhances the



(152)

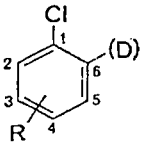
TABLE 48. Rates of hydrogen exchange of halobenzenes **152** in CH_3O^-/CH_3OH at 100° [148]

X	Y	$k \times 10^6$ (l mole^{-1} s^{-1})
F	F	978
F	Cl	151
Cl	Cl	20·2

rate by a factor of about 7. This effect appears to be additive. Moreover, no halide ion was found, showing that proton capture by the aryl anion is, in this case, faster than halide ion loss from it.

Two methods have been developed to estimate the relative rates of proton capture and halide ion loss. Roberts and coworkers[149] evaluated this ratio (k_{-1}/k_2, see equations 13 and 14) for the *o*-chlorophenyl anion by measuring the yield of chloride ion and the change in deuterium content during reaction of *ortho*-deuterated chlorobenzene with KNH_2 in liquid ammonia. Hoffman[150] has shown that the above ratio can be obtained, when the *o*-bromophenyl anion is generated in an alcoholic solvent, by the yields of bromobenzene recovered and bromide ion formed.

Bunnett and coworkers reported the ratio k_{-1}/k_2 for *o*-chloro-[151] and *o*-bromo-[152] phenyl anions. The *o*-chlorophenyl anions were generated in liquid ammonia–diethylether (60 : 40) by reaction with KNH_2 of the appropriate chlorobenzene (**153**). The ratios k_{-1}/k_2, evaluated following Roberts and coworkers[149], are reported in Table 49. Both electron-releasing (CH_3, OCH_3) and electron-attracting (Cl, CF_3) substituents increase the k_{-1}/k_2 ratio.



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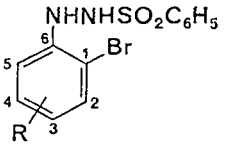


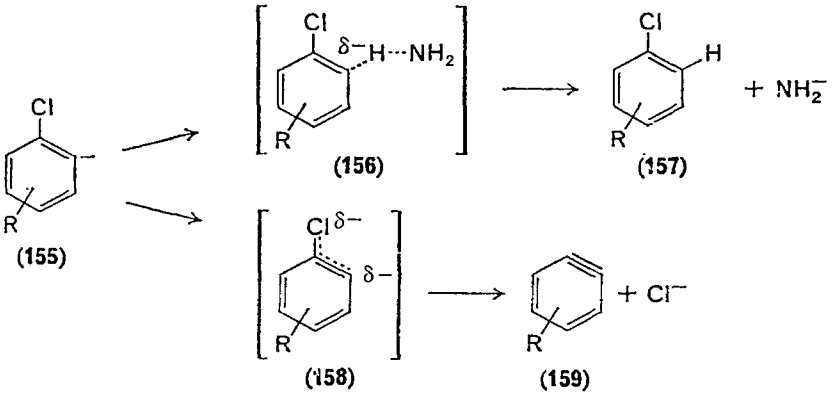
(154)

TABLE 49. Proton capture/halide ion loss ratio (k_{-1}/k_2) for reaction of substituted chlorobenzenes **153** with KNH_2 in ammonia–diethyl ether (60 : 40) and of substituted 1-(*o*-bromophenyl-)-2-sulphonhydrazides (**154**) with CH_3ONa/CH_3OH at 61° [151, 152]

R	153	154
H	7·6	7·8
2-Cl	41·0	—
3-Cl	—	21·0
4-Cl	240·0	43·0
5-Cl	240·0	—
4-CH_3	11·4	11·3
4-CF_3	230·0	46·0
4-OCH_3	99·0	26·0

The electron-attracting substituents (Cl, CF_3) are known to stabilize negative charges on ring carbons through inductive and electrostatic effects. They indeed accelerate, in aromatic substrates, proton abstraction by bases[140,147] and therefore stabilize the phenyl anions formed. A similar effect should be present also in transition states **156** and **158**, leading to proton capture and chloride ion loss, respectively. The amount of stabilization will depend on the amount of negative charge in the transition state.

The fact that proton capture is favoured over chloride ion loss implies that the energy of transition state **156** is decreased more than that of **158**, and therefore it may be deduced that **156** is more 'phenyl anion-like' whereas **158** is 'aryne-like'[151].



By the principle of microscopic reversibility, **158** is also the transition state for chloride ion addition to aryne. Following the above discussion it must be concluded that the transition state for this addition occurs very early on the reaction coordinate. This conclusion was indeed reached by Huisgen and Zirngibl[153] and used to explain the small steric effects found in the addition of nucleophiles to 1,2-naphthalyne.

The effects of CH_3 and OCH_3 substituent are more difficult to explain. They should destabilize phenyl anions[140,147] and, possibly, increase the energy level of the aryne-forming transition state[151].

Similar behaviour was found in the reaction of substituted 1-(*o*-bromophenyl)-2-sulphonhydrazides (**154**) with 2M CH_3ONa in CH_3OH at 61°[152]. Also in this reaction, which involves decomposition of **154** to aryl anions, the ratio k_{-1}/k_2, evaluated following Hoffmann[150] is increased both by electron-attracting and electron-releasing substituents (see Table 49). The substituent effects, while somewhat lower, closely parallel those observed for chlorobenzenes in liquid ammonia.

The finding that substituents increase the ratio of proton capture over halide ion loss is of great practical importance, since it makes it possible to have reactions of aryl anions with acids or other electrophiles without excessive decomposition to halide ion and aryne. Examples of these reactions will be reported in the following section.

B. Effects on Reactivity

1. Alkyl anions

Decarboxylations of trihaloacetic acids are first-order reactions of the carboxylate anions and very probably[154,155] they involve the rate-determining formation of **161**, which is then trapped by water. The relative

$$\underset{\textbf{(160)}}{X_3C{-}CO_2^-} \longrightarrow \underset{\textbf{(161)}}{X_3C^-} + CO_2 \qquad (16)$$

$$\underset{\textbf{(161)}}{X_3C^-} + H_2O \longrightarrow \underset{\textbf{(162)}}{X_3CH} + {}^-OH \qquad (17)$$

decarboxylation rates of **160** follow the order[154–157]: $X_3 = Br_3 > Br_2Cl > Cl_3 > BrClF \gg F_3$ (see Table 50).

The sequence is in agreement with the rates of carbanion formation from CX_3H even if probably other factors, such as the bulkiness of halogen atoms, may help to expel the CO_2 from carboxylate anions. For instance,

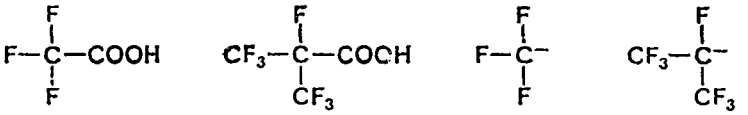
TABLE 50. Rates of decarboxylation of trihaloacetate ions ($CX_3{-}COO^-$) at 70° in water

X_3	ks^{-1}	Reference
I_3	Very fast	155, 158
Br_3	$6{\cdot}5 \times 10^{-4}$	155
Br_2Cl	$3{\cdot}0 \times 10^{-4}$	156
Cl_3	$1{\cdot}7 \times 10^{-5}$	154
BrClF	$1{\cdot}0 \times 10^{-6}$	156
F_3[a]	$2{\cdot}8 \times 10^{-11}$	157

[a] In ethyiene glycol, extrapolated from data at higher temperatures; in the same solvent the rate of decarboxylation for trichloroacetate ion is $2{\cdot}48 \times 10^{-6}$ s^{-1} at 55·5°C.

it has been reported[155,158] that triiodoacetic acid decarboxylates rather rapidly at room temperature, and hence much faster than tribromoacetic acid (see Table 50), even if the triiodomethyl anion is not formed from haloform significantly faster than the tribromomethyl anion[126].

It is interesting to compare the behaviour of trifluoroacetic **163** and perfluoroisobutyric acid **164**. The former is very stable in water and

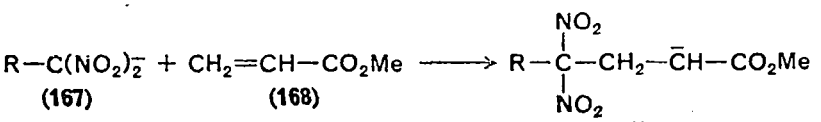


(163) **(164)** **(165)** **(166)**

measurable rates of decarboxylation are attained only at high temperature: at 170° in ethylene glycol the rate of decomposition is $k = 2{\cdot}98 \times 10^{-5}$ s^{-1} [157]. The latter[159] is completely decomposed after 45 min in basic aqueous solution at 100° ($k_{dec} > 10^{-3}$ s^{-1}).

If the stability of the resulting carbanions **165** and **166** is the most important factor in determining the rates of acid decomposition, we must conclude that **166** is much more stable than **165**. This is reasonable in the light of the discussion in the previous sections on the destabilizing effect of fluorine on α-carbanions because of lone pair–lone pair repulsion.

A similar example of influence in carbanion reactions of α-fluorine, though in the opposite sense, is found in the addition of dinitromethide ions to methyl acrylate[160].



(167) **(168)** **(169)**

The specific rates and activation parameters are collected in Table 51 for several methide ions. The rates of addition lie in a fairly narrow range for all R but fluorine: the fluorodinitromethide ion (**167**; R = F) adds to methyl acrylate about 2000 times faster than the other ions in either solvent system. This increase in reactivity is clearly reflected in the ΔH^* term: the fluoro substitution decreases it by 5 kcal/mole. This has been attributed to destabilization of the ground state of **167** by fluorine substitution[160]. It must be remembered that fluorodinitromethane has a pK_a in water at 25° of about 3·9 pK units higher than chlorodinitromethane[131,132]. Both effects may be rationalized on the basis of lone-pair repulsion between fluorine and the negative charge on the α-carbon.

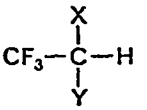
Easy expulsion of halide ions makes it difficult to observe β-halogenocarbanions in saturated systems. The only example refers to a carbanion stabilized by β-fluorine, which has the least ability to depart as an anion from saturated carbon.

TABLE 51. Specific rates and activation parameters for the addition of substituted dinitromethide ions [R—$C(NO_2)_2^-$] to methyl acrylate in water and 50% dioxan at 30° [180].

R	H_2O			50% Dioxan		
	$k \times 10^4$ (l mole^{-1} s^{-1})	ΔH^* (kcal/mole)	ΔS^* (cal mole^{-1} deg^{-1})	$k \times 10^4$ (l mole^{-1} s^{-1})	ΔH^* (kcal/mole)	ΔS^* (cal mole^{-1} deg^{-1})
CH_3	13·5	~14·4[a]	−23·7[a]	17·2	~12·5[a]	−29·5[a]
C_2H_5	16·1			18·4		
Cl	21·4			25·6		
F	49,800	9·5	−24·0	72,400	7·4	−30·4

[a] This is the average of three similar values for the three compounds.

1,1,1-Trifluoro-2,2-dihalogenoethanes (**170**) in alkaline methanol undergo H/D exchange at a rate faster than fluoride ion elimination[161,162]. Data are collected in Table 52.



(170)

TABLE 52. Rates of hydrogen exchange (k_{exch} at 20°) and dehydrofluorination (k_{el} at 55°) of 1,1,1-trifluoro-2,2-dihalogenoethanes (**170**) in alkaline methanol[161,162]

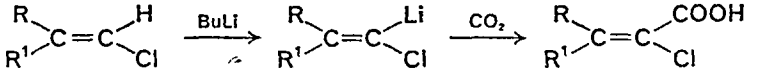
X	Y	$k_{exch} \times 10^3$ [a] (l mole^{-1} s^{-1})	$k_{el} \times 10^6$ (l mole^{-1} s^{-1})
Cl	Cl	10·2	1·5
Br	Br	74·0	5·5
Br	Cl	22·0	2·9
I	I	29·0	51·0

[a] Evaluated on deuterated **170**.

The α-halogens and β-fluorines facilitate the hydrogen abstraction: for comparison in the same conditions, the rate of exchange of $CDCl_3$ is $8{\cdot}9 \times 10^{-3}$ l mole^{-1} s^{-1}. This fact, together with the well-known reluctance of fluorine to depart as an anion from saturated carbon, increased by the presence on the same carbon of other halogens[72,163], provides us, possibly, with the only clean example of the E*l*c*B* mechanism in reaction of saturated halogenoalkanes[164].

2. Vinyl anions

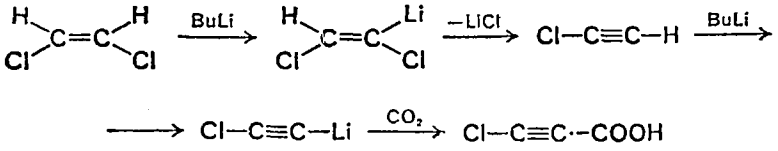
Kobrich and coworkers[165,166] reacted several halogenoethylenes with butyllithium in ether at low temperature and then with CO_2. They obtained the corresponding α,β-unsaturated carboxylic acids in yields usually better than 70% but decreasing with increasing temperature.



(18)

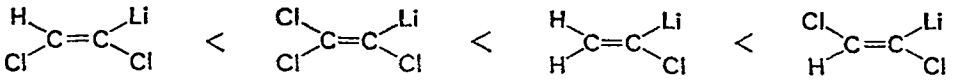
R = R' = H, Cl or aryl; R = H, R' = Cl; R = Cl, R' = H

The only exception was the reaction with *cis*-dichloroethylene where chloropropiolic acid was formed.

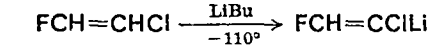


(19)

From the yields of the carboxylic acids the following stability scale was set up[166]:



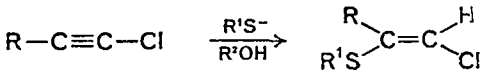
It is interesting that 1-chloro-2-fluoroethylene (*cis* or *trans*) metalates on the chlorine-bearing carbon[101]:



(20)

this is in agreement with the rates of hydrogen exchange of halogenoethylenes (see section III. A) and with the general finding that α-fluorine does not favour carbanions.

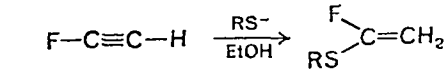
Other examples are provided by the nucleophilic additions to halogenoacetylenes[101]. The base-catalysed addition of thiols and alcohols to chloro- and chloroalkyl-acetylenes occurs directiospecific β to the halogen[101,167–172]:



(21)

R = H, Me, *n*-Bu, *t*-Bu
R¹ = Alkyl, Ph
R² = Me, Et

On the contrary, the addition of the thiophenolate anion to fluoroacetylene[173] occurs with opposite orientation:



(22)

This is another manifestation of the destabilizing effect of fluorine on α-carbanions by lone pair–lone pair repulsion.

Reactions of thiolates, as well as other nucleophiles, with bromo- and iodo-acetylenes are complicated by concurrent attacks at the carbon and

at the halogen atom. Recent papers have been published dealing with factors affecting the two possible reaction paths[174–176]. It is enough to say here that the ease of attack at halogen decreases in the order I > Br > Cl [174].

Halogenovinyl carbanions have been proposed as intermediates in the ElcB hydrogen halide eliminations from 1,2-dihaloethylenes[177]. These ethylenes, in fact, undergo elimination at a slower rate than H/D exchange. The rates of exchange in alkaline D_2O are similar for *cis*-dibromo- and dichloro-ethylene, whereas the *trans* derivatives follow the series:

$$CHCl{=}CHCl > CHBr{=}CHBr > CHI{=}CHI$$

Moreover, the isotope effect found for elimination in the *cis*-dibromo compound at 35·2°C is 1·03, a very low value[178], which suggests that the rate-limiting step is indeed the halide ion elimination from the β-halogenovinyl anion. The rates of dehydrohalogenation, collected in Table 53,

TABLE 53. Rate coefficients and activation parameters for the dehydrohalogenation of dihalogenoethylenes with sodium methoxide in methanol, at 60° [177]

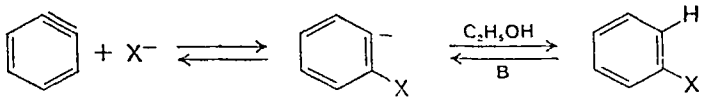
		k (1 mole^{-1} s^{-1})	E_a (kcal/mole)	ΔS^* (cal mole^{-1} deg^{-1})
$C_2H_2Cl_2$	*cis*	$1{\cdot}4 \times 10^{-6}$	35·1	+22
	trans	$4{\cdot}2 \times 10^{-9}$	29·0	−12
$C_2H_2Br_2$	*cis*	$1{\cdot}8 \times 10^{-2}$	28·1	+16
	trans	$3{\cdot}3 \times 10^{-8}$	33·4	+5
$C_2H_2I_2$	*cis*	1·6	24·7	+14
	trans	$1{\cdot}2 \times 10^{-5}$	35·8	+24

show the expected decrease in the order I > Br > Cl. Moreover, since the rates of hydrogen exchange of dichloro- and dibromo-ethylenes were found to be much higher than rates of *cis–trans* isomerization, a lower limit for the inversion of halogenovinyl carbanions was estimated in the range 28–35 kcal/mole[178]. This value was confirmed by theoretical calculations[179].

3. Aryl anions

Several examples of benzyne formation through *o*-halogenoaryl anions are available and since they have been collected in a recent book[180] they will not be discussed here.

Ortho-halogenoaryl anions are obtained via addition of halide ions to dehydrobenzene in tetrahydrofuran or ethanol:



(171) (172) (173) (23)

This is the reverse of the formation of dehydrobenzene from aryl halides and demonstrates the reversibility of the processes[181].

Judging from the yields, the relative reactivity of halide ions is I : Br : Cl = 65 : 8 : 1. For the reverse reaction, loss of halide ion from **172**, the relative reactivities are[150] I : Br : Cl = 100 : 40 : < 2. This made it possible to calculate the ratios of the equilibrium constants in the reaction **171** ⇄ **172**. The results obtained were about 3·2 for the ratio K_I/K_{Br} and about 2·5 for the ratio K_{Br}/K_{Cl}.

Orientation in the addition of nucleophiles to substituted benzynes may be influenced by several factors[180], such as electronic and steric demands of the substituent, nucleophilicity of the attacking base, solvent, etc. Some examples of additions to 3- and 4-halogenobenzyne (**174** and **175** respectively) are reported in Tables 54 and 55.

(174) (175)

TABLE 54. *Meta*/*ortho* isomer ratio in nucleophilic additions to 3-substituted benzynes **174**

	Reacting system[a]			
X	KNH_2/NH_3	Reference	LiPip/Pip	Reference
F	100	182	16	184
Cl	Large[b]	183	—	—
Br	Large[b]	183	4·9	185
CH_3	0·8	182	1·95	184

[a] KHN_2/NH_3 = potassium amide in liquid ammonia at boiling point (~ −33°); LiPip/Pip = lithium piperidide in the presence of piperidine in ethyl ether at room temperature (~20°).

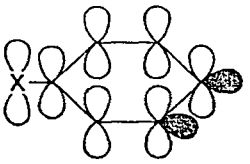
[b] No numerical value is reported; $NaNH_2$ in liquid ammonia at reflux.

TABLE 55. *Para/meta* isomer ratio in nucleophilic addition to 4-substituted benzynes **175**

	Reacting system[a]			
X	KNH_2/NH_3	Reference	LiPip/Pip	Reference
F	4·0 ± 0·2	182	1·95	184
Cl	4·2	151	—	—
Br	—	—	1·4	185
I	—	—	(1·55)[b]	186
CH_3	0·67	182	0·83 ± 0·05	187

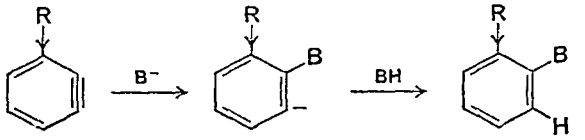
[a] See footnote *a* to Table 54.
[b] The adding compound is benzoic acid in benzene.

The substituent effect may be explained in two alternative ways. The orbitals at which the polar addition occurs (see **176**) are orthogonal to those of the aromatic π-system, including the lone pairs on the substituent. The conjugative effect of the substituent will influence the aromatic system, but not, at first approximation, the reactive site. Only the inductive effect of the substituent, therefore, is transmitted to the reacting centre.

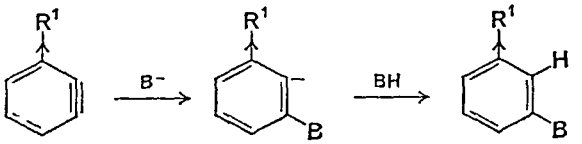


(176)

This inductive effect will direct the approaching nucleophile in the way which allows the best stabilization of the resulting negative charge. That is, the more acidic of the two possible products will be formed in higher yield. This is illustrated by schemes (24) and (25), where the substituents R and R^1 are electron-donating and electron-attracting, respectively.



(24)



(25)

The alternative explanation calls for a kinetic control of the isomer ratio, which thus reflects the electron density of the two carbon atoms of the formal triple bond polarized by the inductive effect of the substituents. In other words, the transition state for nucleophilic additions to benzynes should come early along the reaction coordinates and resemble the reactants more than the resulting anion. Since evidence in favour of this point has been presented in section III. A, we feel the last explanation more adequate, although in the benzyne series both theories lead to the same conclusion. Moreover, experiments in the dehydroheterocycle series seem in agreement with the latter hypothesis[180].

The nucleophilicity of the attacking reagent should also play a relevant role since the more nucleophilic reagent is expected to be the more reactive and therefore less selective: the isomer ratio should therefore approach unity for the better nucleophile.

Detailed studies by Bunnett and coworkers[188,189] shed some light on this point. They examined the addition of methanol to 4-chlorobenzyne in the presence of various amounts of methoxide ion[189]. The *para/meta* chloroanisole ratio depends on the amount of base (see Table 56).

TABLE 56. Influence of base concentration on the *para/meta* chloroanisole ratio obtained in the reaction of 4-chlorobenzyne and methanol[189]

CH_3ONa (M)	0	0·2	0·4	0·8	1·9
p/m	4·7	3·2	2·8	2·5	2·1

The change in the *para/meta* ratio with increasing sodium methoxide concentration clearly shows that methoxide ion is more reactive than methanol toward 4-chlorobenzyne[188]. The ratio of rates of methoxide and methanol attack was evaluated as 157 and 70 for the *meta* and *para* positions, respectively[189].

The different response of chlorine atom to orient attack by methanol or methoxide is in the expected sense. With a weak nucleophile, like methanol, the transition state for the addition should be attained later on the reaction coordinate than with a strong nucleophile such as methoxide[190]. It follows that the transition state should resemble the intermediate anion more and that the orienting effect of chlorine should be stronger.

According to the previous discussion, a change is expected in the isomer ratio on passing from a protic to an aprotic solvent. This was indeed observed in the addition of lithium chloride and lithium bromide to 4-chlorobenzyne (**175**, X = Cl) (see Table 57)[191].

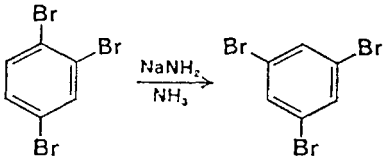
In dimethyl sulphoxide (DMSO) solution the nucleophilicity of the halide ions is increased[192] and the *p/m* ratio, as expected, decreased.

TABLE 57. *Para/meta* isomer ratios as a function of the solvent in the addition of LiCl and LiBr to 4-chlorobenzyne (175, X = Cl)[101]

Solvent	LiCl	LiBr
EtOH	3·7 ± 0·8	2·0 ± 0·2
DMSO/$MeNO_2$	2·1 ± 0·3	—
DMSO	1·5 ± 0·2	1·3 ± 0·2

The discovery that electron-attracting groups enhance the rate of proton capture versus that of halide ion expulsion in *o*-halogenophenyl anions[151,152], is of particular importance to understanding the behaviour of trihalogenobenzenes in strongly basic media.

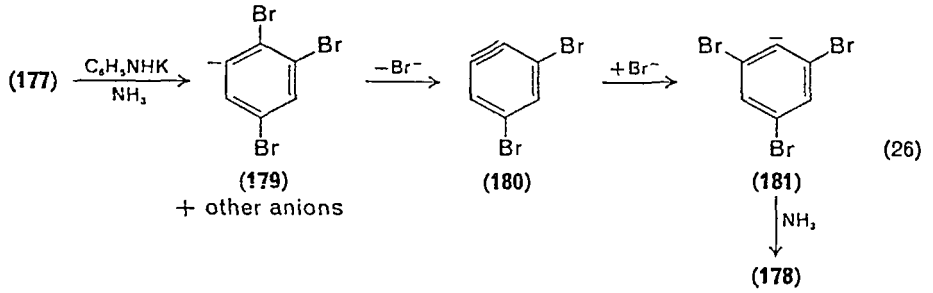
It was observed by Wotiz and Huba[183] that the recovered neutral material from the reaction of 1,2,4-tribromobenzene (**177**) with sodium amide in liquid ammonia was 1,3,5-tribromobenzene (**178**).



(177) (178)

This reaction was subsequently reinvestigated by Bunnett's group[193–195], who also observed similar isomerizations in several other polyhalogenobenzenes.

It was found[193] that by reacting perdeuterated **177** with potassium anilide in liquid ammonia the recovered **178** and **177** were completely deuterium free. This is a clear indication that aryl anions are indeed formed. It could suggest that **178** is formed via aryne **180** (see equation 26).



(26)

The analysis of the data reported in Table 58 indicates that the aryne path cannot account for the experimental results. In fact (i) reaction of **177** in the presence of added KI does not give iodide ion-incorporated

TABLE 58. Percentage of tribromobenzene isomers formed in the reactions of 1,2,4- (**177**) and 1,3,5-tribromobenzene (**178**) in strongly basic media.[a]

Starting material	Solvent[b]	Base	Reaction time (min)	177%	178%
177	NH_3	$NaNH_2$	1080	85	15
177	NH_3	KNH_2	480	77	23
177	NH_3	PhNHK	480	48·6	51·4
177 + KI	NH_3	PhNHK	480	80	20
177	NH_3—Et_2O	KNH_2	120	71·4	28·6
177	NH_3—Et_2O	PhNHK	120	41	59
177	NH_3—Et_2O	PhNHK	480	41	59
178	NH_3—Et_2O	PhNHK	480	0	100
178 + **182**[c]	NH_3—Et_2O	PhNHK	147	24	76
177	DMF	*t*-BuOK	0·45	49·4	50·6
177	DMF	*t*-BuOK	5400	48·6	51·4
178	DMF	*t*-BuOK	76·0	0	100
178 + **182**[c]	DMF	*t*-BuOK	1·67	49·1	50·9
177	HMPA	*t*-BuOK	2·67	59·7	40·3
177	HMPA	*t*-BuOK	1500	63·9	36·1
178	HMPA	*t*-BuOK	1	63·6	36·3

[a] Various amounts of dibromo- and tetra-bromobenzenes were also formed, together with bromide ion; for details see references 193 and 194.

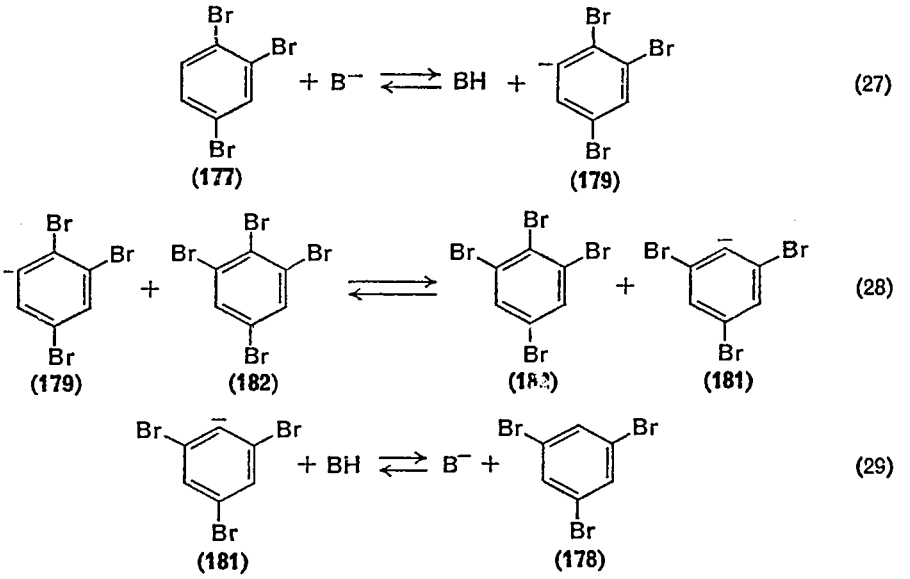
[b] NH_3—Et_2O stands for a 50 : 50 mixture of the two solvents; DMF is dimethylformamide, and HMPA is hexamethylphosphoramide.

[c] **182** is 1,2,3,5-tetrabromobenzene, in catalytic amounts.

products, despite its higher ability to add to benzyne when compared to the bromide ion; (ii) from the scheme above, according to the observed orientation of halide ions to 3-haloarynes, a much higher **178**/**177** ratio than that observed should be expected.

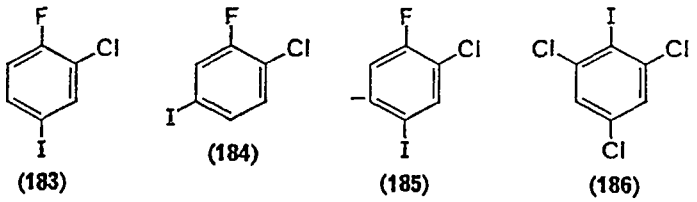
Bunnett and Scorrano[194] investigated the **177** $\rightleftarrows$ **178** isomerization in more detail. It was found that the isomerization of 1,2,4- into 1,3,5-tribromobenzene is actually an equilibrium reaction. However the establishment of the equilibrium seems to require catalysis by 1,2,4,5-tetrabromobenzene (**182**) or other suitable positive bromine donors. The presence of dibromobenzenes among the reaction products indicates that the catalyst may be formed by disproportionation of the tribromobenzenes

and more easily from **177** than from **178**. The following scheme explains the experimental data:



It is important to notice that the aryl anion (**179**) is stabilized by two halogens, other than the one *ortho* to the negative charge, which may explain why it reacts with the positive halogen donor faster than it loses bromide ion to give arynes.

Another example[194] of this reaction path for halogenoaryl anions was found by attempting isomerization of 1-fluoro-2-chloro-4-iodobenzene (**183**) into 1-fluoro-2-chloro-5-iodobenzene (**184**).

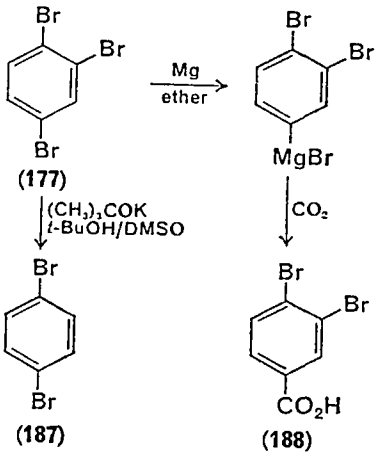


It was found that conversion was possible only via reaction of aryl anion **185** with an iodine donor as 1-iodo-2,4,6-trichlorobenzene (**186**). No isomerization was observed in absence of catalyst **186** ruling out a conceivable 1,2-iodine shift[194].

Equilibrium between **177** and **178** is also attained with potassium *t*-butoxide in dimethylformamide (DMF) and hexamethylphosphoramide (HMPA). The **178/177** ratios are 1·6 in liquid ammonia/ether 50 : 50 at −29°, 1·4 in DMF and 0·55 HPMA at ca. 25°[194]. It is interesting that the recovered 1,2,4-tribromobenzene also appears to have undergone reaction. McLennan and Bunnett[195] studied the reaction of 1,2,4-tribromobenzene-1-^{82}Br under the same reaction conditions leading to the **177** ⇄ **178** equilibration.

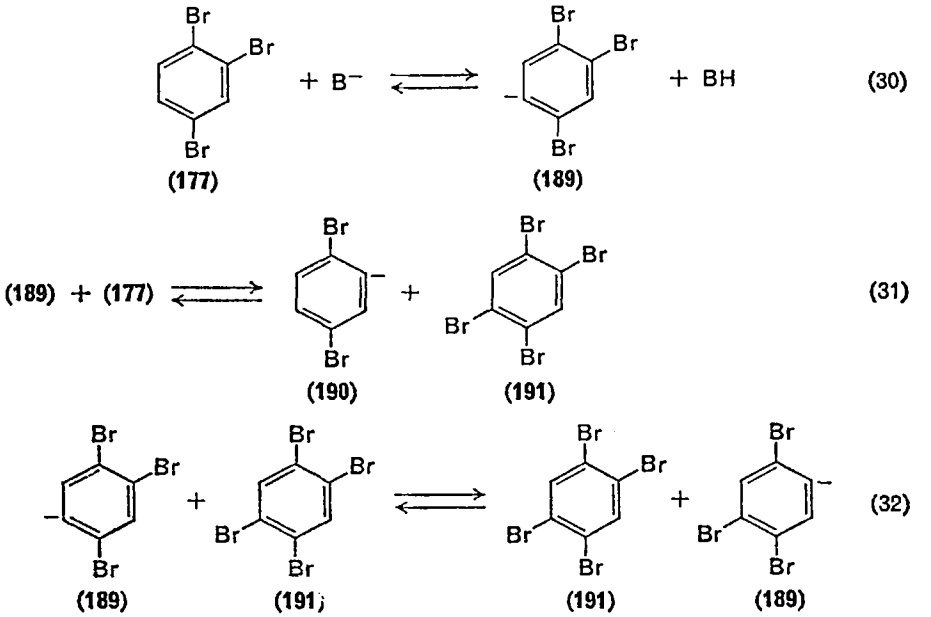
The recovered 1,2,4-tribromobenzene was degraded according to the following scheme. The reaction leading from **177** to **187** was studied in detail by Bunnett and Victor[196].

The radioactivity count in **187** and **188** represents the radioactivity of the original sample minus that of the 2- and 4-bromine respectively.



The results of the radiochemical analysis indicate an equal distribution of the label among the three positions. This may be easily explained by a reaction scheme similar to equations (27)–(29) in which the key step is the positive bromine transfer from 1,2,4,5-tetrabromobenzene to 2,4,5-tribromophenyl anion (see equations 30–32). Notice that the four bromines of **191** are equivalent and hence each one participates in the exchange.

This reaction can be proved only by radioactive labelling of bromine and it is always present in the transformation of **177** into **178**. It shows another aspect of the reactivity of trihalogenoaryl anions. Isomerization and disproportionation have also been reported, and explained with similar positive halogen transfer as described above, for halogenothiophenes[197], halogenoisothiazoles[198] and halogenoimidazoles[199].



IV. EFFECTS ON RADICALS

In the previous sections the effects of halogens were considered mainly from the point of view of polar interactions with positive and negative centres.

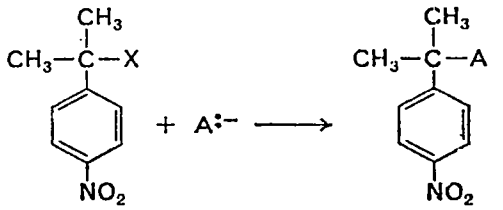
As far as radical stability and radical reactions are concerned, the polar effects, in first approximation, should not play any major role since no formal charges are formed or destroyed in the production of radical intermediates by homolysis of a covalent bond (equation 33) or by addition of a radical to a multiple bond (equation 34).

$$R{-}X \longrightarrow R^{\bullet} + X^{\bullet} \tag{33}$$

$$R + X^{\bullet} \longrightarrow \dot{R}{-}X \tag{34}$$

However, much evidence indicates that polar effects do play a role in radical reactions. On the other hand, the classical sharp separation between homolytic and heterolytic processes is under critical revision and numerous well-documented cases of formally nucleophilic reactions which in fact occur via electron transfer to give radical ion intermediates are now in the literature.

Kornblum and coworkers[200], for example, reported that substitutions such as equation (35) occur via radical anions.



X = NO_2, Cl (35)

Recently Bunnett and Kim[201] reported that unactivated halogenobenzene may react with strong nucleophiles following the scheme (36). The other conceivable electron transfer processes (37), (38), (39) have not,

(36)

$$A + R^+ \longrightarrow A^{\bullet+} + R^\bullet \longrightarrow \text{Products} \quad (37)$$

$$A + R^\bullet \longrightarrow A^{\bullet-} + R^+ \longrightarrow \text{Products} \quad (38)$$

$$A + R^\bullet \longrightarrow A^{\bullet+} + R^{:-} \longrightarrow \text{Products} \quad (39)$$

so far, been clearly identified. However, transition states of reactions between a radical and a molecule in which a partial electron transfer occurs concurrently with the formation of the new bond have often been invoked to explain polar effects, sometimes large[202], observed in radical reactions.

A. Radical Stabilization

The stabilization energy due to substitution of a hydrogen with a halogen on a radical may be evaluated through measurements of the appearance potential in mass spectroscopy. These data refer to gas phase and they may not always be applied to solution reactions because of the solute–solvent interactions[28].

The data of Taft[27] and coworkers on the dissociation energy of the C—H bond of halogenomethanes indicate that halogens stabilize methyl radicals by 15–20 kcal/mole and that the various halogens have similar effects.

$$\text{S.E.} = D[CH_3—H] - D[X—CH_2—H] \quad (40)$$

The stabilization energies (S.E.) of the halogenomethyl radicals (relative to $CH_3^\bullet$) were obtained by the relationship (40) taking for $D[CH_3—H]$ the revised value[203] of 104 kcal/mole (see Table 59).

Halogens have much less stabilization effect on radicals than on the corresponding cations[27]. As far as the order of the halogens is concerned, the data presented in Table 59 are opposite to what is expected on the basis of conjugative ability. Possibly other kinds of interaction intervene

TABLE 59. Dissociation energies of C—H bonds in halogen-substituted methanes and stabilization energies of mono-substituted methyl radicals (R•) [27]

R	D[R—H] (kcal/mole)	S.E.
CH_2—H	104[a]	—
CH_2—CH_3	98[a]	6
CH_2—F	89 ± 3	15 ± 3
CH_2—Cl	88 ± 5	16 ± 5
CH_2—Br	83 ± 5	21 ± 5
CF_3	103 ± 4	—
CCl_3	90 ± 4	—

[a] Taken from reference 203.

as, for example, electron–electron repulsion on adjacent atoms, ground-state stabilization or other effects like polarizability, which seems to be more important in gas than in liquid phase[28].

The relative stabilizations of halogen-containing radicals have also been evaluated by estimating the dissociation energy of the carbon–halogen bond by kinetic methods, and from heats of formation of the radicals and the parent compounds[203].

The data reported in Table 60 show that whereas the results of chlorine and bromine abstraction parallel those discussed above, the dissociation energy of the carbon–fluorine bond seems not to be affected by chlorine substitution. This might be due to ground-state effects.

TABLE 60. Carbon–halogen (R—X) dissociation energy (in kcal/mole)[203]

R	F	Cl	Br
CH_3	108	84	70
C_2H_5	106	81	69
CCl_3	106	73	54

Halogen substitution may also affect the geometry of the radical since it may have either pyramidal or planar structure depending on whether the free electron occupies an sp^3-hybridized or a p-orbital[204].

Much evidence is available showing that alkyl radicals, and in particular the methyl radical, are nearly planar with the unpaired electron occupying a p-orbital whose axis is perpendicular to the molecular plane[205–207]. Halogen substitution seems to modify this geometry. Fessenden and Schuler[208] reported e.s.r. spectra of fluorinated methyl radicals trapped in inert gas matrices. The hyperfine constants are reported in Table 61.

TABLE 61. Hyperfine splitting (in gauss) of radicals trapped in xenon matrices at about −188° [208]

Radical	a_H	a_F	a_C
$CH_3^{\bullet}$ [a]	23·0	—	38·5
$CH_2F^{\bullet}$	21·1	64·3	54·8
$CHF_2^{\bullet}$	22·2	84·2	148·8
$CF_3^{\bullet}$	—	142·4	271·6

[a] Transient signal in krypton.

The ^{13}C splitting is a very sensitive measure of the planarity of the radical site. Any non-planarity introduces s-character into the orbital occupied by the free electron[209, 210], and causes a rapid rise of the hyperfine constant because the contribution from an electron in a carbon $2s$-orbital is ~1190 gauss[209].

From data in the literature[210] it was estimated[208] that in $CF_3^{\bullet}$ the electron is in an orbital having 21% s-character ($\widehat{FCF} = 111{\cdot}1°$; θ = angle between the bonds and a plane normal to the threefold symmetry axis = 17·8°) and in $CHF_2^{\bullet}$ in one having 10% s-character ($\theta = 12{\cdot}7°$). The $CH_2F^{\bullet}$ is near planar ($\theta < 5°$).

Thus the $CF_3^{\bullet}$ radical almost maintains tetrahedral geometry ($\theta = 19{\cdot}5°$, 25% s-character).

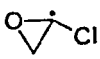
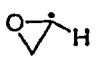
Similar results have been obtained from theoretical calculations[211] using the LCAOSCF method in the INDO approximation (see Table 62). The agreement between the two sets of data is very good. The pyramidal structure of fluoro radicals is also suggested by the fairly large values calculated for barriers to inversion which are related with the energy difference between planar and pyramidal structures.

TABLE 62. Calculated bond angles in fluoromethyl radicals[211]

CH_3	$H\hat{C}H$	119·7		
CH_2F	$H\hat{C}H$	121	$H\hat{C}F$	114
CHF_2	$F\hat{C}F$	109	$F\hat{C}H$	116
CF_3	$F\hat{C}F$	112		

In Table 62 a selection of data obtained by different calculation methods are reported[212–214]. In some cases theoretical data are confirmed by experimental evidence[212,215]. The stabilizing effect of fluorine on the pyramidal

TABLE 63. Calculated barriers to inversion of several halogeno radicals

Radical	Barrier to inversion (kcal/mole)	Calculation method	Reference
	10·5	CNDO/2	212
	10·5	CNDO/2	212
	5·4	CNDO/2	212
	4·0	CNDO/2	212
	1·9	CNDO/2	212
	0·8	CNDO/2	212
$^{\bullet}CHFCl$	0·7	CNDO/2	212
$^{\bullet}CH_2F$	0·6	LCAO-MO-	213
$^{\bullet}CF_3$	27·4	SCF	213
$^{\bullet}CH_3$	−4·9[a]	SCF-MO (MINDO)	214

[a] Energy difference between the less stable pyramidal and the more stable planar structure.

structure is also found in other compounds: the barrier to pyramidal inversion has been estimated[179,216] for NF_3 to be 56–59 kcal/mole compared with 5·8 kcal/mole for ammonia[179,217].

B. Effects on Reactivity

Homolytic reactions, when chain processes, may be generally formulated as shown in Schemes A (equations 41–44) and B (equations 45–48).

SCHEME A:

$$X_2 \rightleftharpoons 2X^{\bullet} \tag{41}$$

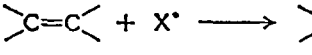
$$RH + X^{\bullet} \longrightarrow R^{\bullet} + HX \tag{42}$$

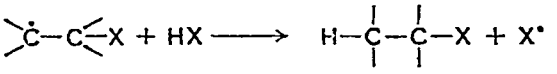
$$R^{\bullet} + X_2 \longrightarrow RX + X^{\bullet} \tag{43}$$

$$2R^{\bullet} \longrightarrow R{-}R \text{ and other terminating reactions} \tag{44}$$

SCHEME B:

$$HX \rightleftharpoons H^{\bullet} + X^{\bullet} \tag{45}$$


(46)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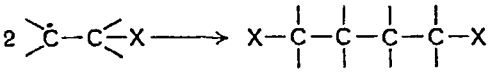

(48)

and other terminating processes

The length of the chain depends on the relative rates of reactions (42) and (43) [or (46) and (47) for Scheme B] in respect of the chain termination processes (reactions 44 and 48, respectively), whereas the overall rate depends also on the rate of formation of the chain carrier (reaction 41).

The effects of halogens in the organic moiety will be manifest in the rates of process (42) and, to a lesser degree, (43) as well as in the 'orientation': i.e. which hydrogen will be abstracted when R is more complex than CH_3 and whether an α or β carbon will be attacked in reaction (46). Moreover halogen substituents may affect the stereochemistry of the overall process (which is definitively fixed by reaction 47).

I. Homolytic substitution[218]

The halogenation of hydrocarbons is one of the most studied homolytic substitutions. The halogens have different reactivity depending largely on the energy of the bonds involved in the reaction.

Reactions (42) and (43) may be very exothermic (F) or endothermic (I). Examples for halogenations of methane are in Table 64.

TABLE 64. Bond energies[1, 203, 218] and estimated ΔH for reactions (42) and (43) in the halogenation of methane

	D[R—H]		D[X_2]	D[H—X]	D[R—X]	ΔH_{42}	ΔH_{43}
$R = CH_3$	104	X = F	37	136	108	−32	−71
		Cl	58	103	84	+1	−26
		Br	46	87	70	+17	−24
		I	36	71	55	+33	−19

The activation energy of reaction (42) is somewhat dependent on the energy of the bond to be formed (see, for example, Table 65).

TABLE 65. Activation energies of the hydrogen abstraction reaction by halogen atoms (X·) from ethane[218]

X	D(H—X)	E_a (kcal/mole)
F	136	0·2
Cl	103	1·0
Br	87	13·3

It follows that the reactivity order of the halogens in respect to hydrogen abstraction is F > Cl > Br ≫ I. In fact, fluorine reacts sometimes with explosive violence, while iodine is unreactive for all but the most highly activated benzylic C—H bonds. The rule that the most reactive is also the least selective reagent is confirmed for the halogenation reaction by the data in Table 66.

TABLE 66. Selectivity of different radicals at 300 K[218]

X·	$-CH_3$	$>CH_2$	$>CH-$
F	1	1·2	1·4
Cl	1	3·9	5·1
Br	1	82·0	1600

The different reactivities of primary, secondary and tertiary hydrogens can be simply explained on the basis of the different stabilities of primary, secondary and tertiary radicals. The different selectivity of halogens may reflect different degrees of bond breaking, and hence radical character at carbon, in the transition state[190].

However there is evidence for polar influences in radical reactions and many radicals, in particular halogen radicals, have electrophilic character[202,218]. Typical examples are chlorination[219] and bromination[220] of substituted toluenes whose reaction rates are correlated by the Hammett relationship with ρ values of $-0{\cdot}76$ and $-1{\cdot}05$, respectively.

Polar effects were invoked to explain the directing effect of halogens in the halogenation of halogenoalkanes[218]. Some data for the gas-phase reactions:

$$X^{\bullet} + Y-\overset{1}{C}H_2-\overset{2}{C}H_2-\overset{3}{C}H_2-\overset{4}{C}H_3 \qquad (49)$$

where X, Y = Hal, CF_3 are collected in Table 67. According to the common use, data are reported in the form of Relative Selectivity (R.S.), that is the relative reactivity for hydrogen atoms at each carbon atom, the

TABLE 67. Relative reactivity at the various carbon atoms in the gas-phase halogenation (X) of *n*-butyl derivatives (Y—C_4H_9-*n*, reaction 49)[221,222]

X•	Y	1	2	3	4	*T* (°C)
F	H	1	1·3	1·3	1	20
	F	0·3	0·8	1·0	1	20
	Cl	?	1·7		1	21
Cl	H	1	3·9	3·9	1	35
	H[a]	1	3·6	3·6	1	75
	F	0·8	1·6	3·7	1	35
	F[a]	0·9	1·7	3·7	1	75
	Cl	0·7	2·2	4·2	1	35
	Br	0·5	—	4·0	1	35
	CF_3[a]	0·04	1·2	4·3	1	75
Br	H	1	82	82	1	146
	H[a]	1	80	80	1	150
	F	10	9	82	1	146
	F[a]	9	7	90	1	150
	Cl	34	32	82	1	146
	CF_3[a]	1	7	90	1	150

[a] From reference 222.

primary hydrogen atoms in *n*-butane taken as unity. The results show that the halogen atoms retard abstraction of the hydrogen from a β-carbon following the order CF_3, F > Cl.

Data on substitution β to a bromine atom are not easily obtained because of the instability of the intermediate radical which breaks down at moderate temperature to give the alkene[221]. However, the very important

$$\begin{array}{l} CH_2-\dot{C}H-CH_2CH_3 \\ | \\ Br \end{array}$$

feature is that the hydrogen atoms *on the same* carbon atom as the substituent are comparatively easily abstracted by halogen atoms.

As the selectivity of the halogenating agent is increased in the series F < Cl < Br, the α-position becomes less deactivated and is actually *activated* to bromination. This can be explained by considering the possibility of stabilization of the incipient alkyl radical by conjugation:

$$X-\dot{C}H-C_3H_7 \longleftrightarrow {}^{\bullet}X=CH-C_3H_7$$

The more the transition state resembles the radical intermediate, the more important will be the conjugative stabilization (e.g. in bromination). In the less selective reaction (fluorination) the more important factor will be the inductive effect of the substituent which deactivates to the attack of the electrophilic radical.

In the chlorination reaction the slight deactivation at the α-position follows the order Br > Cl $\simeq$ F which suggests a balance of inductive and conjugative effects.

That the α-activation is mainly due to resonance effects is shown by the reactions on 1,1,1-trifluoropentane. The CF_3 group has almost the same inductive effect of a fluorine atom (pK_a of fluoroacetic and 3,3,3-trifluoropropionic acid 2·58 and 3·07, respectively)[4], but it strongly deactivates even the bromination at α-carbon[222].

Table 68 collects data[223] on the gas-phase reaction (50).

$$X^{\bullet} + \overset{1}{C}H_3-\underset{\underset{Y}{|}}{\overset{2}{C}H}-\overset{3}{C}H_2-\overset{4}{C}H_3 \qquad (50)$$

The features discussed in connexion with the reaction of *n*-halides are also apparent from the data of Table 68. The more selective reagent ($Br^{\bullet}$) attacks almost exclusively the halogen-substituted secondary carbon to give a resonance-stabilized radical, whereas the attack by the least selective radical ($F^{\bullet}$) occurs preferentially at positions far away from the halogen substituent. The chlorine atom has an intermediate behaviour.

TABLE 68. Relative reactivity (for X = Cl) or percentage of isomer formed (for X = F or Br) at the various carbon atoms in the gas-phase halogenation by X•, of *sec*-butyl derivatives (reaction 50)[223]

X•	Y	1	2	3	4	T (°C)
F	H	26·8%	23·2%	23·2%	26·8%	20
	F	23·9%	0	31·9%[a]	44·2%	21
	Cl	7·9%	0	25·5%[a]	66·6%	21
Cl	H	1	3·9	3·9	1	35
	F	0·1	3·6	2·1[a]	0·7	35
	Cl	0·2	3·2	3·1[a]	0·8	35
Br	H	0·6%	49·4%	49·4%	0·6%	146
	F		92%	8%[a]		146
	Cl		100%			146
	Br		100%			146

[a] Mixtures of *erythro* and *threo* isomers (see Table 69).

Therefore, the early generalization that the halogen directs the attack of an electrophilic radical away from itself is only valid for the very reactive fluorine atom. For the fluorination reaction a transition state very 'reagent-like' can be postulated; in which the deactivating $-I$ effect is expected to be important. With the less reactive bromine radical, a 'product-like' transition state can be assumed: this implies that the halogen substituent may stabilize the incipient radical by resonance.

The halogenation of *sec*-butyl halides gives, as expected, two isomeric 2,3-dihalogenobutanes. The two isomers, however, are formed in different amounts (see Table 69)[223]. Different explanations for the stereochemistry of the reaction will be discussed in section IV. B. 3.

TABLE 69. Percentage of *erythro*- and *threo*-2,3-dihalogenobutanes formed in the halogenation (X•) of *sec*-butyl halides (RY)[223]

	Y = F			Y = Cl	
X	F[a]	Cl[b]	Br[c]	F[a]	Cl[b]
erythro (%)	60·2	59·4	64·3	66·6	71·4
threo (%)	39·8	40·6	35·7	33·4	28·6

[a] At 21°.
[b] At 35°.
[c] At 146°.

Solvents may affect the selectivity of homolytic reactions[224], since they may interact with radicals. As an example it was reported that chlorination of aliphatic hydrocarbons is less selective in the liquid than in the gas phase[225].

More recently Tedder and coworkers[226] showed that the relative rates of chlorination at the primary (p) and secondary (s) carbons of n-hexane at 313 K are 3·11 and 2·14 in the gas phase and CCl_4 solution, respectively. They found also that the different selectivity is caused by different contributions of the pre-exponential factors and of the activation energies. The values reported are:

$$\text{(gas) } k_s/k_p = (2{\cdot}2 \pm 0{\cdot}6)\exp(214 \pm 127 \text{ cal/RT})$$

$$\text{(liquid) } k_s/k_p = (0{\cdot}8 \pm 0{\cdot}2)\exp(597 \pm 20 \text{ cal/RT})$$

On this basis the selectivity in the gas phase was attributed largely to 'cage effect', whereas in the liquid phase it was related to solvation of the chlorine atom[226].

In certain solvents the selectivity may become greater than in the gas phase, as shown by Russell[227] for the chlorination of hydrocarbons in aliphatic and aromatic solvents and in CS_2, and by Walling and Mayahi[228] for chlorination of alkanes in aromatic solvents and in carbon disulphide.

The great effect of carbon disulphide enhancing the selectivity in the chlorination of n-butane is shown by the data reported in Table 70.

TABLE 70. Reactivity ratios in the chlorination of n-butane at 68° [228]

	Gas phase	Liquid phase	9M in C_6H_6	11M in CS_2	13M in CS_2
s/p	3·6	2·69	5·1	6·6	8·0

However, when n-butyl chloride was chlorinated the results collected in Table 71 were obtained[228].

TABLE 71. Isomer distribution in the chlorination of n-butyl chloride at 68° (relative to 1,3-dichlorobutane)[228]

Solvent	1,1/1,3	1,2/1,3	1,4/1,3
—	0·158	0·478	0·397
7·9M in CS_2	0·138	0·430	0·265
11·1M in CS_2	0·122	0·397	0·208
5·7M in C_6H_6	0·114	0·443	0·317
7·5M in C_6H_6	0·120	0·444	0·267

Ashton and Tedder[229] also observed that the selectivity of chlorination of chlorocyclohexane does not increase from the gas phase to carbon disulphide solution as does the halogenation of hydrocarbons (Table 72).

TABLE 72. Relative selectivities (R.S.) for chlorination of chlorocyclohexane relative to 1,4-dichlorocyclohexane ($R.S._{1,4} = 1$)[229]

	Gas	CCl_4	CS_2
1,1	0·23	0·13	0·22
1,2	0·78	0·33	0·25
1,3	0·72	0·68	0·58
1,4	1·00	1·00	1·00

Probably the different dependence of selectivity on the various media is due to the intervention of different effects. In the case of aromatic hydrocarbons and CS_2 the main effect of the solvent is to complex the halogen atom, making it less reactive and hence more selective. In the case of halogenated hydrocarbons the polar effects are more important and the ability of the solvent to stabilize polar transition states intervenes. As a consequence the transition state acquires a greater polar character, the polar effects become more important and effective at greater distances. On the other hand, stabilization by the solvent of the transition state is in itself an activation energy-lowering effect and hence tends to decrease the selectivity.

2. Homolytic additions[230]

The relative facility of the addition of a molecule to a double or triple bond via a radical chain mechanism (see reactions (45)–(48) Scheme B, section IV. B) depends on the balance among the strength of the bonds formed and broken in the process[230, 231].

For example, whereas the radical addition of HBr to an olefinic double bond is facile, the formally similar addition of HCl and HI are both difficult because of the great strength of the HCl bond in the former case and the weakness of the C—I bond in the latter[231].

Substituents at the double bond affect the rate and the orientation of the addition in a more or less marked way depending on the properties of the attacking radical and in particular its electrophilic or nucleophilic character. An example is given in Table 73 where the relative rates of addition to

TABLE 73. Relative rates of addition of radicals to ethylene derivatives

	$CH_3^{\bullet}$ [a]	cyclo-$C_3H_7^{\bullet}$ [a]	$Br^{\bullet}$ [b]	$CF_3^{\bullet}$ [b]
$CH_2=CH_2$	1	1	1	1
$CH_2=CHF$	0·53	0·69	0·014	0·16, 0·24[c]
$CH_2=CHCl$	5·7	1·7	0·301	0·61
$CH_2=CHBr$	7·6	3·4	0·676	0·79
$CH_2=CF_2$	0·65	0·48	0·012	0·088
$CF_2=CF_2$	10·1	—	—	0·15
$CH_2=CHCH_3$	—	—	—	1·5[c]

[a] At 65°C, from reference 232.
[b] At 40°C, from reference 233.
[c] At 200°C, from reference 234.

several halogenoethylenes of two nucleophilic ($CH_3^{\bullet}$ and cyclopropyl) and two electrophilic ($Br^{\bullet}$ and $CF_3^{\bullet}$) radicals are reported.

These results show that nucleophilic radicals attack electrophilic double bonds faster (see in particular the large increase in rate with tetrafluoroethylene). On the other hand, electrophilic radicals react more slowly when electron-withdrawing groups are present on the double bond.

The reactivity sequence Br > Cl > F, observed in the vinyl halides, is common to electrophilic and nucleophilic radicals. It recalls the order of stability of halomethyl radicals as measured by mass spectroscopy (see section IV. A), and, perhaps, the relative stability of the radical to be formed contributes significantly to the overall reactivity.

The polar character of the radical may also affect the orientation, as shown in Table 74 where the relative yields of isomers obtained in the addition of several compounds to trifluoroethene (**192**) are reported (see equation 51).

$$XY + CF_2=CHF \;(\mathbf{192}) \rightarrow \begin{cases} CF_2(X)-CH(Y) & (\mathbf{193}) \\ CF_2(Y)-CH(X) & (\mathbf{194}) \end{cases} \qquad (51)$$

Although the isomer ratios appear to depend, to some extent, on the reaction conditions, the tendency for nucleophilic radicals to attack preferentially the most electronegative carbon (CF_2) whereas electrophilic

TABLE 74. Addition of XY to CF_2=CHF (192) (see equation 51)

XY	Radical (X·)	Attack (%) to		Reaction conditions	Reference
		CF_2 193	CHF 194		
CF_3I	$CF_3^{\bullet}$	11	89	Thermal + I_2	234
		26	74	Photochemical	235
		32	68	Thermal	234
HBr	$Br^{\bullet}$	42	58	Photochemical	235
SF_5Cl	$Cl^{\bullet}$	5	95	Peroxide initiated	236
		27	73	Photochemical	236
$(CF_3)_2PH$	$(CF_3)_2P^{\bullet}$	2	98	Photochemical	237
H_3P	$H_2P^{\bullet}$	15	85	Photochemical	238
$(CH_3)_2PH$	$(CH_3)_2P^{\bullet}$	52	48	Photochemical	237
CCl_3Br	$CCl_3^{\bullet}$	23	77	Photochemical	239
C_3F_7I	$C_3F_7^{\bullet}$	20	80	Photochemical	240
$CH_3N{=}NCH_3 + CH_3I$	$CH_3^{\bullet}$	88	12	Photochemical	241

radicals behave in the opposite way is quite evident. For example, the attack at CF_2 occurs more easily with the $CH_3^{\bullet}$ radical (88%)[241] than with the $CF_3^{\bullet}$ radical (10–30%)[234, 235].

Also typical is the series of phosphine radicals, in which the nature of the radical is gradually changed by the substituents and where, concurrent with increasing nucleophilicity, the attack at CF_2 increases from 2% to 50%[237, 238].

On the other hand, the orientation of the addition of CF_3I and HBr to a series of monosubstituted olefins (195) does not appear to be much affected by the substituent polarity, and in this attack the least substituted carbon is always favoured (see equation 52). Probably in this case the stability of the radical to be formed directs the course of the reaction (see Table 75).

$$XY + \underset{(195)}{R{-}CH{=}CH_2} \rightarrow \begin{cases} R{-}\underset{X}{CH}{-}\underset{Y}{CH_2} \quad (196) \\ R{-}\underset{Y}{CH}{-}\underset{X}{CH_2} \quad (197) \end{cases} \qquad (52)$$

When both carbons are substituted a more delicate balance of effects makes it difficult to predict the preferred orientation: some examples are reported in Table 76.

TABLE 75. Percentage of isomers formed in the addition of CF_3I and of HBr to ethylene derivatives (see equation 52)

R	X = CF_3; Y = I		Reference	X = Br; Y = I		Reference
	197	**196**		**197**	**196**	
CH_3	89	11	234	~100	—	57
F	91	9[a]	242	~80[c]	~20[c]	233
	89	11[b]	234			
Cl	~100	—	234	~100	—	57
Br	—	—		~100	—	57
CF_3	~100	—	243, 244	~100	—	243, 244

[a] Benzoyl peroxide initiated.
[b] Thermal reaction at 200°.
[c] At 60°, lower **197/196** ratios obtained at higher temperatures.

TABLE 76. Percentage of isomers formed in the addition of CF_3I and HBr to ethylene derivatives

Attack to	CF_3I		Reference	HBr		Reference
	CF_2	CRR_1		CF_2	CRR_1	
$CF_2{=}CH_2$	—	100	245	—	100	59
$CF_2{=}CHF$	11	89[a]	234	—	—	—
	26	74[b]	235	42	58	235
	32	68[c]	234	—	—	—
$CF_2{=}CHCl$	90	10	246	100	—	246
$CF_2{=}CHCF_3$	40	60	247	72	28	247
$CF_2{=}CFCl$	100	—	248	100	—	249
$CF_2{=}CFCF_3$	80	20	234	62	38[d]	250
	—	—	—	58	42[e]	250

[a] Thermally initiated, in the presence of I_2.
[b] Photochemically initiated.
[c] Thermally initiated.
[d] U.v. initiated.
[e] X-ray initiated.

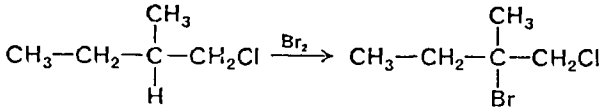
The results reported in Table 76 as well as those in the previous tables of this section show that there are many factors which co-operate in determining the rates and orientation of the homolytic addition to carbon–carbon double bonds. The relative stabilities of the radicals to be formed always play an important role but polar interactions between the attacking radical and the substituents at the ethylenic carbons also contribute to the observed reactivity. It must be expected that in the addition reactions also,

as in the substitutions, the position of the transition state along the reaction coordinate may modify the balance between the various effects. Several other examples of radical additions to halogenated alkenes have been collected in recent reviews[251, 252].

3. Stereochemistry

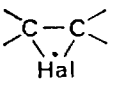
The stereochemistry of the substitution reaction has been studied by a number of authors and there is some evidence that the reaction may be in some circumstances stereospecific.

Although earlier works[253] reported that chlorination of (+)-1-chloro-2-methylbutane (**198**) in the pure liquid yielded inactive 1,2-dichloro-2-methylbutane, it was more recently found[254] that the photobromination of the same compound (**198**; $\alpha = +1{\cdot}38$) gives optically active 2-bromo-1-chloro-2-methylbutane (**199**; $\alpha = -1{\cdot}45$).



(198) (199)

Similar results[254] were obtained in the photobromination of (+)-1-bromo-2-methylbutane ($\alpha = +4{\cdot}89$) which gives (−)-1,2-dibromo-2-methylbutane ($\alpha = -2{\cdot}86$). The bromination with *t*-butyl hypobromite of the same substrates gave similar results although with lower optical yields ($\alpha = -1{\cdot}8/-2{\cdot}0$), whereas the chlorination with *t*-butyl hypochlorite or chlorine yields inactive material. These results were tentatively explained on the basis of the halogen behaving as a configuration holder, possibly by bridging.

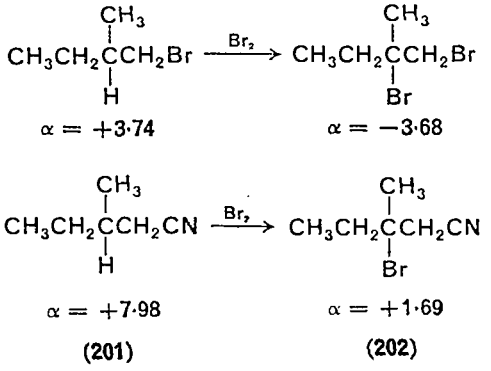


(200)

The hypothesis that halogens, particularly bromine and iodine, are able to bridge with the adjacent radical centre (**200**) has been advanced to explain the stereochemistry of other radical reactions (see below) and it finds support in e.p.r. studies[255] on β-halogeno radicals in solid matrices which suggest a bridged structure of the radical. However, these studies refer to conditions quite dissimilar to those in which radical reactions are usually studied. In particular the lifetime of the radical species is much longer in solid matrices than in the gas or liquid phases.

The intervention of bridged species in these reactions has been questioned by Haag and Heiba[256]. They confirmed the results of Skell and

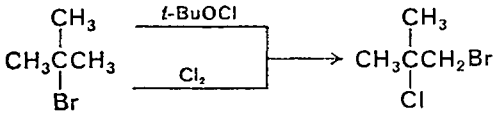
coworkers[254] on the photobromination of 1-bromo-2-methylbutane but on the other hand they also found stereospecificity in the photobromination of 1-cyano-2-methylbutane. Since it is quite unlikely that a cyano group



(201) (202)

would act by bridging, and the changes in optical rotation are similar, some other explanation for the stereospecificity must be sought. The authors[256] suggested that the initially formed pyramidal radicals may be trapped by bromine faster than inversion or conversion to a planar structure occur. This may also explain why stereospecificity was not found in the chlorination with *t*-butyl hypochlorite.

However, there is other evidence which may suggest that halogens act as bridging atoms at a radical centre. The chlorination of *t*-butyl bromide (**203**) with *t*-butyl hypochlorite at −78° and the photoreaction with chlorine at 24° gives only 1-bromo-2-chloro-2-methylpropane (**204**)[257].

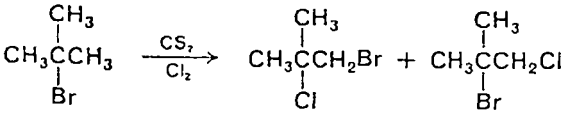


(203) (204)

The authors took into consideration the possibility of bromine elimination from the intermediate radical followed by readdition of BrCl. However, even in the presence of excess of chlorine no 1,2-dichloro compound was detected. Therefore the elimination–addition path is compatible only if the addition occurs within the solvent cage, which cannot be ruled out although it is not very likely.

The formation of 1-bromo-2-chloro-2-methylpropane requires the 2 → 1 bromine shift and may be explained by bromine bridging across the two carbons. The classical controversy, whether the bridged structure is representative of the transition state of the shift or of an intermediate

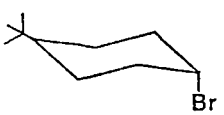
along the reaction path, cannot be resolved on the basis of these results alone. It is interesting that on changing the solvent (from pure liquid to CS_2 solutions) the photochlorination of the same *t*-butyl bromide (**203**) with *t*-butyl hypochlorite yields both 1-bromo-2-chloro (**204**) and 2-bromo-1-chloro (**205**) 2-methylpropane[258].



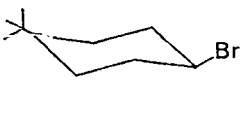
(**203**) (**204**) (**205**)

The authors[258] suggested that the rearranged product derives, at least in part, via an elimination–addition path whereas the unrearranged product derives from direct quenching of the primary radical. However, the results are also consistent with the rate of chlorine abstraction being competitive with the rate of rearrangement to *t*-butyl radical or to the bridged species.

Intervention of bridged structures was also invoked to explain the high yields of 1,2-dibromo derivatives obtained in the photobromination of bromocyclohexane and bromocyclopentane[259]. Moreover, the greater reactivity of *cis*-4-bromo-*t*-butylcyclohexane (**206**) in respect to the *trans*-isomer (**207**) ($k_{cis}/k_{trans} > 15$)[260] may suggest an anchimeric effect of the



(**206**)



(**207**)

axial bromine. Similarly Thaler[259] found a high reactivity for liquid-phase hydrogen abstraction β to a bromine in *n*-alkanes whereas chlorine is much less effective (see Table 77).

TABLE 77. Relative reactivities[a] in the liquid-phase halogenations ($X^{\bullet}$) of 1-halogenobutanes (RY) at 60° [259]

$X^{\bullet}$	Y	1	2	3	4
Cl	Cl[b]	0·158	0·478	1	0·397
	Br	0·093	0·434	1	0·455
Br	Cl	0·439	0·488	1	—
	Br	0·062	5·78	1	—

[a] Reactivity of $C_{(3)}$ taken arbitrarily as unity.
[b] From reference 228.

The assistance of β-bromine seems to depend on the media. In fact the bromination in the liquid phase of 2-bromobutane gives results (see Table 78) similar to those reported above for 1-bromobutane[259] whereas the gas-phase bromination occurs exclusively at the α-position with respect to

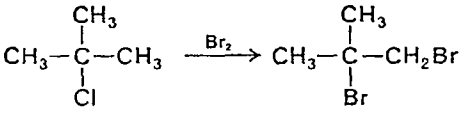
TABLE 78. Relative reactivities[a, b] in the liquid-phase bromination of *sec*-butyl halides (RY) at 60° [250]

Y	1	2	3	4
Cl	—	1·00	0·0858	—
Br	—	1·00	5·13	—

[a] Reaction run in 1 : 5 bromine/alkyl halide mixture.
[b] Reactivity of $C_{(2)}$ taken arbitrarily as unity.

the halogen (see Table 68)[223]. These results emphasize the point that the assistance of bromine is much higher than that of chlorine.

The same conclusions may be suggested by the results obtained[257] in the photobromination of *t*-butyl chloride (**208**), which yields 1,2-dibromo-2-methylpropane (**209**) probably via elimination–addition, in the sense that the lack of assistance makes the elimination path predominant.



(**208**) (**209**)

The intervention of the elimination–addition mechanisms has been recently stressed[261, 262]. Ashton, Tedder and Walton[262] observed that hydrobromic acid promotes elimination and, since it is formed in the abstraction step of bromination reactions, the elimination–addition process becomes more important at later stages of the reaction. It has also been observed that the composition of the products changes with hydrobromic acid concentration and hence with the progress of the reaction[261, 262]. These very recent results may call for a revision of earlier work in this area and of the hypothesis advanced.

The bridging by bromine in the liquid-phase bromination of 2-bromobutane to give 2,3-dibromobutane has been claimed[259] to explain the preferential formation of the *meso* isomer.

However *meso* (or *erythro*) isomers were also found to be predominant in the halogenation of 2-chloro- and 2-fluorobutanes (see Table 69)[223].

Since in the latter cases the intervention of bridged species seems unlikely, the observed stereochemical course might be better explained on the basis of preferred conformations in the reagents and intermediate radicals.

Similar problems arise in the analysis of the stereochemistry of the radical addition of HBr to olefins[263]. The addition to 1-bromo-[264] and 1-chloro-cyclohexene[265] gives more than 99% of the *cis*-1,2-dihalogeno-cyclohexane. Similar preference for *anti* addition[266] was also found in other cyclic 1-bromoalkenes (see Table 79), although in the small rings, possibly

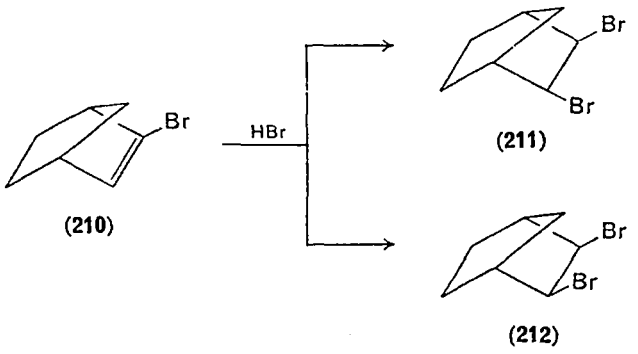
TABLE 79. Percentage of *anti* adducts in the hydrobromic acid addition to 1-bromocycloalkenes[266]

1-Bromocyclobutene	79
1-Bromocyclopentene	94
1-Bromocyclohexene[a]	99
1-Bromocycloheptene	91

[a] From reference 264.

because of *cis* repulsion of the halogens, substantial amounts of products derived from *syn* addition are formed.

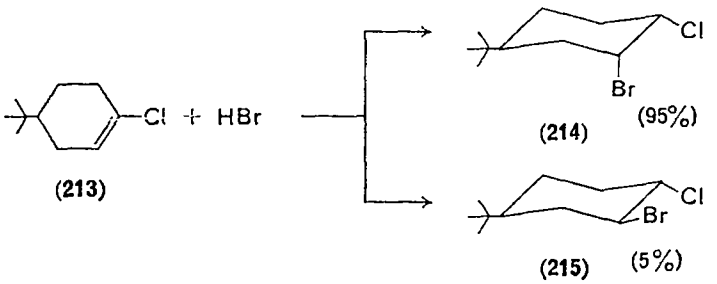
On the other hand, the stereochemistry of addition to 2-bromo-2-norbornene (**210**), which gives 5/7 of *trans*-2,3-dibromonorbornane (**211**) and 2/7 of *exo-cis*-2,3-dibromonorbornane (**212**), indicates that both the attack of the bromine radical and of HBr occurs from the least hindered *exo* side and hence that conformational factors are important[267].



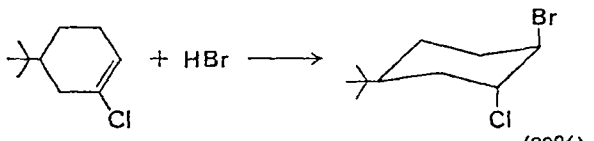
(210) (211) (212)

The addition of hydrobromic acid to 1-chloro[268] (**213**) and 2-chloro[269] (**216**) -4-*t*-butylcyclohexene, which gives the products reported in equations (53) and (54) may again be explained on the basis of the requirement for

t-butyl groups to be equatorial throughout the reaction. Consequently the bromine must assume the axial position in both cases, and the hydrogen too must enter axially to avoid two halogens in the axial position. The intervention of bridged species was postulated but it does not seem compulsory.

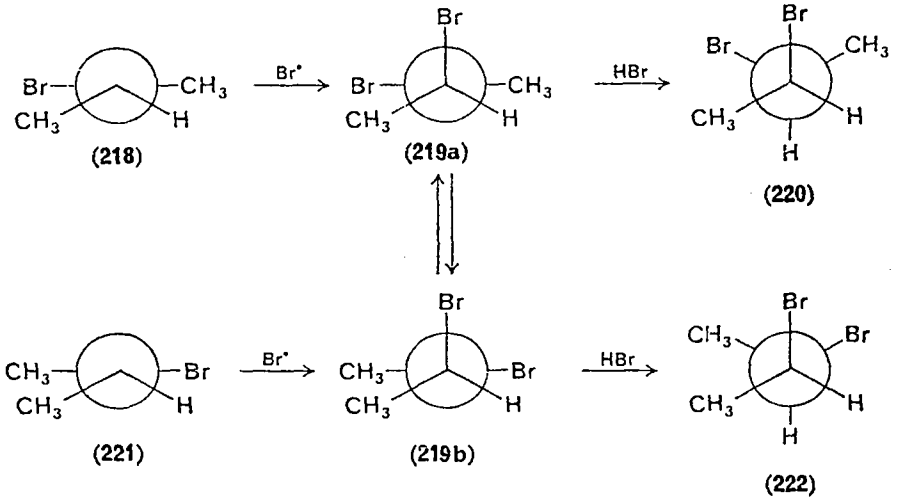


(213) (214) (95%) (215) (5%) (53)



(216) (217) (80%) (54)

The addition of HBr to open-chain halogenoolefins may be stereospecific in some particular instances. Thus the radical addition to *cis* (**218**) and *trans* (**221**) 2-bromobut-2-ene at −78° in excess liquid HBr is *anti* stereospecific but at room temperature a mixture of *meso* (25%) and *racemic* (75%) products is formed[270] from either olefin.



The stereochemistry observed was related to the formation of a weakly bridged β-bromo radical. This may easily open at higher temperatures and hence allow for decreasing selectivity with increasing temperature.

The above results might also be explained by assuming that at low temperatures the rotation around the C—C bond is slower than hydrogen abstraction and that the attack from the less hindered side to give a staggered conformation is favoured over attack from the opposite side to give an eclipsed conformation.

4. Homolytic aromatic substitution

Substituent effects in homolytic aromatic substitution are usually small and therefore large differences in the behaviour of the four halogens cannot be expected[1, 271].

As already seen in the previous sections the nature of the radical, its electrophilic or nucleophilic character, may affect both overall rates and partial rate factors. The rates of attack by phenyl radicals, a presumed 'neutral' radical, on halogenobenzenes are slightly faster than attack on benzene (see relative rates in Table 80) but halogens are not very effective

TABLE 80. Relative rates of substitution of C_6H_5X with benzoyl peroxide at 80°C [272]

	X						
	H	NO_2	F	Cl	Br	I	CH_3
Relative rates	1·00	2·94	1·03	1·06	1·29	1·32	1·23

as typical resonance interacting substituents[272]. Although the differences in relative rates are small there is a clear trend of increasing reactivity with increasing atomic weight. All halogens have similar orienting effects, as shown in Table 81, where two other substituents are also reported for comparison.

TABLE 81. Isomer ratios in the phenylation of C_6H_5X with benzoyl peroxide at 80°

X	*ortho*	*meta*	*para*	Reference
F	54	31	15	273
Cl	50	32	18	274
Br	50	33	17	275
I	52	31	17	275
CF_3	29	41	30	276
CH_3	67	19	14	277

Bromo- and chlorobenzene react more slowly with electrophilic radicals and faster with nucleophilic radicals than the phenyl radical[271].

TABLE 82. Relative rates of arylation with substituted phenyl radicals ($XC_6H_4^{\bullet}$) at 80° [271]

X	Relative rates (C_6H_6 = 1)		
	$O_2NC_6H_5$	ClC_6H_5	BrC_6H_5
p-NO_2	0·94	1·17	1·5
p-Cl	1·5	1·02	—
p-Br	1·8	—	—
p-OCH_3	2·9	1·6	—
H	4·0	1·5	1·7
p-Me	5·1	2·0	—

The polar effects are more evident when the differences in the attacking radicals are greater. In Table 83 the relative rates of attack on substituted benzenes are reported for a nucleophilic (cyclohexyl), an electrophilic (phenylethynyl) and a 'neutral' (phenyl) radical. All the halogenobenzenes

TABLE 83. Relative reactivities (C_6H_6 = 1) for reactions of substituted benzenes (C_6H_5X) with radicals

X	Radical		
	Cyclohexyl[a]	Phenyl[b]	Phenylethynyl[c]
F	1·9	1·0	0·57
Cl	3·5	1·1	0·50
Br	—	1·3	0·35
CH_3	0·76	1·2	2·25
CF_3	2·0	1·0	—

[a] From reference 278.
[b] From reference 278 evaluated on the basis of data in Table 81; see also Table 80.
[c] From reference 279.

are less reactive than benzene toward the phenylethynyl radical and more reactive toward the cyclohexyl radical.

The isomer ratios are differently affected by the halogens when radicals have more pronounced polar character. However, the differences are always small in an absolute sense (see Table 84). The effect of substituents on the orientation depends on the electronic demand of the attacking radical. Even though the differences are not great, fluorine, the effects of

TABLE 84. Isomer ratios of homolytic substitution in C_6H_5X

Radical	X = F			X = Cl			X = Br			
	ortho	*meta*	*para*	*ortho*	*meta*	*para*	*ortho*	*meta*	*para*	Reference
$CH_3^{\bullet}$	57	37	6	62	28	10	55	34	11	280
cyclo-$C_6H_{11}^{\bullet}$	61	35	4	54	34	12	58	32	10	278
$C_6H_5^{\bullet}$	54	31	15	50	32	18	50	33	17	[a]
p-$O_2NC_6H_4^{\bullet}$	—	—	—	60	24	16	61	25	14	281
C_6H_5-$C{\equiv}C^{\bullet}$	42	28	30	52	26	22	50	30	20	279

[a] See Table 83.

which are exalted, shows an increased preference for *para* orientation as the electrophilic character of the radical increases. It is of particular interest to compare partial rate factors for attack at the *para* position in halogenobenzenes (see Table 85).

TABLE 85. Partial rate factors for *para* position in homolytic substitutions of halogenobenzenes (C_6H_5X)

X	cyclo-$C_6H_{11}^{\bullet}$	$C_6H_5^{\bullet}$	C_6H_5—$C{\equiv}C^{\bullet}$
F	0·47	0·86	1·04
Cl	2·5	1·2	0·66
Br	—	—	0·43

With nucleophilic or 'neutral' radicals the *para* position is deactivated whereas with the electrophilic phenylethynyl radical it is slightly activated. This suggests that in the fluorobenzene reactions the polar effects are more discriminating than with other halogenobenzenes, probably because the transition state occurs late on the reaction coordinate resembling rather the intermediate radical where stabilization through resonance will be important.

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The Chemistry of The Carbon-Halogen Bond: Part 1
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CHAPTER 7

Heterolytic mechanisms of substitution involving carbon–halogen bonds

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I. INTRODUCTION: CLASSIFICATION OF REACTIONS AND MECHANISMS

In discussing *reactions* of organic compounds, our first preoccupation is with the structure of starting materials and products. The range of molecules with which we are concerned is limited by the techniques which we have available for the study of entities which can be isolated, and by the kinetic stability of these entities. As the techniques become more and more sophisticated, we can hope to recognize more and more fleeting intermediates, and so to characterize an increased complexity in sequential reactions.

As soon as we start to consider the *mechanism* of a chemical reaction, we are attacking a problem which is very much more complicated, and the inferences that we may wish to draw from our experimental data are likely to be less certain than those that we can reach relating to structures. A complete knowledge of the mechanism of a chemical reaction at the least requires a precise knowledge of the energies and entropies of all those geometrical states which have a finite probability of being attained by the reactants in the course of conversion into the products. Most of these states have an existence for no longer than the duration of a molecular collision or two, and so they are not capable of observation as isolated entities.

In practice, we concern ourselves mainly with sections through an energy surface which can be used to describe the overall transformation. The section which we use is that which relates to the bonds being made or broken. Maxima are the transition states dividing reactants from intermediates and products; minima represent the starting materials, intermediates and products. Kinetic methods help us to define (a) the stoicheiometry and (b) the change in energy and change in entropy in going from starting materials to transition state. Various physical methods involving examination of the system during reaction help us to recognize intermediates; the existence of these can sometimes also be inferred from

experiments designed to remove or 'trap' a fleeting substance, though interpretation of such experiments is fraught with the danger that some new reaction may have been evoked by the trapping reagent.

In principle, theoretical calculations may also be used to define the properties of transition states; ultimately it may be possible to define mechanisms in this way. In this chapter we shall discuss one important example of this approach as applied to reactions of organic halides. In practice, however, experimental recognition of mechanistic complexities has generally preceded theory, as the examples which we need to draw upon in discussing organic halides will establish clearly.

One further general point is relevant to the reactions we shall be considering. Chemical reactions can occur both in the gas phase and in solution; most of those to be discussed in this chapter are in the latter category. The involvement of the solvent involves energies of solvation and energy changes during the reaction, often quite as important in determining the course of reaction as the strengths of the forming and breaking bonds. The solvent may also have the dual role of solvation and of reaction; and the mechanics of the process of collision in solution are rather different from those involving collision in the gas phase, since once two particles have come together within their sheath of solvent molecules, they may undergo repeated collision before becoming separated again. Such repeated collisions are referred to as 'encounters', and for non-reacting particles the average behaviour over a large number of encounters may be approximately the same as that associated with the larger number of more random collisions that would have occurred if the solvent were not there. If, on the other hand, reaction occurs at some time during the encounter, it is difficult to know whether the assembly of particles involved in the encounter should be regarded as an intermediate or not; if a solvent molecule is one of the particles specifically concerned in the reaction it is hard to define its role as distinct from that of the solvating solvent molecules.

If we consider in very general terms the physical process which we are describing when we draw an energy diagram of the conventional kind (e.g. Figure 1) to represent the changes occurring along a reaction path leading from A to products in a thermal reaction, we must realize that we are implying a physical process (e.g. collision between molecules) which transfers energy (e.g. kinetic energy) into the mode of vibration which leads to passage through the transition state, and having reached the transition state we imply a further process (which may also involve collision) which allows deactivation as the transition state is transformed into products. The simplification usually made is to consider only the mode of vibration which leads to passage through the transition state to one

particular product, as from A to B. The very process of deactivation, however, may contribute to the determination of the product. Thus if this collisional deactivation involves the solvent, the possibility of diversion of the still highly activated system at some intermediate point (e.g. as indicated in Figure 1) is a very real one, and is not describable in terms of a discrete intermediate on the reaction path, though it may be important in defining the exact nature of the product; as for example whether this comprises B or C (Figure 1), or a mixture of the two.

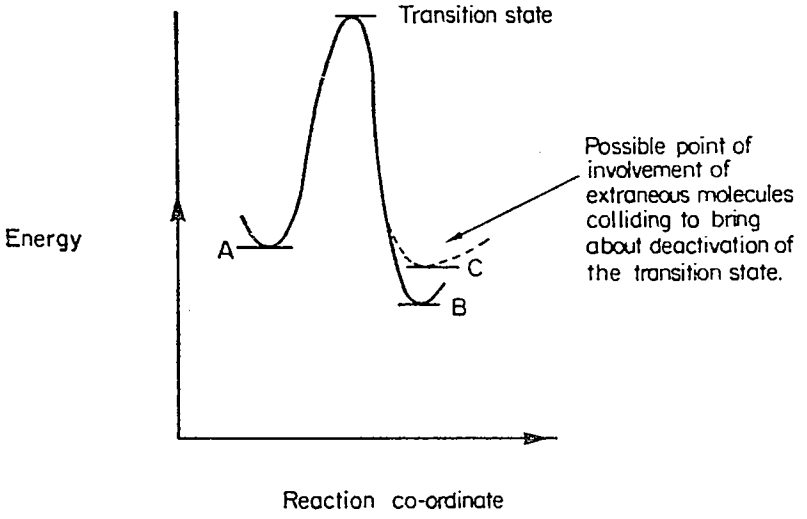


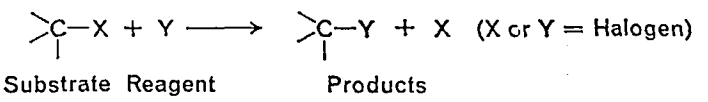
FIGURE 1.

Considerations of this kind leave areas of uncertainty in mechanistic discussion of any reaction in solution. In this chapter we shall attempt to show that there are various major groupings of mechanisms of the reactions with which we are concerned, and that these major groupings each have some important common characteristics which are distinguishable by experimentally observable phenomena of major importance in determination of products.

Authors have from time to time sought to simplify mechanistic discussion by invoking 'Occam's razor', '*Entia non sunt multiplicanda praeter necessitatem*'[1]. The present writers maintain that, even if we agree on some free translation of this doctrine, the simplification thereby introduced is wholly illusory as applied to the scientific situations under discussion. If 'Occam's razor' has any application outside the field of abstract philosophy, it can be applied only to a closed system of logic. In dealing

with mechanisms in the present state of knowledge, we are always dealing with open systems, where more can be discovered by experiment and where our present theories are an approximation to a truth which can be defined only within the limits determined by our restricted techniques and insight. Application of 'Occam's razor' applies an additional blinker which may appear to help us in the short term, but in so doing tends to leave us satisfied not to speculate beyond the immediate realm of knowledge.

The reactions with which we will be concerned are of the type:



We shall use the terms 'substitution', 'replacement' and 'displacement' synonymously to describe such a process. Substrates, $\rangle\overset{|}{C}-X$, will include saturated and unsaturated compounds. As far as the broad classification of mechanisms is concerned, we shall include reference to nucleophilic substitution, where the reagent Y attacks by way of a pair of electrons, and the leaving group is displaced as X^-; to electrophilic substitution, where attack is by an electron-deficient centre in the reagent, which may be a simple ion (e.g. Cl^+) or a complexed form (e.g. Cl—Z) and the displaced group leaves behind its bonding pair, thus being removed as X^+; and to homolytic substitution, where the bond-fission involves the departure of X as a halogen atom.

The Brønsted approach is accepted, namely that the overall charge-type of the reaction is for many purposes of secondary importance; electrophiles can be neutral or positive, nucleophiles can be negative or neutral without affecting, except in matters of detail, the general nature of the chemical reaction under study. With this framework in mind, we can classify the two main types of heterolytic substitution involving carbon–halogen bonds as electrophilic and nucleophilic; we shall deal separately under each heading with reactions at saturated and unsaturated centres.

In discussing the mechanisms of these reactions, we make no attempt to be exhaustive. Most of the processes with which we are concerned have been the subjects of excellent reviews; our purpose is to draw attention to the range of mechanisms available, to the most important characteristics of and variations within each mechanistic category, and to recent developments which give further insight into the complex phenomena which can be observed.

In most cases, the mechanistic possibilities available for any one kind of carbon–halogen bond are in principle available for the others. Qualitative

differences between the halogens relevant to the mechanistic discussions with which we shall be concerned include the following[2]:

(i) The bond energies of C—X bonds follow the sequence F > Cl > Br > I.

(ii) The hydration energies of the halide anions follow the sequence $F^- > Cl^- > Br^- > I^-$.

(iii) The hydrogen-bonding power of the halogens decreases in the order F ≥ Cl, Br, I.

(iv) The van der Waals radii of the covalently bound halogens decrease in the order I > Br > Cl > F, so that non-bonding interactions with equally distant molecules or groups are least for fluorine and greatest for iodine.

(v) The covalent bond-lengths of the halogens decrease in the order I > Br > Cl > F.

(vi) The first ionization energies of the halogens decrease in the order F > Cl > Br > I, so that the ease of formation of isolated cationic halogen follows the reverse order.

(vii) The availability of *d*-orbitals allowing expansion of the octet of the halogen involved in a C—X bond decreases in the order I > Br > Cl > F.

(viii) The influences described under (iv), (v), (vi) and (vii) are all probably concerned in determining that the ease of bridging to a cationic centre decreases in the order I > Br > Cl > F.

(ix) The electronegativities of the halogens decrease in the order F > Cl > Br > I. As a result, adjacent atoms can be partly denuded of electrons; fluorine, because of its small size and short bond length, is particularly effective in this way.

(x) The polarizability of halogens decreases in the order I > Br > Cl > F, so that in systems where direct interaction with external reagents can be important, the importance of sequence (iii) becomes diminished.

These factors interact in a complicated way in any real situation, so that it is often not possible to predict the order of reactivity of a series of compounds containing halogens. Experimental observation, however, often tells us which of the various influences are the most important in a particular instance. We shall draw attention as far as possible to the range of halogens over which each of the mechanistic possibilities has been investigated.

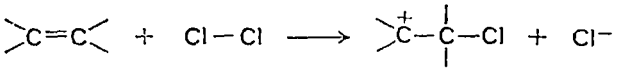
Classification of mechanisms. The common use of labels for the classification of organic reaction mechanisms started with the realization that more than one mechanism was possible for a single reaction; the familiar terms S_N1 and S_N2 are particular examples deriving from this concept. When only the limiting simple cases represented by such examples are considered, it is reasonably easy to define precisely what the symbols are intended to mean. Application to multi-stage processes, however, becomes complicated

and introduces difficulties, some of which are semantic, but others which are real and may be at present unresolved and in practice unresolvable. Some of these difficulties have produced unprofitable and acrimonious controversies. We shall refer to some of them in the course of the text; at this point some general remarks will save later repetition.

We hold that none of the currently used classificatory symbols for organic mechanisms are wholly satisfactory in giving a comprehensive way of describing multi-stage reactions. But we think that it is convenient to use symbols such as S_N1, S_N2, S_E1 where appropriate because they are so familiar as used in current literature.

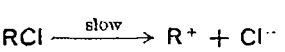
In using these, the symbol S refers to an overall stoicheiometric substitution (e.g. $R—X+Y \rightarrow R—Y+X$), quite independent of the reaction path and any mechanistic detail. Addition processes (Ad) and elimination processes (E) are other classes of reaction for which it is common to use a label indicating the stoicheiometry.

The subscript E or N has mechanistic connotation because it defines reactant and substrate in a heterolytic process. Thus $OH^- + RCl \rightarrow ROH + Cl^-$ is a nucleophilic substitution of chlorine in RCl regarded as the substrate. Likewise $PhH + RCl \rightarrow PhR + HCl$ is a nucleophilic substitution in which RCl is the substrate. This may be further extended as in the example



which is a nucleophilic substitution at chlorine. The common characteristic of these reactions is that the leaving chlorine takes with it the bonding pair of electrons; any reaction sequence, or any step in any reaction sequence which may be analysed in this way, can be called a nucleophilic substitution. In the same way, if in a particular step or in a particular stoicheiometry (e.g. $R—X+Y \rightarrow R—Y+X$) the bonding electrons of R—X may be analysed as becoming the bonding electrons of R—Y, then the reaction is called an electrophilic substitution and given the symbol S_E. If the subscript H is used, then one electron of the bonding pair becomes associated with each fragment.

Each step in a multistep reaction may be given such a descriptive label. The convention was early established that the rate-determining step was given a nomenclature appropriate to the overall process. Thus S_N1 refers to the process



occurring as part of a nucleophilic substitution whose stoicheiometry is represented

$$RCl + Y^- \longrightarrow RY + Cl^-$$

The qualifying numeral then refers to the number of molecules necessarily involved in covalency change in the rate-determining stage; it carries a prime if the reaction has proceeded with accompanying rearrangement. Further qualification is then sometimes necessary, essentially when it becomes necessary to indicate that a simple one-stage mechanism is not under observation: too mechanical an association of such labels will bring together some strange bed-fellows. The reader will appreciate this if he thinks about the terms S_N2, $S_N2(C^+)$, $S_N2(Ar)$. All of these are used quite commonly; all refer to nucleophilic substitutions with two molecules necessarily undergoing covalency change in the rate-determining stage, but they involve very diverse sequences.

The possibility of isomeric transition states of the same kind (even perhaps involving the same bonds) is not excluded in the use of any such symbolism and becomes a very real possibility in some cases. Furthermore, the use of a particular symbol to describe a reaction having a particular transition state implies no particular assumption as to what intermediate stages, if any, precede formation of the transition state.

The question of whether or not covalency is changing, and if so in what particles, is perhaps one of the most difficult to answer by reference to definitive experiment. It brings one immediately into the situation of having to argue whether or not forces of solvation involve covalent bonding. We shall take the view that they need not. Applying ourselves now to reactions of nucleophiles, reasonable criteria for covalent interaction are (*a*) whether a better nucleophile interacts more strongly, and (*b*) whether an isotope-effect can be observed on the formation or breaking of the appropriate bond.

In any real case, we recognize that we often either do not have the information or have an experimental result which is ambiguous because our experimental probe is not sufficiently sensitive.

II. NUCLEOPHILIC REPLACEMENTS

A. Nucleophilic Replacement of Halogens at Saturated Centres

1. Bimolecular (S_N2) processes

a. Kinetic criteria. The existence of bimolecular processes of nucleophilic displacement of halogen from saturated centres are part of the very obvious fabric of organic chemistry; alkyl halides react with anions and with

neutral molecules at different rates and under different conditions, and thereby give products of substitution. Any of the methyl halides, for example, can act as alkylating agents for a wide variety of nucleophiles, as in the cases mentioned below.

$$MeBr + PhS^- \longrightarrow MeSPh + Br^- \quad (1)$$

$$MeBr + \bar{C}H(CO_2Et)_2 \longrightarrow MeCH(CO_2Et)_2 + Br^- \quad (2)$$

Kinetic measurements which establish the second-order, and hence bimolecular, nature of the process can be traced back into the early history of physicochemical investigations; examples include the bimolecular reactions of alkyl halides with the thiosulphate anion[3].

$$MeBr + S_2O_3^{2-} \longrightarrow MeS_2O_3^- + Br^- \quad (3)$$

The necessity of categorization arose when it began to become clear that more than one mechanism is available for these reactions. Hence arose the use of the symbol S_N2 to refer to a bimolecular nucleophilic substitution; the term *bimolecular* was specified as implying that two molecules were necessarily undergoing covalency change in the rate-determining stage of the reaction.

The experimental characteristic which is most cogent in identifying this type of process is that which establishes that the formation of a new bond makes easier the breaking of the old one; where it can be shown that one reagent performs the reaction more rapidly than another (as when ethoxide ion is more effective than ethanol), or that the kinetic form is bimolecular, good evidence for the existence of the S_N2 mechanism is provided. Difficulties arise with processes which are called *solvolytic* because the solvent is the reagent; here we cannot apply the kinetic criteria without varying the solvent and so vitiating our conclusion. We shall return to this problem later.

b. Comparison of halogens. The results quoted in Table 1 show that the relative reactivities of corresponding fluorides, chlorides, bromides and

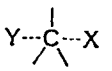
TABLE 1. Relative reactivities (RCl = 1) of aliphatic halides in bimolecular nucleophilic displacements with sodium ethoxide in ethanol

	X: F	Cl	Br	I
n-C_4H_9X at 50°	0·004	—	29	—
C_2H_5X at 55°	—	1·00	29	58

iodides by the S_N2 mechanism are unambiguously in the sequence F < Cl < Br < I; only a limited number of investigations of fluorides have been made, and these have been summarized[4]. The comparison given in Table 1 is illustrative and is derived from data summarized elsewhere[5]. This sequence establishes that bond-breaking is a very important factor influencing the rates of reaction, even in quite strongly solvating solvents: as we shall see, aromatic halides behave quite differently.

c. Stereochemical criteria. The most notable structural feature of the S_N2 mechanism is derived from the fact that it requires a new bond to be formed at the same time as the old bond is broken in order to facilitate the latter process. Since carbon is a small element in the first row of the Periodic Table, with a maximum covalency of four (i.e. effectively having only *s* and *p* orbitals available for bonding, and being able to expand its octet by the use of *d* orbitals only with the expenditure of much energy), any transition state involving a fifth bond to carbon and an excess of electron-density must of necessity be highly congested.

It turns out, furthermore, that the accommodation of five groups around carbon, two of them being partly bonded to the centre by four electrons,



(1)

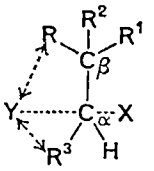
(2)

has rather precise geometric requirements. The geometry **1** is favoured over geometry **2** by such a large energy-difference that even when the entering and leaving groups initially have opposite charge, so that electrostatic interaction would favour the latter, it is the former that is experimentally observed. This is established experimentally through the observation that bimolecular nucleophilic substitution is accompanied by inversion of configuration (Walden inversion) over a very wide range of substrates and nucleophiles. It has been stated, for example[6], that 'inversion of configuration in S_N2 reactions is one of the most unqualified and absolutely dependable phenomena ever observed in the field of organic stereochemistry'.

Ingold (reference 7, p. 516) discussed the theory of this phenomenon from a qualitative quantum-mechanical viewpoint, considering that the geometric arrangement **1** would minimize the repulsive exchange integrals between the altered and preserved bonds and so give a transition state of lower energy. Only recently have attempts been made[6,8] to calculate the relative energies of **1** and **2** taking into account the energies of all the bonds. The case chosen was the hypothetical symmetrical exchange involving attack on methane by the hydride ion (X = Y = H) and it was concluded

that for this reaction in the gas phase, inversion is preferred to retention by about 0·64 eV(ca. 15 kcal mole^{-1}). In this calculation, only contributions from *s* and *p* orbitals were considered; Gillespie[9] had previously discussed the possible intervention of *d* orbitals and had reached qualitatively similar conclusions.

A consequence of the crowded nature of the transition state is that the introduction of bulky groups at the reaction centre is generally associated with a decrease in reaction rate. The rather precise geometric requirements are partly responsible for a further feature, that large groups in the β-position (e.g. R, R^1 in 3) can be just as effective in hindering replacement as are similar groups in the α-position (e.g. R^3 in 3). The most spectacular illustration of this comes from the extraordinary unreactivity of neopentyl halides (e.g. Me_3CCH_2Br)[10]; this was shown to be associated with the



(3)

S_N2 mechanism by Dostrovsky, Hughes and Ingold[11], and can be illustrated by the rate and energy sequences in Table 2.

TABLE 2. Relative rates and Arrhenius activation energies for bimolecular substitutions of primary alkyl bromides, RBr, with ethoxide ions in ethanol

R:	Me	Et	*n*-Pr	iso-Bu	neo-Pentyl
Relative rate of reaction of RBr with OEt^- in ethanol at 55°C	17·6	1	0·28	0·030	0·0000042
E_A (kcal mole^{-1})	20·0	21·0	—	22·8	26·2

d. Calculation of steric effects. These studies led Hughes, Ingold and coworkers to attempt to calculate the influence of steric hindrance on reactions of this kind. For arithmetical simplicity, the symmetrical exchange reactions

$$X^- + RX \longrightarrow XR + X^- \qquad (4)$$

were considered and the reactions of methyl halides were taken as the standard of reference. Among a number of other simplifying assumptions was the important one that there is no appreciable internal steric strain in any of the *initial* states of the halides concerned.

The results of the calculations were compared with experimental results

(i) for the symmetrical exchange reactions to which they referred, but carried out in acetone, with the lithium salt of the exchanging anion;

(ii) for the similar unsymmetrical exchange reactions in the same solvent;

(iii) for other bimolecular exchange reactions in other solvents, where relevant data were available. For full details, the original papers[11,12] should be consulted; results particularly relevant to the present discussion are presented in a slightly modified form in Table 3.

TABLE 3. Comparison of experimental results with theoretical calculations of Arrhenius parameters for symmetrical bimolecular exchange reactions, $RBr + Br^-$ in acetone.

Series:	α-Alkylated			β-Alkylated		
R:	Methyl	Ethyl	iso-Propyl	*n*-Propyl	iso-Butyl	*neo*-Pentyl
E_A (kcal mole^{-1}, obs.)	15·8	17·5	19·7	17·5	18·9	22·0
E_A (kcal mole^{-1}, calc.)[a]	27·4	28·2	29·0	28·2	29·7	34·7
ΔE_A ($E_A^R - E_A^{Et}$; kcal mole^{-1}, obs.)	−1·7	0·0	2·2	0·0	1·4	4·5
ΔE_A (calc.)	−0·8	0·0	0·8	0·0	1·5	6·5
$\log_{10}B$ (B in l mole^{-1} s^{-1}, obs.)	10·7	10·1	9·7	9·8	9·6	8·6
$\log_{10}B$ (B in l mole^{-1} s^{-1}, calc.)[a]	13·1	12·6	12·2	12·3	12·1	11·1
$\Delta\log_{10}B$ ($\log_{10}B^{Et} - \log_{10}B^R$, obs.)	−0·6	0·0	0·4	0·3	0·5	1·5
$\Delta\log_{10}B$ (calc.)	−0·5	0·0	0·4	0·3	0·6	0·9

[a] Gas-phase values, see text.

A feature of the calculations was the relatively small degree of extension of the C—Br bond calculated for the transition state (initial state, 1·91 Å; transition state, 2·25 Å). This implies that both the breaking and the forming bond are quite strong in the transition state. This feature was also apparent in the calculated results for hydride exchange referred to above.

Since the calculations refer to a hypothetical reaction in the gas phase, comparison of these values with those observed [e.g. for R = Me, E_A (calc.) = 27·4 kcal mole^{-1}, E_A (obs.) = 15·8 kcal mole^{-1}] show the importance of solvation in this reaction. The calculated Arrhenius

frequency factors [e.g. for R = Me, $\log_{10}$B (calc.) = 13·1, $\log_{10}$B (obs.) = 10·7] were also somewhat lower than the calculated values, and this again was held to be a reflexion of solvation in all its forms, including solvent–ion and ion–ion interactions. It was considered, however, that solvation differences between initial and transition states would be nearly independent of the alkyl residue and so could be neglected in discussion of structural effects. In the β-alkylated series (Table 3), the observed increments in activation energy are very close to those calculated; the calculations reflect also the fact that the introduction of the last methyl group to form the neopentyl structure has by far the largest effect. Calculations of increments in Arrhenius B-values (which can of course be translated into increments in entropy of activation) were also in quite reasonable agreement with the observed values.

The overall picture derivable from the comparison between theory and experiment for the β-alkyl-substituted series of compounds is that of a quite good agreement, establishing the soundness of the assumptions made concerning the transition state and of the physical basis of the calculations, including the approximations involved. Turning now to the α-alkylated series, where polar effects might be expected to be more significant, the Arrhenius B-factors were well predicted by the calculations. In this series, however, the energies of activation showed systematic discrepancies, which could be removed if it were assumed that methyl groups had a polar effect which resulted in an increased energy of activation to the extent of ca. 1·0 kcal mole^{-1} per α-methyl group. We adopt this as a conclusion to be drawn from the comparisons in Table 3; Hughes, Ingold and coworkers preferred to include this as a theoretical correcting factor and then to compare theory with experiment over the whole range of α- and β-methyl substitution.

It is probable now, by the use of a computer and by using more recent information concerning bonding and non-bonding potential functions, that the energy surfaces for such exchange reactions could be defined theoretically in greater detail. Two important experimental extensions of the original papers have been made. Winstein and coworkers[13] showed that the exchanges observed between *t*-butyl bromide and halide ions in acetone probably come mostly through elimination–addition processes, rather than by S_N2 reactions*.

* The results in Table 3 stand on their own feet, without inclusion of the results for *t*-butyl bromide. For the latter compound, the values of E_A and $\log_{10}$B calculated from the results for methyl bromide by using Hughes, Ingold and coworkers' assumptions were respectively 21·3 kcal mole^{-1} and 10·5; the experimental values for the reaction now known to be mainly

Cook and Parker[17] have re-examined one of the unsymmetrical exchange reactions ($RBr + Cl^-$) in another solvent (*N*,*N*-dimethylformamide). Their results in general terms confirm the earlier findings.

e. Kinetic isotope effects in S_N2 *reactions.* Kinetic isotope effects are useful in studies of reaction mechanism because they can reveal the nature of the changes in bonding brought about by going from the initial state to the transition state. They arise from changes in zero-point energy of the vibrations of the system under study and so are very dependent on the relative masses of the particles involved. For this reason they are greatest in magnitude for the lightest element, hydrogen; but they are still significant for heavier atoms and, if sufficiently precise experimental measurements can be made, the results can be helpful, especially since the theory of isotope effects can be made quantitative to the extent that the direction and maximum possible isotope effect associated with any given bonding change can be calculated[18].

A number of results are available for halides known to be reacting by the S_N2 mechanism. For a direct displacement, we need to distinguish between isotope effects resulting from change in the entering group, in the leaving group, and in the central carbon atom at which substitution is occurring. Effects resulting from isotopic change in the entering group tend to be small, thus the maximum value expected for a $^{12}C : {}^{14}C$ isotope effect is ca. 1·12 at 25°; but for the reaction of methyl iodide with cyanide ions[19], values of $k_2(^{12}CN^-) : k_2(^{13}CN^-)$ around 1·01 have been obtained. Such relatively small values arise because of opposing, partially cancelling, components in the frequency changes[18].

Changes in the leaving group, however, can be larger in relation to the theoretical maximum. Thus for second-order reactions of substituted benzyl chlorides with various anions in ethanol or aqueous dioxan, $^{35}Cl : {}^{37}Cl$ isotope effects of ca. 1·006–1·007 were obtained[20], the theoretical maximum here being about 1·01. This work establishes that a relatively large chlorine leaving-group isotope effect is characteristic of S_N2 reactions, and that in these particular examples the C—Cl bond is substantially extended and weakened in the transition state.

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elimination were 21·8 kcal mole^{-1} and 10·7. This implies that the exchange should have made a major contribution to the observed reaction. It is by no means impossible that the rather constrained and heavily congested transition state normally leading to substitution actually decomposes to products of elimination; if so the concept of merged substitution and elimination first proposed by Winstein, Darwish and Holness[14], and subsequently abandoned[15], should be revived for this case, though probably not for most others[16].

Related results for nucleophiles reacting with *n*-butyl chloride and with some substituted benzyl chlorides[21] are summarized in Table 4. For the same substrate, the more reactive thio-anion gives isotope effects larger than those found for the corresponding oxy-anion; and for the same nucleophile the more reactive benzyl chlorides have isotope effects larger

TABLE 4. Rates and chlorine leaving-group isotope effects for some S_N2 reactions in methanol

Substrate:	*p*-$MeOC_6H_4CH_2Cl$	$C_6H_5CH_2Cl$	*p*-$O_2NC_6H_4CH_2Cl$	C_4H_9Cl
T °C:	20°	20°	20°	40°
Nucleophile, PhS^-; 10^4k_2	820	130	760	2·3
$k_2(^{35}Cl) : k_2(^{37}Cl)$	1·0098	1·0095	1·0092	1·0084
Nucleophile, PhO^-; 10^4k_2	—	—	0·080	—
$k_2(^{35}Cl) : k_2(^{37}Cl)$	—	—	1·0079	—
Nucleophile, *n*-$C_4H_9S^-$; 10^4k_2	—	—	1000	3·1
$k_2(^{35}Cl) : k_2(^{37}Cl)$	—	—	1·0087	1·0081
Nucleophile, CH_3O^-; 10^4k_2	—	0·12	0·20	0·01
$k_2(^{35}Cl) : k_2(^{37}Cl)$	—	1·0080	1·0076	1·0074

than that observed for the less reactive *n*-butyl chloride. Within the series of benzyl chlorides, however, the size of the isotope effect is better correlated with the extent of conjugative electron release from the aryl group, and hence with the expected weakness of the C—Cl bond in the transition state.

It is obvious that complicated factors, including probably factors of solvation[18,21], contribute to the small differences and it will be seen later that the magnitude of these effects does not distinguish clearly the S_N2 from other mechanisms. Few results have been recorded for other halogens; the report[22], that the exchange of iodide ions with methylene di-iodide exhibits an 'inverse' isotope effect, is surprising and deserves careful confirmation and extension to other systems.

Central-carbon-atom isotope effects have also received attention. Some of the results[18,19,23,24,25] are summarized in Table 5.

The first point to be made from consideration of these results is that S_N2 reactions show central-atom isotope effects of quite substantial

magnitude; clearly the change in bonding around the reaction centre is reflected by the existence of this effect. Different halides when reacting with the same nucleophile show only small differences, but in so far as the differences are significant, the effect is smaller the weaker the bond to be displaced. Different nucleophiles reacting with the same halide can show

TABLE 5. Central-atom carbon isotope effects for S_N2 reactions of methyl and substituted aralkyl halides

Halide	Nucleophile	Solvent	T°C	$k_2(^{12}C) : k_2(^{14}C)$	Reference
p-$MeC_6H_4CH_2Cl$	CN^-	80% Dioxan	40	1·09	18
p-$ClC_6H_4CH_2Cl$	CN^-	80% Dioxan	40	1·11	18
$C_6H_5CH_2Cl$	CN^-	80% Dioxan	40	1·10	18
$C_6H_5CH_2Br$	OMe^-	MeOH	0	1·10[a]	23
$C_6H_5CH(Me)Br$	OEt^-	EtOH	0	1·07[a]	23
MeCl	CN^-	H_2O	11	1·15[a]	19
MeBr	CN^-	H_2O	11	1·15[a]	19
MeI	CN^-	H_2O	11	1·14[a]	19
MeI	$PhNEt_2$	MeOH	63	1·12	24
MeI	OH^-	50% Dioxan	25	1·09	25
MeI	Pyridine	Benzene	25	1·14	25
MeI	NEt_3	Benzene	25	1·10	25

[a] The original experimental result was obtained by determining $k_2(^{12}C) : k_2(^{13}C)$ and has been corrected appropriately[18].

different isotope effects, and these do not obviously depend on the charge-type of the reaction. The relatively low value for the reaction of methyl iodide with the hydroxide ion may be attributable to the unsymmetrical nature of the transition state, with its relatively highly weakened C—I bond.

The reactions of the aralkyl halides show further that the isotope effect can be reduced by structural features which would tend to increase the extent of bond-breaking in the transition state by stabilizing the positive charge on the reaction centre. Thus 1-phenylethyl bromide reacting with sodium ethoxide has an isotope effect smaller than that observed for benzyl bromide. Electron-release from within the aryl group also somewhat reduces the isotope effect.

All these isotope effects in S_N2 reactions have 'normal' temperature coefficients, slightly decreasing with increased temperature.

f. Structural ('polar') effects. The effect of change in structure on the rates of S_N2 reactions has been a matter of some controversy, which has become confused from time to time in different ways: sometimes through

failure to recognize the great importance of steric hindrance in these bimolecular reactions, and sometimes through an unwillingness to accept the complex ways in which change in structure can alter reactivity. Theoretically, one would expect that electron-release towards the centre at which replacement was occurring could increase the ease of separation of the departing halogen, but could at the same time reduce the ease of attack by the nucleophile. Early reviews[26,27] clearly recognize the conflicting requirements of bond-making and bond-breaking, and exemplify them. Thus Baker and Nathan[28] showed for the reaction of nitrate ions with substituted benzyl bromides that the rate-sequence was as shown in Table 6. So in a situation where steric hindrance by the new substituent should be minimal, both electron-withdrawing and electron-releasing substituents can facilitate the reaction.

TABLE 6. Rates of displacement of bromide by nitrate ion from substituted benzyl bromides in acetone at 40°C

Bromide	10^4k_2
2,4-Dinitrobenzyl	ca. 33
p-Nitrobenzyl	8·2
Benzyl	4·3
p-*t*-Butylbenzyl	6·8
p-Methylbenzyl	7·5

When such substituents are attached directly to the reacting centre, their effects would be expected to become larger and, qualitatively, the dual possibilities can be exemplified here also. From among the many examples that could be chosen, we select three because they are well documented as to mechanism, and because the influence of steric hindrance can be allowed for semi-quantitatively. Some of the relevant results[29] are given in Table 7: they refer to symmetrical halide exchanges in acetone.

These results may be analysed in terms of a polar effect, which may have an inductive and a conjugative component and may either increase or decrease the rate of reaction, and a steric effect, in which congestion produced by the replacement of a smaller by a larger group will raise the energy of the pentacovalent transition state and so reduce the reactivity. In the series CH_3Br, $PhCH_2Br$, Ph_2CHBr, hydrogen is being successively replaced by the undoubtedly larger phenyl group. Since the observed rate is not reduced by the introduction of one phenyl group, this group must

surely be exerting a facilitating polar influence which is only overcome by the steric effect when two such groups are introduced.

Secondly, consider the bromine substituent, which is powerfully electron-withdrawing by its inductive effect, with a less dominant electron-releasing influence ($-I$, $+R$). The inductive effect must be important in determining the very modest reactivity of methylene dibromide and its analogues.

TABLE 7. Rates (k_2) and Arrhenius parameters (E_A, B) for symmetrical bimolecular isotopic exchange reactions of halogen between organic halides and lithium halides in acetone.

Substrate	Nucleophile (M)	$10^5 k_2$ 0°C (1 mole^{-1} s^{-1})	E_A (kcal mole^{-1})	$\log_{10}B$ (B in 1 mole^{-1} s^{-1})
CH_3Cl	LiCl (0·028)	0·16	20·2	10·4
$PhCH_2Cl$	LiCl (0·028)	0·16	18·3	8·9
CBr_4	LiBr (0·024)	Very small	—	—
CH_2Br_2	LiBr (0·024)	0·23	20·9	10·7
CH_3Br	LiBr (0·024)	1120	15·8	10·7
$PhCH_2Br$	LiBr (0·024)	1120	—	—
Ph_2CHBr	LiBr (0·024)	3·3	17·2	9·2

Comparison of the increment in activation energy, ($BrCH_2Br—CH_3Br$, $\Delta E_A = 5{\cdot}1$ kcal mole^{-1}: Table 6) with the corresponding value for the methyl substituent ($MeCH_2Br—CH_3Br$, $\Delta E_A = 1{\cdot}7$ kcal mole^{-1}: Table 3) shows that the former value is substantially larger, despite the fact that the methyl group is similar in size to the bromine substituent[30].

Thirdly, consider the methoxyl substituent, which is powerfully electron-releasing by the conjugative effect but only modestly electron-withdrawing by the inductive effect ($-I$, $+R$). This group, when attached directly to the reaction centre, very strongly facilitates S_N2 substitution. An approximate estimate of the extent of this facilitation has been given[31]; methoxymethyl chloride is more reactive than methyl chloride with ethoxide ions in ethanol at 0° by a factor of about 10^5.

The theoretical description of the facilitation of bimolecular substitution by conjugative electron release (as with the methoxyl and phenyl substituents) can be put in the following way, by using valence-bond language. One of the contributors to the resonance hybrid which describes the transition state is such a structure as **4**, and a conjugatively electron-releasing group R (R = OMe, Ph, etc.) allows further contribution of an extra structure **5**, absent if the substituent does not have the power of

conjugative electron-release. Hence reaction must be facilitated by this structural feature.

(4) (5)

g. Modified S_N2 *transition states.* From the above results, it can be deduced that the transition states for S_N2 substitutions are often very closely balanced in their response to polar effects; the rate can be enhanced by either electron-releasing or electron-withdrawing conjugative effects, and it can be diminished by either electron-withdrawing or electron-releasing inductive effects. Further complexities are indicated by some comparisons given in Table 8 from the work of Cook and Parker[32], who

TABLE 8. Rates of bimolecular (S_N2) reactions of some alkyl bromides, RBr, with chloride ions

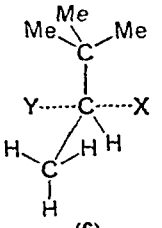
R	Solvent	T °C	$\log_{10}k_2$
$MeCH_2$	Dimethylformamide	100	0·95
t-$BuCH_2$	Dimethylformamide	100	−3·26
MeCH(Me)	Acetone	100	−1·0
t-BuCH(Me)	Acetone	100	−3·4

point out that the rate-diminution through introducing a t-butyl group in place of a methyl group is much greater in the primary system ($\Delta\log_{10}k_2$, 4·2) than in the secondary system ($\Delta\log_{10}k_2$, 2·4). They consider several possible interpretations. One is that the transition state for substitution in t-BuCH(Me)Br is so much loosened by C–Hal bond extension, as compared with the situation in neopentyl bromide, that steric effects are no longer so large. Consideration of distortion of the calculated energy surfaces around the transition-state configuration for neopentyl bromide[12], however, indicates that this is unlikely; loosening of the transition state occurs whenever new bulky groups are introduced, but one can reduce steric strain in this way only at the cost of bonding energy of incoming and outgoing groups, and this bonding energy is substantial enough to keep the transition state fairly tight.

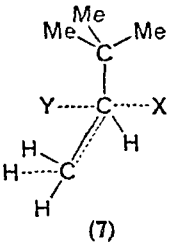
A second possibility, which the present writers favour, is that the polar effect has become modified in the neopentyl system by such loosening of the C–Hal bond as has occurred; so that there is now more carbonium character in the transition state, and in consequence the methyl group when

introduced to form the secondary system of *t*-BuCH(Me)Br is now by its hyperconjugative effect a facilitating, rather than by its inductive effect a retarding, influence. This hypothesis is consistent with the views developed in the previous section; we may note also the possibility that the entropy of activation is higher for the reaction of *t*-BuCH(Me)Br than for that of neopentyl bromide.

Yet a third possibility considered by Cook and Parker is that the transition state for S_N2 substitution should be considered to be not like **3**, as was proposed by Hughes, Ingold and coworkers[12], but more like the so-called *E*2C transition state. As applied to Cook and Parker's particular example, the representations under consideration are **6** (S_N2), **7** (*E*2C-like) and **8** (intermediate between **7** and the transition state for an *E*2 elimination, though considered to be leading to substitution).



(6)



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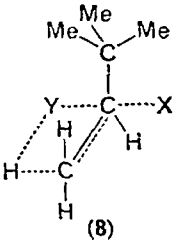


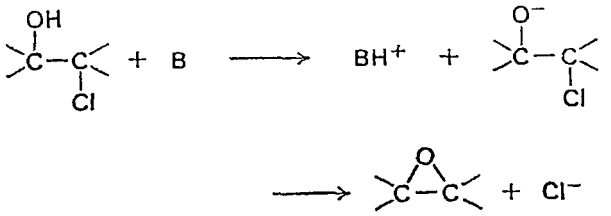
(8)

The hyperconjugative structure **7** must bring one hydrogen atom of the methyl group into such great proximity to the entering group Y that the steric repulsion between them would, on the usual assumptions concerning non-bonding interactions, be prohibitive. Structure **7**, therefore, provides no rationale for its adoption in preference to **6**, which minimizes the total energy of the system by minimizing those repulsions which lie on the steepest part of the repulsive potential energy curves. Structure **8**, however, does provide a new feature: the bond indicated as partly formed between H and Y allows some additional stabilization which in principle might offset the non-bonding steric interaction. Not enough is yet known to enable calculations to be made which would determine whether or not this is a real possibility; it seems to raise again the question of whether in certain cases the transition state which normally would lead to substitution might lead concurrently to elimination (see footnote in section II. A. 1. d).

2. Intramolecular ('internal') processes

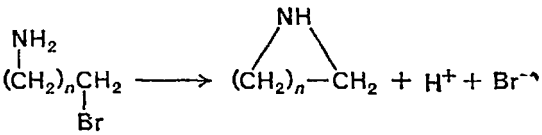
We have already noted that the formal definition of an S_N2 reaction requires the involvement of two particles in covalency change in the rate-determining stage of the reaction. There are a number of well-known

reactions in which a nucleophilic centre can displace a halogen within the same molecule by a process so closely analogous to a normal S_N2 reaction that differentiation as a separate class seems at first sight to be artificial. Thus the reactions of chlorohydrins with bases proceed much more rapidly than reactions of simple alkyl halides with alkoxide ions under the same conditions: equation (5) shows the type of sequence involved[33].



(5)

Chlorohydrins with the reactive substituents more distant from each other react similarly, providing that the stereochemistry allows them to come within effective bonding distance and to give an S_N2-like transition state. Similar considerations apply to the ring-closures of bromo-amines according to equation (6). The ease of formation of these products as it

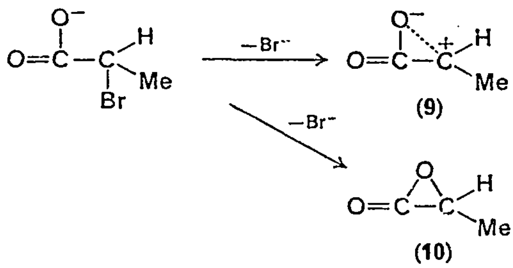


(6)

relates to ring-size was reviewed by Bennett[34]. It has been well established that the stereochemistry of these intramolecular reactions is similar to that of the corresponding intermolecular S_N2 processes, and proceeds with formal inversion of configuration at the centre of displacement.

Despite the obvious analogies between these inter- and intramolecular reactions, there has been some argument as to whether this mode of description is proper. For in the rate-determining step of the intramolecular process, only one molecule is formally involved in the rate-determining step, and so by analogy with the customary use of the term S_N2, it would be possible to describe these reactions as proceeding by a unimolecular mechanism, which could be called S_N1. We shall be discussing S_N1 reactions in some detail below (cf. section II. A. 7); the problem of classification would probably not result in argument if cases such as those mentioned above were the only ones with which we were concerned. But the analogy with bimolecular nucleophilic substitutions of the intermolecular kind becomes more strained, the more unstable the product of nucleophilic displacement becomes. Perhaps the case that has invoked the

most discussion is that of the solvolysis of the α-bromopropionate ion. This has been regarded as an S_N1 process with retention of configuration (reference 7, pp. 523 ff.) giving an intermediate **9**, and classifiable in a way different from that appropriate to the corresponding reactions involving a carboxylate-ion substituent β-, γ- or δ- to the departing halogen[35], where the sequence is S_N2, followed by S_N2, giving overall retention of configuration by way of two formal inversions.



(7)

The question of whether the reaction actually gives an α-lactone (**10**), and so differs from the other cases only because α-lactones undergo subsequent reactions different from those of their β-, γ- and δ-analogues, has been discussed by other workers: Winstein, Grunwald and coworkers[36] concluded that no firm distinction could be made between the intermediacy of **9** and **10** on the basis of the existing evidence.

The writers consider that most rigid schemes of classification, if pressed too far, introduce unhelpful semantic difficulties; the intramolecular reactions clearly have analogies both with S_N2 and with unimolecular processes, and we shall return in a later section to the kinetics and stereochemistry associated with the formation of unstable intermediates of displacement such as **9** or **10**.

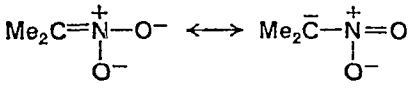
3. Bimolecular radical-ion processes

These reactions have recently been reviewed[37]. When the salts of nitroparaffins are allowed to react with an alkyl halide, the usual mode of reaction is a normal bimolecular replacement of halide, giving the product of *O*-alkylation; this product is not isolated, but is decomposed to give oxime and aldehyde, as in equations (8) and (9). Kornblum and coworkers[38]

$$RCH_2X + Li^+[Me_2CNO_2]^- \longrightarrow RCH_2O\overset{+}{N}(O^-){=}CMe_2 + LiX \qquad (8)$$

$$RCH_2O\overset{+}{N}(O^-){=}CMe_2 \longrightarrow RCHO + Me_2C{=}NOH \qquad (9)$$

have shown that for benzyl halides the reaction takes this course, giving good yields of benzaldehyde, whether the leaving group is chlorine, bromine or iodine. These nucleophilic anions are potentially ambident in character; being resonance-hybrids between such forms as **11** and **12** below, they might be able to initiate nucleophilic attack from the carbon instead of from the oxygen centre. The latter type of reaction can in certain



(11) (12)

cases become dominant, especially for the reactions involving attack on *p*- and *o*-nitrobenzyl chlorides. In the example of equation (10)

$$p\text{-}O_2NC_6H_4CH_2Cl + Li^+[Me_2CNO_2]^- \longrightarrow p\text{-}O_2NC_6H_4CH_2CMe_2NO_2 + LiCl \quad (10)$$

the yield of the product of alkylation on carbon was 92% in dimethylformamide as solvent.

An interesting feature which arose from more detailed study was that the corresponding iodide gave only 8% of the C-alkylated product, the remainder being that of normal S_N2 replacement and subsequent decomposition. The results are summarized in Table 9. For *O*-alkylation, the

TABLE 9. Rates and products in the reaction of some nitrobenzyl halides with the lithium salt of 2-nitropropane in dimethylformamide at 0 °C

Halide	Second-order rate-coefficients (k_2, l mole^{-1} s^{-1})		
	k_2(total)	k_2(carbon)	k_2(oxygen)
p-$O_2NC_6H_4CH_2Cl$	0·023	0·02	0·002
p-$O_2NC_6H_4CH_2Br$	0·34	0·068	0·27
p-$O_2NC_6H_4CH_2I$	1·9	0·15	1·8
m-$O_2NC_6H_4CH_2Cl$	0·0013	—	0·0013
m-$O_2NC_6H_4CH_2Br$	0·28	—	0·28
m-$O_2NC_6H_4CH_2I$	1·4	—	1·4

sequence of reactivity, I > Br > Cl, and the spread through the series, is that observed for other S_N2 reactions both for *m*- and for *p*-nitrobenzyl halides. The much smaller spread for the C-alkylation of the *p*-nitrobenzyl halides, and the consequent change in product-ratio with change from iodide to

chloride, would be unexpected for an S_N2 process. It was shown by using electron spin resonance spectroscopy that a solution of the lithium salt of 2-nitropropane in dimethylformamide converts other nitro-compounds into detectable amounts of their radical-anions by electron-transfer and that the inclusion of modest proportions of otherwise inert nitro-compounds in the medium in which *p*-nitrobenzyl chloride was reacting with the lithium salt of 2-nitropropane diverted the product of reaction to that of mainly *O*-alkylation. It was proposed, therefore[38], that carbon-alkylation in this system is effected through the intermediacy of a radical anion. Later work[39] showed that a chain-process was involved, so we can amplify the mechanism as in equations (11)–(15).

Chain-initiating process:

$$\underset{(11)}{p\text{-}O_2NC_6H_4CH_2Cl} + \underset{(12)}{[Me_2CNO_2]^-} \longrightarrow \underset{(13)}{[p\text{-}O_2NC_6H_4CH_2Cl]^{\bullet -}} + \underset{(14)}{[Me_2CNO_2]^{\bullet}} \quad (11)$$

Chain-propagating processes:

$$(13) \longrightarrow \underset{(15)}{[p\text{-}O_2NC_6H_4CH_2]^{\bullet}} + Cl^- \quad (12)$$

$$(15) + [Me_2CNO_2]^- \longrightarrow \underset{(16)}{[p\text{-}O_2NC_6H_4CH_2CMe_2NO_2]^{\bullet -}} \quad (13)$$

$$(16) + p\text{-}O_2NC_6H_4CH_2Cl \longrightarrow \underset{\text{(product)}}{p\text{-}O_2NC_6H_4CH_2CMe_2NO_2} + (13) \quad (14)$$

Chain-terminating process:

$$(15) + (14) \longrightarrow p\text{-}O_2NC_6H_4CH_2CMe_2NO_2\ \text{(product)} \quad (15)$$

In still later work[40] it was shown that the C-alkylation of some β-keto-esters by nitrophenyl-substituted alkyl halides (particularly tertiary halides, such as *p*-nitrocumyl chloride) can also involve chain-reactions with radical-anions as intermediates; these could often, but not always, be inhibited by traces of such chain-breakers as cupric ions and could be trapped by oxygen to give products of oxidation. Aliphatic amines have been shown also to be able to act as nucleophiles in such radical-chain processes[41].

It would seem that the formation of radical-anions under conditions normally conducive to the heterolytic bimolecular (S_N2) mechanism is particularly important only for nitrobenzyl halides. When radical-anions are preformed from aromatic hydrocarbons, they are known to be excellent reagents for the removal of halogen from organic halides. For example, the decomposition of organic halides, including many relatively unreactive fluorides, with sodium biphenyl is a basis for the determination of halogen

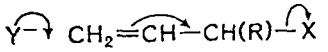
in organic compounds[42]. Some measurements of relative reactivities of organic halides with radical-anions have been made[43,44]; the reactions are bimolecular in dioxan as solvent, and alkyl chlorides seem to react more rapidly than the corresponding bromides or iodides, thus reinforcing Kornblum's view that these reactions are differentiable from ordinary S_N2 processes through a study of structural effects.

4. Bimolecular replacements with rearrangement (S_N2' processes)

When a simple allylic halide is allowed to react with an anionic nucleophile, an S_N2 reaction usually occurs and the product is that of replacement without rearrangement (e.g. equation 16).

$$CH_2{=}CHCH(Me)Cl + OEt^- \longrightarrow CH_2{=}CHCH(Me)OEt + Cl^- \qquad (16)$$

It was first proposed independently by Hughes[45] and by Winstein[46] that the analogous bimolecular mechanism giving rearrangement could exist. The process can be formulated as in **17**. The simplest form that could be



(17)

taken by any such reaction might be considered to be that in which attack by Y^- and displacement of X were synchronous, and no intermediate of life longer than a molecular vibration existed before the transition state was reached, but more complex elaborations are possible, leaving unchanged the essential feature that both bond-forming and bond-breaking processes are concerned in the rate-determining step.

Systems in which this mechanism has been realized are essentially those in which steric or polar influences inhibit attack at the centre to which the displaceable group is attached, at the same time preferably facilitating attack by the nucleophile on the double bond by withdrawal of electrons. Some neutral nucleophiles, including secondary amines in particular, seem to promote reaction by this mechanism, though the reason for this is not completely clear. Since one of us[47] has reviewed in some detail the scope and characteristics of this type of rearrangement, we shall concentrate here on some recent publications in the area.

First, and perhaps most important, is the report[18] that the reaction of diethylamine with 3-chlorobut-1-ene (equation 17) gives substantial isotope effects. Values obtained were:

$$k_2(^{12}C_1) : k_2(^{14}C_1) = 1{\cdot}057; \quad k_2(^{12}C_2) : k_2(^{14}C_2) = 1{\cdot}074$$

$$k_2(^{12}C_3) : k_2(^{14}C_3) = 1{\cdot}079; \quad k_2(^{35}Cl) : k_2(^{37}Cl) = 1{\cdot}011$$

These results should be compared with those quoted earlier for S_N2 reactions; they establish that in the transition state considerable bonding changes are occurring involving the leaving chlorine and all three carbon atoms of the allylic system. The view is therefore supported that a synchronous mode of displacement is under observation.

$$Et_2NH + CH_2{=}CH{-}CH(CH_3)Cl \longrightarrow Et_2NCH_2{-}CH{=}CHCH_3 + HCl \quad (17)$$

Secondly, an important comparison has been made between allylic chlorides and allylic bromides reacting with and without rearrangement by bimolecular mechanisms[48]. The results for bimolecular exchanges between isotopically labelled bromide ions and the isomeric 1- and 3-methylallyl bromides and between chloride ion and the corresponding allylic chlorides are summarized in Table 10.

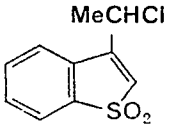
TABLE 10. Rates (k_2) and activation parameters for exchange and rearrangement of 1- and 3-methylallyl halides in acetone (bromides) or acetonitrile (chlorides)

Compound	Halide	Mechanism	$10^6 k_2$ at 25°C (l mole^{-1} s^{-1})	$\Delta H^{\ddagger}$ (kcal mole^{-1})	$\Delta S^{\ddagger}$ (e.u.)
$CH_2{=}CHCH(Me)Br$	Br^-	S_N2	879	15·9	−19·1
$CH_2{=}CHCH(Me)Br$	Br^-	S_N2'	14·9	18·8	−17·7
$BrCH_2CH{=}CHMe$	Br^-	S_N2	141,000	14·1	−15·0
$BrCH_2CH{=}CHMe$	Br^-	S_N2'	5	ca. 18	ca. −19
$CH_2{=}CHCH(Me)Cl$	Cl^-	S_N2	2·87	20·8	−13·9
$CH_2{=}CHCH(Me)Cl$	Cl^-	S_N2'	0·0133	24·2	−13·4
$ClCH_2CH{=}CHMe$	Cl^-	S_N2	315	18·8	−11·6
$ClCH_2CH{=}CHMe$	Cl^-	S_N2'	0·0053	24·3	−14·9

The use of isotopic tracers in such an investigation has the advantage that exchange does not change the starting material chemically, so that both S_N2 and S_N2' processes can be investigated under the same conditions, even if the first is much more rapid than the second. The pattern of results for the very labile bromides is reproduced for the chlorides, which are very much less prone to spontaneous rearrangement. For the 3-halogenobutenes, with these reagents as with others, the 3-carbon atom is the preferred site of nucleophilic attack, and the S_N2 mechanism predominates; but this preference over attack on the 1-position with consequent rearrangement is not very great, so that suitable structural modifications of the system would be expected to reverse the major mode of attack. It was the realization of this fact that led to the investigations of such compounds as

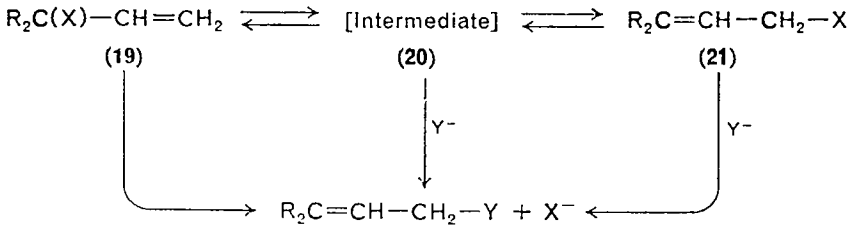
CH_2=CHCHCl$_2$ and CH_2=CHCH(*t*-Bu)Cl referred to in the review mentioned above[47].

Thirdly, Bordwell and coworkers[49] have added significantly to their earlier contributions in the study of the S_N2' mechanism by examining the reactions of a further number of cyclic unsaturated sulphones with nucleophiles. Bimolecular substitutions with allylic rearrangement have been identified for the reactions of secondary amines with a number of substrates, of which **18** is a representative example.



(18)

These workers have expressed reservations concerning the mechanistic classification of most of these allylic substitutions with rearrangement which other reviewers and investigators have been prepared to include in the category of S_N2' processes. Classification of reactions which could follow a multi-stage path is, of course, to some extent a matter of subjective judgement; difficulties of this kind associated with the exclusion of the route involving normal substitution followed by rearrangement (S_N2, then S_Ni) for certain examples in this field have been considered by one of us[47], as also by others[50]. One path which Bordwell considers[51] not to be excluded for a number of cases is the sequence involving intramolecular



SCHEME 1. Some possible routes for bimolecular substitution accompanied by anionotropic rearrangement of $R_2C(X)—CH=CH_2$

rearrangement followed by bimolecular substitution, elaborated by the inclusion of an intermediate which could react with the nucleophile, as in Scheme 1.

This view has been criticized[52], and the writers consider that, Bordwell's view to the contrary notwithstanding, the path **19** $\rightleftarrows$ **21** $\rightarrow$ **22** has in fact been made quite improbable for a number of important representative

examples. The route **19** $\rightleftarrows$ **20** $\rightarrow$ **22**, on the other hand, is not so easily excluded; it deserves discussion in the more general context below (section II. A. 10), since it has been proposed also for simpler systems. Here we shall note only that the transition state for this route is isomeric with that for the S_N2' conversion of **19** into **22**, and in our view could be described as 'not S_N2'' only if the C—X bond were *completely* broken before reaction with Y^-.

Other elaborations of and variants on the S_N2' mechanism have been referred to in the review already cited[47]. Attention on one of these may be focused by reference to the inclusion by Bordwell and coworkers[49] of comparisons of chlorides, bromides and iodides as leaving groups in some of the reactions they assert to be S_N2' processes. They find that, although the sequence of reactivity for organic halides, I > Br > Cl, is on the whole maintained in these systems, there are considerable variations in the magnitude of the differences between the different halogens. Instances are quoted in which the rates of displacement of these three halogens by the same nucleophile are nearly equal. This result suggests that bond-breaking has begun to make less contribution to the transition state than it does in the corresponding S_N2 reactions of simple alkyl and allyl halides. The possibility then arises that some of these processes might be examples of the sequence:

$$RX + Y^- \rightleftharpoons [YRX]^- \longrightarrow YR^1 + X^- \qquad (18)$$

Here we consider $[YRX]^-$ as an intermediate rather than as a transition state, and either its formation or its decomposition could be rate-determining. The formal analogy with the route **19** $\rightleftarrows$ **20** $\rightarrow$ **22** (Scheme 1) is obvious; we are considering other possible transition states isomeric with that implied by the label S_N2'. Elaborations of the S_N2 displacement, first recognized clearly through exactly the same type of observation, are referred to in relation to bimolecular nucleophilic substitution at unsaturated centres (section II. C), and related problems arise in categorizing electrophilic substitutions at unsaturated centres (section III. A). The most powerful criterion enabling us to establish which bonds are undergoing covalency change in the rate-determining step involves measurement of primary isotope effects, and study of the effect of the change in the leaving group (the so-called 'element effect')[53] is only a partial substitute in diagnosing whether or not the breaking bond is making a contribution to the transition state. Among the halogens, the comparison of fluorine with chlorine, bromine and iodine as leaving groups gives the most sensitive experimental probe, and it is a pity that Bordwell and his group have not been able to include the fluorides in their investigations.

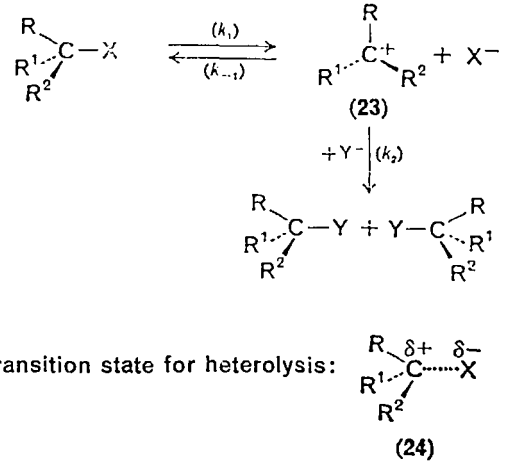
There have in fact been rather few mechanistic investigations of the reactions of allylic fluorides. A number of preparative examples of bimolecular displacements with rearrangement have been recorded for highly substituted fluorocompounds, as has been discussed elsewhere[47].

5. Unimolecular (S_N1) reactions

The idea of ionization as a mechanism for replacement had been adumbrated by a number of investigators prior to 1933, but it was only in that year that Hughes, Ingold and Patel[54] set out clearly for the first time the important proposal that there are two distinctive mechanisms for nucleophilic substitution in an organic halide. One of these is the S_N2 mechanism which we have already considered; the other is one in which the rate-determining stage is the ionization of the organic halide (equation 19).

$$R{-}X \longrightarrow R^+ + X^- \qquad (19)$$

Equation (19) does not, of course, represent the whole process; in Scheme 2 the reaction path is elaborated and for future reference we include an indication of the stereochemistry of reactants, intermediate **23** and



SCHEME 2. First approximation to a description of the reaction path in S_N1 replacements of alkyl halides.

products. The geometry of the transition state for the rate-determining heterolysis is shown approximately in **24**. Provided that the rate of the combination of the intermediate carbonium ion with Y^- is fast in comparison with the rate both of ionization and of the ionic recombination of

the carbonium ion with X^- (i.e. provided that k_2 is greater than both k_1 and k_{-1}), then replacement proceeds at the rate of equation (20), and we are

$$d[\text{products}]/dt = k_1[RR^1R^2CX] \quad (20)$$

describing a unimolecular process (with only one molecule involved in covalency change in the rate-determining stage), nucleophilic in character (because the departing X leaves with its bonding pair of electrons), and giving products of substitution; the categorization S_N1 is complete.

The most satisfactory experimental criterion for such a reaction is achieved when it is possible to show that with two nucleophiles of widely different nucleophilic power (e.g. a hydroxylic solvent and the derived lyate ion) the reaction proceeds at the same rate. This gives clear evidence that the nucleophile is not concerned in covalent bonding with the alkyl halide in the transition state to an extent sufficient to contribute to the stabilization of the transition state. It is not assumed that the solvent is not concerned in the reaction at all; in the S_N1 process, as indeed also for the S_N2 mechanism, the solvent plays a vital role in solvating ions and ionic intermediates, and so allowing the whole process to take place. But only in the S_N2 mechanism, and not in the S_N1 sequence that we are now considering, does the nucleophile (be it solvent or anion) play the role of a reagent which by its covalent bonding facilitates the departure of the leaving group.

There are a number of systems in which the kinetic behaviour approximates to the limiting situation that we have just described; important examples include the hydrolyses and alcoholyses of *t*-butyl halides, 1-phenylethyl halides and diphenylmethyl halides.

Some of the criticism which followed this proposal was answered by reviews which revealed how extensive was the experimental evidence supporting the general concept[26,45]. The criticism had led to the focusing of attention on the limiting properties of the particular carbonium ionic sequence indicated in Scheme 2, as illustrated by the behaviour of a range of compounds which, though including a large number of solvents and structural types, did not exhaust the field of possibilities. The kinetic method was used to analyse the effects of added salts in terms of departures from the behaviour expected under the conditions that $k_2 \gg k_1$; when this condition does not hold, then the effects of added anions X^- (common with the displaced anion), Y^- (effecting replacement) and others (not effecting replacement) on rates and products can be predicted to differ in characteristic ways; in particular, added X^- retards the reaction whilst other anions do not. Good agreement between theory and experiment was reported in a number of illustrative cases and the conclusions have been confirmed and extended in later work[55,56].

The stereochemistry of the products of the reaction has also been established to be diagnostic of mechanism in favourable cases. Whereas reaction by the S_N2 mechanism gives complete inversion of configuration, the sequence of Scheme 2 gives complete racemization provided that the intermediate carbonium ion becomes completely free from the influence of the departing group. Behaviour approximating to this was recorded for the solvolysis of 1-phenylethyl bromide.

Product-composition was also shown to be diagnostic in certain cases. Where more than one product can be produced from the intermediate carbonium ion, and where two or more different substrates can be used to produce the same ion, then if the sequence is as indicated in Scheme 2, and if the carbonium centre becomes completely free from the departing group before it undergoes further reaction, then the same products would be expected from the different sources. Various tests of this kind have been devised: one, involving a mesomeric carbonium ion and rearranged products, is the allylic system in which 1,1-dimethylallyl chloride and 3,3-dimethylallyl chloride can give the same mesomeric carbonium ion (**25**) and hence the same products. The results for aqueous solvolysis under neutral conditions show the expected limiting behaviour[57].

$$[Me_2\overset{+}{C}-CH=CH_2 \longleftrightarrow Me_2C=CH-\overset{+}{C}H_2]$$

(25)

From 1940 onwards, therefore, organic chemists began to find it acceptable to write carbonium ionic structures for unstable intermediates. The most important and obvious departure from the limiting behaviour of Scheme 2 is shown by study of the stereochemistry of the products, and was recognized at an early stage in the work of Hughes, Ingold and coworkers. Reactions proceeding by the S_N1 mechanism give the limiting stereochemical result, complete racemization, only if the carbonium ion has long enough life to lose chirality by interaction with the environment before reaction with the nucleophile occurs. In fact, this limiting situation is only rarely achieved, and often the observed result is racemization accompanied by an excess of inversion of configuration, the amount of inversion depending very critically on the conditions of reaction.

A qualitative explanation for this result was given in terms of a shielding effect exerted by the leaving group[45]. It was suggested that, after passage through the transition state, subsequent reaction with the nucleophile is sufficiently rapid that the carbonium ionic centre is still affected by the nearness of the leaving group in the sense that there is greater ease, or greater probability, of capture of the nucleophile from the side of the originally asymmetric centre remote from the leaving group.

This view has never been disproved and, although it has been criticized as 'vague', it remains as a clear interpretation of inversion accompanying racemization in S_N1 reactions. A number of other phenomena in the chemistry of reactions proceeding through carbonium ionic intermediates can be explained in similar terms[58]. It is not, however, the only possible interpretation. Doering and Zeiss[59] proposed an alternative in terms of discrete intermediates, the formation of which follows the original rate-determining ionization. Streitwieser[60] gave an analysis and extension of these views, making use of free-energy diagrams to illustrate the sequence of events envisaged as starting materials are transformed into products. We present an expansion of his treatment in Figure 2, though the strict

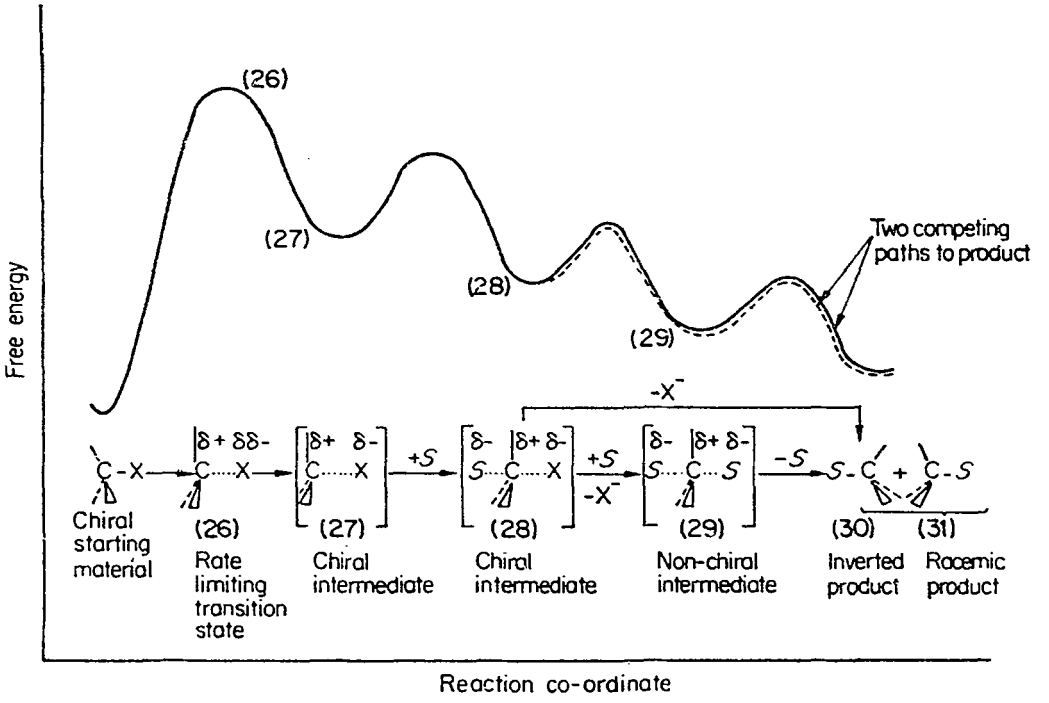


FIGURE 2

propriety of describing reactions in terms of sections of free-energy surfaces might be thought hard to justify, and the nature of the reaction co-ordinate, which must change as the new reagents are successively introduced along the reaction path, is difficult to specify.

It can be seen that the successive stages on the reaction path are envisaged as follows:

(i) A transition state, **26**, rate-determining for the whole reaction, with what may be called a relaxed tetrahedral geometry, and a stretched C···X bond.

(ii) An intermediate, **27**, still retaining its chirality, but with the three bonds which will be retained in the product more nearly coplanar with the central carbon atom.

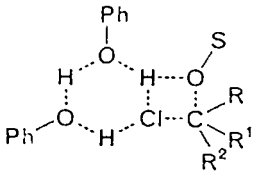
(iii) A very rapid conversion, still needing some energy of activation, of **27** to a new, still chiral, intermediate, **28**, in which the solvent is now partly bonded to the reaction centre.

(iv) The decomposition of **28** by alternative pathways, both of which must involve some energy of activation. The first of these leads to inverted product, the second to yet a third intermediate, **29**, which has now lost chirality with its loss of X^- and decomposes to give racemic product.

It will be noted that the concept of 'shielding' is still invoked in this description; all the way from starting material to inverted product **30**, one face of the carbonium ion is shielded from *S* by X. The new feature is that the conversion of starting material to inverted **30** or racemic **31** product can be treated as a competition of two activated processes leading from the common intermediate **28**; hence the relative proportions in the final product can be used to calculate the ratio of the rate-coefficients for these two processes. It is true that this description is less vague; something is to be gained from it if it is correct, but if it is incorrect for any reason (e.g. if there is some by-pass route to either inverted or retained product), then our precise description becomes precisely wrong.

The kinetics of the overall solvolysis do not help in resolving this problem; it should be emphasized that we are discussing a situation in which the rate-determining transition state does not contain the solvent covalently bound to the reaction site. The solvolyses of *t*-alkyl halides[61] and of 1-phenylethyl halides[62] normally fall into this category. At least two new phenomena have to be accommodated in our description of the reaction. The first, which may have been adumbrated by Read and Taylor[63], was put on a firm footing by Okamoto and coworkers[64]. They made extensive studies of the solvolyses of 1-phenylethyl chloride in solvents containing alcohols and phenols and showed that, although the earlier reports of overall inversion of configuration are correct and apply over quite a wide range of conditions, yet other solvent mixtures (particularly those containing phenols) give products (alcohol or ethers) of excess retention of configuration.

The classical scheme, even in its elaboration shown in Figure 2, does not allow such a result except when special configuration-holding groups are present. Okamoto's interpretation[64] is essentially that particular types of hydrogen-bonding between the departing group and the nearby solvent can bring one of these into the vicinity of the developing carbonium ionic centre in such a way that retention of configuration is effected (e.g. as is represented in **32**, in which SOH can be phenol or another hydroxylic component of the solvent mixture). This concept can be developed as an extension either of the 'shielding' or of the 'intermediate' type of formulation, and has been supported by still more recent experiments relating to the structural effect of the leaving group[65].



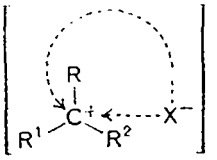
(32)

Further new information is sometimes revealed if the overall rate of reaction can be followed by more than one technique. In particular, there have been a number of studies in which it has been shown that the rate-coefficient for a solvolysis followed by titrimetric measurement of the production of the displaced group can, in suitably chosen systems, be smaller than that for what would have been expected to be the same reaction followed by change in optical activity. Among the reactions for which this type of behaviour has been established are those of *p*-chlorobenzhydryl chloride in aqueous acetone[66] and of 1-phenylethyl chloride in aqueous acetone and other solvents[67, 68].

This observation implies that the starting material has in part racemized or undergone some other change before solvolysis is complete. This could happen in a number of ways, a trivial one of which would involve bimolecular exchange between the developing halide ion and the unchanged organic halide. Another, which would not require the postulation of a new intermediate, involves ionic recombination of the carbonium ion and its counter-ion. This could be described[64, 65, 69] as indicated in **33**, in which the nucleophilic component of the partly separated ions finds its way to the opposite face of the carbonium ionic centre through appropriate motions of the two components.

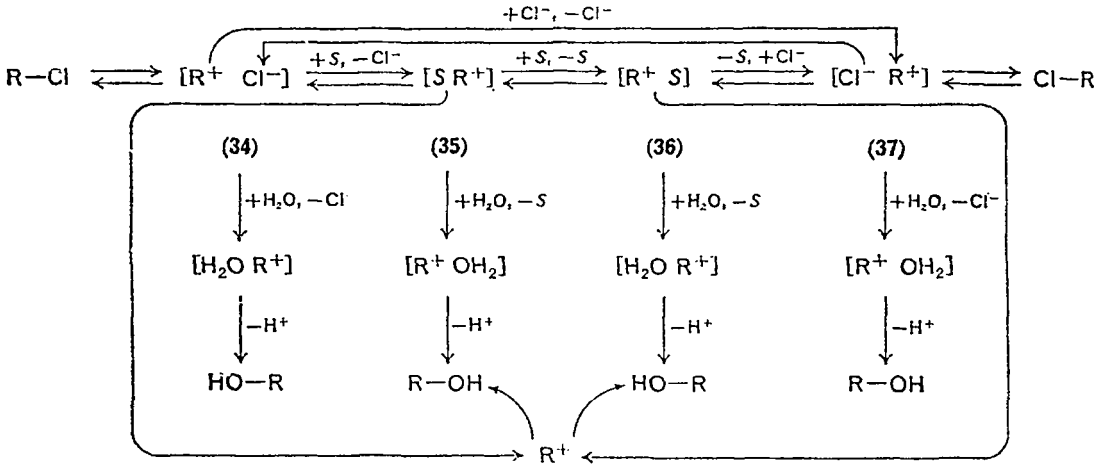
Analysis of the effects of added salts on the various rates of reaction, including the rate of exchange of added radiochloride ion between starting material and solution, indicates that the effects of electrolytes are

very specific. Ingold (reference 7, p. 497 ff.) has argued that results of this kind do not necessitate the assumption that intermediates other than the fully formed carbonium ion are involved on the reaction path. Taking now a different point of view, it has been suggested[67] that all of the results that



(33)

we have mentioned so far can be accommodated by the rather elaborate Scheme 3. This assigns a very positive role to the solvent, as in Doering and Zeiss's proposal[59], variants of which have been adopted by a number of writers[60, 70, 71].



SCHEME 3. Possible role of a co-ordinating solvent (*S*) on the course of solvolysis in a mixed solvent.

In the original publication[67], the by-pass route from **34** to **37** was omitted, and the scheme was specialized to describe the situation with an inert co-ordinating solvent, such as acetone or dioxan. The more general situation is presented here; when *S* is hydroxylic, a further set of products add to the complexity of the situation, but do not alter the general principle.

In the formulation of the scheme, it is implied that R—X is enantiomeric with X—R, R—OH with HO—R, and that structures **34** and **37** are enantiomeric, as are structures **35** and **36**. Each interchange (e.g. **34** ⇄ **35**,

35 ⇄ **36**) is considered as proceeding with inversion of configuration because of some form of shielding; partial racemization could be allowed to accompany any of these processes without altering the conclusions. The initial ionization is held to be only partly reversed, and not to include either component of the solvent in covalent bonding with the reaction centre.

The formal advantage of such a scheme, at least as it appears to the present writers, is that in principle, whilst not excluding the concurrent operation of still more processes involving other intermediates, it enables almost any combination of results to be accommodated. The following are examples.

(i) When the polarimetric rate exceeds the titrimetric rate, this is ascribed to the fact that interchanges between **34**, **35**, **36** and **37** compete effectively with the onward reactions leading from these intermediates to products of solvolysis, but when the polarimetric rate equals the titrimetric rate, then the onward reactions supervene over the interchanges.

(ii) When the exchange reaction can be shown to be internal, there must be a direct path from **34** to **37**.

(iii) When the equilibrium between **34** and **35** is established more rapidly than is that between **35** and **36**, then exchange can involve overall retention of configuration; but in the converse situation exchange will involve racemization.

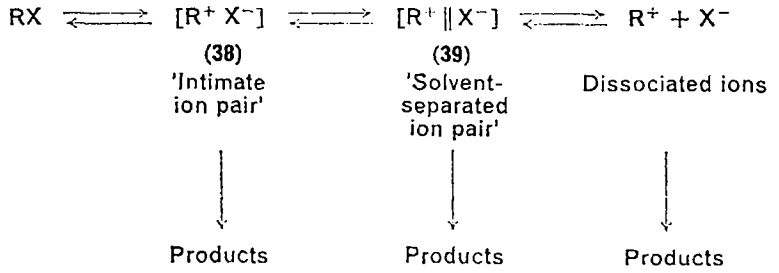
(iv) If the bulk of the product is derived from **34**, then solvolysis will proceed with overall inversion of configuration.

(v) Alternatively, if the bulk of the product is derived from **35**, because its reaction with water is faster than its reaction with solvent to form **36**, then solvolysis will involve retention of configuration.

The above scheme includes all the concepts of the earlier proposals, including two different types of intermediate, $[R^+ Cl^-]$ and $[R^+ OH_2]$, which must both be considered to have lifetimes longer than a molecular collision. Arguments by analogy for the existence of both types of intermediate are implicit in most discussions of such reactions; the main warnings against the indiscriminate postulation of discrete intermediates are those in the writings of Hughes and Ingold. Ingold (reference 7, p. 497 ff.) gives a careful analysis of the position as he assesses it. It is clear that the precision gained from the description given in Scheme 3 is largely illusory from a predictive point of view since, even if the proposal be in essence correct, very subtle changes in the relative rates of the various proposed reactions could modify the overall results (rates, salt-effects, and stereochemistry) in a way which would be difficult to analyse except *a posteriori*.

So far, we have confined attention to results obtained in solvents of relatively high dielectric constant, in which we might hope to find that electrolytes can be treated as behaving according to the limiting form of the Debye–Hückel equation at accessible dilutions. Studies in solvents of very low dielectric constant, however, require the consideration of ionic aggregates higher than ion pairs, and studies in some of these solvents have provided further evidence concerning the potential complexity of reaction paths which start with ionization of an alkyl halide. Winstein and coworkers[72] for example, have examined the unimolecular solvolyses of a number of alkyl halides and arenesulphonates in acetic acid. This solvent dissolves many salts, but because of its low dielectric constant (ca. 6) the ion pairs thus formed are not extensively dissociated under equilibrium conditions. Any pair of ions closer than about 40 Å will attract each other by more than the average kinetic energy, and so can be considered to form an ion pair.

For many substrates, it was found that the effects of added salts were similar to those found in the more conventional solvents; typically, for non-common-ion salts (e.g. $LiClO_4$) the rate increases approximately linearly with salt concentration. Some organic halides, however, of which cholesteryl chloride is an example[73], showed also a 'special' salt effect, which took the form of an initial rapid acceleration of the rate, curving off into the normal, more-or-less linear, behaviour when the concentration of added salt reached about 10^{-3}M. Two theories have been proposed for interpretation of the results. The first is that indicated in Scheme 4 and advocated by Winstein and coworkers[72].

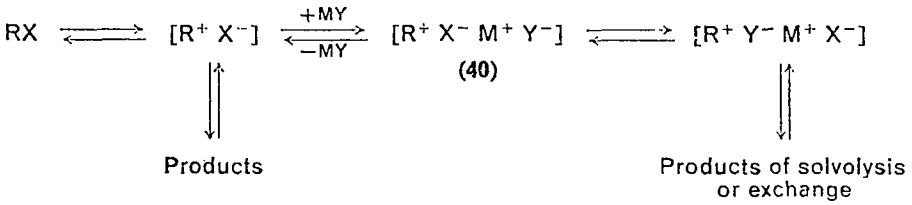


SCHEME 4. 'Two ion pairs' interpretation of solvolyses in acetic acid.

The reaction is here considered to involve up to three different discrete intermediates, separated by activation barriers: the 'intimate ion pair' (38), the 'solvent-separated ion pair' (39) and the carbonium ion. All of these are considered to be affected by salts in different ways, all can lead to

products of solvolysis or exchange, or indeed sometimes of other reactions. The special salt effect is considered to arise because the added salt scavenges away the solvent-separated ion pair and thus suppresses reversibility through this intermediate.

The second possibility was considered by Topsom and is presented in Scheme 5 following Ingold's formulation of it (reference 7, p. 507); in principle, the carbonium ion should be added as a possible intermediate.



SCHEME 5. Ion-quadruplet formulation of solvolyses in acetic acid in the presence of an added electrolyte, MY.

In this proposal, a slightly more specific interpretation of the scavenging process is given, and the activated process separating the two routes to the products is regarded as the internal reorganization of the ion-quadruplet **40**. It is agreed that the results establish the existence of one intermediate other than the carbonium ion on the pathway to solvolysis, but, retaining consistency with his views concerning reactions in aqueous media, Ingold prefers to leave open the question of whether two such discrete intermediates are involved, as Winstein's interpretation (Scheme 4) requires.

In benzene as solvent, similar principles apply, though even more complicated behaviour has been recorded. The reactions of triphenylmethyl chloride with anions and with alcohols have been studied by Hughes, Ingold and coworkers[74], and by Swain and his group[75,76]. Ingold (reference 7, p. 503 ff.) has summarized the results and his interpretation. He stresses that the application of that form of the kinetic theory based on the assumption that intermediates are present in stationary states[76,77] may be invalid in solvents of such low dielectric constant (benzene has dielectric constant 2·25) because of the great distance over which interionic forces are operative. For example, two univalent ions might be considered to be 'ion pairs' at any separation less than about 500 Å, and ion pairs themselves are expected to aggregate into higher multiplets as soon as they are formed. As far as the nucleophilic substitutions are concerned, activated processes involving internal reorganization of ion-quadruplets are considered to intervene on the reaction path.

6. The S_N2 (C^+) mechanism

When reaction involves initial ionization of the alkyl halide, but the later processes have higher activation energies than the initial ionization, these processes become partly rate-determining. The kinetic form then reverts to second-order and the rate-determining transition state again involves two molecules, though one of these is not the original alkyl halide but instead the carbonium ion. This situation can arise when the carbonium ion is relatively stable (or is stabilized by complex-formation) and reacts relatively slowly with the substituting nucleophile, as for example in the reaction of triphenylmethyl chloride with hydroxylic solvents in nitromethane[78] (equations 21, 22). This mechanism can be categorized as $S_N2(C^+)$ on the convention that the whole process (equations 21, 22) is a

$$S_N2(C^+)\begin{cases} Ph_3CCl \underset{}{\overset{fast}{\rightleftharpoons}} Ph_3C^+ + Cl^- & (21) \\ Ph_3C^+ + ROH \underset{}{\overset{slow}{\rightleftharpoons}} Ph_3COR + H^+ & (22) \end{cases}$$

substitution, the reagent which effects the substitution is a nucleophile, two molecules are concerned in the rate-determining stage of the reaction, and this involves not the organic halide, but the carbonium ion. Of course the mechanism is a variant of the S_N1 mechanism and situations intermediate between the two can exist, as for example in some of the circumstances which can be consequent on reaction according to earlier schemes.

Pocker and Buchholz[79] have recently discussed the behaviour of triphenylmethyl chloride in diethyl ether as solvent, with added electrolytes to modify the properties of the medium. Kinetic studies of exchange with labelled chloride ion were supplemented with calorimetric, conductometric and spectrometric studies of various solutes, which included lithium salts and hydrogen chloride. A relatively simple kinetic form was observed, but both the equilibrium position for the ionization of triphenylmethyl chloride and its rate of exchange with chloride ions were very powerfully promoted by the presence of lithium perchlorate. The reaction path was described in terms of the equilibria shown in equations (23) and (24). These

$$Ph_3CCl + 2[Li^+ ClO_4^-] \rightleftharpoons [Ph_3C^+ ClO_4^- Li^+ ClO_4^-] + [Li^+ Cl^-] \quad (23)$$

$$Ph_3CCl + 2[H^+ ClO_4^-] \rightleftharpoons [Ph_3C^+ ClO_4^- H^+ ClO_4^-] + HCl \quad (24)$$

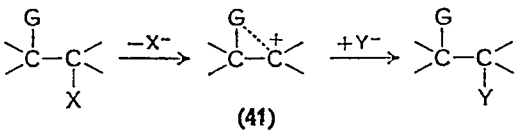
results focus further attention on the importance of ionic aggregates in determining the course and rate of such a reaction.

Leffek[80] has recently re-examined salt effects on the methanolysis of triphenylmethyl chloride in benzene and has reached the conclusion that the results are accommodated no better by Winstein's than by Ingold's mechanism.

7. Unimolecular processes with internal nucleophilic participation by groups bearing lone pairs of electrons

We have already noted in section II. A. 2 that there exists an important mode of replacement of halogen (and of other related leaving groups) in which a group bearing a lone pair of electrons suitably located in the molecule undergoing substitution can assist the ionization of the halogen by internal nucleophilic attack in a process which is formally unimolecular. In Winstein's terminology, such groups are called 'neighbouring groups'; and we can note that a neighbouring group, like an external nucleophile, can be negatively charged (e.g., O^-) or neutral (e.g. NH_2), and may be located at any distance from the centre of substitution, provided that in the transition state it can get near enough to the reaction centre and can be suitably disposed geometrically to give a transition state approximating to that of an S_N2 reaction. The geometric requirements are in part illustrated by the effect of ring-size on the rate of reaction, as has already been noted. The additional stereo-electronic restrictions are particularly evident in the reactions of 2-substituted cyclohexyl halides, where it has been established that *trans* disposition of the 2-substituent is necessary for effective participation[81,82].

Neighbouring-group participation in nucleophilic substitution reactions can have a variety of consequences, depending critically on the structure and chemistry of the intermediate which results from the initial ionization. The simplest situation that can arise is when the ring-closed intermediate is stable and reaction onwards to give the product of overall substitution does not occur, or occurs so slowly that it is easily studied as a separate reaction. Some cases of this kind are mentioned in section II. A. 2. Another limiting situation exists when the intermediate is very unstable under the conditions of reaction, and the bonding of the neighbouring group to the carbonium centre is unsymmetrical (**41**) throughout the course of substitution. The overall reaction sequence then results in retention of configuration (equation 25), as in the solvolysis of the α-bromopropionate ion discussed earlier (section II. A. 2).



(41) (25)

This reaction sequence has considerable historical significance, since the realization of its mechanistic consequences led to the unravelling of the mystery of the Walden inversion, a problem which had puzzled organic

chemists for many years. Reviews[7,83] summarize the main features and we do not need to give details here. We should stress, however, that the *stereochemical* consequences are independent of the nature of the bonding between G and the carbonium centre in **41** (i.e., for example, whether it is covalent or electrostatic in character), of whether or not measurable assistance is given to the heterolysis by the formation of this bond, and indeed of whether or not the formation of this bond is synchronous with the loss of the leaving group, always provided that the bond when established is sufficiently strong to prevent loss of stereochemical specificity at the carbonium ionic centre, and that the further reactions at this centre are slow relative to the development of the bond in question.

If, however, the development of the bond between G and the carbonium ionic centre is synchronous with the ionization, then the latter will in principle be facilitated by the presence of the neighbouring group. To establish whether or not this has happened, it is necessary to be able to evaluate what influence the group G would have had on the rate of reaction in the absence of neighbouring-group interaction in the transition state. Winstein and coworkers[81,82] made efforts in this direction by producing estimates of the 'driving force' contributed by representative substituents in certain specified systems. Their results, some of which are given in Table 11, showed that, other things being equal, neighbouring-group participation makes a larger contribution to the rate of substitution

TABLE 11. Estimates of 'driving force', L_0, for replacement assisted by neighbouring groups G in 1,2-disubstituted ethanes, $G—CH_2CH_2—X$

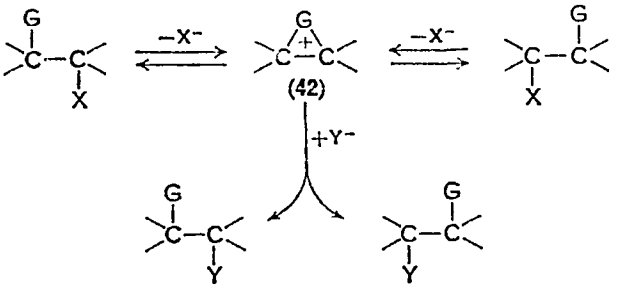
G in GCH_2CH_2X:	$HOCH_2CH_2S$	I	NH_2	O^-	Br	OH	Cl
L_0 (kcal mole^{-1}, 25°C)	13	8·7	8·0	6·0	4·5	1·3	0·0

for replacement at primary than at secondary or tertiary centres, and also makes a greater contribution when the group G is attached to a tertiary centre than when it is attached to a secondary or primary centre.

For weakly interacting groups, however, it remains difficult to establish whether or not there is significant covalent assistance to the ionization in the heterolysis, despite the substantial or complete stereochemical control of the overall course of the reaction. The chlorine substituent is one such group, and another is the important CO_2^- group, discussed earlier (section II. A. 2).

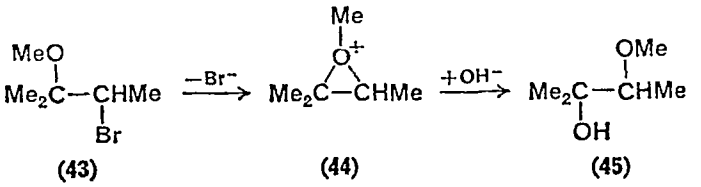
We now need to consider the situation in which the participation by the neighbouring group G gives an intermediate which, though reactive enough

to proceed onwards under the conditions of heterolysis, yet develops a full covalent bond to saturate the carbonium ionic centre before further reaction destroys the intermediate thus formed. Some of the consequences are set out in Scheme 6.



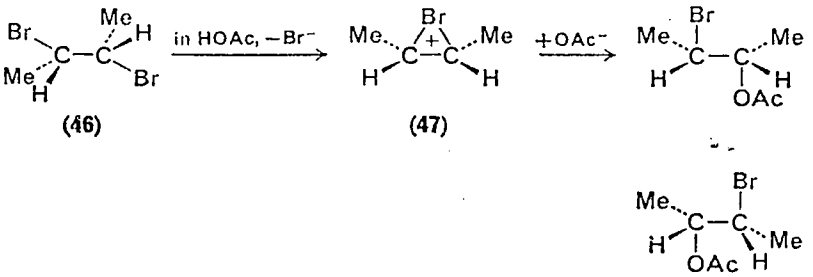
SCHEME 6. Some chemical and stereochemical consequences of heterolysis assisted by neighbouring-group participation.

Two methods have been used for establishing this type of behaviour. The first is applicable when the two carbon atoms to which G is attached in the intermediate **42** have different substituents attached to them. Then, if reaction is followed from the appropriate starting material, the existence of an intermediate such as **42** is made probable by the observation that part or all of the product is derived by migration of the group G. An example is the conversion of 3-methyl-3-methoxy-2-bromobutane (**43**) into 3-methoxy-2-methylbutan-2-ol (**45**) by treatment with aqueous silver nitrate (equation 26)[82].



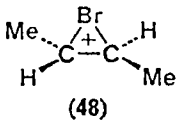
(43) (44) (45) (26)

The second method is applicable when the two carbon atoms of the system are symmetrically substituted. Then, migration through an intermediate such as **42** can be established through examination of the stereochemistry of starting materials and products. Thus (Scheme 7) the optically active *threo*-2,3-dibromobutane (**46**) gives racemized acetate, since the replacement with retention of configuration is accompanied by an equal proportion of replacement with migration of bromine through the intermediacy of the non-chiral bromonium ion (**47**). The diastereoisomeric



SCHEME 7. Acetolysis of a *threo*-2,3-dibromobutane.

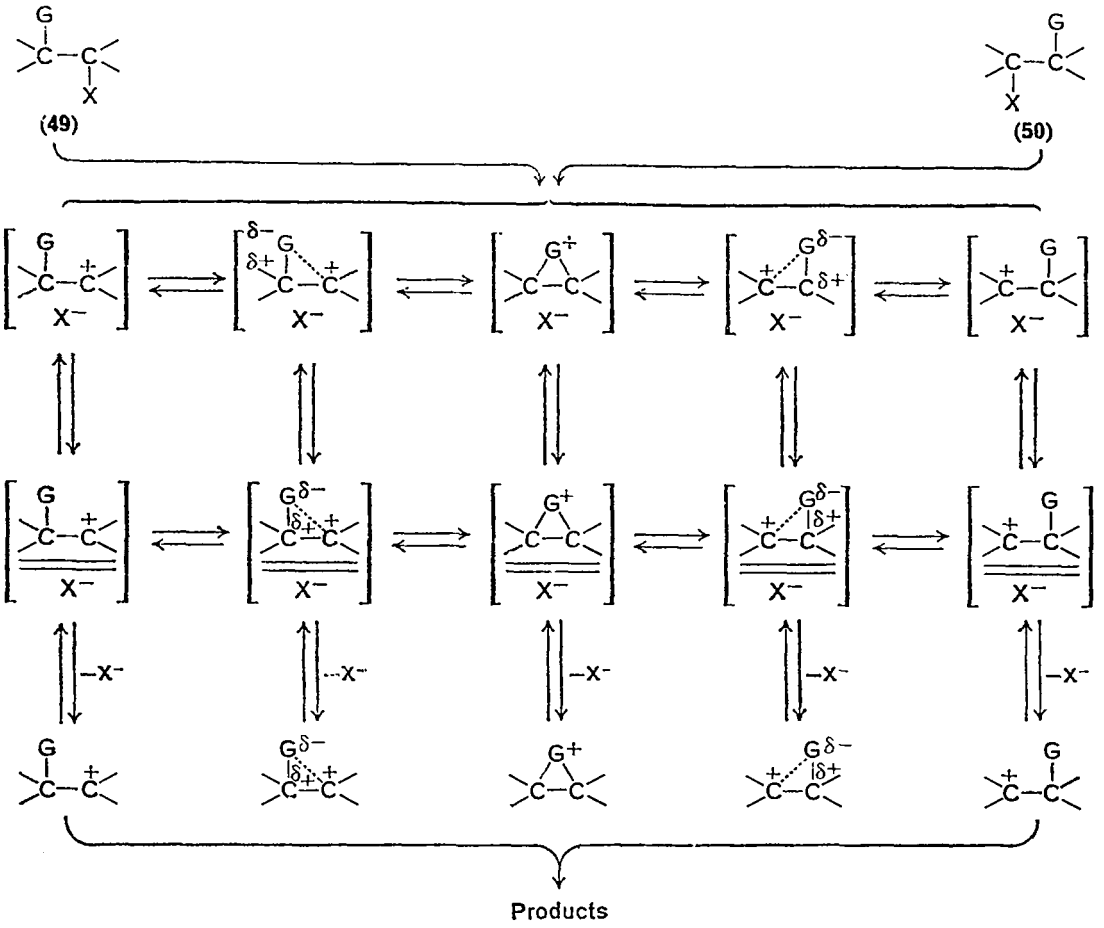
starting material, on the other hand, gives the chiral intermediate (**48**), and so gives replacement with retention of optical activity despite the accompanying migration.



(48)

Scheme 6 can be elaborated even further, to take account of the possibility that there are activation barriers separating the open carbonium ion, the partly bridged ion and the fully bridged ion and also, in appropriate solvents, between one or more different kinds of ion pair. The complex of possibilities is indicated in Scheme 8. Here the first row of intermediates are 'intimate ion pairs', the second row are 'solvent-separated ion pairs' and the last row are free carbonium ions. Product-determination at any stage prior to the formation of fully bridged species (whether involving an intermediate or the interception of an activated species as it loses energy by collision) can be used to interpret any situation in which the alternative starting materials **49** and **50** give different product-mixtures. The scheme has the advantage of symmetry and generality, and can be extended by the inclusion of any other kind of intermediate that might be appropriate to a particular situation; the predictive power is, however, not great, nor is it easy to assign definite intermediates to any particular experimental situation.

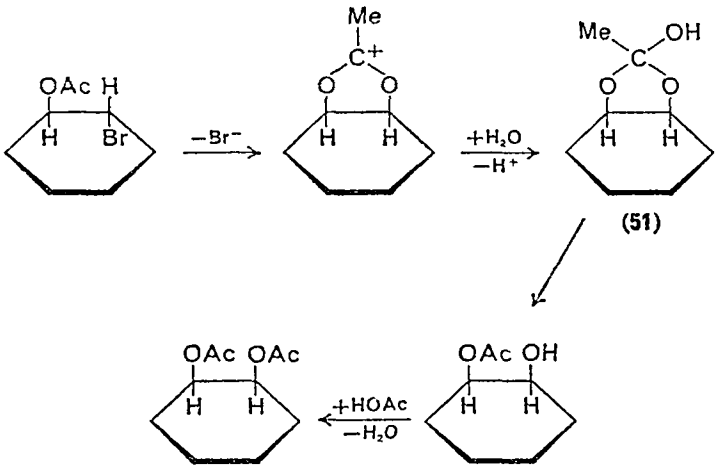
These considerations do not exhaust the ramifications of substitutions controlled by neighbouring-group participation. With certain complex neighbouring groups, the chemistry of the intermediate written for generality as **41** is such that its further reactions may not necessarily involve either of the two carbon atoms indicated in the formula. Under these circumstances, replacement may be effected with inversion of configuration



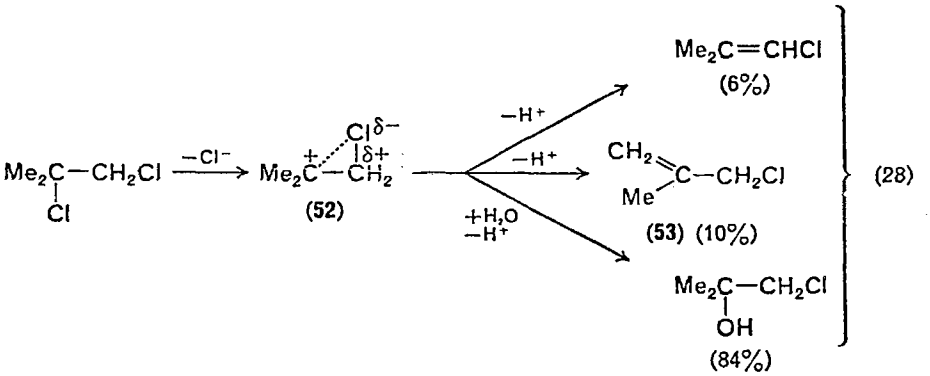
SCHEME 8. Elaborated scheme, using 'Winstein-type' intermediates, for replacements accompanied by neighbouring-group participation.

at the reaction centre, sometimes with modification of the participating group. The conversion of *trans*-2-acetoxycyclohexyl bromide into the diacetate of *cis*-cyclohexane-1,2-diol through the ortho-ester (**51**) is a well known example (sequence 27)[84]. These considerations give such reaction sequences considerable importance in stereospecific synthesis.

Neighbouring-group interaction can also modify the course of other reactions accompanying nucleophilic substitution. Thus the proportion of the isomeric products of elimination formed in the hydrolysis of 1,2-dichloro-2-methylpropane[85] is probably modified in favour of **53** through the neighbouring-group interaction indicated in **52** (sequence 28).



(27)

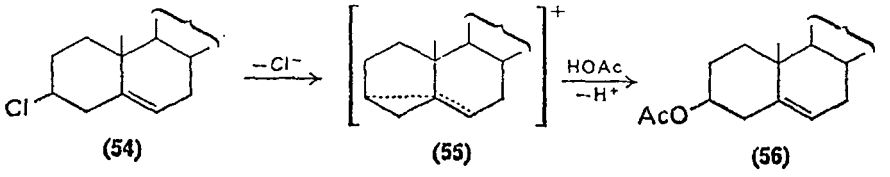


(28)

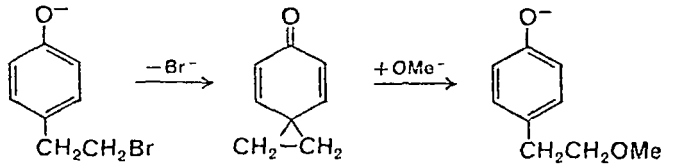
8. Unimolecular processes with participation by neighbouring carbon or hydrogen

Interaction between a neighbouring group and a carbonium ionic centre is not confined to groups bearing a lone pair of electrons. Shoppee[86] showed that the acetolysis of cholesteryl chloride (partial formula **54**) occurs with retention of configuration, whereas the saturated analogues undergo substitution with inversion of configuration. The generally accepted interpretation is that the double bond can provide electrons for the interaction indicated in **55**, and hence protect the carbonium centre at the 3-position to allow overall retention of configuration in the formation of **56**.

Aryl groups can also participate in a similar way. Baird and Winstein[87] have exemplified this by examination of a case in which the intermediate is sufficiently stable to be isolated (equation 30).

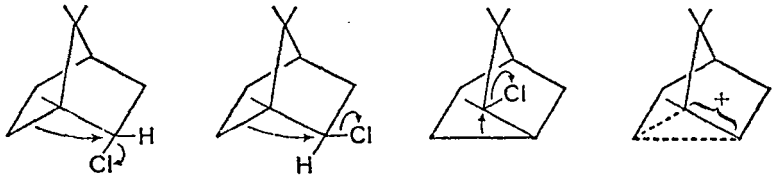


(29)



(30)

The possibility that saturated groups might similarly participate in replacement reactions was first indicated by Nevell, de Salas and Wilson[88]; see also reference 7, p. 767. We can illustrate several situations that may arise by reference to the solvolyses of camphene hydrochloride, isobornyl chloride and bornyl chloride[89]. All of these compounds give products derived from the camphene hydrate system. The first-order solvolysis of bornyl chloride (**57**) takes place at a rate which is of the same order of magnitude as that of a secondary chloride such as isopropyl chloride. The corresponding reaction of isobornyl chloride (**58**), however, is much faster, by a factor of several powers of ten. The rate of the non-rearranging solvolysis of camphene hydrochloride (**59**) is also much faster than that of its structural analogue, *t*-butyl chloride.



(57) (58) (59) (60)

The most direct interpretation of these results is that the electron movements shown in **57** have to be consecutive, for steric reasons; so this solvolysis is non-accelerated, though it gives rearranged products. The movements shown in **58**, on the other hand, can be concerted, so that an accelerated rearrangement can occur; so can those in **59**, but here the intermediate (**60**), which in its simplest form is the same for all three isomers, gives non-rearranged products.

The type of intermediate concerned in such reactions has been termed 'non-classical', 'synartetic' and 'anchimeric' by different groups of workers.

Subsequent investigation has documented many related examples and there has been much argument concerning the possible contributions of steric hindrance and steric acceleration to the rates of these reactions. Since there have been excellent summaries and assessments of the evidence[7,90] we need not do more than state that there is excellent kinetic, stereochemical, spectroscopic and isotopic-tracer evidence that bridging by alkyl groups across two alternative carbonium ionic centres can occur in stereo-electronically suitable situations. By analogy with the situation occurring with simpler carbonium ions, however, it is not surprising that the simple formulation of solvolysis through an intermediate (e.g. **60**) common to more than one starting material needs to be modified when completion of the reaction can occur before the ion has had time to relax to its equilibrium conformation.

The corresponding bridging by hydrogen accompanying the solvolysis of halides undoubtedly can occur, but the scope of this reaction can hardly be claimed to have been delineated fully. Rearrangements of isobutyl into *t*-butyl systems have long been recognized (equation 31)[91]. One of the

$$Me_2CHCH_2I \xrightarrow[HOAc]{AgOAc} Me_3COAc \qquad (31)$$

best-documented examples is the hydrolysis of 2-chloro-2-methylpropan-1-ol, which reacts unimolecularly in water to give 21% of isobutyraldehyde (equation 32). It was considered that the rearrangement of the cation **61**

$$Me_2C(Cl)CH_2OH \longrightarrow Me_2C^+CH_2OH \longrightarrow Me_2\overset{+}{C}HCHOH \longrightarrow Me_2CHCHO \qquad (32)$$

(61)

probably occurred intra-, rather than intermolecularly, since it had been shown that the analogous cation $Me_2C^+CH_2OMe$ could undergo intramolecular hydrogen-shift[92]. It may be noted that the related cation $Me_2C^+CH_2Cl$ gives only a very small proportion of rearrangement to isobutyraldehyde under analogous conditions[85]. Recently it has been shown[93] that only minor amounts of interconversion of isomeric secondary carbonium ions by hydrogen shift occur in the solvolysis of 3-bromopentane in 60% ethanol.

Hydrogen shifts are well known also in the solvolyses and rearrangements of bicyclic systems[94].

9. Electrophilically assisted processes

Electrophilic assistance to the heterolysis of the C—X bond is possible in principle for either unimolecular or bimolecular processes. For

solvolysis of halides in hydroxylic solvents, catalysis by acids has been established for alkyl fluorides, but not for chlorides, bromides or iodides. It would seem[4,95,96] that primary and secondary alkyl fluorides, when undergoing solvolysis in solvents such as aqueous ethanol, use a bimolecular mechanism. Catalysis is shown by added hydrogen fluoride, and autocatalysis by the hydrogen fluoride formed in the reaction. The transition states are probably of the type $H_2O\cdots R\cdots F\cdots H\cdots F$, and no doubt the difference between fluorides and other halides arises because of the relatively great strength of hydrogen bonds involving fluorine. It is a matter of taste whether significant covalent character should be attributed to the new bond involved in the catalytic process.

Tertiary alkyl halides show little autocatalysis, but considerable specific hydrogen-ion catalysis. Here we see a catalysed ionization, with a transition state of the form $[R\cdots F\cdots H]^+$, rather than a catalysed bimolecular replacement. This type of reaction seems to be established also for suitable arylalkyl chlorides (e.g. 1-phenylethyl chloride) undergoing exchange with chloride ions in aprotic solvents[97]. In these solvents, it seems that the hydrogen chloride molecule can act as a general acid in catalysing the exchange reaction.

Catalysis by salts of metals appears normally to be S_N1-like, with transition states of the form $[R\cdots Hal\cdots M]^+$. The most cogent argument supporting the availability of transition states of this form derives from the nature of the products; both heterogeneous silver-catalysed and homogeneous mercury-catalysed solvolysis of neopentyl halides have been shown to give rearranged products[98,99]. It is hardly likely, with such a hindered substrate, that the anion can be directly concerned in the transition state.

In the solvolyses of substituted benzhydryl chlorides in 80% acetone, evidence for the importance of ion pairs as intermediates in the reactions assisted by mercuric ions has been adduced[100]. Mercuric ions also promote racemization and halogen exchange: complicated sequences of intermediates clearly are implicated, particularly in dipolar aprotic solvents. Other studies have been made with simpler secondary substrates[101]. The reactions of various tetra-alkylammonium and silver salts with 2-octyl chloride and with 2-octyl bromide in acetonitrile, and of the latter compound with silver perchlorate in benzene, are powerfully catalysed by silver ions, and the catalytic process also requires the participation of the anion as a kinetic partner. In benzene, the role of the anion could be environmental, but acetonitrile has a relatively large dielectric constant. It seems more reasonable, then, to deduce from the kinetic form that the anion must in this solvent be involved in covalency change in the transition state. The

products are like those of an S_N1 process, being partly racemized and accompanied by products of elimination. Ingold (reference 7, p. 482) writes the rate-limiting stage of the reaction as in equation (33), the products being regarded as determined by stages still later on the reaction path.

$$X^- + R{-}Hal\cdots Ag^+X^- \xrightarrow{slow} [X^- R^+ Hal^- Ag]^+ + X^- \qquad (33)$$

The reactions of fluorides and of iodides do not seem to have been examined extensively in relation to these mechanisms, though electrophilic catalysis by silver ions of solvolyses of iodides is well recognized preparatively. A mode of electrophilic catalysis of replacement of halide which is perhaps accessible only for iodides has been examined recently by Noyes and coworkers[102,370]. The kinetic form and the effect of change in structure on the rate of exchange between iodine and substituted diphenylmethyl iodides, Ar_2CHI, in carbon tetrachloride and in hexane as solvents, indicate that the reaction can proceed through a carbonium ionic intermediate, the iodine molecule behaving as an electrophilic catalyst by assisting heterolysis as indicated in equation (34). In the solvent used for

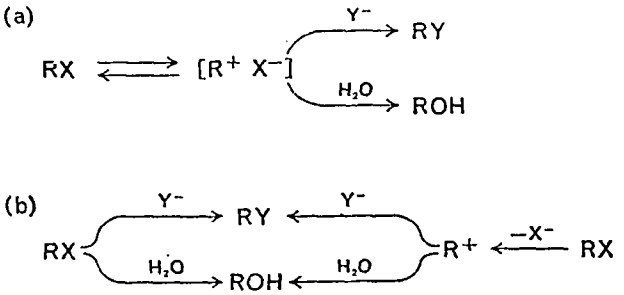
$$Ar_2CHI + I_2 \longrightarrow [Ar_2CH^+ I_3^-] \qquad (34)$$

the kinetic measurements, the intermediates and transition states must have the nature of ion pairs rather than of free ions; kinetic evidence for the participation of more than one iodine molecule was obtained also.

10. Mixed and other multi-stage reactions

We have already noted some of the controversies that have developed around the mechanisms of nucleophilic substitution. These have been particularly acute in the field of solvolytic processes: here the kinetic criterion of mechanism cannot be applied directly, since the concentration of the solvent cannot be changed without varying its properties. Such reactions have been the subject of a detailed and informative review[60]. The rather natural desire to produce a fully unifying theory has led to a recurrence from time to time of the view that nucleophilic substitutions are always bimolecular; fundamentally, this hypothesis always founders on the observation that with some substrates the reactivity is clearly not dependent on the strength of the nucleophile. The alternative view that all these reactions require both a nucleophile to displace and an electrophile to assist the departure of the leaving group[103] is excluded on similar grounds; there are many cases, for example, where if the solvent were acting as an electrophilic catalyst for heterolysis, a proton or a general acid should be more effective, and is found not to be.

Rather recently, Sneen and coworkers[71,104] have suggested that perhaps all reactions hitherto regarded as bimolecular in fact proceed through ionization to give an ion pair, which is then attacked nucleophilically. This view has been supported by claims concerning the relationship between rate and product-composition particularly in the presence of added azide ions, the substrates being substituted benzyl and secondary halides. Relationships between rate and product-composition in the presence of more than one nucleophile are, however, rather difficult to analyse; earlier, Olson and Halford[105] used such a relationship as evidence that any solvolysis of an alkyl halide is bimolecular. Kohnstam and coworkers[106] have analysed Sneen and Larsen's examples, and also their own data on the solvolysis of 4-methoxybenzyl chloride, in terms of the two alternatives shown in Scheme 9, both of which are themselves rather simplified



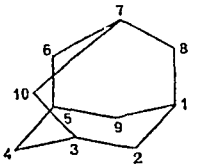
SCHEME 9. Alternative simplified reaction pathways in the 'border-line' area of solvolytic displacements.

versions of the sophisticated elaborations we have already discussed. The results establish that the rates and product-compositions can be fitted equally well by Scheme 9(b) as by Scheme 9(a).

Criteria based on this type of kinetic relationship are likely always to be ambiguous; the fundamental reason seems to be that the substrate considered to be attacked in Scheme 9(a) is isomeric with the starting material, and leads to a transition state isomeric with that under consideration for the bimolecular component of Scheme 9(b). More sophisticated mechanistic probes, however, can give a less ambiguous answer. The most cogent objections to the view that all nucleophilic substitutions involve prior ionization come from the incidence and magnitude of heavy-atom isotope effects in representative nucleophilic substitutions: these isotope effects, characteristically greater for bimolecular than for unimolecular processes, establish unequivocally the importance of the bond-breaking process in the rate-determining stages of both these reactions[18]. Similar

deductions have been made[107] from the relative rates of displacement in charged and uncharged systems such as $BrCH_2CO_2H$ and $BrCH_2CO_2^-$.

Evidence which further defines the degree of nucleophilic participation by solvent in the solvolyses of some halides in the region of the mechanistic border-line, where concurrent S_N1 and S_N2 mechanisms might be expected, has recently been obtained by Schleyer and coworkers[108]. They have examined the response of rate to change in solvent for the solvolyses of a number of secondary and tertiary halides and toluene-*p*-sulphonates, using as reference compounds those derived from the adamantane system (**62**).



(62)

For 1-adamantyl bromide, for example, solvent-participation whether in solvolysis or in elimination is precluded for steric reasons; the back face of the bridge-head carbon atom is inaccessible and strain defeats the development of a double bond at the bridge-head. Comparison with *t*-butyl bromide and with *t*-butyl chloride shows that there exists an excellent correlation between the rates of solvolyses in these tertiary systems over a solvent-range giving a rate-spread of at least five powers of ten; illustrative rate-comparisons are given in Table 12. Schleyer concluded, therefore, that

TABLE 12. First-order rate-coefficients ($10^9 k_1$ s^{-1}) for solvolyses of 1-adamantyl bromide, *t*-butyl bromide and *t*-butyl chloride at 25°C

Solvent	*t*-Butyl chloride[109]	*t*-Butyl bromide[109]	1-Adamantyl bromide[108]
40% EtOH	$1{\cdot}29 \times 10^6$	—	$1{\cdot}21 \times 10^5$
HCO_2H	$1{\cdot}1 \times 10^6$	—	$8{\cdot}25 \times 10^4$
60% EtOH	$1{\cdot}27 \times 10^5$	$3{\cdot}76 \times 10^6$	$7{\cdot}19 \times 10^3$
90% EtOH	$1{\cdot}73 \times 10^3$	$7{\cdot}14 \times 10^4$	$2{\cdot}47 \times 10$
CH_3CO_2H	$2{\cdot}13 \times 10^2$	—	2·38

the *t*-butyl compounds undergo solvolysis by a limiting S_N1 mechanism, free from any significant contributions from nucleophilic solvent-participation and rate-determining elimination. With 1-adamantyl bromide, it was noted also that the inclusion of azide ion in the solvent resulted in very little capture of this nucleophile.

Marked divergences of behaviour were noted, however, for simple secondary substrates, a result which was taken as suggesting that, in the reactions of these compounds, some degree of nucleophilic assistance was under observation. No doubt this result can be accommodated in terms of concurrent S_N1 and S_N2 processes, as in Kohnstam's treatment, with appropriate elaboration of the former mechanism when ion pairs can be implicated. In secondary systems where for steric reasons solvent participation is inhibited, limiting behaviour is observed, an example being the solvolysis of 2-adamantyl toluene-*p*-sulphonate.

Kohnstam and coworkers have used two further criteria to explore the nature of the mechanistic border-line. One of the methods employed[110] involves study of the variation of salt effects with structure. *p*-Phenoxybenzyl chloride solvolyses faster in 70% dioxan than *p*-methoxybenzyl chloride does, although both are unimolecular. In the presence of salts with anions more nucleophilic than the perchlorate anion, the rates are increased by an amount too large to be attributable to a salt effect. The relative rates for the bimolecular reaction now observed are reversed, but the catalytic rate increases with the nucleophilic power of the anion more rapidly for the compound least reactive in solvolysis. This is what would be expected if the nucleophile were contributing to the ease of reaction by covalent bonding in the transition state of the rate-determining stage of the reaction.

Kohnstam has used another line of approach by way of studies of the temperature coefficient of the enthalpy (otherwise the heat capacity) of activation, $\Delta C^{\ddagger}$. It has been found that the ratio of $\Delta C^{\ddagger} : \Delta S^{\ddagger}$ for unimolecular solvolyses in aqueous acetone is nearly independent of the nature of the substrate provided this is a halide or toluene-*p*-sulphonate, and that its value is consistently greater than that for avowedly bimolecular solvolyses under the same experimental conditions. Table 13 shows the

TABLE 13. Entropies of activation, and $\Delta C^{\ddagger} : \Delta S^{\ddagger}$ ratios, for solvolyses of 4-$YC_6H_4CH_2Cl$ in aqueous acetone at 50°C

Y:	NO_2	H	Me	*p*-$MeOC_6H_4$	PhO	MeO
$-\Delta S^{\ddagger}$, 50% acetone	23·5	22·4	15·7	—	—	—
70% acetone	—	24·0	17·5	12·8	12·0	12·0
$\Delta C^{\ddagger} : \Delta S^{\ddagger}$, 50% acetone	0·84	0·95	0·34	—	—	—
70% acetone	—	0·91	1·19	2·31	3·60	3·83

application of this criterion to the hydrolyses of 4-substituted benzyl chlorides[111].

Only the last two entries in the table show values of the ratio, $\Delta C^{\ddagger} : \Delta S^{\ddagger}$, approximating to those expected for typical S_N1 reactions (2·9 in 50%

acetone, 3·7 in 70% acetone). It was concluded that the solvolyses of the remaining compounds probably have considerable bimolecular character.

The use of this method has some difficulties: partly because of the need to determine rate-coefficients over a wide range of temperature with very great accuracy, and partly perhaps because of the difficulty of allowing for the temperature coefficient of the solvation energy and entropy of the initial state. In favourable cases, however, it leads to conclusions similar to those obtained by other methods, identifying a class of reaction in which the solvent can be attributed no covalent role in the formation of the transition state, and another class for which varying degrees of covalent participation by the solvent can be inferred.

B. Nucleophilic Replacement by Halogen at Saturated Centres

1. Halogen exchange reactions

The halide ions are well established as nucleophiles, and the general principles and mechanisms of replacement are as applicable to the formation as to the displacement of carbon–halogen bonds. In the discussion above we have covered some of the more important aspects of the former type of process, and have indicated their considerable part in the development of mechanistic theory.

One of the best known uses of halide exchange reactions and their close analogues is the preparation of iodides from chlorides, bromides or aryl sulphonates in acetone (equation 35)[112]. This reaction would proceed to an

$$R{-}X + KI \longrightarrow RI + KX\downarrow \qquad (35)$$

unfavourable equilibrium but for the precipitation of the insoluble potassium salt. The reaction was used by Conant and coworkers[113] in pioneer studies of the kinetic form and effect of structure on the rate of such reactions, but was abandoned by later investigators[11,12] because of the possible uncertainties arising from the heterogeneity of the reaction mixtures.

These exchange reactions, when carried out in homogeneous solution, go to fairly balanced equilibrium positions, despite the fairly wide variations in the carbon–halogen bond energies (C—F, 116; C—Cl, 81; C—Br, 66; C—I, 57 kcal mole^{-1}) and in the solvation energies of the individual ions (in water, F^-, 121; Cl^-, 87; Br^-, 80; I^-, 70 kcal mole^{-1})[2]. This makes it clear that the rates of the individual exchange processes must depend on the balancing of a number of opposing factors, their differences becoming small because of the partial cancellation of opposing differences[114]. For a single substrate in hydroxylic solvents, the

established[115] order of nucleophilicity for attack on carbon is $I^- > Br^- > Cl^- > F^-$. This order is partly determined by the fact that the ions have to become partly desolvated in the transition state. In acetone, a dipolar aprotic solvent, the same order of reactivity, $I^- > Br^- > Cl^-$, is found[12]. The counter-ion can be considered, however, as contributing to the solvation energy of the nucleophile by the formation of ionic aggregates, including ion pairs.

The reactivity can be treated by using Acree's 'dual theory', in which it is assumed that the solvated ions can be regarded as two species, one a reactive free ion and the other an unreactive, or much less reactive molecule or ion pair[116]. Treatments of this kind have been used for reactions in ethanol[116] and in acetone[117]. With acetone, however, the low dielectric constant introduces a number of theoretical difficulties. One is the fact that any pair of ions within a radius of ca. 13 Å should be considered to form an ion pair, so that to describe the salt in terms of the properties of two species having the limiting properties respectively of free ions and ion pairs seems inappropriate[118]. Furthermore, ion-pair dissociation constants have to be calculated from measurements of conductivity made very far from the range of concentration where the theory of electrolytes is satisfactory. By using the dual theory, however, Parker[119] obtained the orders of reactivity: $Br^- \sim I^- > Cl^-$ for reaction with MeI; $Br^- > I^- \sim Cl^-$ for reaction with MeBr and MeCl; and $Cl^- > Br^- > I^-$ for reaction with *n*-butyl-*p*-bromobenzene sulphonate. No doubt the limiting order, $F^- > Cl^- > Br^- > I^-$, the reverse of that obtaining in hydroxylic solvents, would be observed if the reactivities of the unsolvated gaseous ions could be measured, when the influence of bond-formation would not be obscured by the conflicting requirements of solvation.

It would be valuable to have measurements of the heats of solution of the relevant salts in a number of dipolar aprotic solvents; failing this, a number of workers, including Parker[118,119] and Winstein and coworkers[13,120] have emphasized the sensitivity of reaction rate to change in solvent by comparing the relative rates of displacement of iodide from methyl iodide by chloride at 25°C as follows:

Solvent:	MeOH	H_2NCHO	MeNHCHO	Me_2NCHO	Me_2CO
Relative rate:	1	12	45	$1{\cdot}2 \times 10^6$	$1{\cdot}6 \times 10^6$

Many of the preparative procedures involving the formation of alkyl fluorides by exchange with anhydrous hydrogen fluoride, or with potassium fluoride under homogeneous or heterogeneous conditions, no doubt make use of the bimolecular mechanism; the use of catalysts[121] such as $SbCl_3$

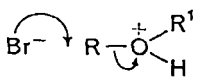
suggests the intervention also of mechanisms involving electrophilic catalysis, but mechanistic work on these reactions is lacking.

2. Reactions of ethers and of alcohols with hydrogen halides

The cleavage of ethers by hydrogen halides is analogous in mechanistic character. Both the proton and the nucleophile play a vital part in the reaction: the proton by forming an oxonium ion, so facilitating the heterolysis, and the nucleophile by attack on carbon to effect the displacement. The importance of the kinetic role played by the latter is exemplified by the course of the Zeisel reaction, which can be used for determining methoxyl groups because the methyl group is (particularly for steric reasons) very readily attacked by the powerfully nucleophilic iodide ion (equation 36). The kinetics of the cleavage of diethyl ether by hydrogen

$$MeOR^1 + HI \longrightarrow MeI + HOR^1 \text{ (not } MeOH + R^1I) \qquad (36)$$

bromide have been examined in a number of solvents, acetyl bromide being added to combine with the alcoholic product[122]. The rate was found to be proportional to the concentration of diethyl ether and to $[HBr]^2$ in toluene and some other solvents, to $[HBr]^{\frac{1}{2}}$ in chloroform and to [HBr] in acetic acid. It would seem that the bimolecular process (**63**), which in its simplest form involves attack by halide ion on the oxonium ion, can result in more than one kinetic form, depending on whether or not the nucleophile is provided by the same molecule that provides the proton.



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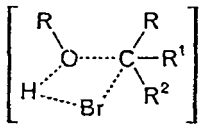


(64)

These results, and those of related studies, have led to general acceptance of the view that primary ethers are cleaved by hydrogen halides by an S_N2 attack on an oxonium ion formed in pre-equilibrium[123]. Lewis acids, such as boron trichloride, can also act as catalysts, taking over the role of the proton by co-ordination with the oxygen atom. Electron-release to the reaction centre, however, increases the importance of S_N1-like processes, so that secondary alkyl, and to a still greater extent tertiary alkyl, benzhydryl and trityl ethers tend to adopt the unimolecular mechanism[124]. Considerable interest arises in the possible part played by the S_Ni mechanism[83, 125]. In this, the transition state (**64**) would lead to replacement with retention of configuration. It has been shown that 1-phenylethyl phenyl

ether reacts with hydrogen chloride in solvents toluene, 3-pentanone and isobutyl alcohol to give the corresponding chloride with 85–90% retention of configuration, the rates and stereochemistry of the reaction being only slightly affected by the nature and dielectric constant of the solvent[126]. It was considered that the transition state was S_N1-like, but involved a rather tight ion pair; the insensitivity of rate to change in solvent probably results from opposing solvent effects on protonation and heterolysis.

Similar results have been obtained for the formation of alkyl halides from alcohols and hydrogen halides. Here the kinetic results tend to be complex, because the rates of reaction are markedly affected by the accumulating products. The influence of change in structure on the rate can be interpreted as indicating the intervention of the S_N2 mechanism for methyl alcohol and the primary alcohols, and of the S_N1 mechanism for secondary and particularly for tertiary alcohols[124]. The rate-sequences Me > Et, and *t*-Bu > *i*-Pr > *n*-Pr, seem to be well documented, in agreement with the above deductions[127,128]. As far as the stereochemistry is concerned, it has been shown that 3,7-dimethyloctanol-3 with hydrogen chloride in pentane as solvent can give either of the enantiomeric chlorides: at 25°, inversion of configuration predominated, whereas at much lower temperatures (e.g. −78°), retention was observed[129]. Arcus[130] surveyed the experimental results for the reactions of the phenyl alkyl carbinols with hydrogen bromide, and concluded that they could be interpreted sensibly in terms of competition between three mechanisms, S_N2, S_N1 and S_Ni. The last mechanism seemed to be favoured by electron-release to the reaction centre, suggesting that its transition state must have considerable carbonium ionic character.

3. Replacement of hydroxyl by halogen by the use of thionyl chloride and related reagents

Similar conclusions have been drawn from the stereochemistry of replacement of hydroxyl by halogen through the use of non-metallic acid halides. The conversion of alcohols to chlorides by the use of thionyl chloride involves the intermediate chlorosulphite, formed by nucleophilic attack on sulphur, and decomposing according to equation (37). Since

$$ROSOCl \longrightarrow RCl + SO_2 \qquad (37)$$

inversion with some racemization is observed for the first-order decompositions of secondary chlorosulphites in iso-octane as solvent, it has been presumed that the S_N1 mechanism is implicated[131]. There is evidence that the three bonds not directly concerned in the reaction have to be able to relax from tetrahedral towards trigonal geometry in the transition state,

since apocamphyl chlorosulphite (**65**), which is made fairly rigid by the bridging ring, does not decompose to give the chloride[132]. Retention of configuration in the formation of cholesteryl chloride from cholesterol[86] is taken as evidence that the configuration-holding properties of neighbouring groups characteristic of reactions proceeding by the S_N1 mechanism are revealed also in chlorinations by thionyl chloride. The holding of

(65)

configuration by the phenyl group, together with accompanying group-migration, has been established also through the stereochemistry of replacement in the 3-phenyl-2-butyl system[133].

In all of these studies, it is clear that the rate of decomposition of the chlorosulphite responds to electron-release to the reaction centre. Chloride ions catalyse the decomposition of the chlorosulphite and promote reaction by the S_N2 mechanism, with characteristic inversion of configuration[134]. Primary systems are relatively unreactive by the S_N1 mechanism; 1-butyl-1-deuteriochlorosulphite decomposes only slowly, with predominant inversion, presumably through the S_N2 route[135].

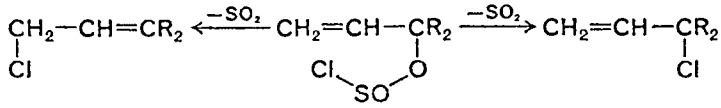
The conversions of alcohols into halides by reaction with one or other of the halides of phosphorus have generally been presumed, because of the stereochemistry of the reactions, to follow similar paths[7,136]. The stoicheiometry of typical reactions can be represented as in equations (38) and (39). General experience would suggest (reference 7, p. 535 ff.) that

$$ROH + PBr_3 \longrightarrow ROPBr_2 \longrightarrow RBr + POBr_2 \qquad (38)$$

$$ROH + PCl_5 \longrightarrow ROPCl_4 \longrightarrow RCl + POCl_3 \qquad (39)$$

retention of configuration is less often encountered with halides of phosphorus than with thionyl chloride, though retention resulting from neighbouring-group interaction is known[86]. Where retention of configuration is found in the absence of any such special structural influence, it has often been assumed that the S_Ni mechanism is under observation; examples which can be cited are the decomposition of secondary chlorosulphites in dioxan (rather than in iso-octane) as solvent[131]. Related cases occur in the reactions of allylic chlorosulphites. Here, despite the competition that can exist between the reactions depicted in equation (40), rearrangement can

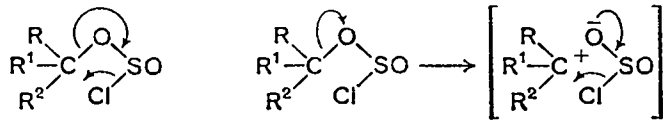
apparently become the exclusive path[57]. The circumstances which can lead to replacement with rearrangement through a six-membered transition state, rather than replacement with retention or with inversion of configuration, have been reviewed elsewhere[47,57]; the results generally support the



(40)

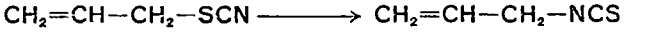
picture of these replacements that has been built up from studies of non-rearranging systems.

It seems to the writers that, although the experimental results establish the existence of unimolecular and of bimolecular reaction paths in the formation of halides from alcohols, the exact status of the S_Ni mechanism remains uncertain. Observation of predominant retention of configuration is not sufficient to characterize such a mechanism, even in the absence of neighbouring groups, since Okamoto and coworkers[64,65] have shown that the phenolysis of 1-phenylethyl chloride can give retention of configuration. Other routes to retention involving nucleophilic attack by solvent are theoretically possible and difficult to rule out in individual cases. The



(66) (67) (68)

fundamental point at issue, formulated for the decomposition of a chlorosulphite, is whether in the transition state the breaking and forming of the two bonds concerned in the reaction are concerted processes, as indicated by the arrows in **66**, or sequential, as in **67** → **68**. A reaction can be held to be 'not S_Ni' provided that it can be established that the bond broken in **67** is *completely* broken before the formation of the C—Cl bond (in **68**) begins. The commonly discussed examples in which the S_Ni mechanism might be operative provide scant definite evidence on this point. In other systems, however, a case can be made for the existence of the concerted mechanism. Thus the rate of rearrangement of allyl thiocyanate to allyl isothiocyanate (equation 41) does not respond to change in solvent[137]. Here an intramolecular concerted process may be implicated; whereas the corresponding rearrangement of cinnamyl thiocyanate ($PhCH{=}CHCH_2SCN$) is slower,



(41)

occurs without allylic shift, is sensitive to change in solvent, and is catalysed by zinc chloride. In the latter case, reaction through an ion pair is suggested. If this view is correct, the thiocyanate system provides examples of both types of mechanism within a relatively small range of structural change. It may be, therefore, that the decomposition of chlorosulphites, chlorophosphites or chlorophosphates can also provide examples from each class.

C. Nucleophilic Replacement of Halogen at Unsaturated Centres

1. The bimolecular mechanism: general considerations and the possible existence of the synchronous mechanism

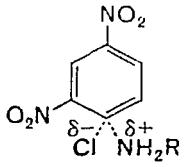
Aryl and vinyl halides are commonly considered to be rather inert to nucleophilic replacement and in this respect contrast sharply with the alkyl halides, most of which are relatively reactive. In order to realize bimolecular substitution of halogen at unsaturated carbon, some facilitating feature must be present. This may be structural; thus *p*-$O_2NC_6H_4Hal$ is much more reactive than C_6H_5Hal; $N{\equiv}CCR{=}CR^1Hal$ than $HCR{=}CR^1Hal$; and $O{=}CRHal$ than $H_2C{=}CRHal$. Other possible facilitating features include temperature, an alteration in the relative solvation of initial and transition states (as when a dipolar aprotic solvent is used instead of a hydroxylic solvent), and the use of a catalyst.

One of the tasks in investigating these reactions is to define the limits of usefulness of the various forms of facilitation since in altering conditions in favour of a bimolecular process, other competing mechanisms may also be helped and may then supervene. As an example of this, nucleophiles which are strong bases may attack at hydrogen and thus bring about replacement by an elimination–addition sequence. Other examples will be outlined later in this article.

Direct replacement of one nucleophile by another in a bimolecular reaction analogous to the S_N2 process is conceptually perhaps as simple a process as could be envisaged for these reactions at unsaturated centres. It has been known for very many years[138] that second-order kinetics characterize such reactions as that shown in equation (42). It was natural,

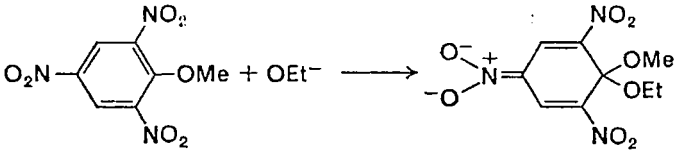
$$2,4\text{-}(O_2N)_2C_6H_3Cl + OEt^- \longrightarrow 2,4\text{-}(O_2N)_2C_6H_3OEt + Cl^- \qquad (42)$$

therefore, at an early stage in the discussion of the mechanisms of these and related reactions, for some authors[139,140] to favour strongly the simple hypothesis that the transition state is that of a direct displacement, with forming and breaking bonds both incomplete, as is illustrated in **69** for displacement by an amine. On the other hand, it had been known also[141,142] that similar compounds could react with anions to form identifiable



(69)

complexes (equation 43). It was, therefore, equally natural for other workers[143, 144] to prefer the view that the mechanism normally involves the stepwise co-ordination–heterolysis* sequence (44), in which either the



(43)

(70)

formation of the complex **71** or its breakdown could in principle be rate-determining.

$$ArX + Y^- \rightleftharpoons [ArXY]^- \rightleftharpoons ArY + X^- \qquad (44)$$

(71) (72)

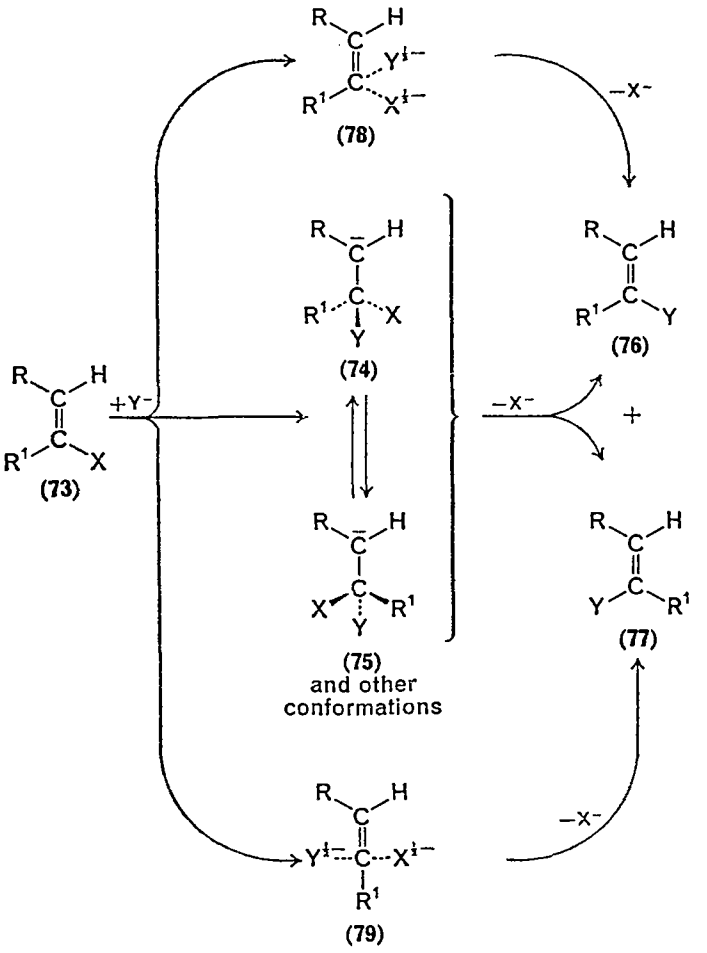
A number of important and comprehensive reviews and books[143, 145–148] are available to document the evidence that the stepwise mechanism, which has often been labelled $S_N2(Ar)$ to distinguish it from the synchronous S_N2 process, is important for nucleophilic replacements at aromatic centres and that the rate-determining transition state may indeed lie on either side of the central intermediate. In this article, our discussion of the two-stage mechanism will be limited to a consideration of a few special points of interest. The question of the existence or otherwise of the one-stage mechanism remains unresolved, though *caveats* have been entered[149] with regard to the assumption of its non-existence†.

The general characteristics of nucleophilic substitution at a vinylic centre are essentially the same as those of nucleophilic aromatic substitution,

* We here follow Ingold's[7] terminogy: co-ordination is the converse of heterolysis, just as colligation is the converse of homolysis, see also section II. C. 6.

† The logical situation of anyone who wishes to exclude mechanisms on the basis of 'simplicity' or of 'Occam's razor' (which says nothing about simplicity, despite statements[150] to the contrary), having at one time been that the synchronous should be preferred to the non-synchronous mechanism, must now be the reverse.

but the two reactions have the important difference that any long-lived intermediate formed by co-ordination with a nucleophile can now in principle undergo rotation about the original double bond and that the



SCHEME 10. Some possible reaction paths in nucleophilic replacement at vinylic centres.

product can in principle have the same geometrical configuration as the starting material or the 'inverted' configuration. Scheme 10 illustrates some of the possibilities.

In Scheme 10 we have included indication of the nature of transition states which would lead by synchronous processes to replacement with

respectively retention (**78**) or inversion (**79**) of geometric configuration. Both these possibilities were the subject of early theoretical discussion[143, 151–153].

The experimental facts relating with certainty to such reactions are available only for a limited number of cases. For the ethyl β-chlorocrotonate system (Scheme 10: R = EtOCO, R^1 = Me), it has been shown that the reactions with thiolate ions follow second-order kinetics and give mixtures of products predominantly involving retention of geometric configuration, whether **73** or its geometric isomer is the starting material. Reaction paths involving prior elimination, or prior prototropic rearrangement, have been excluded and the starting material did not rearrange during the course of reaction. The formation of both isomers from a single starting material was interpreted as indicating that the reactions were stepwise rather than synchronous. Other cases more stereospecific in character are known, however[152, 154], as has recently been reviewed by Rappoport[155], and the possibility must be recognized that these cases give the nearest known approximation to a synchronous displacement of this kind, the favoured transition state for which must be **78** (as is forced in the S_N2(Ar) reaction) rather than **79**. Studies of heavy-atom isotope effects would probably be useful in throwing light on the extent of bond-breaking in the transition states for some of these reactions.

2. The co-ordination–heterolysis sequence

We have noted already that reaction by the sequence involving co-ordination followed by heterolysis from the same centre (equation 44) has been reviewed extensively, both in connexion with aromatic[145–148] and with vinylic[155] replacements, and only a few special points will be made here.

a. Comparison of the halogens as leaving groups. One of the important lines of argument which focused attention on the existence of this mechanism was the observation that the relative leaving abilities of the halogens as nucleophiles from aromatic systems were very different from those prevailing in aliphatic systems. In the latter case, fluoride is the most difficult anion to displace, the order being F < Cl < Br < I (see section II. A. 1). In the former case, however, though chlorine, bromine and iodine are all replaced at rather similar rates, fluorine undergoes reaction much more rapidly. Table 14, taken from Miller's compilation[148], exemplifies this.

Similar ratios have been noted for the picryl halides reacting with hydroxide ions: in their reactions with water[156] the F : Cl replacement ratio can be as high as 22,000 : 1. Such results are hard to rationalize except on the basis that for the fluoro-compounds the C—F bond-breaking has not become very important in the rate-determining transition state.

This transition state probably therefore, in this case, lies to the left of the intermediate **71** (equation 44)[53]. The results do not, however, constitute a disproof of the synchronous mechanism, particularly for the heavier halogens.

As far as the writers are aware, no valid comparisons of the full range of halogens being displaced from a vinyl centre under circumstances establishing the co-ordination–heterolysis mechanism have been made, though

TABLE 14. Relative reactivities (RCl = 1) of aromatic halides in bimolecular nucleophilic replacements with sodium methoxide in methanol

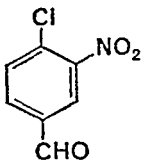
X in RX:	F	Cl	Br	I
R = C_6H_5 at 200°C	1960	1	—	—
R = 4-$O_2NC_6H_4$ at 50°C	312	1	0·85	0·36
R = 2-$O_2NC_6H_4$ at 50°C	722	1	0·70	0·33
R = 2,4-$(O_2N)_2C_6H_3$ at 0°C	890	1	0·69	0·15

reactivity-sequences in which fluorine is replaced more readily than chlorine at a vinylic centre have been reported[155,381], together with some relative rates of displacement of chlorine and bromine.

b. The identification of stable complexes. Meisenheimer's beautiful experiments[141] which established the existence of complexes between nitro-substituted aromatic compounds and anions, and showed that these complexes could be decomposed to give products of replacement, have been followed by very wide documentation of their formation, and a recent review[157] summarizes some aspects of their chemistry which seem particularly important at this time. Both anionic[141] and neutral[158,159] complexes are known and of course it will be clear from what has been said already that much information concerning the intervention of unstable substances of this general type has been derived from kinetic studies by a number of research groups. Reference to some of these has already been made; other important contributions come from work by Zollinger and coworkers[160], by Bunnett and his group[161], by Bourns and his group[162] and by Illuminati and coworkers[163]. In general, complexes are less readily obtained in bulk concentration for halides than for aromatic ethers reacting with nucleophiles.

Careful attention should be paid to the fact that in a complex organic molecule, and particularly in unsaturated compounds, there may be alternative sites for effective attachment of a reagent, that attack at only one of these sites can initiate replacement by a particular mechanism, that

the reaction under study need not necessarily involve the most thermodynamically stable of these potential intermediates, and that the establishment of the physical existence of one of these intermediates does not necessarily implicate it in the particular reaction path under study. We will meet this situation again in our discussion of electrophilic aromatic substitution; we can illustrate it in relation to nucleophilic aromatic replacements by noting that the kinetics of methanolysis of **80** and of **81** are affected by the reversible formation of complexes by attack on the carbonyl or cyano groups respectively, though the final product of reaction involves displacement of the chlorine substituent in each case[161]. General chemical intuition tells one in such a case that the reversibly formed complex is not concerned with the main reaction, but the kinetic form in itself gives no information on this point.



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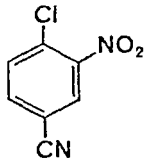


(81)

Unsubstantiated conclusions concerning the orders of stability of anionic intermediates have been reached through neglecting the above considerations. Whenever a halogen-substituted alkene reacts with a nucleophile, the possibility exists of attack on either of the two vinylic carbon atoms (e.g. equation 45). A substitution product results from only one of these

$$R_2C{=}CHF + Y^- \rightleftharpoons R_2CY{-}\bar{C}HF \rightleftharpoons R_2\bar{C}{-}CHFY \qquad (45)$$

carbanions, but to draw conclusions concerning orders of stability of such anions[165,166] has no sound basis.

c. Isotope effects. The study of isotope effects would seem to provide a potentially important method of studying nucleophilic aromatic substitution. Some information is available from this source[162], but none for the reactions of halides as far as we know, although one study of vinylic compounds has been made[167]. There have been some attempts to examine deuterium isotope effects in the reactions of secondary amines with aromatic halides[145,149]. They show that the proton-loss from nitrogen is of little importance in the rate-determining steps of the reactions investigated, of which an example is the reaction of piperidine and [1-^{2}H]-piperidine with 4-chloro-3-nitrobenzotrifluoride[159], a result which is not very revealing as to the detailed mechanism.

Recently, solvent medium isotope effects have been examined using EtOH and EtOD as solvents[167]. Results are given in Table 15. Comparison

TABLE 15. Solvent medium isotope effects in some typical nucleophilic substitutions and comparison with elimination

Substrate	Reagent	T°C	$\frac{k_2(\text{EtOD})}{k_2(\text{EtOH})}$
1-Chloro-2,4-dinitrobenzene	OEt^-	25	1·84
1-Chloro-2,4-dinitrobenzene	Pyridine	90	1·30
1-Chloro-2,2-di(*p*-nitrophenyl)-ethylene	OEt^-	25	1·83
n-Butyl chloride (S_N2)	OEt^-	70	1·34
n-Butyl chloride (*E*2)	OEt^-	70	1·71

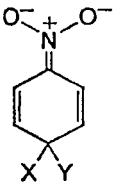
being restricted to nucleophilic substitutions by ethoxide ions, it seems that attack on unsaturated centres is subject to a larger solvent medium isotope effect than is attack on a saturated centre. Further study is needed to clarify whether this generalization is of wide utility.

d. Structural effects. It is well known that nucleophilic aromatic and vinylic replacement is powerfully accelerated by electron-withdrawing groups. One of the earliest systematic investigations was by Berliner and Monack[168], and there have been a number of more recent surveys[148,163,169] in which the Hammett equation and its modifications have been used for correlation of structural influences in this and other reactions.

We draw attention here to some points of special interest. First, nucleophilic aromatic substitution is one of the few reactions which are inhibited by electron-release and yet show the Baker–Nathan order of substituents, Me > *t*-Bu > H, thus giving a reactivity-sequence affected by *para*-substituents (R) in the order R = H > *t*-Bu > Me. The inhibition of reaction-rate by an alkyl group can be attributed to electronic effects of polarization and polarizability operating by hyperconjugation, thus giving the characteristic Baker–Nathan order of reactivity. Other interpretations, particularly those which would associate this order with steric effects on bond-contraction, break down, as has been discussed in more detail by Berliner[170].

Secondly, activation of nucleophilic aromatic substitution can be essentially inductive in nature, as is shown by the power of the NMe_3^+ substituent[143,171]. Conjugative effects can contribute also: this is shown by the fact that a *p*-nitro is considerably superior to a *p*-NMe_3^+-group in activating power for these reactions[143,171]. In valence-bond language, this implies that structures like **82** contribute to the resonance hybrid of the intermediate anion, helping to delocalize the attacking electron pair, and

related structures help to stabilize the transition state relative to the initial state. In support of this view, steric interference with the co-planarity of the



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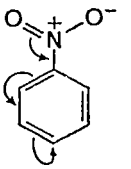


(83)

nitro-group and the aromatic ring reduces the activating power of the nitro-group[143,149,172]. There exists an interesting difference between the nitro- and the NMe_3^+-groups in relation to their effects in nucleophilic and electrophilic substitution; the nitro-group is much superior in activating the former, but the two groups have almost the same effect in deactivating the latter reaction[173]. It seems possible to the writers that this difference may indicate the operation of the form of electron-movement shown in **83**, evoked by an electron-deficient reagent as a manifestation of the molecule's polarizability. This would operate in the direction of diminishing the deactivating power of the nitro-group in electrophilic substitution, but would not be operative in nucleophilic substitution[174].

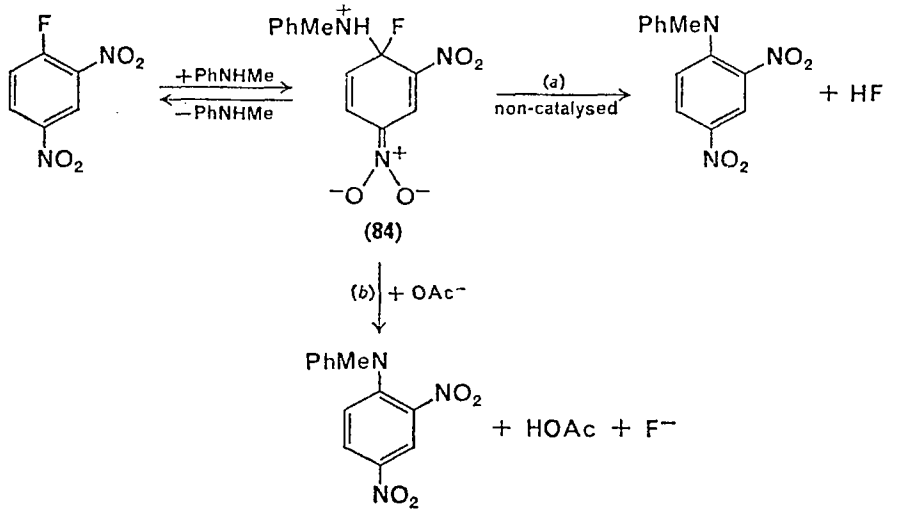
Thirdly, it should be noted that both secondary and primary steric effects can be significant in determining the rate and orientation of nucleophilic aromatic substitution[149].

Fourthly, Bunnett and his group have drawn particular attention to the fact that influence of polarizability involving London forces of attraction can become important in nucleophilic aromatic substitution, particularly when a polarizable reagent such as the benzenethiolate ion attacks adjacent to a polarizable substituent. Thus, whereas in reaction at 0°C a 2-methyl substituent inhibits the reactions of 4-nitrofluorobenzene with OH^-, with OCH_3^-, with NH_3 or with $C_5H_{10}NH$, by factors in the range 2–30, it accelerates by a factor of nearly 2 the reaction with the benzenethiolate ion[175].

e. Possible catalysis by electrophiles. In cases where the reaction of **71** (equation 44) to give products is the rate-determining stage of the reaction, catalysis by electrophiles might be observed. In particular, since separation of fluoride ion from carbon is known to be susceptible to catalysis by acids in saturated systems, the reactions of aromatic fluorides might be suitable for observation of such facilitation, which, however, would not be observed if (as has been deduced from the F : Cl leaving-group ratio), the rate-determining stage were earlier in the reaction path.

Bunnett and Nudelman[176] made a particularly careful kinetic search for acid-catalysis in the reaction of the benzenethiolate ion with 2,4-dinitrofluorobenzene, and found no evidence for such enhancement of reactivity under a number of experimental conditions. They concluded that these results supported the view that the formation of the intermediate is rate-limiting in this case, and presumably also in many related ones.

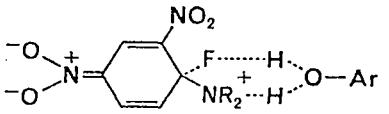
f. Examples in which the second (heterolysis) stage of the reaction can become rate-determining. For aromatic halides, therefore, it would seem that the situation in which the decomposition of the intermediate **71** (equation 44) becomes rate-determining is difficult to realize. Illustrations have been found, however, in the reactions of some amines with 2,4-dinitrofluorobenzene. Thus Bunnett and Randall[161] found that the reaction of *N*-methylaniline with 2,4-dinitrofluorobenzene is sensitive to base-catalysis, whereas reactions of the chlorine and bromine analogues are not. They suggest that the considerable accelerations observed for the fluoro-compound are consistent with reaction according to Scheme 11. Here the



SCHEME 11. Possible paths in reaction of *N*-methylaniline with 2,4-dinitrofluorobenzene in ethanol with and without added acetate ions.

non-catalysed reaction path labelled (*a*), and the general-base-catalysed path labelled (*b*), both contribute independently; in the latter, the second stage is rate-determining. More recently, Bunnett and Garst[161], whilst confirming this interpretation, have expressed doubt concerning its extension to other cases involving less spectacular catalysis. There are, however, several points about reactions of this kind which are not fully

understood[146]. In particular, it is not clear whether the stage of proton-loss from the intermediate **84** or the stage involving loss of fluoride is rate-determining. From the effects of phenols and of bifunctional catalysts such as 2-pyridone, Pietra and Vitali[177] have proposed a cyclic transition state, one representation of which would be **85**, thus indicating the further possibility that both these stages may in some cases become merged[145,177].



(85)

The corresponding situation in vinylic systems has been discussed very recently by Rappoport and Ta-Shma[382] with reference to the reactions of 1,1-dicyano-2-*p*-dimethylaminophenyl-2-halogenoethylenes, p-$Me_2NC_6H_4C(X)=C(CN)_2$ (X = F, Cl), with aromatic amines in various solvents. Variations in the kinetic form depending on the substrate, the halogen and the medium were noted, and the F : Cl rate-ratio varied also with the conditions of reaction. From the careful discussion it becomes apparent that the several reaction paths discussed above (which in some cases can be elaborated by detailed consideration of the influence of hydrogen-bonding), may all compete in suitable circumstances.

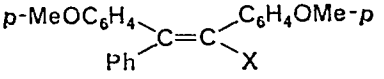
3. The unimolecular mechanism

For many years it was assumed that the unimolecular route for replacement of halogens at unsaturated centres is not available. Recent work, however, has put this reaction path on a firm basis for vinylic cations. Grob and coworkers[178] examined kinetically the solvolyses of substituted α-bromostyrenes in 80% ethanol. The reactions were shown to follow first-order kinetics, and to give a mixture of products of substitution and elimination (sequence 46). The reaction was considerably faster in a more

$$ArCBr{=}CH_2 \xrightarrow{-Br^-} ArC^+{=}CH_2 \begin{array}{l} \xrightarrow{H_2O} ArC(OH){=}CH_2 \longrightarrow ArCOCH_3 \\ \xrightarrow[-H^+]{} ArC{\equiv}CH \end{array} \qquad (46)$$

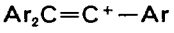
polar solvent, as is expected for the situation where charge becomes well developed in the transition state, and electron-releasing groups very powerfully increased the rate of reaction. The unimolecular mechanism of solvolysis, with the first stage of sequence (46) rate-determining, was proposed to account for these results, and it has been generally accepted[155].

More recent evidence relating to this mechanism has come from study of the effect of change in the leaving group. Rappoport and Gal[179] have shown for the reactions of trianisylvinyl halides in 80% ethanol at 120°C, the rate ratio $k_{Br}:k_{Cl} = 58$, a result which supports reaction by the unimolecular mechanism. Further details concerning the intermediate stages have been given by Rappoport and Apeloig[180]. The 1,2-dianisyl-2-phenylvinyl halides (**86**; X = Cl, Br) and their geometric isomers on



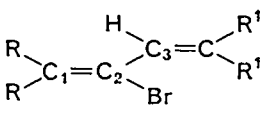
(86)

solvolysis with and without added nucleophilic anions in a variety of solvents give almost indiscriminate formation of mixtures of geometrically isomeric products. This makes it almost certain that the product-forming intermediate **87** is linear, rather than bent. A further important feature,



(87)

which throws light on the geometry not only of the product-forming intermediate but also of the transition state, has been revealed by the work of Grob and coworkers[181]. They have examined the solvolyses of substituted butadienes (e.g. $CH_2{=}CBr{-}CMe{=}CHMe$ and more highly C-methylated derivatives) in 80% ethanol. The reactions are not affected by added triethylamine; they respond in rate to increase in the ionizing power of the solvent and to increase in electron release to the unsaturated system as would be expected for a unimolecular reaction. The substituted 2-bromo-1,3-cyclohexadienes, however, do not solvolyse under the same conditions. This result is very strong evidence that the attainment of the rate-determining transition state by heterolysis from **88** requires a considerable approach towards linearity of the $C_1{-}C_2{-}C_3$ system, as is possible in the reactions of substituted butadienes but not in those of the cyclic system of **89**. This



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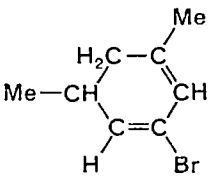
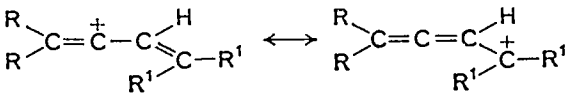


(89)

geometry allows contribution of structure **91** to the resonance hybrid structure of the cation (**90**↔**91**). Reaction is thus facilitated, and in the

open-chain substituted butadienes the replacement giving the normal products (alkenynes and α,β-unsaturated ketones) is accompanied by the formation of the allenic products of rearrangement.



(90) (91)

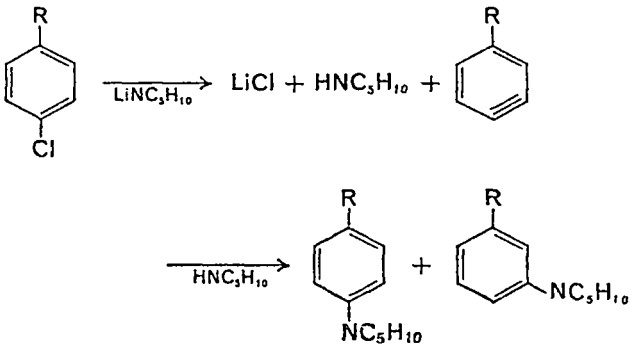
Bergman and coworkers[182] have investigated the properties of systems in which a cyclopropyl group is attached to an olefinic centre with special reference to the solvolyses of the *cis*- and *trans*-isomers of 1-cyclopropyl-1 iodoprop-1-ene in acetic acid. Each isomer gives substantially the same mixture of products of substitution, elimination and rearrangement to cyclobutenyl and other products. From this result it would appear that a vinylic cation is a common intermediate in the reaction; details of the reaction paths were considered, including the possibility that ion pairs or ion-molecule complexes can be concerned as intermediates.

Other examples of rearrangements have been reported accompanying solvolyses of substituted vinyl trifluoromethanesulphonates[183]. Further cases are known[184] in which allenic halides undergo solvolysis by a reaction path which is probably unimolecular in character. The various criteria that have been used to distinguish the unimolecular mechanism of replacement from the elimination–addition and addition–elimination sequences considered in subsequent sections have been surveyed by Rappoport, Bässler and Hanack[185], who emphasize how important is the kinetic criterion and particularly the dependence of the rate on the acidity or basicity of the medium.

4. Elimination–addition sequences

Competing with the mechanisms already discussed, particularly for reactions in sufficiently basic media, are those processes in which elimination to give a more highly unsaturated compound is followed by addition to regenerate the original degree of formal unsaturation. Such reactions are not very commonly encountered in saturated systems, since the product of elimination is usually more stable than any possible product of addition, but, since nucleophilic additions to triple bonds are relatively easy, they are not uncommon at unsaturated centres. The reactions of aryl halides with strong bases to give benzynes and hence products of substitution (sequence 47) have been reviewed extensively[148,186,303], and we need not give details here, except to note that aromatic fluorides, chlorides, bromides and

iodides all react at similar rates (e.g. with lithium piperidide in ether at 20°C). The fact that the back-addition can reverse the position of the



(47)

substituent provides one criterion for reaction by this mechanism. Substituent effects in these additions have been discussed by various groups[187–189].

An equally comprehensive account of the availability of the elimination–addition route in replacements at vinylic centres has been given by Rappoport[155] and discussions of the availability of the competing possibilities will be found in a number of the papers already cited[153,154,185]. In certain cases, where the potentially intermediate acetylene is stable under the conditions of elimination, the characteristics of the elimination stage have been examined kinetically. For the 1,1-diphenyl-2-haloethylenes reacting with potassium *t*-butoxide in *t*-butanol at 95°C, the order of reactivity Br > I > Cl, was observed[190] and rearrangement of the vinyl anion (**92**) accompanied the final stage of the dehydrohalogenation, which can be represented as in sequence (48). Various forms of elimination and rearrangement can characterize reaction by this mechanism[155].

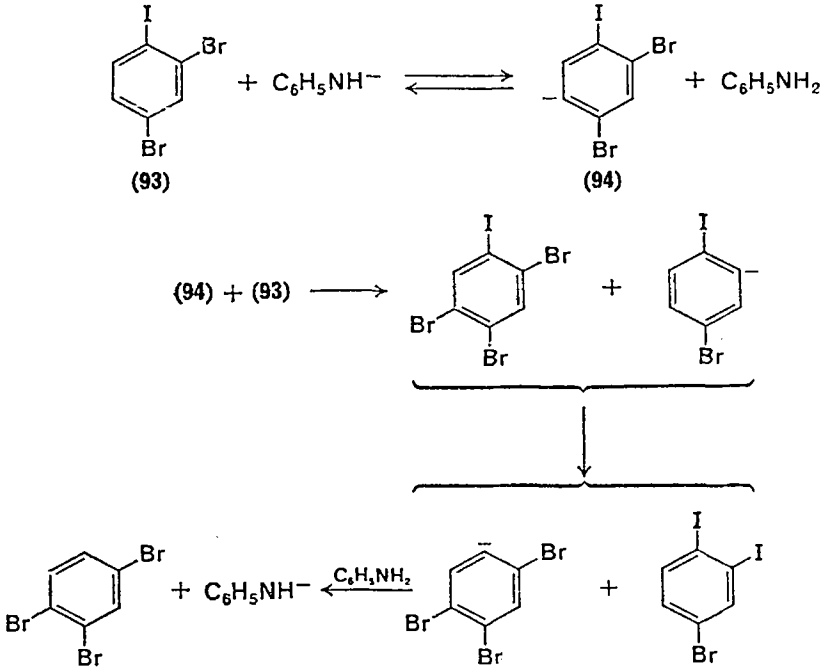
$$Ph_2C{=}CHX \underset{-H^+}{\overset{t\text{-BuOK}}{\rightleftharpoons}} Ph_2C{=}\bar{C}X \xrightarrow{-X^-} PhC{\equiv}CPh \qquad (48)$$

(92)

5. Replacements and rearrangements involving nucleophilic attack on halogen

Some polyhalogenobenzenes have been shown by Bunnett and coworkers[191–193] to undergo base-catalysed isomerization and disproportionation by yet another mechanism which involves nucleophilic attack by a suitably substituted phenyl anion on a phenyl-bound halogen, as in Scheme 12. The possibility of formation of an anionic centre adjacent to a halogen seems critical for the realization of reaction by this mechanism. From a

formal point of view, the replacement occurring in this reaction (e.g. in the formation of 1-bromo-3,4-di-iodobenzene from 1,3-dibromo-4-iodobenzene) is an electrophilic replacement at carbon.



SCHEME 12. Reaction path in the rearrangement and disproportionation of 1-iodo-2,4-dibromobenzene.

6. Replacements and rearrangements involving addition–elimination sequences

We define an *addition* reaction as one in which a double bond has become saturated, or a triple bond converted to a double bond, during the course of reaction. This definition is consistent with organic terminology. Distinction is therefore made from the co-ordination stage of a co-ordination–heterolysis sequence, which is not regarded as an addition, despite the usage (which we regard as confusing) adopted by some writers[155].

Addition–elimination sequences are not normally adopted for nucleophilic reactions of benzenoid systems, but they can be adopted for replacements involving a wide variety of other unsaturated compounds. Reactions of this kind involving vinylic centres have been reviewed by Rappoport[155], and can have ramified implications. Here we shall discuss only a few special topics; it should be noted generally that either electrophilic or nucleophilic additions could initiate such a sequence, that either

the electrophilic or the nucleophilic stage of the addition could be rate-determining, as could either of the two possible stages of the final elimination.

The difficulties of distinguishing the possibilities, particularly where the kinetics of the reaction are the main source of information, have been very cogently pointed out by Silversmith and Smith[194]. Thus in the reaction of 1,1-diphenyl-2-fluoroethylene with ethoxide ions in ethanol to give 1,1-diphenyl-2-ethoxyethylene, the observed second-order kinetic form is equally consistent with the intermediacy of the carbanion $Ph_2\bar{C}$—CH(OEt)F, or of the adduct Ph_2CH—CH(OEt)F. In reviewing the ionic reactions of fluoro-olefins, Chambers and Mobbs[195] noted that such alternative routes existed generally, and that in many cases the evidence does not yet allow proper distinction between them. Some authors have preferred for particular examples to postulate the carbanionic route[196,197] but the structures of the products may sometimes be more convincingly explained in terms of intermediate adducts which eliminate hydrogen fluoride[198]. Neither kinetic measurements nor studies of product structures and ratios are likely, taken separately, to give decisive evidence as to which of these alternative routes is under observation. The direct detection of the relevant intermediates by physical means is sometimes helpful, and an example of this kind (sequence 49) has recently been characterized[199] by ^1H n.m.r. spectroscopy of the reacting mixture.

$$\begin{aligned} PhCOCBr{=}CHMe &\longrightarrow PhCOCH(Br)CH(N_3)Me \\ &\longrightarrow PhCOCH(N_3)CH(N_3)Me \longrightarrow PhCOC(N_3){=}CHMe \end{aligned} \qquad (49)$$

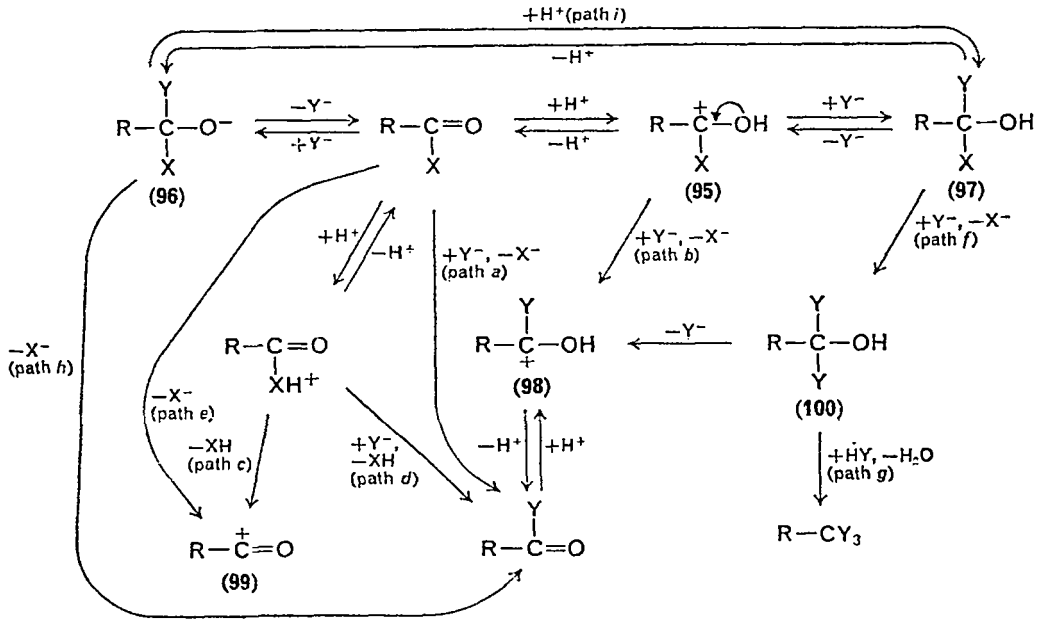
The direct conversion of the unsaturated bromide to the corresponding azide was considered also to contribute to the reaction. It should be remembered in any such case that again this type of evidence alone is not necessarily compelling or conclusive, since the supposed intermediate may merely represent a temporary diversion of the starting material, and may be isolatable from the reaction mixture but may give the final product only by first reverting to starting material or to some common alternative intermediate (see also section III. A. 3. e).

7. Replacements of halogen in carbonyl halides

a. General considerations. Carbonyl halides are known to be generally reactive in nucleophilic displacements, being extensively used as acylating agents. Several good reviews[200,201] consider the main reactions of this kind which they undergo. Just as with vinyl halides, mechanisms initiated by

co-ordination, rather than by displacement, are more important than with saturated compounds, as would be expected with triligant carbon, and this feature has indeed become even more pronounced, for two reasons: first, electrophilic attack on oxygen is rapid, though reversible, and secondly, nucleophilic addition is favoured by the polarization of the $\rangle C{=}O$ bond towards the formal structure $\rangle C^{+}{-}O^{-}$.

Some of the various ways in which a carbonyl halide might react to give products of nucleophilic replacement are set out in Scheme 13. We might



SCHEME 13. Some possible routes leading to displacement in acyl halides.

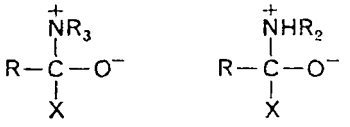
expect that bimolecular nucleophilic replacement (path *a*) would be more rapid than with saturated halides[202], both because of the polarization indicated and because the attacked carbon atom must be less congested. Attachment of an electrophile (a proton or a Lewis acid) to the oxygen atom, as in **95**, would be expected to make the carbonyl carbon atom even more prone to displacement (path *b*). Alternatively, the electrophile might attack halogen, and then would catalyse the loss of halide ion, either in a unimolecular or in a bimolecular process (paths *c* and *d*). Again, with suitable structures direct ionization to form the acylium ion (path *e*) might become available.

If, on the other hand, addition occurred to saturate the carbonyl double bond, we obtain such an intermediate as **97**, and the possible intervention of compounds of this type introduces some special features in the reaction. Such compounds, whether formed by initial nucleophilic or electrophilic attack, are in general very labile. Their high reactivity in S_N1 reactions, which lead first to the hydroxy-substituted carbonium ion **95**, comes about because the transition state leading from **97** to this ion is enormously stabilized by electron-release from the hydroxyl group. This is shown for **95** by the curved arrow in the formula, then representing the limiting case when the heterolysis is complete. The extent of rate-enhancement arising from this electron-delocalization in simple halides of analogous structure (e.g. $MeO—CH_2Cl$) is known[203] to be of the order of 10^{14}; it accounts, among other things, for the fact that the glycosyl halides are chemically rather similar to the acyl halides*.

Furthermore, the saturated adduct **97** may have available to it paths for reaction with nucleophiles other than S_N1 heterolysis. Thus, its reactivity by a bimolecular process (path *f*) is considerably enhanced in rate as compared with saturated compounds not having as powerful an electron-releasing group on the attacked centre[203], and in the presence of Lewis acids, routes involving the hydroxyl group itself may become important, especially S_Ni processes, as in the final stages of path *g*.

A further set of routes becomes available if nucleophilic attack on the acyl halide precedes attachment of the proton. This can lead through the tetraligant species **96** either directly to product (path *h*) or to the adduct **97** (path *i*).

The nucleophile, which we have depicted in Scheme 13 as an anion Y^-, may equally be neutral, and then such an intermediate as **96** will be a zwitterion, as in **101** (below) when a tertiary amine is concerned. When such an intermediate has an exchangeable proton, as in **102** for reaction with a



(101) **(102)**

secondary amine, further possibilities involving proton-migration or loss at an intermediate stage in the reaction path can become significant and

* Replacement of halogens in the glycosyl halides is not dealt with in this article but it has many features of general mechanistic interest. A valuable review has been given by Capon[204].

examples have been given[205] through comparative studies of isotope effects in catalysed and uncatalysed reactions. With such a ramification of possibilities to be considered, it is not too surprising that many ambiguities remain as to the paths adopted even in some cases which have been studied extensively. In the following sections we shall try to indicate the extent to which the possibilities have been identified.

b. Second-order processes involving direct displacement (path a) or co-ordination–heterolysis (path h). Conant and coworkers[206] studied the kinetics of the reactions of a number of organic chlorides with potassium iodide in acetone. The reactions were uniformly of the second order, and for saturated halides would generally be considered to be typical examples of reactions by the S_N2 mechanism. Benzoyl chloride was included in these comparisons and the relative reactivities were:

PhCOCl, 700 $PhCH_2Cl$, 197 *n*-BuCl, 1

This reaction of benzoyl chloride may well be an example of the S_N2 mechanism. Bunton and Lewis[207] have mentioned that the exchange of labelled chloride between $Li^{36}Cl$ and 2,4,6-trimethylbenzoyl chloride in dry acetone is much slower than that of benzoyl chloride, as would be expected for a bimolecular reaction subject to steric hindrance. The results for the second-order reactions of morpholine with benzoyl fluoride, chloride, bromide and iodide[208] can be interpreted similarly. Here the relative reactivities were as shown in Table 16.

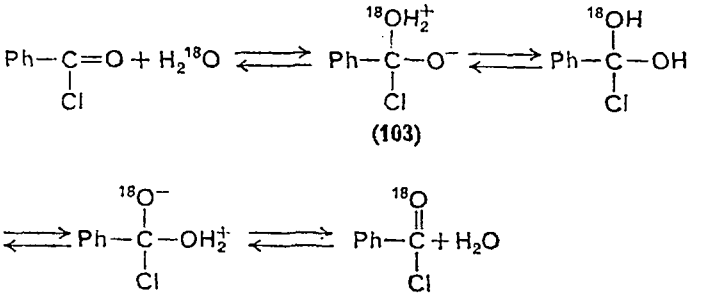
TABLE 16. Relative reactivities of benzoyl halides with morpholine in cyclohexane at 25°C

Compound:	PhCOF	PhCOCl	PhCOBr	PhCOI
Relative rate of second-order reaction	1	2800	71,000	254,000

This reaction clearly shows the operation of a large 'element effect', with a considerable contribution from bond-breaking in the transition state for the displacement, as is found also in S_N2 reactions (section II. A. 1) but is by no means typical of displacements from aromatic systems (section II. C. 2). It would be natural, therefore, to presume that the S_N2 mechanism is under observation. Bender and Jones[208], however, prefer to interpret the results in terms of the co-ordination–heterolysis sequence, and ascribe the large 'element effect' to variation of the partitioning of the intermediate, which here would have the form **102**. Distinction between paths *a* and *h* (Scheme 13) does not, however, seem to be clearly based on

experiment in this case, the degree of uncertainty being even greater than in the case of the less activated aryl halides.

Study of reactions of this kind in solvents containing water, whether with or without other nucleophiles, indicates several trends of mechanistic significance. First, the 'element effect', as manifested by the relative ease of displacement of fluoride and chloride, becomes less. Thus acetyl fluoride in water hydrolyses less rapidly than acetyl chloride by a factor[209] of only 47 (cf. 2800 for the related comparison given in Table 16). This result is consistent with the view that the reaction is now of the two-stage variety and some evidence for this has been obtained from experiments in which isotopically labelled solvent is used as a tracer. No exchange between ^{18}O-labelled water and the starting material was detected in the course of neutral or acid-hydrolysis of 4-substituted 2,6-dimethylbenzoyl chlorides in 99% acetonitrile[210], but, in the hydrolyses of benzoyl chloride and various derivatives in mixtures of dioxan and water[211], exchange of ^{18}O from the solvent was observed, and increased with the water content of the medium. Furthermore, 2,4,6-trimethylbenzoyl chloride was more rapidly attacked under these conditions than was benzoyl chloride. These results strongly suggest that an intermediate is formed reversibly, thus partially introducing labelled oxygen through a sequence such as sequence (50); the isotopic replacement must be established at a rate similar to those of the processes



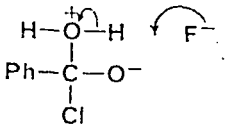
(103)

(50)

leading to hydrolysis. Acid-catalysis could facilitate the proton-transfers within this sequence by further protonation of the tetrahedral intermediate.

It has been noted also[209] that the hydrolysis of acetyl fluoride by this type of mechanism may be catalysed by bases, including fluoride ion, which probably act by helping to remove the proton from the incoming water, as depicted in **104**. Whether this catalytic action is synchronous with or subsequent to the nucleophilic attack has not been made certain; tentatively, we may take this result as exemplifying the theoretical possibility discussed in relation to structure **102**. Related mechanistic complications have been noted for nucleophilic aromatic substitution in section II. C. 2. f. That this

type of route is not always operative, however, is established by the observation of an inverse deuterium isotope effect, $k_2^{ArND_2} : k_2^{ArNH_2} = 1{\cdot}17$, in the second-order reaction of benzoyl chloride with aniline in benzene as solvent[212].



(104)

Fry[18] has recently discussed a study of chlorine isotope effects in the hydrolyses of *p*-substituted benzoyl chlorides, $p\text{-}RC_6H_4COCl$, in 50% acetone. With R = MeO, Me, H, Cl and O_2N, the values of $k(^{35}Cl) : k(^{37}Cl)$ were 1·0089, 1·0085, 1·0082, 1·0067 and 1·0051 respectively; the accuracy was assessed in each case as $\pm 0{\cdot}0004$. The magnitudes of these isotope effects show that in each case the breaking of the C—Cl bond plays an important part in the formation of the transition state, as in the reactions of related benzyl halides discussed in section II. A. The fact that there is a marked change in the magnitude of the isotope effect with change in the substituent, R, suggests the possibility of reaction by more than one mechanism. Possibilities are S_N2 (path *a*) and S_N1 (path *e*), but Fry clearly notes[18] that addition–elimination sequences (e.g. via **97**) also deserve consideration.

c. First-order processes (*Scheme* 13, *routes* e *and* c). A number of other investigations of the hydrolyses of acyl halides in aqueous solvents, and of the accompanying reactions with nucleophiles, have established the general applicability of the second-order mechanism under conditions in which a co-ordination–heterolysis sequence is probable[213–217]. But these studies and other work[210] show clearly a second trend, becoming particularly apparent in solvents of high ionizing power, namely towards the incursion of a mechanism in which the rate has become independent of the concentration of the nucleophile. Further kinetic evidence has been adduced from the effects of substituents on the rate of reaction, and from the salt-effects, including the effects of halide ions common with those derived from the acyl halide undergoing replacement. These experiments give evidence supporting the existence of a unimolecular mechanism for these replacements. It may be presumed that this often involves reaction through the acylium ion **99** (Scheme 13), though it is difficult to exclude that a hydrated or otherwise solvated form of this ion is concerned[216,217].

A number of workers[209,210,216,218] have reported electrophilic catalyses, not only with general acids such as hydrogen fluoride, but also with

protons[215,216,218]. Under similar conditions, acyl chlorides are much less susceptible to acid-catalysis than are acyl fluorides. If acid-catalysis involved protonation on oxygen, there seems no special reason why acyl chlorides should not behave like the corresponding fluorides. It was for this reason that Bender[200] and Satchell[216] attribute catalysis to protonation on halogen. This could lead rather naturally to the acylium cation **99** (path *c*), but the dependence of the rate of reaction on the stoicheiometric concentration of H^+ rather than on the acidity function, h_0, as has been noted for a number of acyl fluorides[216], suggests the involvement of the nucleophile (here a component of the solvent) in the rate-determining stage of the reaction.

Many Friedel–Crafts reactions with acyl halides come into the category of nucleophilic displacements of halogens proceeding through acylium ions formed under catalysis by Lewis acids. There are a number of good reviews[219] of these reactions, and we do not treat them specifically in this article.

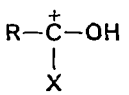
d. Reactions through adducts (*paths* f, i). Evidence that displacements of halogen can be forced through routes involving addition is mostly preparative in character. Many years ago, Hübner and Müller[220] showed that acetyl chloride reacts with phosphorus pentachloride to give first trichloroacetyl chloride and then hexachloroethane (sequence 51). Exactly

$$CH_3COCl \xrightarrow{PCl_5} CCl_3COCl \xrightarrow{PCl_5} CCl_3{-}CCl_3 \qquad (51)$$

what intermediate stages are involved is, of course, uncertain; but the possible route via $CCl_3{-}CCl_2(OPCl_4)$ is the analogue of path *g* (Scheme 13). A similar route could be concerned in the conversion of acyl chlorides and fluorides into trifluoromethyl compounds by the use of sulphur tetrafluoride (sequence 52)[221].

$$C_6H_5COCl \xrightarrow{SF_4,\ HF} m\text{-}Cl{-}C_6H_4{-}CF_3 \qquad (52)$$

e. Reactions through the halogenohydroxycarbonium ion (**95**, *Scheme 13*). It will be apparent from the above sections that mechanistic documentation of reaction paths in which the ion



(**95**) can be established to be a key intermediate has proved difficult; most of the acid-catalysed displacements appear to proceed by way of the alternative site of protonation, and the base-catalysed reactions can start by

way of the anionic intermediate **96**, which has a natural route (path *h*) directly to the product, but by protonation gives **97** (path *i*). It is by no means impossible that the chlorohydroxycarbonium ion is sometimes involved, perhaps through the sequence via **96**, **97** leading to **95**, since it potentially provides such a rapid means of exchanging nucleophiles at the carbonyl centre. It is not known whether direct displacement on this ion (route *b*) rather than indirect displacement via adducts (path *f*) can be significant.

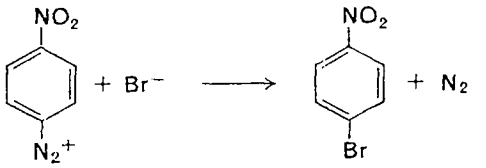
D. Nucleophilic Replacement by Halogen at Unsaturated Centres

1. Second-order processes

Although there are some well-known preparative methods for nucleophilic introduction of halogen at unsaturated centres, there have been few mechanistic studies, and most of these apply to replacement in aromatic systems. In principle, introduction of nucleophilic halogen should be possible by most of the mechanisms available for other nucleophiles. No doubt the most generally available route involves second-order attack by halide ions on some suitably activated substrate. The reactions of this kind noted below probably involve co-ordination–heterolysis sequences, rather than synchronous one-stage reactions, but little definite evidence on this point is available.

Examples of reactions which from the conditions under which they proceed are probably second-order include the activated exchange reactions between α-halogenopyridines and potassium fluoride in dimethyl sulphone or dimethyl sulphoxide (equation 53)[222], and the second-order displacement of nitrogen by bromide ion from activated diazonium ions, studied kinetically by Lewis and coworkers[223] (equation 54).

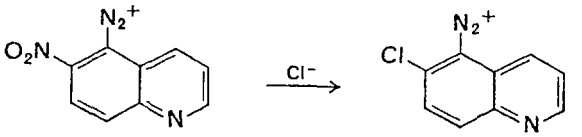
(53)



(64)

The latter reaction probably has a number of preparative counterparts[224], and situations exist in which the diazonium substituent acts as an activating

group, promoting replacements of other substituents by a nucleophilic process (equations 55, 56)[143, 225, 226].



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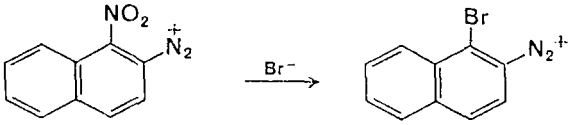


(56)

2. Routes involving aryl cations

There has been considerable mechanistic discussion of the various other reactions of diazonium cations through which nucleophilic halogen can be introduced into an aromatic nucleus. It now seems to be agreed generally that replacements under the usual conditions of the Sandmeyer reaction usually involve free radicals, since products obviously derived from the aryl radical can be detected in the products[227]. The radical-producing process is believed to be that shown in equation (57). Uncatalysed replace-

$$ArN_2^+ + CuCl_2^- \longrightarrow Ar^\bullet + N_2 + CuCl_2 \qquad (57)$$

ments in aqueous solution are, however, thought to be heterolytic and a recent review is given by Chapman[228]. The solvolytic reactions leading to phenols have generally been regarded[229, 230] as initiated by unimolecular loss of nitrogen to give the aryl cation. This conclusion has been based on the effects of substituents on the rates of reaction, and on the relatively small influence of nucleophiles on the rates and on the products[231]. Lewis and coworkers have made extensive studies of kinetics and products of relatively activated diazonium cations in the presence and absence of added anions. Their earlier conclusions[232] have recently been modified[233]; they now consider that attack by nucleophiles on these diazonium cations forms part of the rate-determining step, so that the reactions are all formally bimolecular, but that the transition states are very like the aryl cation, nucleophiles being very unselective in their behaviour. Many of the small kinetic effects on the rate of the reaction are to be interpreted as salt effects. The present reviewers think that it is better to describe these reactions as S_N1 in character and believe that the minor, relatively indiscriminating, influences of salts on product-composition result from the sort of complications that beset all reactions involving the solvolyses of carbonium ions (cf. section II. A. 5).

It is by no means clear why the uncatalysed replacement of the diazonium group by nucleophiles is so much more satisfactory for the preparation of iodides and cyanides than for other derivatives. The mechanisms are usually depicted as involving aryl cations. For iodides, it appears[234] that unidentified oxidative processes produce iodine, and that in some cases the subsequent reaction to form aryl iodide occurs in the only slightly soluble, and therefore precipitated, aryl diazonium tri-iodide.

The Balz–Schiemann reaction[235] involves the conversion of a diazonium tetrafluoroborate into the corresponding aryl fluoride. Customarily, these reactions are carried out by heating the solid, either alone or suspended in an inert solvent. It has been shown for at least one representative reaction, however[236], that a similar product mixture results when the reaction is carried out in homogeneous solution. The reactions are believed to involve relatively free aryl cations, produced as is shown in sequence (58). Evidence

$$ArN_2^+BF_4^- \xrightarrow{-N_2} Ar^+ + BF_4^- \longrightarrow ArF + BF_3 \qquad (58)$$

for this route comes from experiments[236,237] which show that such reactions when carried out in substituted aromatic solvents give as by-products the biaryl derivatives expected for electrophilic aromatic substitution involving an aryl cation, rather than those which would be expected if an aryl radical were being trapped by the solvent. Further support comes from kinetic experiments[238], which show, for example, that the kinetics of decomposition of *N*,*N*-dicyclohexyl benzamido-*o*-diazonium tetrafluoroborates in acetic acid or in methanol are not affected by radical-chain inhibitors. Olah and Tolgyesi[239] have extended the conclusions derivable from product analyses by studying the decomposition of other diazonium salts, including diazonium tetrachloroborates and tetrabromoborates. Reactions were carried out by heating suspensions of the salts in ligroin or in aromatic solvents. Some results are summarized in Table 17.

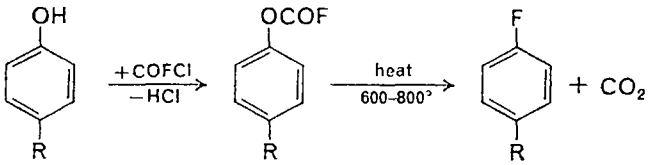
TABLE 17. Products of decomposition of diazonium salts suspended in fluorobenzene

Diazonium salt	T (°C)	Time (h)	Main product	Fluorobiphenyls (% of biphenyl fraction)		
				o	*m*	*p*
$PhN_2^+Cl^-$	25	8	PhCl	26	47	27
$PhN_2^+BF_4^-$	85	48	PhF	45	—	55
$PhN_2^+BCl_4^-$	75	6	PhCl	42	1	57
$PhN_2^+BBr_4^-$	85	16	PhBr	62	—	38

The results show that all these diazonium tetrahaloborates decompose to give isomer-ratios typical of an aromatic substitution; in contrast, the diazonium chloride is believed to decompose by a process involving free radicals, as is witnessed by the very different isomer-distribution in the fluorobiphenyls. Further discussion of the Baltz–Schiemann reaction is given by Suschitzky[240].

3. S_Ni reactions

Fluorides can be prepared also from alcohols or thiols by a reaction path (sequence 59) which has been considered[241] to be S_Ni in character. Reaction conditions involve high temperatures and, for best yields, a platinum catalyst. Replacement occurs without the production of products substituted in other positions, so it seems that free radicals are not implicated.



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III. ELECTROPHILIC REPLACEMENTS

A. Electrophilic Replacement by Halogen at Unsaturated Centres

1. Introduction

Halogenation of aromatic compounds is a well-known reaction of organic chemistry and is met at an early stage of the study of the subject, particularly in the context of the special properties of aromatic systems. Geissman's excellent textbook, for example, (*Principles of Organic Chemistry*, 2nd ed., Freeman, 1962, p. 513) states: 'The most striking differences between aromatic and aliphatic compounds are found in their substitution reactions ... . The substitution of a hydrogen atom by a halogen atom, for example, can be brought about in the case of an aliphatic hydrocarbon, and in its simplest form can be represented by the expression

$$RH + Br_2 \longrightarrow RBr + HBr \qquad (60)$$

For the case of an aromatic hydrocarbon (benzene), the reaction is:

$$C_6H_6 + Br_2 \longrightarrow C_6H_5Br + HBr \qquad (61)$$

These reactions, which appear to be similar in type, are quite different in the mechanism by which they occur ... . Some of the characteristics of the

halogenation of paraffin hydrocarbons ... may be contrasted with the related substitution of aromatic compounds.'

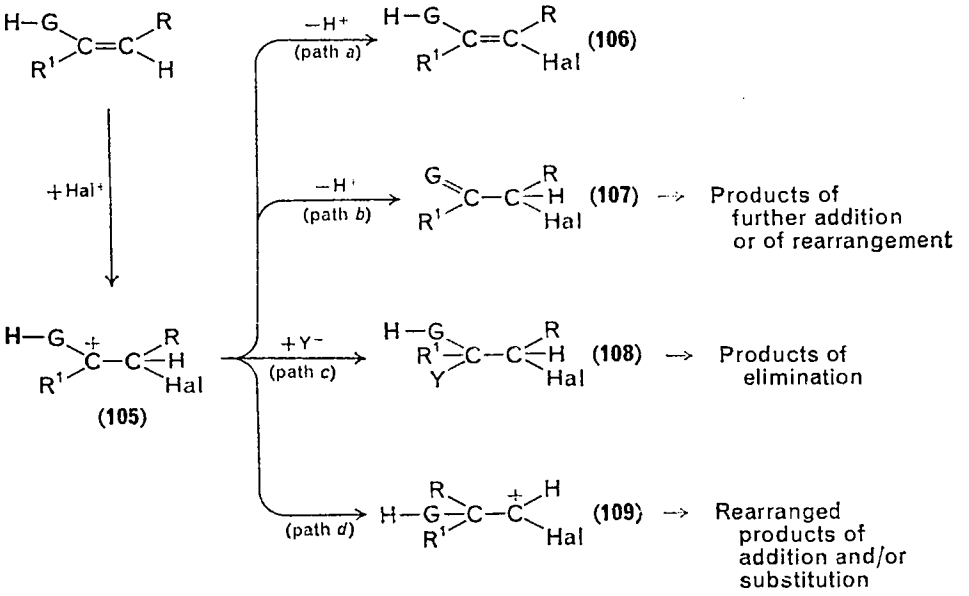
No exception need be taken to such statements, nor to the contrast on the one hand between free-radical halogenations of saturated hydrocarbons and the polar halogenations of derivatives of benzene, and on the other between additions of halogens to aliphatic unsaturated hydrocarbons and substitutions by halogens in aromatic compounds. The emphasis conveyed by these contrasts, however, becomes more difficult to justify when organic chemistry is considered more widely. The destructive fluorinations of aromatic compounds, for example, almost certainly involve free radicals, though they occur in environments where chlorinations and brominations would be expected to adopt polar mechanisms[242]. Both free radical and polar additions of chlorine to aromatic compounds are well known, and give tetra- and hexachlorides[243]. Polar (electrophilic) substitutions by chlorine in simple olefinic substances are also much more widespread than is sometimes believed; an example[292] is the chlorination of isobutene to give 3-chloro-2-methylpropene (equation 62).

$$\begin{matrix} CH_3 \\ CH_3 \end{matrix}\!\!>\!C{=}CH_2 \xrightarrow[-HCl]{+Cl_2} \begin{matrix} ClCH_2 \\ CH_3 \end{matrix}\!\!>\!C{=}CH_2 \qquad (62)$$

In the intermediate state for attack by any reagent on a saturated carbon atom, it is necessary to accommodate five atoms or groups around carbon. In contrast, for attack on an unsaturated carbon centre, only a four-covalent intermediate state is required. Speaking in general terms, then, it is to be expected that substitution at a saturated carbon atom could involve concerted formation and breaking of bonds, a pentaligant state then being a transition state rather than an isolatable entity. In contrast, however, the formation and breaking of covalent bonds to give substitution at an unsaturated centre are more likely to be stepwise, the steps being separated by an intermediate compound of which a number of types are possible.

We have already seen (section II A) that the first of these generalizations can be justified by experiment, and in this section the evidence for the second will be presented in relation to electrophilic substitution. The formation of such an intermediate in electrophilic halogenation introduces into the reaction path a number of chemical possibilities which depend considerably on the nature of the attacked unsaturated system and would not exist in a concerted mechanism. The intermediate, which for illustration we can represent in the partly generalized form **105**, is a substituted carbonium ion, and as such may have many reactions available to it. Some

of these are indicated in Scheme 14. Reaction by path *a* gives the normal product **106** expected for substitution; for aromatic systems it is the path considered in elementary treatments such as that quoted above, and it can be documented widely for olefinic systems also. Path *b* gives first the



SCHEME 14. Some reaction paths available in stepwise halogenation. In this Scheme, G can in principle represent any bi- or polyvalent substituent.

product **107** of substitution with rearrangement; equation (62) gives an example for an olefinic substitution, and it will be seen that it can be documented also in aromatic halogenation. Further reactions may then supervene. Path *c* is an addition, well known both for aliphatic and for aromatic examples, where the adduct may have incorporated any nucleophile available for capture by the intermediate **105**, including a suitable fragment from the solvent. Further reaction by elimination is then possible and the final product may be one of substitution, not necessarily by the original nucleophile. Path *d* illustrates a type of possible carbonium ionic rearrangement; the rearranged ion **109** then undergoes further reaction leading to products of substitution and/or addition. Such reactions also are known both in aliphatic and in aromatic systems.

Aromatic halogenation, therefore, needs to be put into the context of the halogenation of unsaturated compounds generally and, seen in fuller perspective, presents a complex and ramified picture of possibilities. The differing properties of the various halogens lead to notable differences in

mechanistic detail in their reactions and we shall need to consider, among other factors, their relative sizes, the trend in bond-strengths, the fact that the higher halogens more easily interact with adjacent carbonium centres by neighbouring-group interaction, and the fact that the expansion of the octet of the halogen becomes significant for chlorine through the use of *d*-orbitals, and becomes even more important for the heavier halogens (cf. section I).

Although aromatic substitutions with rearrangement have been recognized as possibilities for many years[244], and substitution by addition–elimination also forms part of the history of chemical thought[245], attention has been focused through more recent times rather heavily on displacements from the centre initially attacked (Scheme 14, path *a*). There have been a number of useful reviews of aspects of such halogenations[246]. In the following discussion, particular reference will be made to recent discoveries. It is emphasized that, though the routes which are sometimes described as 'less usual' can often be recognized from the products, this is not always true and so the potential importance of these less usual pathways can be overlooked, as has been done sometimes for nitration[247] and for other aromatic substitutions.

2. Fluorination

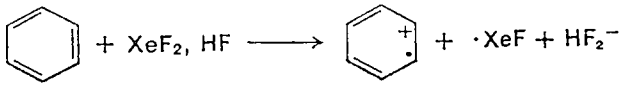
Fluorine reacts violently with most organic compounds, to give complicated mixtures of products. It is generally considered that these reactions involve chain-processes involving free-radicals, initiated easily because of the relative weakness of the F—F bond, the average bond energy of which[2] is 38 kcal mole^{-1}, and the corresponding strengths of the C—F and C—H bonds (116 and 99 kcal mole^{-1} respectively). By reacting with fluorine in acetonitrile at −35°C, however, controlled fluorination of benzene and its derivatives has been effected[248]. No kinetic measurements were made but it was found that electron-withdrawing substituents retarded the reaction, and that the orientation of substitution was that expected for a reaction involving electrophilic fluorine, as is shown by the results summarized in Table 18.

TABLE 18. Proportions of isomeric products of fluorination of RC_6H_5 by fluorine in acetonitrile at −35°C

R:	Me	F	NO_2
o-RC_6H_4F (%)	50	40	13
m-RC_6H_4F (%)	10	10	79
p-RC_6H_4F (%)	40	50	8

Free-radical substitutions are usually less discriminatory than this and give a rather different substitution pattern[249], so the results suggest the operation of an electrophilic mechanism.

Several other potential sources of electrophilic fluorine have been investigated. The reaction of substituted benzenes with chlorine trifluoride in carbon tetrachloride with cobaltous fluoride as catalyst gave products of chlorination and of fluorination consistent with the operation of an electrophilic process[250]. The fact that addition products, substituted biphenyls and tars were produced also, however, makes it probable that radical centres were involved, perhaps concomitantly. For the fluorination of benzene and of fluorobenzene by xenon difluoride in carbon tetrachloride with a trace of hydrogen chloride as catalyst, the radical-ion sequence shown in equations (63)–(65) has been proposed[251].



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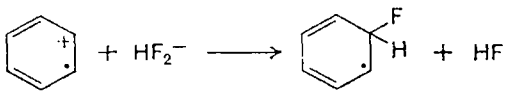

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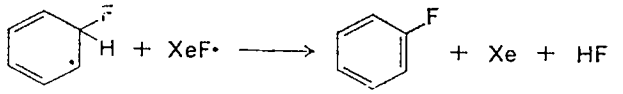
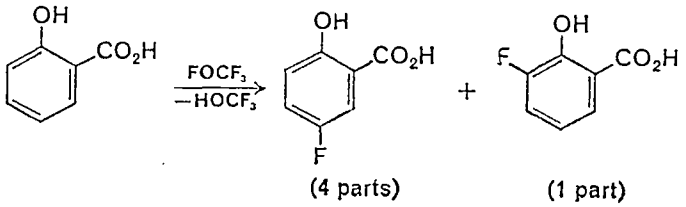


(65)

That radical-ions were involved was indicated by the development of intermediate colours.

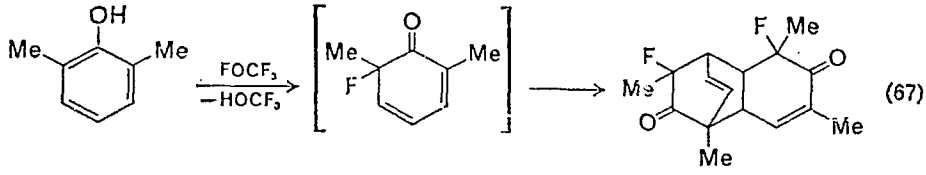
Trifluoromethyl hypofluorite in halogenated solvents has been shown to give a variety of electrophilic fluorinations[252]. With salicylic acid in chloroform at 0°C, for example, it gives the 3- and 5-fluoro-derivatives (equation 66), and with *N*-acetyl-2-naphthylamine it gives *N*-acetyl-1-fluoro-2-naphthylamine; the orientation in each case is that expected for an electrophilic fluorination. Mixtures containing addition products were



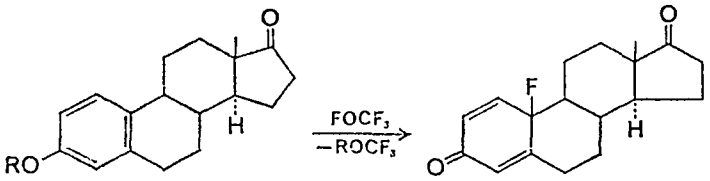
(66)

(4 parts) (1 part)

obtained with *N*-acetyl-1-naphthylamine and with 2,3-dibenzofuran, on the other hand, and reactions with rearrangement were established in the fluorination of 2,6-dimethylphenol (equation 67) and of derivatives of oestrone (equation 68).



(67)



(68)

(R = Me, Ac)

Product-studies are a very incomplete way of defining mechanisms, and it is to be hoped that in due course kinetic measurements may give more definitive evidence concerning some of these reactions. Enough has been done, however, to make it probable that most of the types of reaction illustrated in Scheme 14 can be realized for fluorination.

3. Chlorination, bromination and iodination

a. The electrophiles: positively charged species. Uncatalysed halogenation by molecular chlorine or by molecular bromine normally proceeds through transition states which, though highly polarized, are formally neutral in character. The nitronium ion, NO_2^+, is known to be of widespread importance as a reagent for nitration, so naturally there has been much research seeking to establish the utility of positively charged halogenating species. Berliner[253] has recently summarized the relevant evidence and has analysed some of the matters of controversy. Aspects of these are also treated in the general references already cited[246]. Shilov and Kaniaev[254] established, and several other groups of workers subsequently confirmed, that the kinetics of bromination of aromatic compounds by hypobromous acid in aqueous solution can be represented by equation (69). This kinetic

$$-d[BrOH]/dt = k[ArH][BrOH][H^+] \qquad (69)$$

form establishes that the transition state contains the aromatic compound and positive bromine, but leaves uncertain whether or not it contains water.

At sufficiently high acidities[255], the rate increases more rapidly than the stoicheiometric acidity, corresponding to the use of an acidity function in between the Hammett function (h_0), which measures the extent of protonation of an amine (equation 70); and the function (j_0) which measures the extent of ionization of an aryl carbinol (equation 71). This result still leaves

$$ArNH_2 + H^+ \rightleftharpoons ArNH_3^+ \quad (70)$$

$$ROH + H^+ \rightleftharpoons R^+ + H_2O \quad (71)$$

uncertainty as to whether or not a molecule of water is contained in the transition state.

Whereas molecular bromine reacts only slowly with benzene at room temperature, acidified hypobromous acid is very reactive, and at sufficiently high acidity can be effective even with compounds as deactivated as nitrobenzene, so it is clear that a very effective electrophile is implicated. The response in rate to change in the substituent shows that the reaction responds moderately strongly to electron release; the Hammett ρ-value for the reaction, Brown's σ^+ substituent constants being used, is about the same as in nitration. The linear free-energy correlation with σ^+ was reasonably good for neutral substituents, but a major discrepancy was noted for the NMe_3^+ substituent[255].

Steric effects, though noticeable with sufficiently large groups, were shown to be relatively small in these reactions. Thus, whereas in nitration and in molecular bromination of *t*-butylbenzene there is very little substitution *ortho-* to the *t*-butyl group, in bromination by positive bromine the proportion becomes quite significant[149, 256].

Proton loss from the aromatic compound was shown to be of negligible kinetic importance, since hexadeuterobenzene was brominated at a rate nearly the same as that of benzene[257]. It was found that brominations showing similar kinetic behaviour could be carried out in aqueous dioxan[257] and in aqueous acetic acid[258].

The simplest picture consistent with the above results is that a positively charged halogenating species is formed by a pre-equilibrium protonation of hypobromous acid, and that this species then attacks the aromatic compound in the rate-determining step, giving a σ-complex which subsequently loses a proton (equations 72, 73, 74). Sequences involving a different order of association of the reagents have been favoured by some workers, and are not excluded by the kinetic measurements. Berliner[246] discussed this possibility and recent experiments by Ridd and coworkers[383] provide evidence that for the most reactive substrates at low acidities the transition state can be reached by pre-equilibrium protonation not of

$$BrOH + [H^+] \rightleftharpoons [BrOH_2^+] \; (\rightleftharpoons [Br^+] + H_2O) \qquad (72)$$

$$[BrOH_2^+] \; (\text{or } [Br^+]) + ArH \xrightarrow{\text{slow}} \left[\begin{matrix} Ar \\ \diagdown \\ Br{-}OH_2 \end{matrix}\overset{H}{\diagup}\right]^+ \; (\text{or } \left[\begin{matrix} Ar \\ \diagdown \\ Br \end{matrix}\overset{H}{\diagup}\right]^+) \qquad (73)$$

$$\left[\begin{matrix} Ar \\ \diagdown \\ Br{-}OH_2 \end{matrix}\overset{H}{\diagup}\right]^+ \; (\text{or } \left[\begin{matrix} Ar \\ \diagdown \\ Br \end{matrix}\overset{H}{\diagup}\right]^+) \longrightarrow ArBr + [H^+] + H_2O \; (\text{or } ArBr + [H^+]) \qquad (74)$$

BrOH, but instead of a preformed complex, ArH, BrOH. In either case, it is clear that the steric requirements of the entering halogen in the positively charged transition state are small.

Bromination by Derbyshire and Waters' method[259], in which the aromatic compound is treated with bromine and silver sulphate in sulphuric acid, clearly makes use of a positively charged species, since even quite unreactive compounds are attacked. The orientation of substitution in the quinolinium ion[260] is very like that for nitration by the nitronium ion, 5- and 8-substituted derivatives being produced, but it is not known whether Br^+ or some co-ordinated form (e.g. $BrSO_3^+$ or $BrAgBr^+$) is involved.

Very similar considerations apply to reactions involving positive chlorine. Acidified solutions of hypochlorous acid react with aromatic compounds according to the kinetic form analogous to that of equation (69) and the rate increases more rapidly than the stoicheiometric acidity[261]. Positive chlorine is less favoured thermodynamically than positive bromine, whereas molecular chlorine is a more reactive electrophile than molecular bromine. It is necessary, therefore, when using the more reactive aromatic compounds to reduce the concentration of free chlorine (always present in traces in solutions of hypochlorous acid) by adding a soluble silver salt (e.g. $AgClO_4$). Recently it has been shown[262] that in 95% dioxan a number of aromatic substrates are chlorinated at a rate which is correlated linearly with the Hammett acidity function, h_0 (as measured by the protonation of *o*-nitroaniline), both with and without added silver perchlorate, and that, with added silver perchlorate, the rate is faster and independent of the concentration of added silver perchlorate over a threefold range. These results suggest that, whereas the reagent without added silver perchlorate must be a form of positive chlorine (e.g. $ClOH_2^+$ or Cl^+), in the presence of the added salt the reagent may be the ion $[ClAgCl]^+$.

The other characteristics of either reagent, whether in water or in aqueous dioxan as solvent, are similar to those of hypobromous acid. In particular, the steric requirements of 'positive chlorine' are relatively small[262, 263].

A further kinetic term has been identified in the chlorination of relatively reactive compounds (e.g. anisole) in very dilute aqueous solution in the presence of added silver perchlorate. Under these conditions, the kinetic expression includes a term (equation 75) in which the aromatic compound

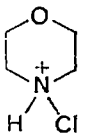
$$-d[ClOH]/dt = k[ClOH][H^+] \quad (75)$$

does not enter[264]. The existence of this term has been confirmed by Swain and coworkers[265,266], and its nature has been the subject of some controversy. Since the reaction is more rapid in deuterium oxide than in water, it seems clear that a proton pre-equilibrium is involved. Originally, it was proposed that the rate-determining process under observation was the heterolysis giving the chlorine cation (equation 76). Other possibilities have

$$ClOH_2^+ \longrightarrow Cl^+ + H_2O \quad (76)$$

been considered, and the matter must be considered still to be open, as Berliner[253] has noted.

Speaking in general terms, then, it can be said that positive chlorine can act as a chlorinating species for aromatic compounds covering a wide range of reactivity. It would seem that, depending on the environment, positive chlorine can be provided from a variety of co-ordinated species[267,268], including $ClOH_2^+$, $ClAgCl^+$, $ClOAcH^+$, and the *N*-chloromorpholinium cation (**110**).



(110)

The characteristics of iodination are rather different from those of chlorination and of bromination, since the transition state usually lies later on the reaction path, and the rate-determining step more often involves the removal of the aromatic proton. Evidence in this direction comes from studies of primary isotope effects, which lie in the range $k_H/k_D = 2–5$ for the iodination in water of aniline and many of its derivatives, anisole, phenol and some of its derivatives and imidazole[253,271]. Observations have also been made relating to iodination by iodine chloride in water[269]. The kinetic form for iodinations by iodine is generally consistent with reaction through the sequence of equations (77) and (78) in which iodine has provided I^+ to the aromatic molecule forming a σ-complex which then loses a proton in the rate-determining step. Examination of the reverse process for the case of the protode-iodination of *p*-iodoaniline has led to a similar conclusion concerning the transition state[270].

$$ArH + I_2 \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \left[Ar\begin{matrix}H\\I\end{matrix}\right]^+ + I^- \qquad (77)$$

$$\left[Ar\begin{matrix}H\\I\end{matrix}\right]^+ \xrightarrow{k_2} ArI + H^+ \qquad (78)$$

Not a great deal is known concerning structural or steric effects in reactions by this mechanism; it is clear that effects of electron-release still dominate, since anisole is much less reactive than aniline[269], and conjugative groups determine *ortho,para*-orientation. There has been some argument concerning which iodinating species is involved in attack on the aromatic molecule in these reactions. Under some circumstances, there seems little doubt that the reagent is in fact molecular iodine. Reaction by the above sequence carries the implication that, if the concentration of iodide ions were sufficiently reduced, the rate of the reversal of the first stage ($k_{-1}[I^-]$) might become too low to maintain a stationary concentration of the intermediate with this stage faster than the forward reaction, k_2. Under these circumstances, the first stage could revert to being rate-limiting, and the primary deuterium isotope effect would diminish. Behaviour of this kind has been established for the iodination of *p*-nitrophenol by iodine in water[271] and of aniline[272].

In other cases, however, even at the lowest accessible concentration of iodide ions (or chloride ions when ICl is used), the isotope effect remains constant[273,274]. Here it is not possible to distinguish kinetically between the above mechanism and that of the sequence shown in equations (79)–(81).

$$I_2 + H_2O \rightleftharpoons H_2OI^+ + I^- \qquad (79)$$

$$H_2OI^+ + ArH \rightleftharpoons \left[Ar\begin{matrix}H\\I\end{matrix}\right]^+ + H_2O \qquad (80)$$

$$\left[Ar\begin{matrix}H\\I\end{matrix}\right]^+ \longrightarrow ArI + H^+ \qquad (81)$$

Unfortunately, solutions of HOI are rather too unstable to allow successful independent studies of the kinetics of iodination in the complete absence of iodide ions.

Iodinations are commonly catalysed by bases, and in some examples it is probable that the base acts as a catalyst for the removal of the proton; in others it may be forming a new iodinating species more reactive than

iodine, but a clear distinction between these possibilities has not been made.

b. The electrophiles: neutral species. The molecular halogens, chlorine and bromine, are often used to effect halogenation of activated derivatives of benzene, but it is not immediately obvious whether these compounds provide the electrophilic halogen themselves, or by way of a pre-equilibrium of which equation (82) is one possibility and others, (83)–(85), become available in suitable solvents. Although Bradfield, Jones and coworkers had

$$X_2 \rightleftharpoons X^+ + X^- \quad (82)$$

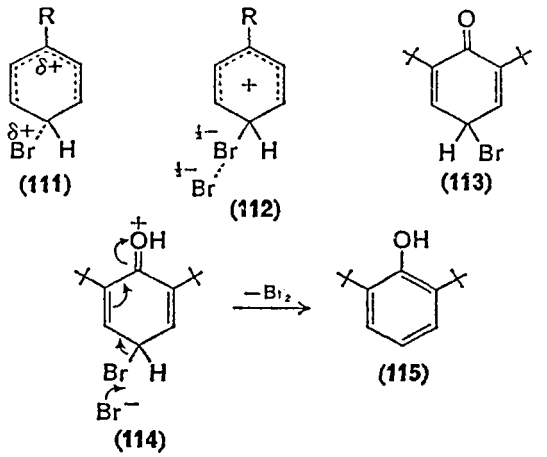
$$X_2 + Py \rightleftharpoons XPy^+ + X^- \quad (83)$$

$$X_2 + SOH \rightleftharpoons XOS + H^+ + X^- \quad (84)$$

$$X_2 + SOH \rightleftharpoons XOSH^+ + X^- \quad (85)$$

earlier examined structural effects in the halogenation of ethers and anilides[275], it was Robertson and coworkers[276] who first examined the kinetics of chlorination and bromination in acetic acid in sufficient detail to establish that molecular halogen in its entirety can be concerned in the transition state. The characteristics of this process have been summarized elsewhere[246, 277]. Proton loss is still normally not part of the rate-determining stage as judged by the absence of primary isotope effects. One of its most interesting features is the very powerful response in rate to change in structure (ρ^+ for chlorination in acetic acid, ca. -10; for bromination in acetic acid, ca. -12). This must come about because the carbonium ionic character of the transition state is very strongly developed; indeed, more so than in nitration or in bromination by 'positive bromine'. As far as structural modification in the organic molecule is concerned, therefore, the transition state for molecular halogenation is further along the reaction path than is that for bromination by 'positive bromine'; the latter can be represented as in **111**, whereas the former should be represented as in **112**, with the breaking of the Hal—X bond incomplete.

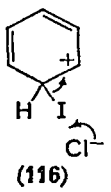
This view of the transition state for molecular halogenation has recently been supported by the direct observation of a rate-determining process which involves the reverse of the formation of **112**. Combined catalysis of the prototropic rearrangement of 4-bromo-2,6-di-*t*-butylcyclohexa-2,5-dienone (**113**) by acid and by bromide ions is accompanied by a substantial proportion of debromination[278]. A proton pre-equilibrium can be shown to be observed through the existence of a reverse solvent deuterium isotope effect. So the transition state must be that indicated by the arrows in **114**



(86)

(equation 86). By the principle of microscopic reversibility, therefore, the bromination of the phenol **115** must be able to have a rate-determining stage having the same composition.

It is possible for catalysts to assist the removal of bromide ion in the rate-determining stage of molecular bromination, and one of the possible catalysts is another halogen molecule, which helps by removing bromide as trihalide ion. For this reason, brominations and iodinations in organic solvents have often been observed to have orders of reaction greater than one in halogen. Halogenations by interhalogen compounds have similar characteristics. Thus orders of reaction greater than one have been observed for brominations catalysed by iodine[279]. The kinetic form for catalysis by chloride ions of the deiodination of iodo-2,4,6-trimethoxybenzene led Batts and Gold[280] to propose **116** as one of the transition states for this process, a result which implies (again through application of the principle of microscopic reversibility) that the iodination of benzene by iodine chloride can involve the rate-determining breaking of the halogen–halogen bond.



(116)

The halogen molecules and the interhalogen compounds are by no means the only potential neutral suppliers of electrophilic halogen. *N*-Halogeno-compounds, alkyl hypohalites, acyl hypohalites and other mixed anhydrides

involving hypohalous acid can all potentially act as halogenating agents. The preparative use of such compounds (e.g. *N*-chloroacetamide, *N*-bromosuccinimide, *t*-butyl hypochlorite) in effecting substitutions and additions is well known[281]. Frequently, however, it has not been established whether such compounds are being effective directly or through the intermediacy of free halogen or some other derived reagent; the presence of even a trace of halide ions may allow reaction through a catalysed path such as that shown in sequence (87). Furthermore, where the species

$$Cl{-}X + Cl^- \rightleftharpoons Cl_2 + X^-; \quad Cl_2 + ArH \longrightarrow ArCl + H^+ + Cl^- \qquad (87)$$

involved has been identified kinetically, the products of the reaction have often not been examined.

Chlorine acetate (Cl—OAc, sometimes called acetyl hypochlorite) is a reagent of this kind which has been investigated most thoroughly from a mechanistic viewpoint. It can be prepared and identified spectroscopically in acetic acid or in dipolar aprotic solvents, and it can be shown to react with aromatic compounds to give products of substitution[267]. It is readily and rapidly hydrolysed by water, but the equilibrium mixture of chlorine acetate and hypochlorous acid (equation 88) still reacts as the former even

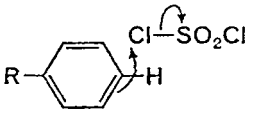
$$ClOAc + H_2O \rightleftharpoons ClOH + HOAc \qquad (88)$$

when the position of equilibrium is unfavourable, since chlorine acetate is a much more effective reagent than hypochlorous acid. It is also a much more reactive electrophile than molecular chlorine, and this feature of its chemistry is not yet fully understood. It seems likely that the explanation has to do with the properties of intermediates with expanded octets on halogen rather than with the strength or electronegativity of the Hal—X bond.

Bromine acetate can also be effective as an electrophile, and appears to resemble molecular bromine in its steric requirements[258].

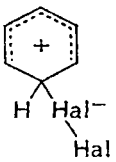
Although sulphuryl chloride can effect chlorination both of aliphatic and aromatic hydrocarbons by routes involving free radicals, yet under controlled conditions in dipolar aprotic solvents a heterolytic mechanism can be shown to occur with suitably activated aromatic systems. Thus it has been shown[282] that aromatic ethers and simple hydrocarbons react with this reagent by second-order processes in nitrobenzene, chlorobenzene and other similar solvents, products of electrophilic chlorination being formed. The kinetic effects of added substances which might conceivably take part in pre-equilibria (e.g. SO_2, n-Bu_4NCl) establish that the reagent is molecular SO_2Cl_2 rather than any derived form and the electrophilic character of the

attack is established by the marked response in rate to change in structure ($\rho^+ = -4$). The absence of a deuterium isotope effect in the reaction with toluene establishes that here at least the breaking of the C—H bond has made little progress in the transition state, which presumably therefore is to be represented as in **117**.

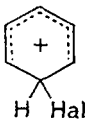


(117)

c. The reaction sequences: displacement by the co-ordination–heterolysis pathway (*Scheme* 14, *path* a). We have already noted that, for a number of chlorinations and brominations, studies of primary isotope effects show that proton loss in the rate-determining stage is insignificant. This makes it probable that the reaction path involves at least two stages, with the carbonium ion (**105**, Scheme 14) as an intermediate. For the case of a benzenoid system, the positive charge is delocalized; if the electrophile is neutral halogen, the zwitterionic structure **118** may be implicated at an early stage in the reaction, but one of its possible fates is to lose halide ion to form **119**.



(118)



(119)

Pfeiffer and Wizinger[283] recognized that the expected properties of ions having the composition of **119** would contribute to an explanation of the course of aromatic substitution. Since Price and Arntzen's demonstration that addition and substitution can be concurrent reactions of aromatic systems[284] and Wheland's use of the delocalized structure **119** as a model of the transition state for the purpose of quantum-mechanical calculations[285], it has been customary to assume their importance as intermediates. Such an assumption is in many cases reasonable; proof would require that evidence be found to show that completion of addition is not a preliminary step essential to substitution. As far as aromatic systems are concerned, we shall continue to assume that substitution by loss of a proton from a halogen-substituted carbonium ion is an important component of reaction paths leading to mono-chloro- or mono-bromo-derivatives. Two important provisos should be noted, however. One is, that the nature of the products

of halogenations needs careful examination in every detail possible before it can be assumed that the isolated and identified products are in fact the primary products of substitution. The second is, that it is frequently possible to establish that part (but not all) of the reaction involves this path; whereas some (though again not all) of the product is derived by way of an alternative route. In this connexion, the examination of crude reaction products by gas–liquid chromatography may be misleading, since this technique often decomposes the primary labile products of reaction to give compounds which could have been derived by direct substitution.

Heterolytic electrophilic substitutions by halogens in olefinic systems are quite well-known processes, though they have been investigated mechanistically very little. From a kinetic point of view, it has been documented thoroughly[286] that the same kinetic forms are in general observed for halogenation of olefinic and of aromatic systems. As far as products are concerned, equations (89)–(91) illustrate some of the cases in which it has been established that an olefinic system is halogenated to give a substantial proportion of the product of substitution, and in which it is reasonable to assume that the product of direct substitution is derived from the carbonium ionic intermediate[283, 287].

$$PhCH{=}CH_2 \xrightarrow[\text{in } CCl_4]{Cl_2} PhCH{=}CHCl\ (\text{ca. } 25\%) + HCl \qquad (89)$$

$$PhCH{=}CHMe \xrightarrow[\text{in } CH_2Cl_2]{Cl_2} PhCH{=}C(Me)Cl\ (\text{ca. } 16\%) + HCl \qquad (90)$$

$$(p\text{-}MeOC_6H_4)_2C{=}CH_2 \xrightarrow[\text{in } CCl_4]{Br_2} (p\text{-}MeOC_6H_4)_2C{=}CHBr + HBr \qquad (91)$$

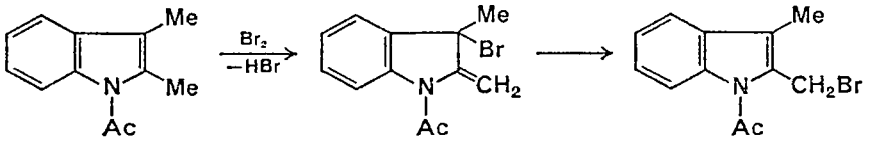
Recently, it has been shown[288] that both *cis*- and *trans*-β-styrylpyridinecobaloximes ($PhCH{=}CHCo(DH)_2Py$; DH = dimethylglyoxime monoanion, Py = pyridine) react with elemental halogens (chlorine, bromine or iodine) in acetic acid by a process presumed to be electrophilic in character to give the corresponding *cis*- and *trans*-β-halogenostyrenes in high yields and with complete retention of configuration. The investigators interpreted this as a two-stage reaction, but it should be noted that a one-stage displacement is not formally excluded here.

d. The reaction sequences: displacement with rearrangement (*Scheme* 14, *path* b). Carbonium ions, when they are produced in chemical reactions, often have more than one site from which a proton can be lost. The resulting problems of orientation, in unimolecular *E*1 reactions for example, have been much discussed; the commonly observed 'Saytzeff' orientation implies that the thermodynamically more stable of two

alternatively accessible olefins is often the predominant product (equation 92)[7].

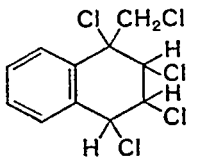
$$CH_3CH_2CMe_2Cl \xrightarrow{-Cl^-} CH_3CH_2CMe_2^+ \xrightarrow{-H^+} \begin{matrix} CH_3CH{=}CMe_2 \\ (80\%) \\ CH_3CH_2C(Me){=}CH_2 \\ (20\%) \end{matrix} \quad (92)$$

Such a route, when taken in a suitably substituted aromatic system, allows (by way of a subsequent allylic rearrangement) heterolytic side-chain replacement by halogen, and there are a number of cases where such products can be identified, sometimes as a minor component of the reaction mixture. Plant and Tomlinson[289] suggested that the bromination of *N*-acetyl-2,3-dimethylindole follows the course shown in equation (93).



(93)

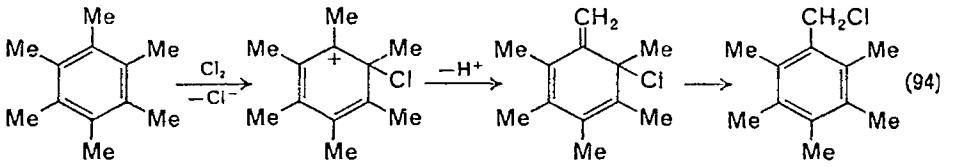
Similarly, one of the products of heterolytic chlorination of 1-methylnaphthalene is the side-chain-substituted compound **120**, for the formation of which a stage involving substitution with rearrangement is required[290].



(120)

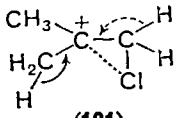
The only kinetic investigations of heterolytic side-chain substitution that we are aware of are by Illuminati and coworkers[291]. They examined the side-chain chlorination of hexamethylbenzene and a number of its analogues. These reactions, which were only a little slower than correspondingly activated substitutions involving displacement of hydrogen (e.g. in pentamethylbenzene) had the usual kinetic form ($-d[Cl_2]/dt = k[ArH][Cl_2]$), and responded to change in substituent as would be expected for an electrophilic substitution. A simple representation of the reaction path is shown in sequence (94).

This type of reaction is not confined to aromatic systems. The chlorination of isobutylene in the liquid phase gives as the main product 3-chloro-2-methylprop-1-ene ($CH_2{=}C(Me)CH_2Cl$), with much smaller amounts of



(94)

1-chloro-2-methylprop-1-ene ($Me_2C{=}CHCl$), so substitution with rearrangement predominates over direct substitution; and, since the same ratio of substitution products is found for reaction with acidified hypochlorous acid in water, it can be presumed[287, 292, 293] that this orientation is typical of reaction by a heterolytic, rather than by a homolytic process. There are several theories to account for this reaction and the reason why substitution occurs predominantly with rearrangement; they have been discussed elsewhere[294] so here we will state merely our preferred view, that interaction between chlorine and the carbonium ionic centre inhibits proton-loss from the attacked carbon atom (dashed arrow in **121**), and thus allows the alternative mode of proton-loss to take predominance (full arrow in **121**).



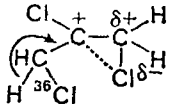
(121)

Evidence supporting the view that the geometry about the group from which the proton is to be lost can affect the ease of this loss comes from a study of the heterolytic chlorination of 2,3-dichloropropene with acidified hypochlorous acid. This reaction gives some 8% of 1,2,3-trichloropropene, and tracer experiments show that the proton is lost predominantly but not exclusively from the 3-, rather than from the attacked 1-position (equation 95)[295]. Heavy-atom isotope effects can be neglected here; the products are

$$CH_2{=}CClCH_2{}^{36}Cl \xrightarrow[-H_2O]{ClOH} \begin{cases} ClCH_2CCl{=}CH^{36}Cl & (6{\cdot}7\%) \\ CHCl{=}CClCH_2{}^{36}Cl & (1{\cdot}3\%) \end{cases} \qquad (95)$$

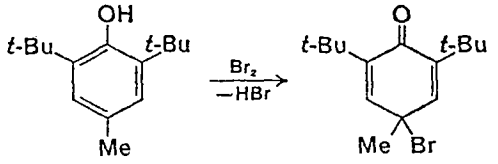
chemically but not radiochemically identical and the intermediate carbonium ion is formally symmetrical. Some factor must be responsible for the preferential loss of a proton from the 3-position, and the theory proposed for isobutene[292] gives a natural and consistent interpretation: in the intermediate carbonium ion as it is formed, interaction between the attacking chlorine and the carbonium centre will be expected to be easy, and it would be expected to take time before the allylic chlorine could become equivalent with the attacking chlorine. Before this can happen

completely, proton-loss can supervene, thus giving the observed result of unsymmetrical behaviour of a formally symmetrical intermediate (**122**)[292, 295].



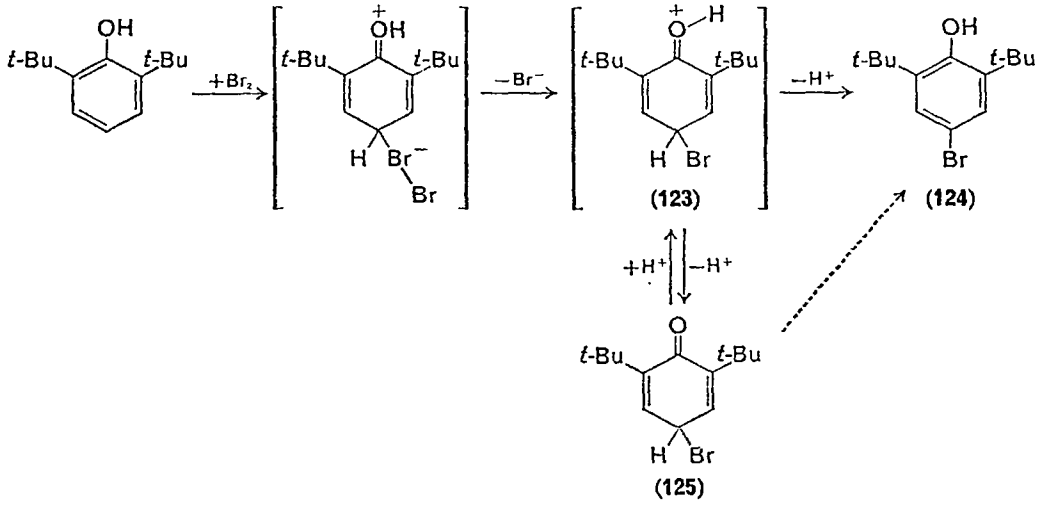
(**122**)

Proton-loss giving aromatic rearrangement in a halogen-substituted carbonium ion need not necessarily be from a carbon atom. There are many examples of the formation of dienones by the halogenation of phenols; equation (96) shows an example involving electrophilic attack at a position bearing a substituent, proton loss from the position attacked being thus precluded[296, 332].



(96)

Rearrangement involving proton-loss from oxygen can also in certain cases be shown to be a consequence of electrophilic attack at a hydrogen-bearing position. A good example is the bromination of 2,6-di-*t*-butylphenol, from which the dienone (**125**) can be isolated in good yield (Scheme



SCHEME 15. Possible reaction path in the bromination of 2,6-di-*t*-butylphenol.

15). Several examples of this type of reaction have been examined kinetically[297-299]. The results can all be analysed in terms of second-order processes involving the phenol molecule and bromine. Little further is known about the intimate details, though these may be as complicated as those involved in the direct substitutions. In particular, it would be valuable to know the extent to which the O—H bond-breaking is concerted, if at all, with the electrophilic attack by bromine.

The isolation of **125** as an intermediate in the bromination of 2,6-di-*t*-butylphenol raises the question whether or not the halogenation of phenols normally involves the intermediacy of such a dienone, which subsequently to its formation can rearrange to give the product of normal substitution, **124** (Scheme 15). Analysis of the rates of bromination of substituted phenols and anisoles[300] indicates that the electron-releasing properties of the hydroxyl group are greater than those of the methoxyl group. Hyperconjugation involving the H—O bond would account for this, and would allow concerted electrophilic attack and proton loss to produce the required rearranged structure, since proton-transfers from oxygen are relatively rapid. It has been shown[301] that deuteriophenol in deuterioacetic acid is brominated 1·9 times more slowly than is phenol in acetic acid; this result suggests that there is some contribution to the rate of the reaction from the breaking of the H—O bond. A similar isotope effect was found for the rearrangement of the bromodienone from 2-naphthol-6,8-disulphonic acid[299]. It seems likely, therefore, that the halogenation of phenols frequently involves dienone intermediates, most but not all of which are capable of rapid rearrangement.

It may often happen that the mechanism of dienone rearrangement in a sequence as shown in Scheme 15 is such that the intermediate for the latter reaction is the same as one of those expected to be involved in the electrophilic substitution leading from the unsubstituted to the substituted phenol. In such a case, the dienone is merely a temporary repository for the starting materials, diverting this substitution without changing its fundamental nature.* The substitution can be regarded as proceeding through the dienone by way of an 'unusual' mechanism only if there is some route leading from the dienone to the final product **124** and not involving **123**. Although normally the mechanism of conversion of **125** to **124** seems to involve **123**, there is evidence also for a base-catalysed path leading directly from one to the other[302]; and certainly the relative rates of the two branching paths leading from phenol to brominated phenol and to dienone can be greatly altered by modification in the medium.

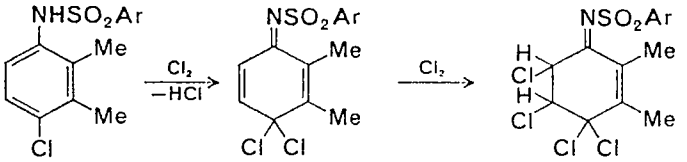
* A similar possibility, involving an *N*-halogeno-intermediate, exists in the case of the halogenation of anilides and amines; see below.

The halogenation of phenols and naphthols have their aliphatic and alicyclic analogues in the halogenation of enols. The mechanistic interest in these processes has, however, mainly centred in the fact that they are the final fast stages in halogenation α- to a carbonyl group, following the rate-determining enolization shown for a ketone in the sequence (97). A survey of such reactions is given by March[303]. It seems probable but by no means certain that such acid-catalysed brominations and chlorinations can involve synchronous attack by halogen on the enol and displacement of a proton; the fast stage indicated in sequence (97) is often, however, assumed to be

$$CH_3COCH_3 \xrightarrow{\text{slow}} CH_3C(OH)=CH_2 \xrightarrow[\text{fast}]{Br_2} CH_3COCH_2Br + H^+, + Br^- \quad (97)$$

stepwise in nature. Bell and coworkers[304] have reported that bromine reacts with the enol form of acetone by a bimolecular reaction at a rate which is at least five times faster than the rate of the corresponding reaction of chlorine, a result which suggests that the rate-determining stages of the reaction paths are different from those normally encountered in electrophilic attack on unsaturated compounds, where chlorine is normally much more effective than bromine.

Since examples are known of sequences involving proton loss from oxygen and from carbon, related sequences involving N—H bonds should be accessible in suitable cases. Robertson[305] has suggested that some complex examples from the chemistry of aromatic sulphonamides can be classified in this way and sequence (98) provides an example.



(98)

e. The reaction sequences: addition–elimination (*Scheme* 14, *path* c). Preoccupation with the chemical criterion for aromaticity and with simplified descriptions of the transition state for aromatic substitution, together with a general sympathy for the simplification that would arise if linear free-energy relationships could be widely applied to electrophilic substitutions, has led to some degree of neglect of addition–elimination routes in these reactions. Yet, especially where halogenations are concerned, paths of this kind are of considerable importance in determining yields of products and details of product composition. Before we consider the consequences that may ensue as far as the course of substitution is

concerned, some mechanistic features of the addition process need to be outlined. Some importance attaches to a comparison of the chlorination of naphthalene and phenanthrene, because these examples give information concerning both kinetics and stereochemistry[306].

Phenanthrene undergoes chlorination by molecular chlorine in acetic acid by the usual second-order process, the rate being increased by the addition of salts or of water to the medium. The reaction gives a mixture of products, all of which are stable in acetic acid under the conditions of reaction; major components, (shown in Scheme 16), are 9-chlorophenanthrene (**133**), *cis*- (**129**) and *trans*-9,10-dichloro-9,10-dihydrophenanthrene (**131**) and *cis*- (**130**) and *trans*-9-acetoxy-10-chloro-9,10-dihydrophenanthrene (**132**); traces of other chlorophenanthrenes are also produced. These results are consistent with a picture of reaction through a carbonium ion, as in Scheme 14; but the influence of added salts on the product composition shows that this is an over-simplification. Added acetate ions divert the reaction somewhat towards increase in the proportion of *trans*-acetoxychloride; but, otherwise, the effects of added salts are marginal, and most significant is the finding that the presence of chloride ions has very little influence on the proportion of 9-chlorophenanthrene or of the *cis*-dichloride. Change in the solvent, too, over the range $MeNO_2$—HOAc—$CHCl_3$ involving a rate-change of several powers of ten, has only minor influence on the product proportions.

It might be thought that the route to the *cis*-dichloride could be different from that which leads to the other products of reaction, but this possibility can be discounted: partly because of the minor influence of solvent on product proportions and partly because the more slowly reacting naphthalene also gives *cis*-adducts in proportion similar to that found for phenanthrene, and by a path which is affected only to a minor extent by the addition of salts, including chloride ions, to the reaction medium.

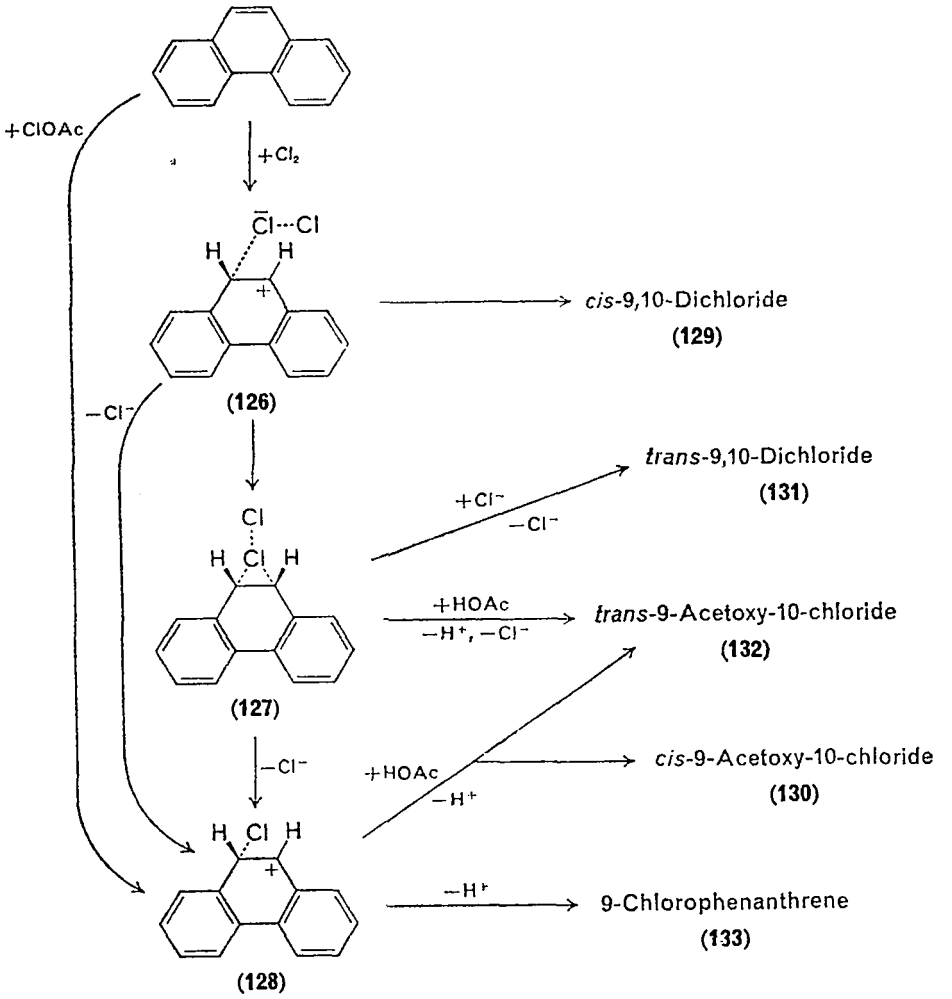
Further information is provided by study of the reaction involving chlorine acetate in the same solvent. This compound, which reacts much more rapidly than chlorine, gives the 9-acetoxy-10-chloro-9,10-dihydrophenanthrenes in a ratio quite different from that determined by molecular chlorine and unaffected by the presence of added acetate ions[307]. The most important of these results are summarized in Table 19.

It is clear that the reaction initiated by molecular chlorine can be diverted by solvent to give the acetoxychlorides, the intermediate undergoing diversion being different from that involved with chlorine acetate since it gives so different a ratio of *cis*- to *trans*-isomers in the product. The former intermediate, in contrast with the latter, gives a rather higher proportion of the *trans*-isomer when diverted by added acetate ions. One

TABLE 19. Products of chlorination of phenanthrene at 25°C

Reagent: / Solvent:	Cl_2 HOAc	Cl_2 HOAc + LiCl	Cl_2 HOAc + NaOAc	ClOAc HOAc	ClOAc HOAc + NaOAc	Cl_2 $CHCl_3$	Cl_2 $MeNO_2$
9-Chlorophenanthrene (%)	35	36	30	40	40	41	66
cis-9,10-Dichloro-9,10-dihydrophenanthrene (%)	38	41	38	—	—	41	23
trans-9,10-Dichloro-9,10-dihydrophenanthrene (%)	10	8	7	—	—	18	11
cis-9-Acetoxy-10-chloro-9,10-dihydrophenanthrene (%)	5	4	6	30	30	—	—
trans-9-Acetoxy-10-chloro-9,10-dihydrophenanthrene (%)	12	11	19	30	30	—	—

set of sequences which could account for the observed results is shown in Scheme 16. Here the *cis*-dichloride, formed in reaction by chlorine, is considered to be derived from the geometrically favourable zwitterion (**126**), which can otherwise lose chloride ion to form the carbonium ion



SCHEME 16. Main reaction paths and intermediates proposed for the chlorination of phenanthrene by chlorine or by chlorine acetate in acetic acid.

(**128**), or rearrange to give the bridged intermediate (**127**). The latter can be captured by acetate ion or by chloride ions to give *trans*-products. It can also lose chloride ions to form the carbonium ion **128**, which reacts rather indiscriminately with solvent to give *cis*- or *trans*-products, and can also

lose a proton to give 9-chlorophenanthrene. Chlorine acetate gives the last ion directly and so determines a simple pattern of products not much altered by the presence of added acetate ions. It is necessary to assume that the environment has little effect on the sequence of intermediates **126–128**, except through slight diversion of **127** on a branching path.

A novel feature at the inception of the investigations leading to the results now summarized was the formation of a major amount of the *cis*-dichloride by what appeared to be a direct reaction. Whatever intermediate is considered to determine the formation of this compound, however, proof has been given that it must have considerable carbonium ionic character; so an interpretation such as that of Scheme 16 with the *cis*-dichloride formed through a zwitterion essential to but early on the reaction path seems entirely reasonable. The further novel feature, clarified through study of the reaction with chlorine acetate, is that the intermediate allowing diversion to predominantly *trans*-products must have some special structure, and is not available for reaction initiated by the latter electrophile. In Scheme 16, we have attributed this special structure to the reaction involving chlorine; if instead we were to attribute the more stereospecific *trans*-additions to reaction through the carbonium ion (as was done in the early papers)[306], then special structures allowing both *cis*- and *trans*-addition would need to be proposed for the reaction involving chlorine acetate. Such a possibility has been considered[307], but since it is more important in regard to addition than to substitution processes, we need not discuss it further here. The properties of the various components of the reaction mixture are, however, important in that a study of them reveals a number of difficulties liable to be encountered in study of aromatic substitutions. In the particular case under investigation, it has been shown that the dichlorides can be decomposed by heat, or by alkali, or sometimes by chromatography; they give 9-chlorophenanthrene accompanied sometimes by phenanthrene. The acetoxychlorides are decomposed by heat, to give a mixture of 9-chloro- and 9-acetoxyphenanthrene with phenanthrene; by alkali, to give 9-acetoxyphenanthrene and hence 9-phenanthrol; and by acid, to give mainly 9-chlorophenanthrene.

A further general point needs to be made in connexion with additions to aromatic systems. A path which leads directly from an aromatic compound to a carbonium ion and thence to a product of substitution does not involve any intermediate particularly susceptible to further electrophilic attack, nor does it involve any considerable change in the geometry of the aromatic skeleton undergoing substitution. Once the intermediate carbonium ion has reacted with a nucleophile to form a product of addition, however, the whole geometry of the ring has suffered a major

change and, furthermore, the resulting adduct may be one which is very susceptible to further reactions of various kinds, including reactions with electrophiles. Phenanthrene, which we discussed in detail above, is an exception to the latter consideration, but naphthalene normally gives naphthalene tetra- rather than di-chlorides, and derivatives of benzene, of which biphenyl and its derivatives have been investigated in some detail[308], also give tetrachlorides among the products of chlorination in acetic acid. Problems not only of geometrical but also of structural isomerism can also arise through competitition between 1,2- and 1,4-addition.

Brominations of aromatic systems can also give adducts[309-311] but these adducts have been less well characterized than those from chlorination, since they are much less stable. It seems quite likely that different mechanisms of bromination can sometimes give different product ratios, but this remains to be established clearly. Speaking generally concerning the addition–elimination route to aromatic halogenation, it can be said:

(i) that adducts are often formed as primary products in competition with those of direct substitution;

(ii) that such adducts are often of varying kinds and comprise complicated product mixtures from a single substrate;

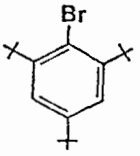
(iii) that the components of the mixture of adducts may decompose in a variety of ways to give secondary products, which can be those of substitution;

(iv) that depending on the conditions of decomposition, these secondary products can be the same as those determined by the primary process of substitution; alternatively they can be new products, or the primary products obtained in different proportions;

(v) that the formation of substitution products of unusual nature or orientation may often be interpretable in terms of addition–elimination sequences.

Two examples in which addition–elimination paths have been postulated are now given. In the first[312] it has shown that the reaction of bromine and silver salts with 1,3,5-tri-*t*-butylbenzene in acetic acid gave the products **134–137**, thus implicating the intermediate adducts **138** and **139**.

The second case involves addition to a heterocyclic system. Bromination and chlorination of quinoline and its derivatives can give two orientations of substitution. The first probably involves a conventional aromatic substitution on the quinolinium cation: for example, bromination by bromine and silver sulphate in sulphuric acid, which gives the 5- and 8-bromo-derivatives[313], just as nitration by the nitronium ion in sulphuric acid gives the 5- and 8-nitroquinolines[314]. Direct reaction between quinoline and bromine, on the other hand, gives first a perbromide (probably



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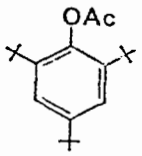

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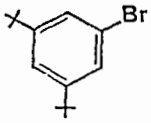

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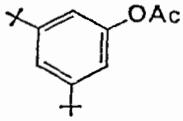

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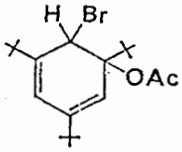

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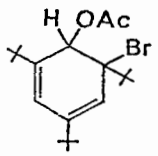
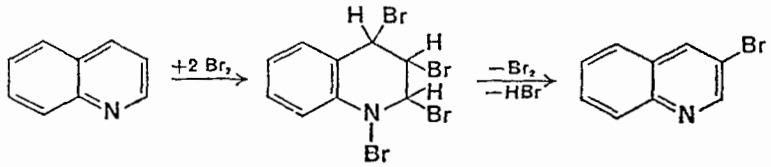


(139)

$C_9H_7NBr^+ Br_3^-$), and then 3-bromoquinoline (in pyridine) or 3,6-dibromoquinoline and 3,6,8-tribromoquinoline (in acetic acid)[315]. The most natural interpretation of these results is that shown in the addition–elimination sequence (99), which indicates the route to 3-bromoquinoline; further reaction involves substitution in the 6- and 8-positions, which in the intermediate **140** are activated through the conjugative effect of the tertiary nitrogen atom. Eisch[316], in a careful and scholarly review of the halogenation



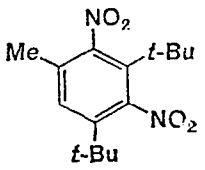
(99)

(140)

of heterocyclic compounds, has discussed other possible interpretations and has pointed out some of the uncertainties involved in making mechanistic deductions from studies of reaction products. Whilst agreeing with all his *caveats*, the present writers think that the evidence to date supports the interpretation given above. It seems even more certain that many aromatic halogenations, particularly in the field of heterocyclic chemistry, can proceed in part by addition–elimination pathways, which may be more common with conventional aromatic compounds than has been recognized generally.

f. The reaction sequences: intramolecular rearrangements of the carbonium ion (*Scheme* 14, *path* d), *and related processes.* In principle, as we have

noted elsewhere[294], the carbonium ion produced by co-ordination of an electrophile with an unsaturated compound may undergo a variety of transformations, including skeletal rearrangements, before reaction is consummated by capture of a nucleophile to give addition, or by proton loss to give substitution. A number of examples of addition of halogen accompanied by skeletal rearrangement have been documented, both in acyclic and in polycyclic systems[294]. Few cases, however, seem to have been well established in which the overall process is one of substitution by halogen. In the aromatic series, nitration provides an illustration. Myrhe and coworkers[317] showed that one product (32%) from the nitration of 2-nitro-1,3,5-tri-*t*-butylbenzene was **141**. It was suggested that some sequence of rearrangement involving shift of a methyl group to the position shown as bearing a positive charge in the postulated intermediate **142** should be used to account for the formation of this component of the product.



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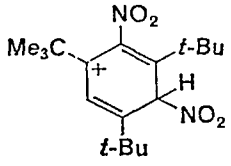


(142)

Analogous sequences in the field of halogenation may ultimately be found; it seems likely to the writer that these should be sought in chlorinations rather than in brominations or iodinations, because neighbouring group interaction by the higher halogens is likely to compete with other processes of rearrangement. Transannular processes in medium-ring olefins may also provide an area in which such rearrangements might sometimes be favoured.

g. The reaction sequences: rate-determining proton loss. Ever since Melander's classic work[318], the criterion which has been accepted as defining whether the stage of an aromatic substitution involving proton loss has become significant in the transition state has been the existence of a primary deuterium isotope effect on the rate of substitution. This criterion can be applied experimentally by the use of several types of procedure; in marginal cases it is subject to the difficulty that a small reverse primary isotope effect, often just within the limit of experimental detection, might be expected to apply to the co-ordination of the electrophile with the aromatic ring. These ideas, together with the experimental information relating to

halogenations and other aromatic substitutions, have been reviewed by Berliner[246], and we will be content here to state only the salient features.

First, no primary isotope effects have yet been observed in chlorination, except the small reverse effects already referred to. Only a few cases have been studied, but these cover several different reagents and conditions of chlorination[267,319].

Most brominations, including representative reactions involving positive bromine, molecular bromine and bromine with Lewis acids as catalysts[320], do not show a primary isotope effect, but in special circumstances such effects can appear. Among the structural factors which seem to contribute to the observation of these, steric congestion around the reaction site seems to be quite important. Illuminati and Stegel[321] showed that the silver-ion-catalysed bromination of 1,3,5-tri-*t*-butylbenzene was subject to a primary isotope effect, $k_H/k_D = 3{\cdot}6$. Similarly, Berliner, Kim and Link[322] have shown from the kinetic form for bromination of 1,5-dimethylnaphthalene in 90% acetic acid that proton loss is partly rate-determining, whereas this is not so for the other dimethylnaphthalenes. It seems intuitively reasonable that congestion around the site of substitution resulting from the presence of the adjacent peri-substituent might make C—H bond-breaking more developed in the transition state.

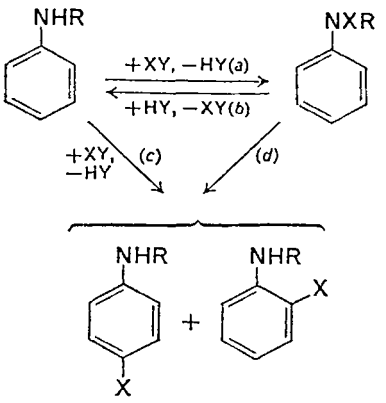
A group of Scandinavian workers[323] have examined a number of poly-substituted benzenes, including trimethyl- and trimethoxy-benzenes, and have focused attention on the possibility that steric inhibition of resonance is also an important factor contributing to the observation of a primary isotope effect. Thus the bromination of 1,3,5-trimethoxybenzene in dimethylformamide shows no primary kinetic isotope effect, but that of 2-bromo-1,3,5-trimethoxybenzene shows quite a large one (k_H/k_D = ca. 4). It can be noted also that the bromination of *N,N*-dimethylaniline and some of its derivatives[324,325] is subject to a large primary deuterium isotope effect in the *ortho*-, but not in the *para*-position. This is consistent with the view that steric interaction between the entering substituent and an adjacent conjugative substituent can through steric inhibition of resonance result in a primary deuterium isotope effect on the rate of substitution.

Reactions involving such primary isotope effects could be envisaged as one-stage processes, with electrophile and nucleophile both partly bonded to the aromatic nucleus in the rate-limiting step. In such a case, the isotope effect would be independent of the concentration of the base, provided that only one base was concerned. The two-stage mechanism involving the sequence similar to that shown in equations (77) and (78) would with appropriate values of the rate-coefficients allow the observation that the

isotope effect would increase in magnitude with increase in the concentration of bromide ions. Two examples have recently been recorded in the field of bromination. The bromodeprotonation of sodium *p*-methoxybenzene sulphonate[326] shows a primary kinetic isotope effect increasing from 1·01 to 1·31 as the concentration of bromide ion is increased from 0 to 2M. A similar variation in the isotope effect has been noted for the bromination of 3,4-dimethyl-*N*,*N*-dimethylaniline in water[325].

We have already referred to the fact that iodinations generally show a kinetic isotope effect characteristic of the two-stage mechanism and further discussion is unnecessary.

h. The reaction sequences: '*indirect substitution*'. The reaction sequence which we describe as involving 'indirect substitution' starts with attack by the electrophile at some centre in the molecule, and then involves stages in which the electrophile is transferred to some other centre in the molecule. Various mechanisms for these stages can be invoked under this heading. The most obvious circumstance under which this possibility can arise, however, obtains when these subsequent stages can be wholly intramolecular. In Scheme 17, substitution in amides or amines is taken as an



SCHEME 17. An example of 'indirect' electrophilic aromatic substitution.

example[327, 328]. Circumstances can exist in which the *N*-substitution (path *a*) is faster than or similar in rate to C-substitution (path *c*), and in which the conversion of starting material into C-substituted product can be effected by way of the conversion of the *N*-substituted compound into the C-substituted compound (path *a* followed by *d*). This provides a new mechanism for C-substitution. Evidence suggesting the existence of such a route can sometimes be obtained by finding that the ratio of isomeric products is different from that obtained with the 'normal' reaction. The

only case in which this type of path is established with certainty is that of nitration, where reaction via the nitramine, which then rearranges, is shown by the formation of a high proportion of *ortho*-substituted product, as is discussed in the cited references.

It is generally believed that halogenation does not normally proceed by such a path. On the contrary, the conversion of a *N*-halogeno-amine or amide into its C-substituted isomer normally proceeds by a path which is the reverse of one of its possible modes of formation (path *b*). If this is true generally, then no new mechanism for C-substitution is provided when the original amine or amide is halogenated to give what may only temporarily be a diversion of the starting material into its *N*-halogeno-derivative. That no examples have yet clearly been documented, however, does not establish that the mechanism involving 'indirect substitution' does not exist for halogenation. It should be noted, too, that some of the possible routes considered by Illuminati and coworkers for substitution with rearrangement (Section III. A. 3. d) and by Eisch for heterocyclic halogenation (Section III. A. 3. e) can be considered to fall into the category of 'indirect substitution'. So far, however, it has proved difficult to distinguish clearly between the various possible ways in which these unusual sequences could proceed.

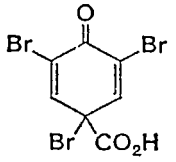
i. The reaction sequences: displacement of groups other than hydrogen. Several of the reviews already mentioned[246] include accounts of the mechanisms established for halogenations involving the displacement of groups other than hydrogen. Although these reactions have not been investigated as systematically as have the corresponding halogenodeprotonations, enough is known to establish that most of the same patterns of behaviour are available.

We may first note that quite a wide variety of groups are known to be displaceable by electrophilic halogen. Among the well known cases are the substituents *t*-Bu, CO_2H, COR, SO_3H, $B(OH)_2$, SiR_3, GeR_3 and SnR_3. The reactions become most prominent in structural situations in which the position occupied by the substituent is strongly activated by an electron-releasing substituent. Where studies have been carried out to establish the response of reactivity to change in structure, the reactions have been shown to have negative Hammett ρ-values, as expected for an electrophilic halogenation, the magnitude of the constant being on the whole rather smaller than those found for the corresponding displacements of hydrogen and varying with the nature of the leaving group.

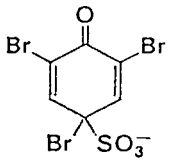
It has also been established that all the usual reagents can be involved. Kinetic studies of chloro- and bromodesilylation[329] indicate that molecular chlorine and molecular bromine in full form part of the composition of the

transition states for these reactions. Molecular iodine has been implicated similarly in studies of iododestannylation[330], and positive bromine, in de-*t*-butylation[256].

Several studies indicate clearly that the two-stage mechanism of halogenation, with a quinonoid compound formed by co-ordination of halogen as a definite intermediate on the reaction path, is available for these substitutions. Examples include the bromodecarboxylation of 3,5-dibromo-4-hydroxybenzoic acid[331] and the bromodesulphonation of sodium 3,5-dibromo-4-hydroxybenzene sulphonate[332]. In each of these cases, the proposed intermediate (**143**, **144** respectively) has already lost a proton, and so is best considered as derived formally from the starting material by substitution with rearrangement (the S_E2' mechanism; Section III. A. 3. d). It would, however, generally be considered probable that, even for systems in which a mobile hydrogen is not displaced, a quinonoid intermediate is still probably concerned at a relatively early stage on the reaction path. Furthermore, the usual elaborations of these early stages are probably available also for removal of groups other than hydrogen; thus kinetics which are second-order in bromine have been recognized for bromodesilylation[333].



(143)



(144)

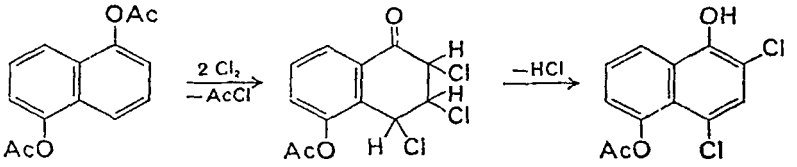
Just as in some circumstances for bromodeprotonations the final stage of the displacement may become rate-determining, so analogous situations have been recognized for the loss of other groups. Thus in bromodecarboxylation[331], a $^{12}C : {}^{13}C$ isotope effect of up to 1·045 in the evolved CO_2 has been recorded, a result which establishes that the final stage of the reaction has become rate-determining. Nucleophilic catalysis has been recognized for bromodeboronations[334]. The stereochemistry of desilylation[335] is also suggestive of nucleophilic help for cleavage of the Si—Ar bond, since inversion of configuration at silicon is observed.

Reactions involving displacements of groups other than hydrogen are not confined to aromatic systems. Thus in acetic acid or in water the *trans*-cinnamate ion reacts with chlorine to give extensive chlorodecarboxylation with the formation of *trans*-β-chlorostyrene and products of further chlorination of this compound (equation 100)[336]. From the

$$\textit{trans}\text{-PhCH=CHCO}_2^- + Cl_2 \longrightarrow \textit{trans}\text{-PhCH=CHCl} + CO_2 + Cl^- \quad (100)$$

stereospecificity of this reaction and the ratios of the accompanying addition products it was concluded that the loss of CO_2 was nearly concerted with the electrophilic attack.

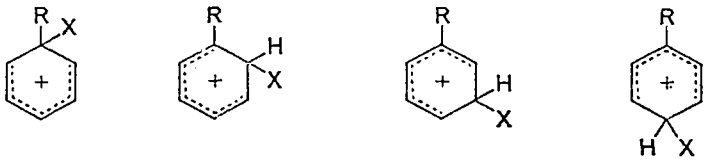
We have already noted that bromodeprotonation with rearrangement can be a first step in a reaction sequence leading to displacement of groups other than hydrogen. Halogenodealkylations and halogenodeacylations are also sometimes available as reaction paths competitive with the more usual substitutions. Thus the chlorination of 1,5-diacetoxynaphthalene gives not the 4- or 4,8-substituted derivative which might have been expected, but instead 5-acetoxy-2,4-dichloronaphthol via the intermediate **145** (sequence 101)[337]. Similarly, the chlorinations and brominations of



(101)

(145)

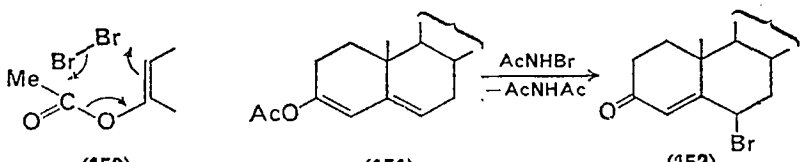
aromatic esters sometimes take the course expected, but in some cases the position of substitution is unexpected, and under these circumstances the reaction is often accompanied by deacylation, which can be catalysed by nucleophilic anions[338]. Formally, the overall processes leading to deacylation in such cases can be regarded as S_E2' reactions, just as normal substitutions can be regarded as S_E2 in character; but for the former (as in some cases for the latter also) it is by no means clear whether addition–elimination sequences are sometimes or always concerned, and if so, whether such additions are usually 1,2- or 1,4-processes. The present indications convey the likelihood that all these pathways, as well as others including proton loss leading to side-chain substitution, may become available in suitable circumstances, as seems to be so also for nitration of esters, ethers, anilides and hydrocarbons[247,339,340]. Detailed knowledge concerning the competing processes available even in the cases investigated to date, let alone in the general case, is lacking, and this is perhaps not surprising in view of the complexities available through the formation of carbonium ionic intermediates. If we consider in a general way the processes which may lead to substitution in a mono-substituted benzene, C_6H_5R, reacting with a source of X^+ as the electrophile, all the intermediate carbonium ions (**146–149**) must be considered to be possible entities concerned in reaction by the conventional two-stage mechanism. We may know the overall rates of formation and decomposition of these entities by study of the product-proportions; but we do not know their stationary



(146) (147) (148) (149)

concentrations in the reaction mixtures, nor have we much evidence concerning their rates of interconversion, nor concerning their possible other reactions.

Halogenodeacylations also occur in olefinic systems, though again the mechanistic details are not yet established. The halogenation of enol acetates is well known and has been documented extensively in the steroid series for chlorination, bromination and fluorination[252,341], and there have been some mechanistic speculations concerning these reactions. Jones and Wluka[342] have proposed the cyclic mechanism indicated in formula **150** as one possibility; in some other circumstances[343], the experimental conditions suggest the possibility that the removal of the acetyl cation is assisted by base, as in some of the examples from aromatic chemistry mentioned above[337,338]. On the other hand, an addition–elimination sequence has been discussed for a formally related case[344]. Such sequence are difficult to disprove when the hypothetical intermediate adducts cannot be isolated.



(150) (151) (152)

One of the most interesting reports in this area relates to observations suggesting that attack by halogen with displacement of an acyl group from a remote centre can become a reality. Reich and Lardon[345] have described the conversion of the enol acetate **151** into the bromoketone **152** by treatment with *N*-bromoacetamide in *t*-butanol or in aqueous acetone. Addition–elimination sequences, as well as cyclic processes, seem unlikely in a case such as this, for which there are other analogies[341].

B. Electrophilic Replacement of Halogen at Unsaturated Centres

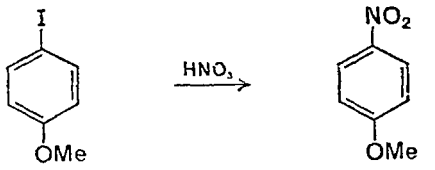
There have been a few mechanistic investigations of protodehalogenations (equation 102), which formally represent the reversal of an electrophilic halogenodeprotonation. The effects of substituents on the rates of

displacement of iodine from iodophenols are as expected for an electrophilic process[346]. The ease of removal of the different halogens is in the order I > Cl, and the reaction is facilitated by steric acceleration if sufficiently

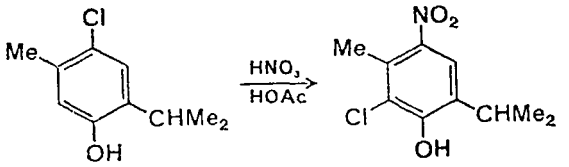
$$\text{ArHal} + \text{HX} \longrightarrow \text{ArH} + \text{HalX} \qquad (102)$$

large and appropriately placed substituents are present. The kinetics of deiodination of *p*-iodoaniline show that the reaction is first-order with respect to the stoicheiometric concentration of the aromatic compound and is independent of the concentration of hydrogen ion and of iodide ion[347]. The reaction was considered to involve the proton attacking the *p*-iodoaniline molecule (present in small concentration under these conditions), and the dependence of the extent of *N*-protonation on acidity was deduced to be the reverse of the acidity dependence of the rate of proton attack at carbon. The reaction was found to be six times faster in H_2O than in D_2O, and no evidence was found for catalysis by iodide ions. The mechanism of deiodination was considered, therefore, to be mechanistically the reverse of iodination.

Nitrodehalogenations are known also (e.g. equation 103); they have been reviewed by Nightingale[348]. They occur most characteristically when the halogen is activated by a strongly electron-releasing group and examples are known for chlorine, bromine and iodine. The ease of the process seems to be greatest for iodine and least for chlorine; when the latter group is displaced, it sometimes resubstitutes elsewhere in the molecule (cf. equation 104).



(103)



(104)

No doubt other types of dehalogenation are possible. Some recent investigations throw light on a major additional mechanistic possibility available for the electrophilic displacement of the higher halogens, particularly iodine and bromine. This involves nucleophilic catalysis, particularly by halide ions, of the removal of positive halogen, and comes

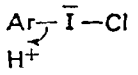
about because the outer electronic shell of the higher halogens can be expanded by the use of *d*-orbitals to hold more than eight electrons (equation 105, cf. equation 106).

$$Ar{-}I + I^- \rightleftharpoons [Ar{-}I{-}I]^- \quad (105)$$

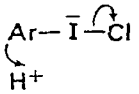
$$I_2 + I^- \rightleftharpoons [I{-}I{-}I]^- \quad (106)$$

The likelihood of the existence of such a mechanism became apparent when it was recognized that complexes having this stoicheiometry are intermediates in the halogenation both of olefinic and of aromatic systems, as we have already noted. In passing, we may comment also that it is by no means clear that the geometry of such an intermediate must necessarily be linear, as in the trihalide ions; angular isomeric forms may also be accessible[349].

Kinetic evidence for the participation of such intermediates in the protodeiodination of iodo-2,4,6-trimethoxybenzene was presented by Batts and Gold[350]. The reaction was found to be catalysed by chloride ions, and the complex kinetic form was analysed in terms of two reaction paths, both involving hydrogen and chloride ions and both competing with the normal acid-catalysed path not involving chloride ions. It seems certain that one of the transition states for protodeiodination catalysed by chloride ions can have the form shown in **153a**, and it was suggested that an alternative isomeric transition state **153b** differs in the timing of the proton loss, and so can differ in the primary and solvent isotope effects to which it is subject.



(153a)

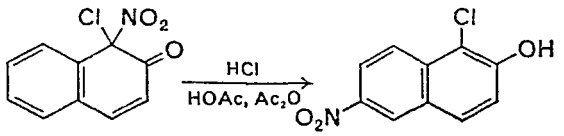


(153b)

An interpretation involving similar intermediates was given of the isomerization and disproportionation of the *p*-bromophenols[351]. When 3-methylphenol, for example, is brominated in an aprotic solvent at 25°C, the kinetically controlled product is, as expected, 4-bromo-3-methylphenol, with lesser amounts of the 6- and 2-bromo-derivatives. If, however, the reaction mixture is allowed to stand, the main product isomerizes and disproportionates, to give much larger amounts of the products of 2-substitution together with some dibromo-derivatives. It was suggested that reversible bromide-catalysed protodebromination had occurred, and was followed by rapid rebromination to give ultimately an equilibrium mixture of products. Direct investigation of the reaction of 4-bromophenol with hydrogen bromide confirmed this interpretation; it was shown also that

hydrogen chloride was a worse catalyst, and that neither toluene-*p*-sulphonic acid nor trifluoroacetic acid was effective. The corresponding chlorophenols did not rearrange under such mild conditions and it is interesting to note also that in the time necessary for the attainment of an apparent equilibrium mixture of products, no products brominated *meta*- to the deactivating group were detected. True thermodynamic equilibrium between all the isomeric products had not, therefore, been obtained; higher temperatures and more powerful catalysts would be needed for this.

The other mechanisms available for halogenodeprotonation can be documented also for dehalogenations. In the reaction of 1-chloro-1-nitro-2-keto-1,2-dihydronaphthalene (**154**) with hydrogen chloride in a mixture of acetic acid and acetic anhydride, the main product involves migration of the nitro-group (equation 107); 1-chloro-2-naphthol is another product.



(154) (107)

For the corresponding bromo-compound (**155**) on the other hand, the sole product was 1-nitro-2-naphthol (equation 108). This reaction, the

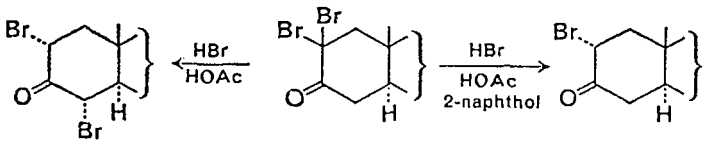
(155) (156) (108)

probable path for which involves the intermediate **156**, is a two-stage protodebromination with rearrangement, falling into the S_E2' classification in the sense in which we have used such terms in this article.

In discussing these reactions in terms of the relative leaving abilities of different groups, Perrin[352] distinguishes between those groups which he regards as generally leaving by S_N1 processes (e.g. NO_2^+, *t*-Bu$^+$, NO^+), and those which he regards as always nucleophilically assisted (e.g. Cl^+, Br^+, RCO^+, H^+). It seems to the writers that no such clear distinction can be made. Certainly the halogens and certain other groups as well (e.g. $MeCO^+$) can have their heterolysis assisted by added nucleophiles, but even in the absence of nucleophilic anions these groups can undergo similar displacements, and then it is probably better to regard the solvent as exercising its influence by solvation rather than by covalent assistance.

Addition–elimination sequences are almost certainly available for dehalogenations also. We have already noted that nitration can be shown in some circumstances (particularly when acetic acid and mixtures of acetic acid and acetic anhydride are used as the solvent) to proceed by routes of this kind[247]. This makes it very probable that some of the nitrodehalogenations already mentioned[348] proceed in part at least by such paths.

Reactions corresponding to those described above are available also for aliphatic compounds, though not a great number of examples have been examined mechanistically. Kirk and Hartshorn[341] have collected a number of cases from the chemistry of steroidal α-halogenoketones. Thus 2,2-dibromo-5α-cholestane-3-one (**157**) rearranges with hydrogen bromide in acetic acid to give the 2α,4-dibromoketone (**158**), but with the same reagent in the presence of 2-naphthol to act as a scavenger for bromine gives the 2α-bromoketone (**159**). It is suggested, therefore, that bromide-catalysed debromination occurs in this system; the axial bromine is removed in preference to the equatorial bromine, in accordance with the known stereochemical preference of the reverse reaction. Whereas hydrogen iodide was shown to be a catalyst also for this reaction, neither hydrogen chloride nor perchloric acid were effective. It appears also that the corresponding chloroketones are not susceptible to this type of reaction, so the analogy with the behaviour of the corresponding aromatic compounds seems to have been documented fairly extensively on a qualitative basis.



(158) (157) (159)

C. Electrophilic Replacement by Halogen at Saturated Centres

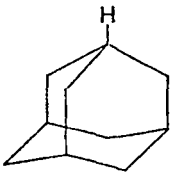
1. Replacements of hydrogen

Direct replacement of hydrogen from a saturated centre by a bimolecular electrophilic process is difficult; the only definite examples[353,354] involve deuterium exchange into methane and other hydrocarbons in solution in a mixture of hydrogen fluoride and antimony pentafluoride at temperatures around 0°C. This mechanism appears to become available easily only under conditions involving very high acidity of the medium. The geometry of the transition state is not known, though Olah and coworkers' treatment[354] postulates a triangular three-centre transition state **160** (equation 109) in

which the electrons of the C—H bond are attacked, thus implying retention of configuration. Since adamantane, with its rigid cage structure **161**, is reported to undergo exchange into the bridgehead protons under these conditions, it would seem that such a route must be available.

$$R_3C{-}H + D^+ \longrightarrow \left[R_3C\!\begin{matrix}D\\H\end{matrix}\right]^+ \longrightarrow R_3C{-}D + H^+ \qquad (109)$$

(160)



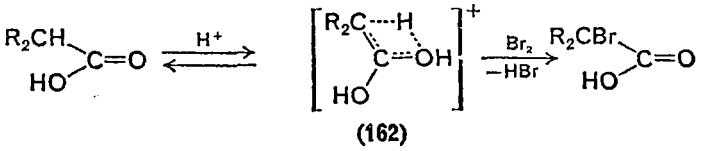
(161)

There are a number of other ways by which halogenation of saturated carbon atoms can be effected, and there is mechanistic information about some of these. The best known are the various processes by which halogen can be introduced adjacent to an electron-withdrawing substituent. We have already mentioned (Section II. A. 3. d; sequence (97) and associated discussion) that in such halogenations the details of the processes which follow the rate-determining proton loss are not known with certainty and need not be the same under all conditions or in all cases.

Although most such reactions characteristically have a rate independent of the concentration or nature of the halogen, it has proved possible in certain cases by study of the reaction at very low concentration of halogen to identify the individual rates of enolization and halogenation[304,355]. Effects of change of structure and of halogen are relatively small. It is not yet clear whether this comes about because of the special nature of the transition state for bromination of the enol or of its anion, or whether the rates of halogenation of these intermediates are so fast that the rate of diffusion limits the observable rate of reaction.

Kwart and Scalzi[356] have measured the rates of bromination of a number of carboxylic acids in dipolar aprotic solvents. Evidence was obtained for partial dependence of the rate on the concentration of bromine. From this, from the effect of structure on the rate of reaction, and from the small magnitude of the primary deuterium isotope effect, they deduced that pre-equilibrium protonation of the C=O group gives a complex in which the potentially migrating hydrogen is partly bonded to three centres (**162**),

but that proton-transfer is not completed until this complex is attacked by halogen (sequence 110). Although their evidence is consistent with this view, it probably cannot be regarded as compelling in character.

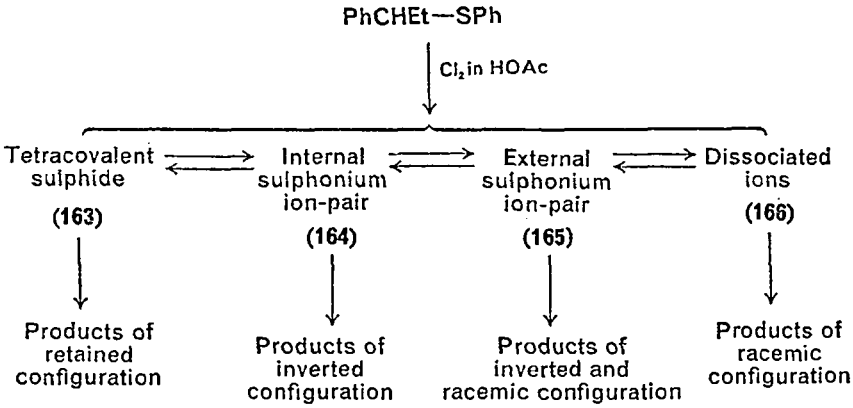


(110)

(162)

2. Replacements of groups other than hydrogen

Studies of the course of the reactions of arylalkyl sulphides and of alkyl and cycloalkyl benzenesulphenates with chlorine in acetic acid indicate complex mechanistic features which provide some instructive comparisons. The reaction of optically active α-ethylbenzyl phenyl sulphide[357] gives inverted arylalkyl chloride with considerable but not complete retention of optical purity, together with inverted arylalkyl acetate with much less retention of optical purity. From the influences of added salts on the extent of racemization and on the product ratio, it was concluded that the intermediates concerned are those shown in Scheme 18

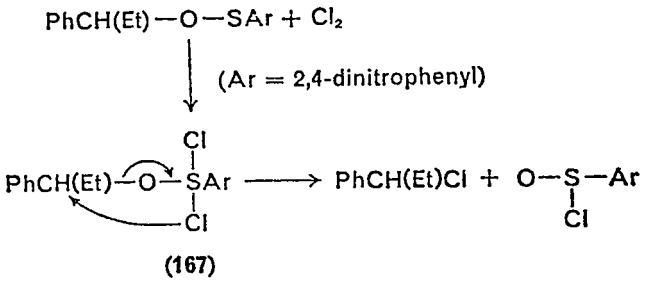


SCHEME 18. Intermediates in the chlorinolysis of arylalkyl sulphides.

(**163–166**). Each of the intermediates indicated in the scheme is multiple in character, depending on the anions concerned (i.e. the tetracovalent sulphide could be $PhCH(Et)SCl_2Ph$ or PhCH(Et)SCl(OAc)Ph or a mixture of these): and the products with which we are concerned are the chloride, PhCH(Et)Cl, and the acetate, PhCH(Et)(OAc). They are considered to be formed in different ratios from the different intermediates: chloride mainly from **163** and **164**, acetate mainly from **165** and **166**. The transition

state leading to products of retained configuration from **163** is believed to be S_Ni in character, whereas those leading to products of inverted and racemic configuration could be of the other kinds involved in chlorinations of alcohols by thionyl chloride.

The chlorinolysis of sulphenate esters, although similar in general characteristics[358,359], shows important stereochemical differences. In particular, in the reaction of α-ethylbenzyl 2,4-dinitrobenzenesulphenate with chlorine in acetic acid, the products were mixtures similar to those obtained for the corresponding sulphide, but by far the largest proportion of the chloride fraction had retained configuration, whilst the acetate was formed with predominantly inverted configuration. Sequence (111) represents one part of the reaction path, with the four-centred S_Ni reaction of the covalent intermediate indicated by the arrows in **167**. Study of the effects of salts on the product ratios implicates complicated multiple ion-pair sequences[357–359].



(111)

(167)

Among the general questions raised by these studies are those of classification. Sequence (111), for example, is clearly a substitution (of OSAr by Cl or by OAc); it is initiated by electrophilic chlorine, it involves initial attack remote from the centre of substitution and the subsequent stages can occur by more than one mechanism. Perhaps the nearest classificational analogy is with what we have called 'indirect substitution' in Section III. A. 3. h; the formation of acetate, however, is reminiscent of the formation of acetoxylated products accompanying nitration, first formulated as an electrophilic acetoxylation but now recognized to proceed by an addition–elimination sequence[247] (Section III. A. 3. e).

Reaction of any substrate, therefore, in which some centre other than that at which substitution is finally to be effected is susceptible to the required initial attack, could potentially proceed by an indirect route of this kind. In the electrophilic example chosen, (sequence 111) the initial reaction (a) brings the reagents together, so favouring the required reaction for reasons of entropy, (b) transforms the attacking species into

one which may be more potent for final reaction and (c) favours the required heterolytic fission necessary for the final replacement.

Since electrophilic replacement at carbon will be promoted by increasing the electropositive nature of the group subject to displacement, it is to be expected that compounds having a C–metal bond will be subject to such reactions. The relatively low bond-strengths of many such bonds will also favour heterolytic reaction and the incursion of mechanisms involving free radicals. In fact, radicals have often been considered to be concerned in the halogenation of C–metal compounds, as in the reaction of bromine with cyclopropyl lithium[360], and in the bromination of alkylmercury compounds[361,362]. In both these cases, it seems that reactions by the radical path usually result in rather indiscriminate formation of racemic, epimeric or geometrically isomeric products, whereas those portions of the reactions in which stereochemical configuration is preserved in the product are thought to be electrophilic substitutions[360–363]. The detailed characters of the transition states are, however, uncertain even when kinetic measurements have been made; often some contribution from bonding to the metal is a very real possibility.

There has been some mechanistic investigation of the cleavage of tin tetra-alkyls by halogens[364]. The stoicheiometry is that given by equation (112). The reactions are first-order in each reactant and the addition of

$$R_4Sn + I_2 \longrightarrow I^- + IR + R_3Sn^+ \qquad (112)$$

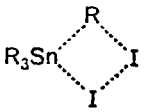
iodide ions has a negligible effect on the rate. Increase in the ionic strength of the medium, however, promotes the reaction. Some effects of structure and of solvent are shown in Table 20.

TABLE 20. Effects of structure and of solvent on the relative rates of electrophilic displacements by halogens on tetra-alkyl tins

Reaction:	$R_4Sn + Br_2$	$R_4Sn + Br_2$	$R_4Sn + I_2$
Solvent:	PhCl	AcOH	AcOH
Relative rate, R = Me	100	100	100
R = Et	1200	84	37
R = *n*-Pr	450	12	4·3
R = iso-Pr	1300	2·5	0·03

It is suggested that the reactions in acetic acid involve electrophilic displacement by halogen; the important influence of steric hindrance in diminishing the rate of reaction is evident from the effect of increasing the

bulk of the alkyl groups around the tin atom, and suggests that the bimolecular process involves approach by the reagent and bonding of it to the centre of substitution. Considerable polarity is believed to develop in the transition state, as indicated by the effect of the solvent and of added salts. In less polar solvents like chlorobenzene, however, where steric hindrance to substitution is less evident or absent, it is suggested that a cyclic mechanism involving a four-centre transition state **168** is more probable.



(168)

The reaction of tetra-allyl tin with iodine is very much faster than that of tetra-*n*-propyl tin, so Gielen and Nasielski[304] propose an S_E2' mechanism (equation 113) in this case.

$$R_3Sn\overset{\curvearrowright}{-CH_2}-CH=\overset{\curvearrowright}{CH_2}\quad I\overset{\curvearrowright}{-}I \rightarrow R_3Sn^+ + CH_2=CH\cdots CH_2I + I^- \qquad (113)$$

It seems likely that variants of such mechanisms are available for the reactions of halogens with many organometallic compounds[372].

D. Electrophilic Replacement of Halogen at Saturated Centres

1. Introduction

In the reaction of equation (114) there are two features which define that electrophilic substitution of halogen is occurring at the organic group

$$E^+ + R{-}Hal \longrightarrow E{-}R + Hal^+ \qquad (114)$$

R: the fact that positive halogen is produced and that the incoming electrophile derives its new bonding electrons from R. There appears to be no well-characterized example of this reaction path occurring at saturated carbon. The reason may be that thermodynamic factors are usually unfavourable, since heterolytic reaction in the reverse direction has been fairly well established. On grounds of electronegativity the formation of positive halogen is likely to be less favoured than the opposite heterolysis to give anionic halogen. We have discussed how the latter reaction may be assisted by electrophiles, as is exemplified by catalysis of the replacement reactions of alkyl and acyl halides by hydrogen halides and by Lewis acids.

It is a reasonable expectation that nucleophilic catalysis of electrophilic substitution would provide an accessible reaction path (equation 115). This

$$E^+ + R{-}Hal \quad :Nu \longrightarrow ER + Hal{-}Nu \qquad (115)$$

process can be regarded as nucleophilic substitution at halogen, and may be expected to occur when R is a good anionic leaving group, or when co-ordination with an electrophile occurs either prior to, or simultaneously with, nucleophilic attack.

2. Reactions which liberate halogen

Nucleophilic attack on halogen occurs when haloketones react with acidified potassium iodide (equation 116) as in Meyer's method[365] for

$$RC^+(OH)CH_2Br + I^- \longrightarrow RC(OH){=}CH_2 + IBr \qquad (116)$$

estimation of enolic content in protropic carbonyl systems. Here the leaving group involves carbon; in analogous cases, it may be a substituted nitrogen as in the chlorine-producing step of the Orton rearrangement[366] of *N*-haloanilides (equation 117), or may be oxygen, as in equation (118).

$$ArNH^+(Ac){-}Cl + Cl^- \longrightarrow ArNHAc + Cl_2 \qquad (117)$$

$$H_2O{-}Cl^+ + Cl^- \longrightarrow H_2O + Cl_2 \qquad (118)$$

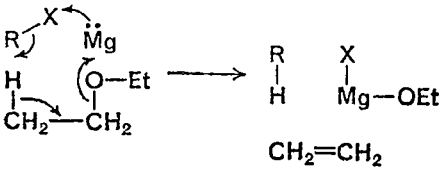
3. Metallation of halides

The formation of organometal compounds by the reaction of metals with alkyl and aryl halides may reasonably be regarded as involving nucleophilic attack on halogen (equation 119). Here a metal behaves as a nucleophile,

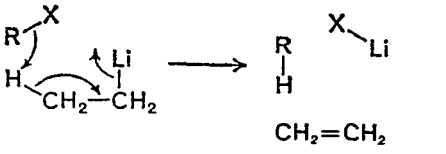
$$R{-}Hal + :Mg \longrightarrow R^- + MgHal^+ \qquad (119)$$

but this is a stoicheiometric description and may not properly depict the mechanism, since electron transfer may be stepwise. The direct syntheses of organometallic compounds have been considered[367], and it is notable that these reactions are frequently catalysed by electrophiles such as bromine. Metallation by magnesium has been reviewed in detail[368]. An optically active Grignard reagent has been prepared[369]. Partial racemization accompanies the preparative step and is interpreted in terms of two one-electron transfers. A two-electron transfer as represented in equation (119) would, however, produce a carbanion which must subsequently react to form RMgX, and such a step could likewise produce racemization. The

reductive side-reaction observed may well involve an ionic process in which the solvent, diethyl ether, acts as a source of electrophilic hydrogen (equation 120). A similar pathway has been proposed[381] to explain the occurrence of reduction (equation 121) instead of the metal–halogen exchange observed in more polar solvents for reaction between lithium alkyls and alkyl halides. Metallation reactions are commonly interpreted as involving radicals, and the mercuration of halides has been described in this way by Makarova and Nesmayanov[362].



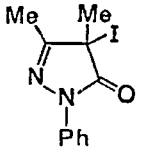
(120)



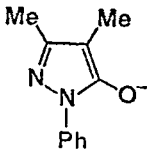
(121)

4. Iodine exchange

Noyes and Körös[370] discuss iodine exchange in some heterocyclic compounds containing iodine. For 1-phenyl-3,4-dimethyl-4-iodo-2-pyrazolin-5-one (**169**), the enolate anion (**170**) would be expected to have

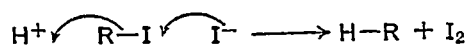


(169)



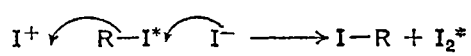
(170)

considerable stability by virtue of an aromatic sextet of electrons. In fact, iodide ion gives iodine in acid solution with this compound (equation 122).



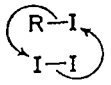
(122)

Exchange with iodide ion in neutral solution is slow, but is rapid with iodine; the mechanism of this process may be written as in equation (123).



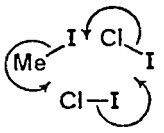
(123)

Where, as in this case, electrophile and nucleophile are combined in the same molecule, the reaction may occur via a cyclic transition state (**171**),

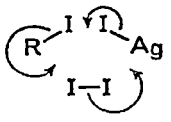


(171)

and considered in terms of electrophilic substitution at R. The transition state for such a reaction need not necessarily be electrically neutral, and for certain other heterocyclic iodides, Noyes and Körös[370] show that the rate of iodine exchange is not altered significantly by light or oxygen, but is accelerated when nitrobenzene is added to increase the polarity of the solvent, a result which indicates considerable development of charge in the transition state. Higher-order terms observed in these and similar exchanges[371] may also have similar polar cyclic transition states (e.g. **172**).



(172)

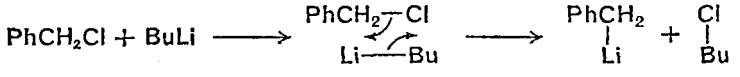


(173)

Catalysis by Hg^{2+} or Ag^{+} in the reactions may be of the form **173**, although alternative possibilities involving intermediates in which R is transferred to the catalysing metal have not been excluded. Transition states of this nature have been discussed by Dessy and Kitching[372]. Oxidative addition of alkyl and acyl halides to Group 8 metal complexes[373,374] show some similarities in kinetic patterns[375] and may be mechanistically analogous.

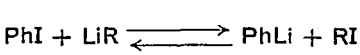
5. Halogen–metal exchange reactions

Halogen–metal exchange reactions (e.g. equation 124) are formally similar to those described above when described by the transition state **174**. These reactions have been regarded as Lewis acid–base reactions in



(174) (124)

which the bases Bu^{-} and $PhCH_2^{-}$ are competing for halogen rather than for a proton. Equilibrium constants have been determined for reaction (125),



(125)

in order to derive an order of carbanionic stability[376]. The aryl and alkyl groups are clearly acting as nucleophilic centres subject to electrophilic replacement, and suitable cases would be expected to show the stereochemistry associated with electrophilic substitution at saturated carbon by the S_E2 or S_Ei mechanism (reference 7, p. 563). An example is the reaction of optically active 2-iodo-octane with butyl lithium, analysed by carbonation, which gave 2-methyloctanoic acid of the same configuration accompanied by approximately 80% racemization[377]. Less racemization and greater retention (60%) were observed for the reaction of optically active 1-bromo-1-methyl-2,2-diphenylcyclopropane with butyl lithium, analysed as the methyldiphenylcyclopropane[378].

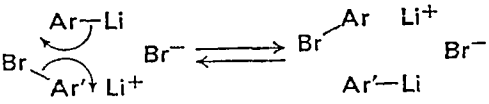
The kinetics of halogen–metal exchange reactions have been investigated by Winkler and Winkler[379] for the reaction of equation (126). They

$$\text{Ar—Li} + \text{Ar'—Br} \rightleftharpoons \text{Ar—Br} + \text{Ar'—Li} \qquad (126)$$

considered various mechanisms involving dimeric ArLi species, and the representation shown in equation (127) would accord with their mechanism

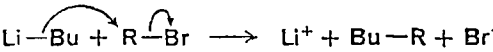
(127)

B. The value of ρ in the Hammett sigma–rho correlation is 4, a fact which indicates that an increase of negative charge in the aromatic nucleus occurs in proceeding to the transition state. The reaction involves a transition state more polar than the initial state, since the rate is increased in changing from ether to tetrahydrofuran as solvent. In the presence of lithium bromide the mechanism changes, and it may be suggested that the reduction in rate is due to a new transition state in which one participating molecule of LiAr is replaced by a molecule of LiBr (equation 128). More complex



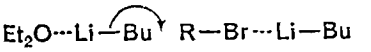
(128)

interpretations are possible; Brown[380] has considered systems involving hexamers in hydrocarbon solvents. Eastham and Gibson[381], from results of a kinetic investigation of Wurtz-type nucleophilic substitutions (e.g. equation 129), consider this reaction to be tetramolecular and to have a



(129)

transition state (**175**) which involves the solvent, diethyl ether (acting as a Lewis base to remove lithium ion) and a further molecule of butyl lithium (acting as a Lewis acid to remove a halide ion).



(175)

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The Chemistry of The Carbon-Halogen Bond: Part 1
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CHAPTER 8

Homolytic mechanisms of substitution

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I. INTRODUCTION

A. General Mechanism

The substitution of a carbon-bonded hydrogen for a halogen atom is one of the more useful chemical reactions available for 'functionalizing' a carbon atom thereby making it labile to reaction with a variety of chemical intermediates. The most facile means of accomplishing such substitutions is by reactions involving free radical intermediates that effect the homolysis of the carbon–hydrogen bond.

Many different carbon–hydrogen bonds are encountered in organic compounds. The facility with which a desired substitution can be attained depends to a great extent on the chemical environment in which that particular carbon–hydrogen bond is found. Furthermore, a variety of reagents are available to serve as the source of the halogen atom (the halogenating agent). In spite of the diversity of reactions that might be expected from the possible combinations of carbon–hydrogen bonds and the halogenating agents, all of these substitutions follow the same general mechanistic path. The reactions proceed by a chain sequence of processes that involve free radicals as reaction intermediates. The substitution of the halogen atom 'X' for hydrogen in reaction (1) is accomplished in the chain

$$-\overset{|}{\underset{|}{C}}H + XY \longrightarrow -\overset{|}{\underset{|}{C}}-X + HY \qquad (1)$$

sequence (2) and (3). The free radical Y$^{\bullet}$ that performs the homolysis of the carbon–hydrogen bond may be either a halogen atom (X$^{\bullet}$ = Y$^{\bullet}$) if molecular halogen is the halogenating agent (XY = X_2) or some free

$$-\overset{|}{\underset{|}{C}}\cdot + XY \longrightarrow -\overset{|}{\underset{|}{C}}-X + Y\cdot \qquad (2)$$

$$Y\cdot + -\overset{|}{\underset{|}{C}}H \longrightarrow HY + -\overset{|}{\underset{|}{C}}\cdot \qquad (3)$$

radical derived from the halogenating agent (e.g. $Y^{\bullet} = Cl_3C^{\bullet}$ if Cl_3CX is the halogenating agent). The facility with which the hydrogen atom is removed from the organic molecule depends both on the nature of $Y^{\bullet}$ and the chemical environment of the hydrogen atom being abstracted by the radical. Most organic compounds have different kinds of hydrogens available for reaction with the hydrogen abstracting radical $Y^{\bullet}$. It is pertinent therefore to determine the specificities displayed by the various hydrogen abstracting radicals for the various kinds of hydrogens since, precluding any rearrangements of the radical formed in this process, the site of the halogen atom in the reaction product is on that carbon from which the hydrogen has been abstracted.

Although the stoicheiometry of a halogenation reaction is determined in the chain sequence (provided the sequence repeats itself sufficiently often), other important processes are a necessary part of the overall halogenation reaction. One of these is the radical-producing or initiation reaction, the process by which free radicals are introduced into the system so that the chain reaction can take place. In many halogenation reactions, initiation is accomplished by photolysis of the halogenating agent, producing two free radicals that start two chain sequences. In some cases, initiation of the

$$XY \xrightarrow{h\nu} (XY)^{*} \longrightarrow X^{\bullet} + Y^{\bullet} \tag{4}$$

chain reaction is effected by the thermal decomposition of appropriate compounds (e.g. peroxides and azo-compounds). The initiator fragments, depending on their structure, may react with either the halogenating agent or the substrate yielding chain-carrying free radicals that start the chain sequence.

$$\text{Initiator} \longrightarrow 2\ \text{Rad}^{\bullet} \tag{5}$$

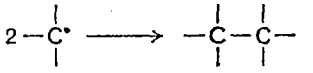
$$\text{Rad}^{\bullet} + XY \longrightarrow \text{Rad}{-}X + Y^{\bullet} \tag{6}$$

or

$$\text{Rad}^{\bullet} + \begin{array}{c} | \\ -C- \\ | \end{array} H \longrightarrow \text{Rad}{-}H + \begin{array}{c} | \\ -C^{\bullet} \\ | \end{array} \tag{7}$$

Free radicals are removed from the reaction medium in bimolecular radical interactions referred to as termination reactions. A chain sequence having two different chain-carrying free radicals has three possible termination reactions, bimolecular reactions of either radical with itself (reactions 8 and 9) or a cross-termination (reaction 10). The particular termination reaction that may be operative depends on the relative concentrations of the two free radicals. The concentrations of the chain-carrying radicals are determined by the reactivities of the free radicals in

their respective chain-propagating reactions and the relative concentrations of the reagents. The kinetic rate laws for the halogenation reactions reflect



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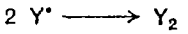

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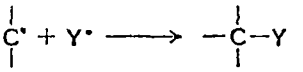

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not only the initiation and chain sequence but also the particular reaction that terminates the chain sequence (see section II. C).

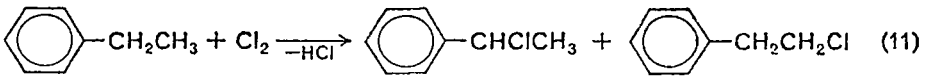
B. Scope of this Chapter

1. Molecular halogens

By far the most economically available halogenating agents are the molecular halogens themselves. Each of the halogens (chlorine, bromine, iodine and fluorine) has its own peculiarities. Some of the general characteristics of the halogens as halogenating agents are outlined here and covered in more detail subsequently in this chapter.

a. Chlorine. Elemental chlorine is a most readily available commercial material and is used extensively as an industrial halogenating agent. Chlorine reacts with most compounds having a carbon–hydrogen bond in free-radical chain reactions having, in some instances, extremely long kinetic chain lengths (the number of times the free-radical chain sequence repeats itself). Initiation of chlorination reactions with molecular chlorine is facilitated by its ease of photolysis although some reactions can be initiated by thermolysis of molecular chlorine.

The chief disadvantages of chlorine as a halogenating agent centre around the reactivity of the chlorine atom as a hydrogen atom abstracting species. Although this characteristic is largely responsible for the long kinetic chain lengths observed for many chlorination reactions, it is also responsible for the lack of its specificity as a hydrogen atom abstractor. Most carbon–hydrogen bonds are labile to attack by chlorine atoms and, unless the compound to be halogenated has only one type of hydrogen (e.g. methane, ethane and the cycloalkanes), mixtures of monochlorinated products are formed. For example, chlorination of ethylbenzene with molecular chlorine yields a mixture of α-chloroethylbenzene and β-chloroethylbenzene. Bromination of ethylbenzene with molecular bromine, on the other hand, yields only the α-bromoethylbenzene.



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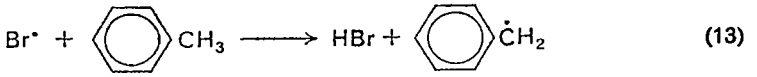
Much of the real interest in the investigations that have been reported concerning chlorinations with molecular chlorine centres around the behaviour of the chlorine atom as a hydrogen abstractor. Being an electronegative species, polar factors in the substrates with which it reacts play a significant role in dictating the site of hydrogen abstraction. Chlorine atoms also complex with many species altering their reactivities as hydrogen abstractors and thereby render chlorination reactions sensitive to certain solvent effects. Both polar and solvent effects encountered in chlorinations with molecular chlorine are discussed in detail in section III of this chapter.

b. Bromine. Molecular bromine is a more specific halogenating agent than chlorine. The hydrogen atom abstracting species in brominations with bromine is the bromine atom, a less energetic and therefore more selective free radical than the chlorine atom. Whereas chlorination often leads to mixtures of monochlorinated products, a single monobrominated product is often formed in reactions of molecular bromine even with compounds having different types of hydrogen atoms available for substitution.

Although the degree of selectivity displayed by the bromine atom as a hydrogen abstractor does give bromine definite advantages over chlorine, it does also have some distinct disadvantages. The less energetic bromine atom reacts readily only with carbon–hydrogen bonds that are chemically labile because of certain polar and resonance factors. Unless such a carbon–hydrogen bond is available for reaction, the kinetic chain length of the bromination chain sequence may be short. For example, bromine reacts with toluene in a reaction having a comparatively long kinetic chain length. The limiting step in the chain is the hydrogen atom abstraction which occurs readily in a reaction involving benzylic hydrogens with bromine atoms. On the other hand, methane reacts with bromine only in



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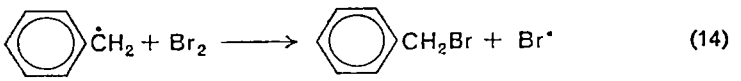


(14)

short kinetic chain length reactions. In this case, the hydrogen atom abstraction reaction renders a serious limiting effect on the chain sequence because of the low reactivity of the carbon–hydrogen bond of methane toward reaction with the bromine atom. Both methane and toluene, on the other hand, react with chlorine in reactions having long kinetic lengths.

$$Br^{\bullet} + CH_4 \longrightarrow HBr + CH_3^{\bullet} \quad (15)$$

$$CH_3^{\bullet} + Br_2 \longrightarrow CH_3Br + Br^{\bullet} \quad (16)$$

Another disadvantage of bromine is its cost. Although this is certainly not a serious limitation for most laboratory preparations, the economic disadvantage of bromine in comparison to chlorine as an industrial reagent does curtail its use to the manufacture of specialty items where either a high degree of specificity is required or the element itself is an essential factor in the reaction product. In contrast, chlorinations with molecular chlorine are used extensively to produce a variety of large-volume products (e.g. chlorinated solvents) and chemical intermediates for the production of other materials.

c. Fluorine. Molecular fluorine is an extremely reactive species that reacts with most compounds having carbon–hydrogen bonds. Reactions with alkanes usually result in extensive fragmentation of the carbon chain ultimately yielding carbon tetrafluoride as the major reaction product. The peculiarities of the free-radical reactions of fluorine with alkanes can be attributed mainly to the reactivity of fluorine atoms as chain-carrying free radicals. Part of the difficulty arises from the oxidizing ability of molecular fluorine itself which reacts with readily oxidizable carbon–hydrogen bonds in a bimolecular process that results in formation of free radicals which initiate the chain sequence. Although seemingly an advantage at first inspection, too much initiation can be unfavourable not only from the standpoint of rate control but also because it leads to the formation of large amounts of undesired termination products. For these reasons, the introduction of fluorine in organic compounds is generally not accomplished by the free-radical chain reaction route.

d. Iodine. Molecular iodine does not react at ordinary temperatures in the free-radical chain sequence shown in equations (2) and (3). Its reluctance to do so can be ascribed to the low reactivity of the iodine atom as a hydrogen atom abstractor. One might expect that if it could react, molecular iodine would be even more selective as a halogenating agent than bromine. Other halogenating agents have been observed that do allow for the substitution of a carbon-bonded hydrogen for iodine but have received little study.

2. Other halogenating agents

Many species containing a halogen atom can be used as halogenating agents. In most cases, the mechanism of the reaction for the halogenation reaction is essentially identical to that for chlorine and bromine. The one distinguishing feature of many of these materials is that the hydrogen abstraction is performed by some free radical other than a halogen atom. The specificity of the hydrogen atom abstraction, therefore, is often different from that encountered in the halogenation reaction using the elemental halogens. Thus, chlorinations with sulphuryl chloride in some instances involve hydrogen abstraction by the chlorosulphonyl radical which is less energetic and therefore more selective as a hydrogen atom abstractor than the free chlorine atom. Other chlorinating agents that

$$ClSO_2^{\bullet} + RH \longrightarrow HCl + SO_2 + R^{\bullet} \quad (17)$$

$$R^{\bullet} + SO_2Cl_2 \longrightarrow RCl + ClSO_2^{\bullet} \quad (18)$$

display a degree of specificity greater than molecular chlorine because of characteristics of the hydrogen atom abstracting radical are Cl_3CSO_2Cl, Cl_3CSCl, PCl_5, $(CH_3)_3COCl$, ICl_3 and $C_6H_5ICl_2$.

Some compounds that have been investigated as brominating agents are $BrCCl_3$, $BrCCl_2CCl_2Br$, BrCl, $(CH_3)_3COBr$ and the *N*-bromoamides. For some of these reagents, a bromine atom is actually the hydrogen atom abstracting radical. The reasons for using brominating agents other than molecular bromine do not, consequently, stem from the specificity that might be found in having a different hydrogen atom abstracting radical participate in the chain sequence. In some cases, a specificity is observed (e.g. the allylic bromination of alkenes with *N*-bromoamides) but it arises from other factors (see section IV. D). In some instances (the major exception being the *N*-bromoamides), the brominating agents have been largely employed in mechanistic investigations directed at the study of free radicals as reaction intermediates.

II. ENTHALPIC AND KINETIC ASPECTS

A. Bond Dissociation Energies

The energy required to break a chemical bond homolytically, a process that yields two free radicals, is determined both by the nature of the bond and by the structures of the free radicals that are produced. The bond-dissociation energies of several carbon–hydrogen bonds are listed in Table 1. Although the same type of bond is broken in each case, the bond-dissociation energies vary considerably, depending on the degree of

resonance stabilization of the free radicals resulting from the homolysis. Since each homolysis yields a hydrogen atom, the stability of which would be the same in each case, the differences in the bond-dissociation energies

TABLE 1. Bond-dissociation energies[a] (kcal/mole)

Bond	ΔH_{Dis}	Bond	ΔH_{Dis}
CH_3-H	104	$F-F$	38
C_2H_5-H	98	$I-I$	36
$(CH_3)_2CH-H$	94·5	$HO-Cl$	60
$(CH_3)_3C-H$	91	CH_3-Cl	84
$CH_2=CHCH_2-H$	85	C_2H_5-Cl	81
$C_6H_5CH_2-H$	85	$(CH_3)_3C-Cl$	79
CH_3COCH_2-H	92	$C_6H_5CH_2-Cl$	68
$H-CH_2CN$	86	CH_3-Br	70
Cl_3C-H	96	C_2H_5-Br	69
$(CH_3)_3CO-H$	103	$(CH_3)_3C-Br$	63
$H-Cl$	103	$C_6H_5CH_2-Br$	51
$H-Br$	87·5	Cl_3C-Br	54
$H-F$	136	CH_3-I	56
$H-I$	71	$C_6H_5CH_2-I$	40
$Cl-Cl$	58	CH_3-F	106
$Br-Br$	46		

[a] Bond-dissociation energies are taken from compilations given in J. A. Kerr, *Chem. Rev.*, **66**, 465 (1966) and S. W. Benson, *J. Chem. Ed.*, **42**, 502 (1965).

must be ascribed to differences in the stabilities of the free radicals that are formed. Included in the table are other bond-dissociation energies that are of value in examining the energetic aspects of free-radical halogenation reactions.

B. Reaction Enthalpies

The enthalpies of chemical reactions can be calculated from the bond-dissociation energies of the chemical bonds that are made and broken in the reaction. For example, chlorination of methane is an exothermic process as calculated from the bond-dissociation energies required to break and make the chemical bonds involved in the reaction. It is pertinent to point out that only the initial and final states of the reaction were considered in making the calculation of the reaction enthalpy as shown in (19).

The enthalpy of a free-radical chain reaction can also be calculated in terms of the chain-propagating reactions that compose the chain sequence. Such calculations are of considerable value in understanding free-radical

$$CH_3{-}H + Cl{-}Cl \longrightarrow CH_3{-}Cl + HCl \quad (19)$$

Bonds broken:

$CH_3{-}H$	+ 104 kcal/mole
$Cl{-}Cl$	+ 58 kcal/mole

Bonds made:

$H{-}Cl$	− 103 kcal/mole
$CH_3{-}Cl$	− 84 kcal/mole
	$\Delta H = -25$ kcal/mole

halogenation reactions. Examination of the reaction of methane and chlorine in this manner shows that the same value for the enthalpy is

$$Cl^{\bullet} + CH_3{-}H \longrightarrow HCl + CH_3^{\bullet} \quad (20)$$

$$\Delta H = +1 \text{ kcal/mole}$$

$$CH_3^{\bullet} + Cl{-}Cl \longrightarrow CH_3{-}Cl + Cl^{\bullet} \quad (21)$$

$$\Delta H = -26 \text{ kcal/mole}$$

obtained (the stoicheiometry of the chain reaction is the algebraic sum of the chain-propagating steps). It is obvious that essentially all of the energy evolved comes from the reaction of the methyl radical with chlorine. The hydrogen abstraction reaction, on the other hand, is an endothermic process in this case.

Reactions of bromine with methane and toluene illustrate how the enthalpic requirements for one of the steps in the chain sequence may influence the course of the homolytic substitution reaction. The bromination of methane is exothermic overall but the hydrogen atom abstraction

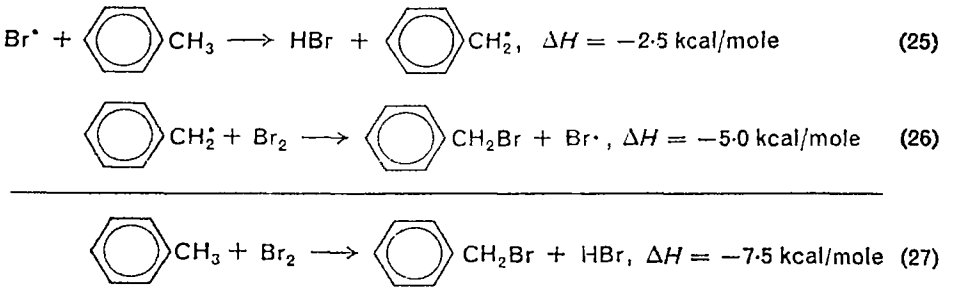
$$Br^{\bullet} + CH_3{-}H \longrightarrow HBr + CH_3^{\bullet}, \quad \Delta H = +16{\cdot}5 \text{ kcal/mole} \quad (22)$$

$$CH_3^{\bullet} + Br{-}Br \longrightarrow CH_3{-}Br + Br^{\bullet}, \quad \Delta H = -24 \text{ kcal/mole} \quad (23)$$

$$CH_3{-}H + Br_2 \longrightarrow CH_3{-}Br + HBr \quad \Delta H = -7{\cdot}5 \text{ kcal/mole} \quad (24)$$

reaction is an endothermic process. The activation energy requirement for the endothermic step in the chain sequence must be at least the endothermicity of the reaction, in this case 16·5 kcal/mole, and presents a sufficiently high energy barrier to introduce a severe limitation to the overall chain reaction. Although methane can be brominated via the chain mechanism shown in equations (22) and (23), the reaction is slow compared to the rate of chlorination of methane under the same conditions.

Toluene, on the other hand, is brominated by molecular bromine in the benzylic position in a free-radical chain process having a long kinetic chain length. The enthalpy for the overall reaction is the same as that of the



$$Br^{\bullet} + C_6H_5CH_3 \longrightarrow HBr + C_6H_5\dot{C}H_2, \quad \Delta H = -2{\cdot}5 \text{ kcal/mole} \qquad (25)$$

$$C_6H_5\dot{C}H_2 + Br_2 \longrightarrow C_6H_5CH_2Br + Br^{\bullet}, \quad \Delta H = -5{\cdot}0 \text{ kcal/mole} \qquad (26)$$

$$C_6H_5CH_3 + Br_2 \longrightarrow C_6H_5CH_2Br + HBr, \quad \Delta H = -7{\cdot}5 \text{ kcal/mole} \qquad (27)$$

bromination of methane. The difference is encountered in that the hydrogen abstraction step in this case is exothermic and does not impose a limiting minimum for the activation energy requirement for the process.

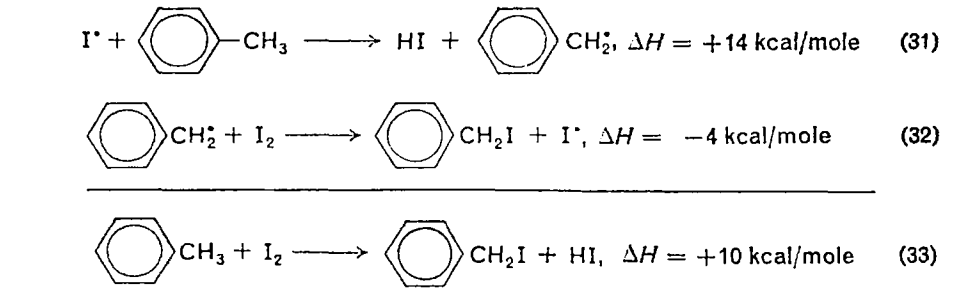
The reactions of iodine with methane and toluene are endothermic. In both cases, the endothermicity of the hydrogen abstraction reaction

$$I^{\bullet} + CH_3{-}H \longrightarrow HI + \dot{C}H_3, \quad \Delta H = +33 \text{ kcal/mole} \qquad (28)$$

$$\dot{C}H_3 + I_2 \longrightarrow CH_3I + I^{\bullet}, \quad \Delta H = -20 \text{ kcal/mole} \qquad (29)$$

$$CH_3{-}H + I_2 \longrightarrow CH_3I + HI, \quad \Delta H = +13 \text{ kcal/mole} \qquad (30)$$

presents a severe limitation on the activation energy minimum for this step in the chain sequence.



$$I^{\bullet} + C_6H_5{-}CH_3 \longrightarrow HI + C_6H_5\dot{C}H_2, \quad \Delta H = +14 \text{ kcal/mole} \qquad (31)$$

$$C_6H_5\dot{C}H_2 + I_2 \longrightarrow C_6H_5CH_2I + I^{\bullet}, \quad \Delta H = -4 \text{ kcal/mole} \qquad (32)$$

$$C_6H_5CH_3 + I_2 \longrightarrow C_6H_5CH_2I + HI, \quad \Delta H = +10 \text{ kcal/mole} \qquad (33)$$

The situation with fluorine is markedly different from that of iodine. The reaction with methane, for example, is very exothermic because of the nature of the reactants and the products. Neither step in the chain sequence

encounters a minimum activation energy requirement and both might be expected to proceed rapidly. The extreme exothermicity of the reaction of

$$F^{\bullet} + CH_3{-}H \longrightarrow HF + CH_3^{\bullet}, \quad \Delta H = -32 \text{ kcal/mole} \tag{34}$$

$$CH_3^{\bullet} + F_2 \longrightarrow CH_3F + F^{\bullet}, \quad \Delta H = -68 \text{ kcal/mole} \tag{35}$$

$$CH_4 + F_2 \longrightarrow CH_3F + HF, \quad \Delta H = -100 \text{ kcal/mole} \tag{36}$$

fluorine with alkanes presents difficulties that render this approach to the introduction of fluorine into organic compounds unfavourable (see section V).

The enthalpies of the halogenation of other species with other halogenating agents can be estimated from the bond-dissociation energies listed in Table 1. Although these enthalpic relationships are informative to some degree, their principal value lies in giving information that is useful in learning something about the kinetic aspects of the steps in the free-radical chain sequence.

C. *Specificities and Kinetic Aspects*

The site of hydrogen abstraction by a free radical is kinetically controlled. The activation energy requirements for the reactions are determined by chemical features of the hydrogen atom abstracting radical, the chemical environment of the carbon atom from which the hydrogen abstraction occurs and, to some extent, the medium in which the reaction occurs. Although many specific examples for hydrogen abstraction from various organic compounds will be given in subsequent sections, certain generalizations will be presented at this time. These generalizations serve as a basis for subsequent discussions of some of the more subtle aspects of the specificities observed in the halogenations of various compounds by different halogenating agents.

Resonance stabilization of the radical formed is not the most important factor in determining the site of hydrogen atom abstraction by the abstracting free radicals that are encountered in most halogenation reactions. The electronegativity of the abstracting radical can be important in determining the nature of the transition state of the hydrogen atom abstraction reaction. Two kinds of polar effects are recognized as operating in free-radical chain-propagating reactions[1]. The chlorine atom is both energetic and electronegative and prefers to react as a hydrogen abstracting radical at sites of high electron density that are generally the result of inductive effects in the substrate molecule. Resonance contributions of the product radical to the reactant-like transition state of these reactions are

probably minimal. A different kind of polar effect involving charge separation in the transition state is observed in hydrogen atom abstractions by less energetic species (e.g. the bromine atom or trichloromethyl radical) where the transition state has considerable product-like character. These transition states can be assumed to be resonance hybrids of the two canonical structures shown in equation (37), one having no charge separation and involving only the free-radical resonance stabilization of the product radical and the other having complete charge separation and in

$$[R\cdots H\cdots X] \longleftrightarrow [R^{+}\cdots H\cdots \bar{X}] \qquad (37)$$

or

$$[R^{\delta+}\cdots H\cdots X^{\delta-}]$$

which the resonance of the resulting carbonium ion contributes to the stabilization of the hybrid. The more stable the carbonium ion counterpart of the resulting radical may be, the greater will be the contribution of the charge–separation structure to the transition state of the reaction. The specificity displayed by bromine atoms in abstracting benzylic hydrogens from alkyl aromatics and tertiary hydrogens from alkanes is probably largely due to the stabilities of the benzylic and tertiary alkyl carbonium-ion character rather than to the corresponding free-radical character in the transition states of the reactions. The hydrogen atom abstractions by radicals other than chlorine and bromine atoms show characteristics that indicate similar transition states are involved. The very energetic radicals such as the alkoxy radicals have reactant-like transition states and are susceptible to inductive polar effects whereas less energetic free radicals participate in hydrogen atom abstractions having product-like character. In the latter cases, the carbonium-ion character of the substrate-derived radical may be a significant factor if the hydrogen atom abstracting radical has a degree of electronegativity similar to that of a bromine atom.

D. Rate Laws for Halogenation Reactions

A general mechanism for free-radical halogenation reactions is shown in equations (38)–(42). The relative importance of certain of these reactions

$$X_2 \underset{k_{-a}}{\overset{k_a}{\rightleftharpoons}} 2\,X^{\bullet} \qquad (38)$$

$$X^{\bullet} + RH \underset{k_{-b}}{\overset{k_b}{\rightleftharpoons}} HX + R^{\bullet} \qquad (39)$$

$$R^{\bullet} + X_2 \xrightarrow{k_c} RX + X^{\bullet} \qquad (40)$$

$$R^{\bullet} + X^{\bullet} \xrightarrow{k_d} RX \qquad (41)$$

$$2\,R^{\bullet} \xrightarrow{k_e} R_2 \qquad (42)$$

depends on the nature of the halogenating agent and the substrate being halogenated. The chain sequence (39) and (40) is initiated by the forward reaction (38) and can be terminated either by the reverse of reaction (38), reaction (41) or reaction (42) or a combination of these radical destroying reactions. The particular termination reaction that may be operative depends on the relative steady-state concentrations of the chain-carrying free radicals $X^{\bullet}$ and $R^{\bullet}$. These steady-state concentrations are determined both by the reactivities of the free radicals in their respective chain-propagating reactions as well as the relative concentrations of the reactants RH and X_2. The importance of the reverse of reaction (39) depends on the reactivity of HX towards attack by $R^{\bullet}$ and the relative concentrations of HX and X_2.

Rate laws can be derived for the halogenation reactions if steady-state concentrations are assumed for the chain-carrying free radicals and only one of the three possible termination reactions is assumed to be operative. If the termination involves only the reverse of reaction (38), the rate law is that shown in equation (43). The derived rate law for the reaction if the

(Termination only reverse of reaction 38)

$$\text{Rate} = k_b\left(\frac{k_a}{k_{-a}}\right)^{\frac{1}{2}} \frac{[X_2]^{\frac{1}{2}}[RH]}{(1+(k_{-b}[HX]/k_c[X_2]))} \tag{43}$$

cross-termination reaction (41) is operative is given in equation (44). The rate equation for the reaction if it is terminated only by the dimerization

(Termination by reaction 41)

$$\text{Rate} = \left(\frac{k_a k_b k_c}{k_d}\right)^{\frac{1}{2}} \frac{[X_2]\,[RH]^{\frac{1}{2}}}{(1+(k_{-b}[HX]/k_c[X_2]))} \tag{44}$$

reaction (42) is shown in equation (45). If the concentration of HX is low, as it would be at the outset of any halogenation reaction, or if the reverse

(Termination by reaction 42)

$$\text{Rate} = \left(\frac{k_a}{k_e}\right)^{\frac{1}{2}} k_c[X_2]^{\frac{1}{2}} \tag{45}$$

of reaction (39) is slow ($k_{-b} \simeq 0$), the fractional terms in rate laws (43) and (44) vanish and the rate laws take on the somewhat simpler forms of (46) and (47), respectively.

$$\text{Rate} = k_b\left(\frac{k_a}{k_{-a}}\right)^{\frac{1}{2}} [X_2]^{\frac{1}{2}}\,[RH] \tag{46}$$

$$\text{Rate} = \left(\frac{k_a k_b k_c}{k_d}\right)^{\frac{1}{2}} [X_2]\,[RH]^{\frac{1}{2}} \tag{47}$$

Another experimental parameter that can have an effect on these rate laws is the mode of initiation. In the general mechanism, initiation is the forward direction of reaction (38). The derived steady-state rate laws (43)–(47) all include the square root of the rate of initiation, namely

$$(\text{Rate of initiation})^{\frac{1}{2}} = (k_a[X_2])^{\frac{1}{2}} \tag{48}$$

Most often, the initiation process for halogenation reactions is the photolysis of the halogenating agent. This being the case, the intensity of

$$X_2 \xrightarrow{h\nu} 2\,X^{\bullet} \tag{49}$$

the illumination becomes a factor in the overall rate under some conditions. If the illumination is of a sufficiently high intensity that light is transmitted through the reaction mixture, the rate of initiation becomes

$$\text{Rate of initiation} = I\epsilon[X_2] \tag{50}$$

where I is the intensity of illumination and ϵ is the extinction coefficient of X_2. This equation assumes 100% efficiency in the photolysis of those molecules that do absorb a quantum of light. The derived rate equations (43)–(47) for light-induced reactions have the quantity $I\epsilon$ in place of k_a which simply means that the reaction rate depends on the square root of the light intensity. If the light intensity is not high enough to have some of it transmitted but is all absorbed by X_2, the rate of initiation is no longer dependent on $[X_2]$ and the rate laws (43)–(47) still include $I\epsilon$ in place of k_a but drop a half power in $[X_2]$.

If some other means of initiation, for example, the decomposition of a chemical initiator, is employed for the reaction, the rate laws (43)–(47) assume a slightly different form. The rate of initiation becomes k_i[Init.]

$$\text{Init.} \xrightarrow{k_i} 2\,\text{Rad}^{\bullet} \tag{51}$$

and the square root of the rate of initiation in the rate equations (43)–(47), namely $(k_a[X_2])^{\frac{1}{2}}$, is replaced by $(k_i[\text{Init.}])^{\frac{1}{2}}$.

These derived rate laws are amply supported by experimental data. The usefulness of such investigations lies in the fact that comparisons of the observed rate laws with the derived rate laws give an indication of the particular termination process that may be operative. Knowing this, one also has information concerning the relative concentrations of the chain-carrying free radicals and the relative facilities of the chain-propagating reactions.

For example, the observed rate law at the beginning of the bromination of methane in the gas phase at a given pressure is that shown in equation

(52)[2]. As the reaction proceeds, the rate is inhibited by the presence of HBr

$$\text{Rate} = k'[CH_4][Br]^{\frac{1}{2}} \tag{52}$$

and the observed rate law becomes that shown in equation (53). Both rate laws indicate that the chain reaction is terminated by recombination of two

$$\text{Rate} = \frac{k'[CH_4][Br]^{\frac{1}{2}}}{1 + k''[HBr]/[Br_2]} \tag{53}$$

bromine atoms, an observation not unexpected in view of the low reactivity of bromine atoms with methane. In order to maintain a steady-state concentration of free radicals, a considerably high ratio of unreactive bromine atoms with respect to the very reactive methyl radicals must be maintained, thereby encouraging termination via the reverse of reaction (38) rather than by either reaction (41) or (42) which would involve reactions of the methyl radical. The retardation of the reaction rate by hydrogen bromide is indicative of the reverse of reaction (39) playing a role. In this case, the facile reaction of hydrogen bromide with the reactive methyl radical is the reverse of reaction (39).

$$CH_3^{\bullet} + HBr \longrightarrow CH_4 + Br^{\bullet} \tag{54}$$

The observed rate laws for chlorinations with molecular chlorine are complex because the concentrations of the chain-carrying chlorine atoms and alkyl radicals are about the same and all three possible termination reactions are operative. Since the reactions of alkyl radicals with hydrogen chloride are slow, the reaction rate is not significantly retarded by the presence of this component and the observed rate law is a hybrid of the rate laws (45)–(47). If one of two possible radical dimerizations predominates over the other, the observed rate law will assume different concentration exponents from those of the rate law (47) to a proportional degree depending on the relative contributions of the rate laws (45) and (46) as dictated by the predominating termination reaction.

Somewhat more satisfying are the rate laws observed for halogenations using other halogenating agents than the molecular halogens. For example, photochlorination of toluene (low concentrations in carbon tetrachloride) using *t*-butyl hypochlorite as the halogenating agent follows the rate law shown in equation (55)[3]. This rate law indicates that the reaction is

$$\text{Rate} = k'[\text{toluene}]^{0.92}[t\text{-BuOCl}]^{0.65} I^{0.55} \tag{55}$$

initiated by the photolysis of *t*-butyl hypochlorite and that the chain sequence (56) and (57) is terminated by the dimerization of two *t*-butoxy

radicals. The latter conclusion is not surprising for a reaction being

$$t\text{-BuO}^{\bullet} + RH \longrightarrow t\text{-BuOH} + R^{\bullet} \quad (56)$$

$$R^{\bullet} + t\text{-BuOCl} \longrightarrow RCl + t\text{-BuO}^{\bullet} \quad (57)$$

$$2\,t\text{-BuO}^{\bullet} \longrightarrow t\text{-BuOOBu-}t \quad (58)$$

$$(R = C_6H_5CH_2)$$

performed with a low concentration of toluene since a comparatively higher steady-state concentration of *t*-butoxy radicals relative to benzyl radicals would be required to maintain steady-state conditions.

Interestingly, chlorination of chloroform with *t*-butyl hypochlorite follows the rate law (59) which suggests that the chain sequence is terminated

$$\text{Rate} = [t\text{-BuOCl}]^{1.30}\,I^{0.5} \quad (59)$$

mainly by coupling of two R$^{\bullet}$ radicals ($Cl_3C^{\bullet}$ in this case). The kinetic study is indicative of the apparently slow reaction of trichloromethyl radicals with *t*-butyl hypochlorite since the concentration of these radicals at the steady-state is evidently high enough to permit termination of the chain sequence by their dimerization.

The benzoyl peroxide induced reaction of $BrCCl_3$ with toluene follows the rate law (60)[4]. This rate law suggests termination of the chain sequence

$$\text{Rate} = k'[RH]^{0.98}\,[Bz_2O_2]^{0.58}\,[BrCCl_3]^{0.13} \quad (60)$$

(61) and (62) by coupling of two trichloromethyl radicals. As in the case of the reaction of *t*-butyl hypochlorite with toluene, the hydrogen abstraction

$$Cl_3C^{\bullet} + RH \longrightarrow HCCl_3 + R^{\bullet} \quad (61)$$

$$R^{\bullet} + BrCCl_3 \longrightarrow RBr + Cl_3C^{\bullet} \quad (62)$$

$$2\,Cl_3C^{\bullet} \longrightarrow C_2Cl_6 \quad (63)$$

reaction appears to be the rate-limiting step in the chain sequence. In the $BrCCl_3$ reaction, the low reactivity of toluene towards hydrogen atom abstraction by the trichloromethyl radical is probably the reason that a high enough steady-state concentration of trichloromethyl radicals is attained to cause termination mainly by their dimerization.

III. CHLORINATIONS

Various aspects of chlorination reactions have been extensively reviewed[5]. The following discussion is in no way an exhaustive survey of the many ramifications of these reactions. Rather, it is an attempt to present some

generalizations that can be reached concerning the substitution of the hydrogens in a variety of organic compounds with a chlorine atom by the use of both molecular chlorine and other chlorinating agents.

A. Alkanes

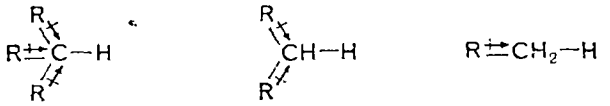
A useful set of rules for the chlorination of alkanes with molecular chlorine was formulated by Haas, McBee and Weber[6]. Most pertinent of these to the following discussion are the statements given here:

1. Every possible monochloride, precluding any rearrangements of the carbon skeleton, is formed.
2. The relative ease of substitution of hydrogens is tertiary > secondary > primary.
3. Increasing the reaction temperature decreases the difference in the ease of substitution of tertiary, secondary and primary hydrogens.

The site of chlorination is determined by the hydrogen atom abstraction reaction which, in the case of chlorinations with molecular chlorine, is performed by chlorine atoms. The energetics of this reaction, owing to the reactivity of the chlorine atom in its role as a hydrogen atom abstractor, are such that this step of the free-radical chain sequence with most alkanes is exothermic (with the exception of methane). The transition states for the abstraction of hydrogen by chlorine resemble the reactants, namely the chlorine atom and the alkane, more than the reaction products. As a consequence, the resonance (hyperconjugative) stabilization of the resulting alkyl radical plays a small role, if any, in determining the activation energy requirements for the reactions. Rather, the relative electron densities at the available reaction sites are more important in determining the activation energy requirements for the reactions. The observed small, but real, differences in the reactivities of primary, secondary and tertiary hydrogens toward reaction with chlorine atoms are possibly best explained in terms of the relative electron densities at the sites of these different hydrogens in the alkane.

1. Polar effects

Alkyl groups are electron-releasing both in a resonance (hyperconjungative) and inductive sense. The electron density at a tertiary carbon is therefore greater than at a secondary carbon which in turn has a higher electron density than a primary carbon. In view of this, it is not unexpected



that the electrophilic chlorine atom displays its observed preferences for abstracting tertiary hydrogens more readily than secondary hydrogens and abstracts primary hydrogens the least readily. The observation that primary hydrogens can be abstracted even when tertiary hydrogens are present suggests either that the differences in electron densities at tertiary and primary reaction sites are not extensive or that the chlorine atom is not remarkably sensitive to electron density differences. Listed in Table 2 are

TABLE 2. Relative reactivities[a] of alkyl hydrogens towards abstraction by chlorine atoms

Compound	Temperature (°C)	Reference
1·0 $CH_3-CH_2-CH_3$ 3·7	25	7
5·6 $CH_3-CH-CH_3$ (1·0) | CH_3	25	7
3·7 1·0 $CH_3-CH-CH-CH_3$ | | CH_3 CH_3	55	8
1·0 2·6 $CH_3-CH_2-CH_2-CH_2-CH_2-CH_3$ 2·45	20	9
0·83 2·16 1·0 $(CH_3)_2CH-CH_2-CH_2-CH_2-CH_2-CH_3$ 2·48 1·45 2·10	20	10

[a] Statistically corrected.

the relative reactivities of various alkyl hydrogens towards abstraction by chlorine atoms. Keeping in mind that these ratios are statistically corrected for the number of available hydrogens at each site, it becomes apparent that considerable amounts of primary chlorides are formed in the reactions of alkanes even with available tertiary hydrogens. For example, chlorination of 2,3-dimethylbutane in carbon tetrachloride at 55° yields a mixture having 63% of the primary alkyl halide and 37% of the tertiary alkyl halide. Although the tertiary hydrogens are 3·7 times more reactive than the primary hydrogens at this temperature, there are six times as many of the latter[8].

The small degree of selectivity displayed by the chlorine atom as a hydrogen abstractor indicates that there are only small differences in the activation energies for the reactions. Indeed, most of the activation energy differences are less than one kilocalorie per mole (e.g. $E_{pri}-E_{tert}=\sim 0{\cdot}54$ kcal/mole for isobutane[11]; $E_{pri}-E_{tert}=0{\cdot}7$ kcal/mole for 2,3-dimethylbutane[7]; $E_{pri}-E_{sec}=0{\cdot}4$ kcal/mole for *n*-butane)[12]. Although increasing the reaction temperature tends to decrease the relative rates of hydrogen abstraction, these differences are not large. For example, chlorination of isobutane at 0° yields a product mixture having 38% *t*-butyl chloride, but the amount of the tertiary chloride at 200° decreases to only 29% yield of the reaction mixture[13]. Likewise, lowering the reaction temperature has little effect in increasing selectivity as evidenced by the 69% yield of 2-chlorobutane obtained from chlorination of *n*-butane at 68° being increased only to 73% by performing the reaction at −78° [13]. Only at relatively high reaction temperatures can the selectivity in the site of chlorination be eliminated and the product distribution of the monochloride approach the statistical distribution of the various hydrogens in the molecule.

The relative reactivities of the hydrogens of cycloalkanes towards hydrogen abstraction by chlorine atoms indicate that, although small, there is some contribution of the alkyl radical to the transition state of the reaction. The observed relative reactivities per hydrogen atom of the C_5 C_6, C_7 and C_8 cycloalkanes at 40° is 1·04 : 1·00 : 1·11 : 1·59[14]. This order of reactivities parallels the relative stabilities of the corresponding cycloalkyl radicals. Since considerably larger differences in the relative reactivities are observed in reactions of more selective hydrogen abstracting radicals (e.g. the reactivity ratio of C_5, C_6, C_7 and C_8 cycloalkanes towards abstraction by $Cl_3C^{\bullet}$ is 1·6 : 1·0 : 3·3 : 9·2)[15], it must be concluded that the contribution of the cycloalkyl free radical to the transition state of the chlorine abstraction reaction is small.

2. Solvent effects

The electrophilic character of the chlorine atom renders Lewis-acid character to the species. In the presence of a suitable Lewis base, the chlorine atom may be effectively complexed and therefore becomes a less energetic species than the free, non-complexed chlorine atom. That this can occur is evidenced by the greater selectivity displayed by chlorine as hydrogen atom abstractor in certain solvents. Table 3 lists the relative reactivities of the tertiary hydrogen with respect to primary hydrogen (k_t/k_p) of 2,3-dimethylbutane towards abstraction in photochlorinations of the alkane in various solvents[8]. Examination of these data shows that

some solvents have a remarkable effect on the selectivity of the chlorine atom as a hydrogen atom abstractor.

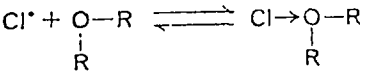
The halocarbons have essentially no effect on the reactivity of the chlorine atoms as a hydrogen abstractor. Oxygen-containing compounds, on the other hand, do increase the selectivity of the chlorine atom to some

TABLE 3. Solvent effects in chlorinations of 2,3-dimethylbutane[8]

Solvent (molar concentrations)	k_t/k_p [a]	
	25°C	55°C
2,3-Dimethylbutane (7·6)		3·7
Cl_4C (4·0)		3·5
$Cl_2C{=}CHCl$ (4·0)		3·6
$(CH_3)_3COH$ (4·0)		4·8
1,4-Dioxan (4·0)		5·6
Nitrobenzene (4·0)		4·9
Chlorobenzene (2·0)	9·0	
Chlorobenzene (4·0)	17·1	
Chlorobenzene (6·0)	27·5	
Benzene (2·0)	11·0	
Benzene (4·0)	20·0	
Benzene (8·0)	49·0	
Anisole (4·0)		18·4
CS_2 (2·0)	15·0	
CS_2 (4·0)	33·0	
CS_2 (11·0)	161·0	
CS_2 (12·0)	225·0	

[a] Statistically corrected.

degree as do the aromatic compounds. The free chlorine atom is in equilibrium with the complexed species, both of which can apparently function as hydrogen abstractors. The complexed chlorine atom, being less energetic than the free chlorine atom, participates in the abstraction reaction in a process having a transition state with a considerable amount



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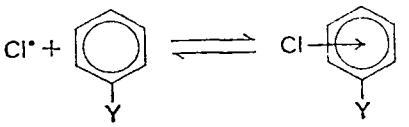

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of product character. As a consequence, tertiary hydrogens are more easily abstracted than primary ones by the complexed chlorine atom. The differences in the reactivity ratios observed in different solvents probably reflect mainly the relative amounts of abstraction performed by the complexed and non-complexed chlorine atoms. Increasing the solvent concentration, as expected, increases the selectivity, since the equilibrium favours the complexed chlorine atoms relative to the non-complexed atoms at the higher solvent concentrations.

In addition to concentration effects of the solvents, there are structural factors that influence the effectiveness of the solvent as a complexing agent. These features relate, for the most part, to the Lewis-base character of the solvent. While alcohols and ethers display comparatively weak Lewis-base character towards the chlorine atom, the aromatics are somewhat more effective. Electron-withdrawing groups (Cl or NO_2) decrease the effectiveness of the aromatic ring relative to benzene in complexing with chlorine atoms. On the other hand, the electron-releasing methoxy group has the opposite effect.

Carbon disulphide is unique as a solvent for chlorinations with molecular chlorine since, in sufficiently high concentrations, it renders the reaction the same high degree of selectivity observed in brominations with molecular bromine. The chlorine atom is very effectively complexed by carbon disulphide, possibly by way of forming a σ-complex which in turn reacts as the hydrogen atom abstracting species.

$$Cl^{\bullet} + S{=}C{=}S \longrightarrow ClS{-}\dot{C}{=}S \xrightarrow{RH} HCl + R^{\bullet} + CS_2 \qquad (66)$$

B. Alkylaromatics

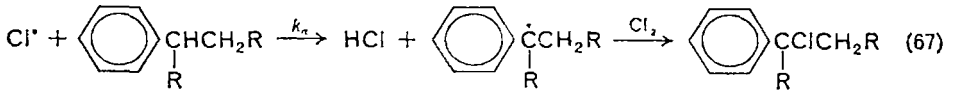
Toluene can be chlorinated in the side-chain to yield a single product, namely benzyl chloride, in high yield. Chlorination of most other alkylaromatics presents the same problems encountered in the chlorination of alkanes, namely, substitution occurs on each carbon of the alkyl chain. As might be expected, benzylic hydrogens are the most reactive towards abstraction by chlorine atoms and the α-chloroalkylaromatics generally are the major monochlorinated reaction product. The amount of hydrogen abstraction from the benzylic carbon, a reaction that leads to the formation of a resonance-stabilized benzylic free radical, is actually somewhat more pronounced than might be expected as a first approximation. For example, the relative reactivity ratios, k_α/k_β, for the reactions of chlorine with ethylbenzene and cumene (see Table 4) are unexpectedly high for reactions that should not have a significant amount of product character in the transition state. This seemingly anomalous situation becomes clarified if

TABLE 4. Chlorinations of ethylbenzene and cumene[16]

Alkylbenzene	(Conc.)	Solvent	k_α/k_β [a]
Ethylbenzene	8·10	None	14·5
Ethylbenzene	5·14	Nitrobenzene	6·15
Ethylbenzene	3·07	Nitrobenzene	3·63
Ethylbenzene	1·49	Nitrobenzene	2·70
Ethylbenzene	0·0	Nitrobenzene	2·00[b]
Cumene	7·05	None	42·2
Cumene	5·04	Nitrobenzene	20·8
Cumene	3·00	Nitrobenzene	10·6
Cumene	1·49	Nitrobenzene	5·24
Cumene	0·0	Nitrobenzene	3·50[b]

[a] Statistically corrected.
[b] Extrapolated values.

the relative reactivity ratios found for the chlorinations of these alkylaromatics in nitrobenzene are examined. Nitrobenzene has little tendency to



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complex with free chlorine atoms whereas, because of the electron-releasing character of alkyl groups, the alkylaromatics do complex free chlorine atoms effectively. Dilution of the alkylaromatics with nitrobenzene decreases the extent of solvation of the hydrogen atom abstracting chlorine atoms, thereby increasing the amount of hydrogen abstraction by free, non-complexed chlorine atoms relative to those complexed by the alkylaromatics. Extrapolation of the experimental data to zero concentration of the alkylbenzene, a situation in which there would be hydrogen atom abstraction only by free, non-complexed chlorine atoms, shows that the relative reactivity ratios of primary, secondary and tertiary hydrogens are similar to those observed in alkanes. It is interesting that the extrapolated values indicate no significant contributions to the hydrogen atom abstraction transition states of the resonance stabilized benzylic radical formed as a product of the process. The exothermicity of the reactions ($\Delta H = -18$ kcal/mole) is substantially greater than that encountered in the hydrogen atom abstractions from the cycloalkanes

($\Delta H = -8$ kcal/mole). Even less product-like character is evident in the transition states of the more exothermic hydrogen atom abstractions from benzylic carbons by non-complexed chlorine atoms than in abstractions from alkanes.

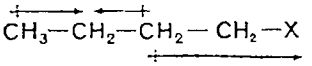
C. Alkyl Halides and Aliphatic Acid Derivatives

Both the lack of an extensive product-like character in the transition state and the electrophilicity of the chlorine atom as a hydrogen abstractor are displayed in the reactions of molecular chlorine with various alkyl halides, aliphatic acids and their derivatives. Table 5 lists the relative amounts of monochlorination observed at different carbons for several such compounds.

TABLE 5. Monochlorination product distribution

Compound	Temperature (°C)	Reference
$\overset{4\cdot2}{CH_3}-\overset{1\cdot0}{CH_2}-\overset{2\cdot2}{CH_2}-\overset{0\cdot7}{CH_2Cl}$	35	17
$\overset{4\cdot0}{CH_3}-\overset{1\cdot0}{CH_2}-\overset{(-)}{CH_2}-\overset{0\cdot5}{CH_2Br}$	35	17
$\overset{3\cdot7}{CH_3}-\overset{1\cdot0}{CH_2}-\overset{1\cdot6}{CH_2}-\overset{0\cdot8}{CH_2F}$	35	17
$\overset{4\cdot3}{CH_3}-\overset{1\cdot0}{CH_2}-\overset{1\cdot2}{CH_2}-\overset{0\cdot04}{CH_2}-CF_3$	75	18
$\overset{4\cdot2}{CH_3}-\overset{1\cdot0}{CH_2}-\overset{2\cdot2}{CH_2}-\overset{0\cdot7}{CH_2}-CO_2CH_3$	75	19
$\overset{3\cdot9}{CH_3}-\overset{1\cdot0}{CH_2}-\overset{2\cdot1}{CH_2}-\overset{0\cdot2}{CH_2}-COCl$	75	19
$\overset{4\cdot2}{CH_3}-\overset{1\cdot0}{CH_2}-\overset{1\cdot5}{CH_2}-\overset{0\cdot08}{CH_2}-COF$	60	20
$\overset{4\cdot4}{CH_3}-\overset{1\cdot0}{CH_2}-CH_2-CH_2-CN$	(-)	21

It is most significant that chlorination is least effective on the carbon atom bearing the halide or acid function. The lack of extensive hydrogen atom abstraction by the chlorine atom at these sites can be ascribed to low electron densities at the carbon atoms bonded to electron-withdrawing functionalities. The data indicate that this effect is operative in decreasing the reactivities of the β-hydrogens, but to a lesser extent. The most reactive hydrogens towards abstraction by a chlorine atom in these compounds are those on the penultimate carbon. Not only is the inductive effect of the electron-withdrawing functionality ineffective this far down the chain, but the electron-releasing character of the terminal methyl group also increases the electron density at this site.



The lack of any significant amounts of hydrogen abstraction from the α-carbons of the acids and their derivatives again points out the reactant-like character of the transition states of hydrogen atom abstractions by chlorine atoms. The α-carbonyl- and α-cyano-radicals formed in these abstractions from the α-carbons are stabilized by resonance contributions of these functionalities to the hybrid free radical. Apparently any contributions of the resonance-stabilized radicals to the transition states of the hydrogen abstractions are very small and essentially negated by the inductive polar effect.

D. Alcohols, Amines, Ethers and Aldehydes

Chlorination of primary and secondary alcohols generally results in oxidation of the alcohol function to the corresponding aldehydes and ketones, respectively. The reactions may be free-radical chain processes involving formation of the halohydrin but non-radical mechanisms are also possible. If, however, the chlorination is performed in strong acid, the protonated alcohol is observed to undergo chlorination at carbon atoms not bearing the protonated hydroxyl group. For example, chlorination of 1-butanol in liquid hydrogen fluoride yields a mixture of 2-, 3- and 4-chlorobutanols in a ratio of 2 : 3 : 3[22]. Attack by chlorine atoms at the 1-carbon of the protonated alcohol does not occur because of the strong electron-withdrawing effect of this functionality. Similarly, chlorination of 1-aminobutane in trifluoroacetic acid yielded 40% of the terminal chloride[23].

Chlorination of ethers generally yields an α-chloroether[24]. A side reaction that may occur in the course of the chlorination is the fragmentation of the intermediate ether-derived free radical before it reacts with

molecular chlorine. For example, *n*-butyl methyl ether may yield a mixture of *n*-butyraldehyde and methyl chloride as reaction products[25]. Fragmentations of the α-alkoxyalkyl radicals occur most readily at higher temperatures[26] and for that reason, successful photochlorinations of the ethers

$$Cl^{\bullet} + CH_3CH_2CH_2CH_2OCH_3 \longrightarrow HCl + CH_3CH_2CH_2\dot{C}HOCH_3 \quad (69)$$

$$CH_3CH_2CH_2\dot{C}HOCH_3 \longrightarrow CH_3CH_2CH_2\underset{\displaystyle H}{\underset{|}{C}}{=}O + CH_3^{\bullet} \quad (70)$$

$$CH_3^{\bullet} + Cl_2 \longrightarrow CH_3Cl + Cl^{\bullet} \quad (71)$$

must be performed at lower temperatures. Chlorinations of cyclic ethers have been accomplished successfully at temperatures in the range of $-30°$ to $-40°$.[27] Epoxides are chlorinated using *t*-butyl hypochlorite yielding the expected α-chloroethers (e.g. propylene oxide is converted to 2-chloropropylene oxide)[28] but reactions with molecular chlorine are complicated by subsequent reaction of the reaction products with the hydrogen chloride formed as the by-product of the chain sequence. Reaction of propylene oxide with chlorine, for example, yields both chloroacetone and propylene halohydrin as reaction products[29].

Aldehydes and ketones having α-hydrogens undergo rapid reactions with chlorine yielding the α-chloro-compounds via an ionic route. Aldehydes having no α-hydrogens react with chlorine at elevated temperatures yielding acid chlorides as reaction products. The reaction probably proceeds by a free-radical path involving abstraction of the aldehydic

$$Cl^{\bullet} + R\underset{\displaystyle H}{\underset{|}{C}}{=}O \longrightarrow HCl + R\dot{C}{=}O \quad (72)$$

$$R\dot{C}{=}O + Cl_2 \longrightarrow R\underset{\displaystyle Cl}{\underset{|}{C}}{=}O + Cl^{\bullet} \quad (73)$$

hydrogen by a chlorine atom followed by reaction of the resulting acyl radical with molecular chlorine[30]. Other halogenating agents, namely carbon tetrachloride[31], sulphuryl chloride[30] and *t*-butyl hypochlorite[28] have also been employed to convert aldehydes to acid chlorides (see next section).

E. Other Chlorinating Agents

The lack of specificity displayed by chlorine has served to promote the investigation of other chlorine-containing compounds as chlorinating

agents. The requirements for such a compound to be of value as a specific chlorinating agent are the following: it must have a chlorine atom that is reactive enough to be abstracted by the free radical that is derived from the substrate being chlorinated. The free radical derived from the chlorinating agent must either be, or give rise to, a hydrogen abstracting radical that has a higher degree of selectivity in this capacity than a chlorine atom. These reagents all suffer from the disadvantage of being more costly than chlorine. When the advantage of specificity outweighs the commercial disadvantages, the value of the quest for such reagents is realized.

I. Sulphuryl chloride

Chlorinations of alkanes with sulphuryl chloride involve the following chain sequence of reactions. Reaction of the alkyl radical with sulphuryl

$$R^{\bullet} + SO_2Cl_2 \longrightarrow RCl + SO_2Cl^{\bullet} \quad (74)$$

$$SO_2Cl^{\bullet} + RH \longrightarrow R^{\bullet} + SO_2 + HCl \quad (75)$$

chloride is a facile process and yields the chlorosulphonyl radical which is a more specific hydrogen atom abstracting species than the chlorine atom. In Table 6, the relative reactivities of tertiary hydrogens with respect to

TABLE 6. Reactions of 2,3-dimethylbutane with chlorine and sulphuryl chloride[32]

Condition	Temperature (°C)	k_{tert}/k_{pri}	
		Cl_2	SO_2Cl_2
Neat	55	3·7	10·0
Neat	25	4·2	12·0
8 Molar benzene	25	4·9	53
4 Molar benzene	55	14·5	27·8
8 Molar benzene	55	32	36

primary hydrogens (k_{tert}/k_{pri}) of 2,3-dimethylbutane towards substitution with both molecular chlorine and sulphuryl chloride are listed. Neat sulphuryl chloride is more selective than chlorine, indicating that significant amounts of hydrogen atom abstraction are probably performed by the chlorosulphonyl radical ($SO_2Cl^{\bullet}$). The reason that the degree of specificity is not greater may be due either to a lack of high specificity of the chlorosulphonyl radical as a hydrogen abstractor or to the fact that the radical is not stable and decomposes to a significant degree, yielding chlorine atoms

which do part of the hydrogen atom abstracting. The relative reactivity

$$SO_2Cl^{\bullet} \longrightarrow SO_2 + Cl^{\bullet} \qquad (76)$$

ratios observed in benzene appear to favour the latter explanation. At the higher benzene concentrations, the reactivity ratios for both halogenating agents are more alike than in either the lower benzene concentrations or in the absence of the aromatic solvent. Apparently the chlorosulphonyl radical is of comparable or less stability than the complex of the free chlorine atom with benzene. At the higher benzene concentrations, the benzene-complexed chlorine atom is the predominant hydrogen atom abstracting species for both chlorine and sulphuryl chloride. With this in mind, one would not expect to find a significant difference in the specificities of the two chlorinating agents in their reactions with alkylaromatics.

2. t-Butyl hypochlorite

Hydrocarbons can be chlorinated with *t*-butyl hypochlorite in a free-radical chain reaction that involves the *t*-butoxy radical as the hydrogen atom abstracting species[33]. The reagent itself is very reactive towards chlorine abstraction by alkyl radicals but, from the kinetic analysis of the chlorination of chloroform[3] with *t*-butyl hypochlorite, it is apparently less

$$R^{\bullet} + (CH_3)_3COCl \longrightarrow RCl + (CH_3)_3CO^{\bullet} \qquad (77)$$

$$(CH_3)_3CO^{\bullet} + RH \longrightarrow (CH_3)_3COH + R^{\bullet} \qquad (78)$$

reactive towards abstraction by electrophilic species such as the trichloromethyl radical. With most hydrocarbons, the kinetic chain lengths of the chain sequence are long and can be initiated either by light or chemical initiators. *t*-Butyl hypochlorite is commercially available but also can be prepared either by passage of chlorine into a mixture of *t*-butyl alcohol and sodium hydroxide or by acidification of a mixture of the alcohol and sodium hypochlorite with an equivalent of acetic acid. *t*-Butyl hypochlorite is a yellow, water-insoluble liquid that can be distilled (b.p. 79°). It is capable of storage for long periods in the dark but may explode when exposed to intense illumination.

The chain sequence outlined above indicates that the *t*-butoxy radical is the hydrogen atom abstracting species and therefore determines the specificity of the reagent as a chlorinating agent. At elevated temperatures, the *t*-butoxy radical fragments, yielding a methyl radical and acetone. Although the methyl radical may function as a hydrogen atom abstractor, it most likely does not do so but rather reacts with the chlorinating agent.

$$(CH_3)_3CO^{\bullet} \longrightarrow (CH_3)_2C{=}O + CH_3^{\bullet} \quad (79)$$

$$CH_3^{\bullet} + (CH_3)_3COCl \longrightarrow CH_3Cl + (CH_3)_3CO^{\bullet} \quad (80)$$

While no specificity that might be rendered by the *t*-butoxy radicals is lost, some of the chlorinating agent is consumed in the chain sequence of reactions leading to the formation of acetone and methyl chloride. A more serious complication arises if the hydrogen chloride resulting from light-induced reactions is formed in large quantities. Hydrogen chloride and *t*-butyl hypochlorite interact to yield molecular chlorine which may

$$(CH_3)_3COCl + HCl \longrightarrow (CH_3)_3COH + Cl_2 \quad (81)$$

function as the chlorinating agent, a complication that becomes serious if the halogenating chain sequence is short and much initiation is required.

$$(CH_3)_3COCl \xrightarrow{h\nu} (CH_3)_3CO^{\bullet} + Cl^{\bullet} \quad (82)$$

$$Cl^{\bullet} + RH \longrightarrow HCl + R^{\bullet} \quad (83)$$

The *t*-butoxy radical is more selective than the chlorine atom as a hydrogen atom abstractor although it resembles a chlorine atom in this capacity more than a bromine atom. The transition states for hydrogen atom abstraction resemble the reactants more than the products of the process. A good linear correlation is observed between the log of the relative reactivities of the *meta*- and *para*-substituted toluenes and the Hammett σ-values of the substituents ($\rho = -0{\cdot}83$ at 40°)[33]. This observation is indicative both of the electrophilicity of the *t*-butoxy radical and the lack of product-like character in the transition state of the hydrogen atom abstraction reaction, at least in the case of benzylic hydrogens.

Like the chlorine atom, the *t*-butoxy radical is subject to solvent interactions. The solvent effects observed for the *t*-butoxy radical are somewhat more subtle than those described earlier for chlorine atoms. For the latter, the solvent interacts with the radical and the solvated or complexed chlorine atom is the actual hydrogen abstractor. The solvation of the *t*-butoxy radical very likely occurs at the radical site, namely the oxygen with the unpaired electron. Hydrogen atom abstraction from a substrate by such a complexed radical cannot readily take place unless some degree of desolvation occurs. The extent of desolvation required for the transition state to be attained depends on the amount of product-like character of the transition state. Thus, more desolvation is encountered in hydrogen abstractions of primary hydrogens than of tertiary hydrogens. This solvent effect does not become apparent in the relative reactivity ratios of various hydrogens with respect to each other as in the case of the

chlorination reactions with molecular chlorine. Table 7 lists the relative reactivity ratios of the tertiary hydrogens with respect to the primary hydrogens in the reactions of 2,3-dimethylbutane with *t*-butyl hypochlorite in various solvents. At any given temperature, the relative reactivity ratios

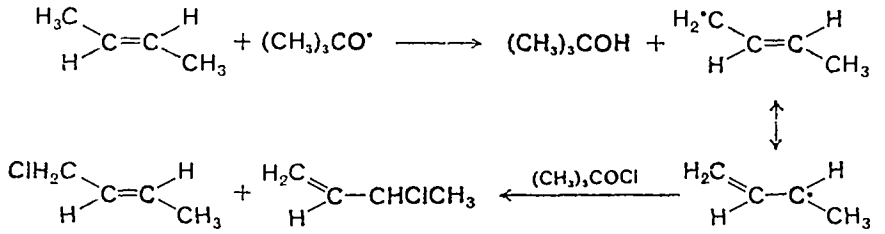
TABLE 7. Reactions of 2,3-dimethylbutane with *t*-butyl hypochlorite[34]

Solvent	k_{tert}/k_{prl}					$E^{\ddagger}_{prl}-E^{\ddagger}_{tert}$[a]
	100°	70°	40°	25°	0°	
None	—	—	44	54	68	1·85
Benzene[b]	—	—	55	70	89	1·99
Chlorobenzene[b]	—	35	54	66	94	2·58
Acetone[b]	20	30	51	76	128	3·77
Acetonitrile[b]	10	17	33	47	—	4·57

[a] kcal/mole.
[b] [2,3-Dimethylbutane] = 0·8 molar and [*t*-BuOCl] = 0·2 molar.

are quite similar in the various solvents. However, on examination of the difference in activation energies, a significant effect for the various solvents becomes apparent. A plausible explanation for this effect is the following: in order to attain the transition states for the hydrogen abstractions, which might be similar in each solvent since the main components would be the *t*-butoxy radical and the substrate, a greater degree of desolvation is required for primary hydrogen atom abstraction than for tertiary hydrogen abstraction. The primary hydrogen abstraction is a less exothermic process than tertiary hydrogen abstraction and therefore has a transition state with somewhat more product-like character and will require more complete removal of the solvent from the radical site for the transition state to be attained. The more tightly the solvent is complexed with the *t*-butoxy radical, the greater will be the energy necessary to remove the solvent molecules from the radical site. This energy appears in the activation energy for the primary hydrogen atom abstraction to a greater extent than in the activation energy for abstraction of the more reactive tertiary hydrogens, which have transition states with less product-like character and therefore do not require the same degree of desolvation of the radical for the transition state to be attained. From the data in Table 7 it can be concluded that the solvation of the *t*-butoxy radical by acetonitrile may involve solvation energies amounting to almost three kcal/mole.

The allylic hydrogens of alkenes are labile to attack by *t*-butoxy radicals, yielding allylic radicals which, on reaction with *t*-butyl hypochlorite, result in formation of a mixture of allylic chlorides. For example, *trans*-2-butene is converted to a mixture of *trans*-1-chloro-2-butene and 3-chloro-1-butene



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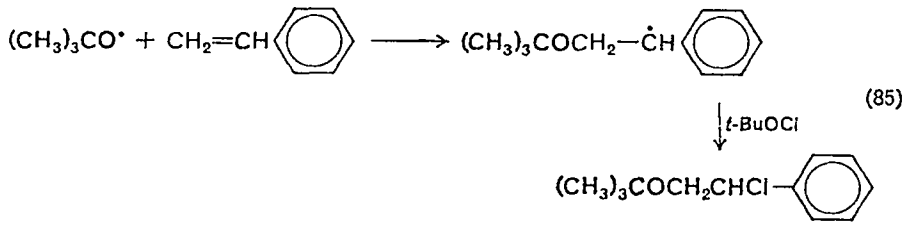
at 40°. The most striking feature of these allylic chlorinations is that the hybrid allylic radical retains its configuration[35]. Chlorinations of other *cis* and *trans* isomeric alkanes with the same reagent also yield allylic chlorides with the same configuration as the alkene indicating the preservation of the stereochemistry of the alkene in the hybrid allylic radical. If no allylic hydrogens are available for abstraction by the *t*-butoxy radical, it will add to the unsaturated linkage, yielding ultimately an addition product of *t*-butyl hypochlorite and the alkene (e.g. reaction with styrene)[36].



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3. Trichloromethanesulphonyl chloride and trichloromethanesulphenyl chloride

Alkanes and alkylaromatics have been chlorinated with trichloromethanesulphonyl chloride (Cl_3CSO_2Cl) in light- and peroxide-induced reactions[37]. The chain sequence for the chlorination reaction most likely involves hydrogen atom abstraction by the trichloromethanesulphonyl radical ($Cl_3CSO_2^{\bullet}$)[38]. The latter radical displays a degree of selectivity considerably greater than that of either a chlorine atom or a *t*-butoxy radical, attacking tertiary hydrogens of alkanes in preference to secondary ($k_{tert}/k_{sec} = 20$) or primary ($k_{tert}/k_{pri} = 20$–30) and only the benzylic

$$Cl_3CSO_2^{\bullet} + RH \longrightarrow Cl_3CSO_2H + R^{\bullet} \quad (86)$$

$$R^{\bullet} + Cl_3CSO_2Cl \longrightarrow RCl + Cl_3CSO_2^{\bullet} \quad (87)$$

hydrogens of alkylaromatics. Trichloromethanesulphinic acid is the product formed in the hydrogen atom abstraction reaction but this species is not stable and decomposes to chloroform and sulphur dioxide, the observed by-products of the chlorination reaction. The kinetic chain

$$Cl_3CSO_2H \longrightarrow HCCl_3 + SO_2 \quad (88)$$

lengths of the reaction sequence are short compared to those of chlorinations with molecular chlorine, sulphuryl chloride or *t*-butyl hypochlorite.

Although the hydrogen atom abstractor is shown above to be the trichloromethanesulphonyl radical, it may be that this radical decomposes, as in the case of the chlorosulphonyl radical, yielding a free trichloromethyl radical which may be the hydrogen atom abstractor. That the reaction

$$Cl_3CSO_2^{\bullet} \longrightarrow Cl_3C^{\bullet} + SO_2 \quad (89)$$

$$Cl_3C^{\bullet} + RH \longrightarrow HCCl_3 + R^{\bullet} \quad (90)$$

does not proceed entirely by this route is evident from the observation that the relative reactivity of cyclohexane with respect to toluene is different for trichloromethanesulphonyl chloride ($k_{cyclohexane}/k_{toluene} = 1{\cdot}86$) and for bromotrichloromethane ($k_{cyclohexane}/k_{toluene} = 0{\cdot}20$), a halogenating agent known to involve the trichloromethyl radical as the hydrogen atom abstracting species.

Trichloromethanesulphenyl chloride (Cl_3CSCl) reacts in light- and peroxide-induced reactions with alkanes according to the following stoicheiometry[39]:

$$RH + 2\,Cl_3CSCl \longrightarrow RCl + HCl + Cl_3CSSCCl_3 \quad (91)$$

The mechanism proposed for the reaction involves hydrogen atom abstraction by a trichloromethanethiyl radical, a species having a degree of

$$R^{\bullet} + Cl_3CSCl \longrightarrow RCl + Cl_3CS^{\bullet} \quad (92)$$

$$Cl_3CS^{\bullet} + RH \longrightarrow Cl_3CSH + R^{\bullet} \quad (93)$$

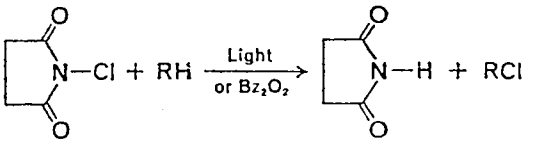
$$Cl_3CSH + Cl_3CSCl \longrightarrow HCl + Cl_3CSSCCl_3 \quad (94)$$

selectivity in this capacity similar to that of the trichloromethyl radical. For example, at 0° the k_{tert}/k_{pri} for 2,3-dimethylbutane is 110 and the k_{sec}/k_{pri} for *n*-pentane is 33. The disulphide formed as a by-product in the reaction can be isolated and converted back to the starting material by treatment with chlorine.

$$Cl_3CSSCCl_3 + Cl_2 \longrightarrow 2\,Cl_3CSCl \quad (95)$$

4. *N*-Chloroamides

N-Chlorosuccinimide can be used to chlorinate hydrocarbons in reactions that are either light-induced or initiated with benzoyl peroxide[40]. The mechanism of the chlorination reactions with this is probably similar to

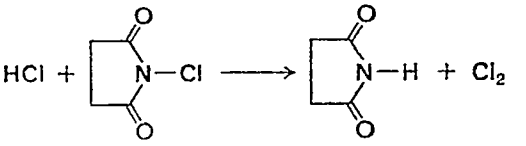


(96)

that of the brominations with *N*-bromosuccinimide in that the actual halogenating agent is the molecular halogen generated by interaction of the *N*-haloamide and the hydrogen halide produced as a product of the halogenation chain sequence. Since the site of chlorination is determined by a chlorine atom, little advantage in terms of selectivity is gained in using this reagent.

$$R^{\bullet} + Cl_2 \longrightarrow RCl + Cl^{\bullet} \tag{97}$$

$$Cl^{\bullet} + RH \longrightarrow HCl + R^{\bullet} \tag{98}$$



(99)

N-Chlorosulphonamides have been used to chlorinate alkanes[41]. The selectivity of these reagents is only slightly greater than that observed for chlorinations with molecular chlorine and has prompted the suggestion that sulphonamide radicals may be the hydrogen abstracting species in these reactions. If so, the sulphonamide radicals do not show a degree of selectivity as hydrogen abstracting radicals significantly different from chlorine atoms. Since the yields of chlorinated products are low in these reactions, little advantage is gained in the use of these reagents as chlorinating agents (see Table 8).

5. Phosphorus pentachloride

Alkanes and alkylaromatics can be chlorinated with phosphorus pentachloride in benzoyl peroxide-induced reactions at 100°[43]. A degree of selectivity displayed by this reagent is observed that is about comparable to that of trichloromethanesulphonyl chloride (see Table 8). Hydrogen atom abstraction is probably accomplished by the $PCl_4^{\bullet}$ radical in these reactions.

$$PCl_4^{\bullet} + RH \longrightarrow PCl_3 + HCl + R^{\bullet} \tag{100}$$

$$R^{\bullet} + PCl_5 \longrightarrow RCl + PCl_4^{\bullet} \tag{101}$$

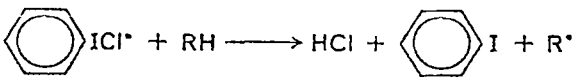
A similar selectivity is noted in the chlorinations of alkanes with molecular chlorine in the presence of phosphorus trichloride, suggesting that the chlorine atom may be effectively complexed with this reagent[44]. The complex is not extremely stable since competition reactions of

$$Cl^{\bullet} + PCl_3 \rightleftharpoons PCl_4^{\bullet} \qquad (102)$$

cyclohexane and toluene with PCl_5 indicate a selectivity comparable to that of molecular chlorine. In this case, the aromatic ring of the toluene possibly complexes the chlorine atom more effectively than the PCl_3 and the selectivity displayed is essentially that observed in the absence of PCl_3.

6. Iodobenzene dichloride

In light-induced reactions, iodobenzene dichloride reacts with alkanes to yield primarily the chlorinated alkane, iodobenzene and hydrogen chloride[45]. The mechanism for the reaction has been suggested to involve the following free-radical chain sequence of reactions in which the hydrogen abstraction is performed by $C_6H_5ICl^{\bullet}$:



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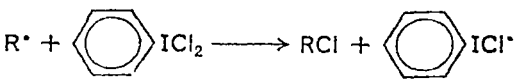


(104)

Iodobenzene itself displays good complexing properties with chlorine atoms as evidenced by its effectiveness in increasing the selectivity of the chlorine atom as a hydrogen atom abstractor in reactions of molecular chlorine. The relative reactivity ratio of tertiary to primary hydrogens of 2,3-dimethylbutane towards substitution with chlorine with iodobenzene dichloride is over 350 at 40°, indicating a high degree of selectivity of the monochloroiodobenzene radical as a hydrogen atom abstractor.

7. Cupric chloride

2,3-Dimethylbutane and toluene have been chlorinated in the photolysis of a mixture of the hydrocarbon in acetonitrile with cupric chloride and lithium chloride (the latter presumably present to increase the solubility of $CuCl_2$). A non-chain free-radical process involving the chlorine atom as the hydrogen atom abstractor has been proposed for the reaction. Both the

TABLE 8. Comparable selectivities of various chlorinating agents[10, 41, 42]

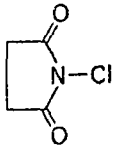
Reagent	Conditions	Substrate	Product distribution (%)[a]
Cl_2	Light, 20°	*n*-Octane	$\overset{14\cdot3}{CH_3}-\underset{30\cdot4}{CH_2}-\overset{28\cdot4}{CH_2}-\underset{26\cdot7}{CH_2}-C_4H_9-n$
$(CH_3)_3COCl$	Light, 20°	*n*-Octane	$\overset{6\cdot3}{CH_3}-\underset{38\cdot2}{CH_2}-\overset{28\cdot7}{CH_2}-\underset{26\cdot2}{CH_2}-C_4H_9-n$
Cl_3CSO_2Cl	Bz_2O_2, 98°	*n*-Octane	$\overset{1\cdot9}{CH_3}-\underset{42\cdot0}{CH_2}-\overset{30\cdot2}{CH_2}-\underset{25\cdot9}{CH_2}-C_4H_9-n$
Cl_3CSCl	Light, 98°	*n*-Octane	$\overset{4\cdot7}{CH_3}-\underset{31\cdot5}{CH_2}-\overset{32\cdot8}{CH_2}-\underset{30\cdot4}{CH_2}-C_4H_9-n$
	Bz_2O_2, 98°	*n*-Octane	$\overset{15\cdot0}{CH_3}-\underset{30\cdot9}{CH_2}-\overset{28\cdot5}{CH_2}-\underset{25\cdot4}{CH_2}-C_4H_9-n$
PCl_5	Bz_2O_2, 98°	*n*-Octane	$\overset{1\cdot5}{CH_3}-\underset{28\cdot4}{CH_2}-\overset{35\cdot1}{CH_2}-\underset{35\cdot0}{CH_2}-C_4H_9-n$
Cl_2	Light, 20°	2-Methylheptane	$\overset{11\cdot6}{CH_3}-\underset{32\cdot4}{CH_2}-\overset{11\cdot2}{CH_2}-\underset{16\cdot7}{CH_2}-\overset{9\cdot2}{CH}(CH_3)_2$ $19\cdot1$

TABLE 8—*continued*

Reagent	Conditions	Substrate	Product distribution (%)[a]
SO_2Cl	Bz_2O_2, 85°	2-Methylheptane	8·5 (CH₃), 34·1 (CH₂), 11·6 (CH₂), 18·9 (CH₂), 13·0 (CH₂), 14·0 (CH) $CH_3—CH_2—CH_2—CH_2—CH_2—CH(CH_3)_2$
$CH_3SO_2N(—Cl)C(CH_3)_3$	Bz_2O_2, 85°	2-Methylheptane	10·8 (CH₃), 38·8 (CH₂), 10·5 (CH₂), 14·1 (CH₂), 11·5 (CH₂), 14·4 (CH) $CH_3—CH_2—CH_2—CH_2—CH_2—CH(CH_3)_2$
Cl_2	Light, 20°	2,3,4-Trimethylpentane	50·8 ((CH₃)₂CH), 17·9 (CH), 20·4 (CH(CH₃)₂), 10·9 (CH₃) $(CH_3)_2CH—CH(CH_3)—CH(CH_3)_2$
Cl_3CSO_2Cl	Bz_2O_2, 85°	2,3,4-Trimethylpentane	4·9 ((CH₃)₂CH), 23·8 (CH), 71·3 (CH(CH₃)₂) $(CH_3)_2CH—CH(CH_3)—CH(CH_3)_2$
$CH_3SO_2N(—Cl)C(CH_3)_3$	Bz_2O_2, 85°	2,3,4-Trimethylpentane	52·6 ((CH₃)₂CH), 19·1 (CH), 19·2 (CH(CH₃)₂), 9·1 (CH₃) $(CH_3)_2CH—CH(CH_3)—CH(CH_3)_2$

[a] Actual observed percentages of monochlorinated products.

lack of specificity and the non-chain character of the reaction render the reagent of limited value as a chlorinating agent[46].

$$CuCl_2 \xrightarrow{\text{Light}} CuCl + Cl^{\bullet} \quad (105)$$

$$Cl^{\bullet} + RH \longrightarrow HCl + R^{\bullet} \quad (106)$$

$$R^{\bullet} + CuCl_2 \longrightarrow RCl + CuCl \quad (107)$$

8. *N*-Chloroamines

The Hoffmann–Löffler reaction is an intramolecular chlorination involving protonated *N*-chloroamines[47]. The reaction can be initiated thermally or, at lower temperatures, with light, with ferrous ions, with hydrogen peroxide or with a combination of the latter two reagents. An intramolecular hydrogen atom abstraction performed by an amino radical is the key step in the free-radical chain sequence for the reaction. For example, *N*-chlorodibutylamine reacts at 20° in 85% sulphuric acid in a light-induced reaction by the path outlined in the chain sequence (108)–(110) which is initiated by the photolysis of the protonated *N*-chloroamine[47].

$$(n\text{-}C_4H_9)_2NCl + H^+ \longrightarrow (n\text{-}C_4H_9)_2\overset{+}{N}HCl \xrightarrow{\text{Light}}$$

$$(n\text{-}C_4H_9)_2\dot{N}H^+ + Cl^{\bullet} \quad (108)$$

$$CH_3CH_2CH_2CH_2\dot{\overset{+}{N}}HC_4H_9\text{-}n \longrightarrow$$

$$^{\bullet}CH_2CH_2CH_2CH_2\overset{+}{N}H_2C_4H_9\text{-}n \quad (109)$$

$$^{\bullet}CH_2CH_2CH_2CH_2\overset{+}{N}H_2C_4H_9\text{-}n + (n\text{-}C_4H_9)_2\overset{+}{N}HCl \longrightarrow$$

$$ClCH_2CH_2CH_2CH_2\overset{+}{N}H_2C_4H_9\text{-}n + (n\text{-}C_4H_9)_2\dot{N}H^+ \quad (110)$$

It is significant that the protonated species is also involved in the chain sequence itself, particularly in the hydrogen abstraction reaction. The charge on the radical must impart a large degree of electrophilicity to the radical as a hydrogen abstracting species. This behaviour becomes evident in intermolecular chlorinations of organic compounds having electron-withdrawing functionalities. The amounts of chlorination at various sites of the following molecules using *N*-chloroamines (R_2NCl) in sulphuric acid (80–90%) and light to induce the reactions illustrate the selectivity of the protonated dialkylamino radical ($R_2\dot{N}H^+$) as a hydrogen atom abstracting radical. It is noteworthy that the penultimate carbon undergoes the most extensive substitution in each case, probably because of the electron-releasing qualities of the terminal methyl group.

$$\overset{4\%}{CH_3}-\overset{78\%}{CH_2}-\overset{13\%}{CH_2}-\overset{5\%}{CH_2}-\overset{0\%}{CH_2}-CO_2CH_3 \quad \text{(Reference 48)}$$

$$\overset{2\%}{CH_3}-\overset{72\%}{CH_2}-\overset{19\%}{CH_2}-\overset{7\%}{CH_2}-\overset{0\%}{CH_2}-CH_2Cl \quad \text{(Reference 49)}$$

$$\overset{1\%}{CH_3}-\overset{93\%}{CH_2}-\overset{6\%}{CH_2}-\overset{0\%}{CH_2}-\overset{0\%}{CH_2}-CO_2H \quad \text{(Reference 50)}$$

$$\overset{6\%}{CH_3}-\overset{90\%}{CH_2}-\overset{2\%}{CH_2}-\overset{2\%}{CH_2}-\overset{0\%}{CH_2}-CH_2OH \quad \text{(Reference 50)}$$

$$\overset{9\%}{CH_3}-\overset{79\%}{CH_2}-\overset{12\%}{CH_2}-\overset{0\%}{CH_2}-CH_2OCH_3 \quad \text{(Reference 50)}$$

IV. BROMINATIONS

A. Alkanes

Bromine atoms are less energetic than chlorine atoms and consequently display a greater degree of specificity as hydrogen abstracting radicals. Hydrogen abstractions from alkanes by bromine atoms involve transition states having a considerable amount of product character and consequently both resonance and polar aspects of the resulting free radical contribute significantly to the structure of the transition state. Owing to the electron-accepting qualities of the bromine atom, the contributions to the transition state of the hydrogen abstraction from an alkane of the canonical structure having complete charge separation may be considerable if the cationic species is itself stabilized by efficient delocalization of the positive charge. Since the order of relative stability of carbonium ions is tertiary > secondary $\gg$ primary $\gg$ methyl, it is not surprising that bromine atoms abstract

$$Br^{\bullet} + RH \longrightarrow [Br\cdots H\cdots R] \longleftrightarrow [Br^{-}\cdots H\cdots R^{+}] \longrightarrow HBr + R^{\bullet} \qquad (111)$$

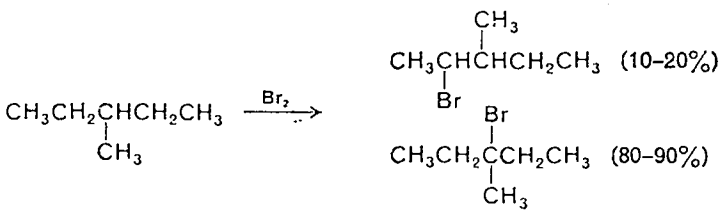
tertiary hydrogens considerably more readily than primary or even secondary hydrogens. Relative reactivities of various hydrogens have been calculated from available rate data and are given in Table 9. It can be deduced from these data that if a tertiary hydrogen is available along with primary and secondary hydrogens, the amounts of primary bromides ultimately formed in the chain process will be negligible whereas the amounts of secondary bromide could be appreciable (depending on the

TABLE 9. Relative reactivities of alkyl hydrogens towards abstraction by bromine atoms[51, 52]

Relative reactivities[a]		
Primary	Secondary	Tertiary
CH_3CH_2—H (1·00)	$(CH_3)_2CH$—H (88)[b]	$(CH_3)_3C$—H (1980)[b]
CH_3CH_2—H (1·00)	$CH_3CH_2CH(CH_3)$—H (43)[b]	$(CH_3)_3C$—H (1980)[b]
$CH_3CH_2CH_2CH_2$—H (1·00)	$CH_3CH_2CH(CH_3)$—H (82)[c]	$(CH_3)_3C$—H (1640)[c]

[a] Statistically corrected.
[b] Relative to the hydrogens of ethane.
[c] Relative to the primary hydrogens of *n*-butane.

statistical availability of secondary hydrogens with respect to tertiary hydrogens). For example, bromination of 3-methylpentane could yield anywhere from 10–20% 2-bromo-3-methylbutane along with the tertiary bromide, 3-bromo-3-methylpentane. The amount of the primary bromide, 1-bromo-3-methylpentane, formed would be less than one per cent of the total mono-brominated product, however.



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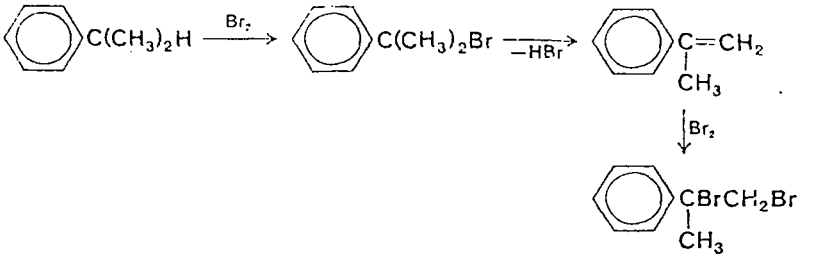
Although dibromides could be obtained by further bromination of the monobromides (see section IV. C), the amounts of dibromide are often observed to be greater than might be expected on the basis of the available monobromides. Formation of excessive amounts of dibromides is particularly evident in branched hydrocarbons which form tertiary alkyl bromides as the initial products. For example, bromination of 2,3-dimethylbutane with 25 mole% bromine at 55° yielded 89% 2,3-dibromo-2-3-dimethylbutane[53]. Similarly, 2-methylpentane yielded 17·5% of 2,3-dibromo-2-methylpentane along with 76% of the tertiary bromide[53]. The amount of dibromides produced in these reactions decreases with decreasing temperature but formation of dibromides has been found to occur in the dark provided some monobromination product is present. It has also been observed that the extent of dibromide formation depends on the nature of the hydrogens on the carbon atom adjacent to that bonded to

the bromine, the order of reactivity being tertiary > secondary > primary. The dark reaction has been suggested to be an ionic process involving dehydrohalogenation of the monobrominated product yielding an alkene that undergoes rapid ionic addition of molecular bromine. The extent of dibromide formation via this route appears, therefore, to be related to the ease of formation of the unsaturated linkage which in turn is determined by the stability of the alkene formed in terms of the substituents that stabilize the unsaturation by resonance. Consequently, it is not surprising that cumyl bromide is readily converted to the dibromide in a dark reaction since the unsaturated intermediate α-methylstyrene is stabilized both by an aryl group and a methyl group.



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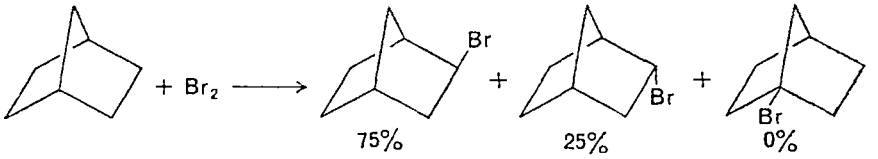
The mechanism for the dehydrohalogenation reaction is not precisely clear but may involve heterolysis of the bromide promoted by either the available hydrogen bromide or molecular bromine. Loss of the hydrogen on the carbon atom adjacent to the carbonium ion site would follow the Saytzev rule producing the most stable of the possible alkenes which then undergoes addition by molecular bromine.

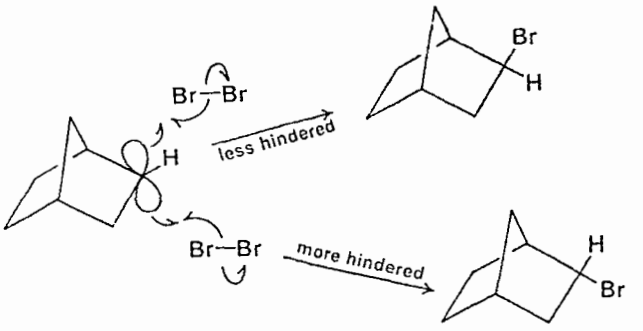
Structural features of certain hydrocarbons render tertiary hydrogens less labile towards abstraction by bromine atoms than secondary hydrogens. Bromination of norbornane[54], for example, yields a mixture of the *endo*- and *exo*-2-bromonorbornanes in a 1 : 3 ratio but none of the 1-bromonobornane that would result from abstraction of a tertiary hydrogen. In this case the tertiary bridgehead hydrogen is not abstracted since, owing to the



(114)

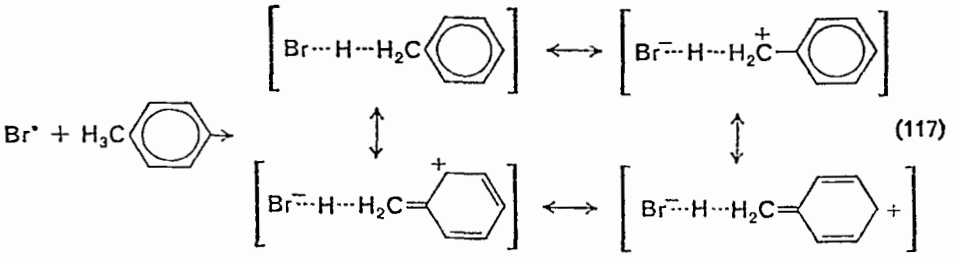
inability of the bridgehead carbon to assume the coplanarity of an sp^2-hybridized carbon, the resulting tertiary alkyl radical is unstable. The predominant formation of the *exo*-2-bromonorbornane reflects the less

hindered approach of the bromine at the *exo*-side of the 2-norbornyl radical relative to the more hindered approach from the *endo*-side.



B. Alkylaromatics

Toluene is readily brominated in the side-chain by molecular bromine in a light-induced reaction. The effect of the aromatic ring in stabilizing the benzyl radical is extensive and decreases the bond-dissociation energy of a benzylic hydrogen to such an extent that, in contrast to alkanes, abstraction of benzylic hydrogens by a bromine atom is slightly exothermic. By way of contrast, the benzylic hydrogens of toluene are 64,000 times more reactive than the hydrogens of ethane toward abstraction by bromine atoms[55]. Although the greater reactivity of the benzylic hydrogens relative to the ethane hydrogens can in part be ascribed to the differences in the bond-dissociation energies of the carbon–hydrogen bonds (85 kcal/mole for toluene and 98 kcal/mole for ethane) and hence the resonance stabilization of the resulting radicals, the polar factor also plays a significant role in lowering the transition state energy requirement for the reaction. There is extensive delocalization of the positive charge of the polar canonical structure that contributes to the hybrid transition state of the benzylic hydrogen abstraction reaction, whereas there is little contribution from the polar canonical structure to the hybrid transition state of the hydrogen abstraction from ethane.

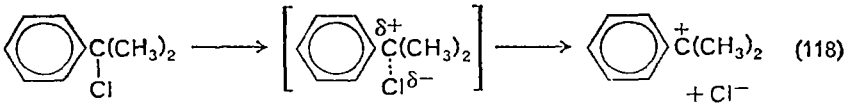


It is interesting that hydrogen atom abstraction from toluene by bromine atoms is only about three times faster than abstraction of the tertiary hydrogen from isobutane. In the latter case, the contribution of the polar canonical structure to the hybrid transition state is significant because of extensive delocalization of the positive charge in the *t*-butyl moiety.

The combination of the radical resonance and cationic resonance factors to the transition states of benzylic hydrogen abstraction by bromine atoms causes those hydrogens to be more reactive than any of the others in alkyl aromatics. As a consequence, only α-bromo-alkyl aromatics are formed as the monobrominated products in the photobrominations of alkyl aromatics.

The nature of the polar effects encountered in benzylic hydrogen abstractions by bromine atoms can be appreciated in terms of the Hammett linear free energy relationship $\log(k/k_0) = \rho\sigma$ observed in examination of competitive brominations of *meta*- and *para*-substituted toluene.

A plot of $\log k/k_0$ for the bromination of *meta*- and *para*-substituted toluene against the σ-values of the substituents is not linear. On the other hand, if $\log k/k_0$ is plotted against Brown and Okamoto's σ^+-values for the substituents[56], a linear correlation is observed. The σ^+-parameters measure the ability of the substituent in the *meta*- or *para*-position relative to the reaction site to delocalize a positive charge that is developed at the reaction site in the transition state, as determined from solvolysis rates of cumyl chlorides (118). Hence, in the transition states of the hydrogen abstractions of benzylic hydrogen by bromine, development of cationic character at the benzylic position can be assumed, also.



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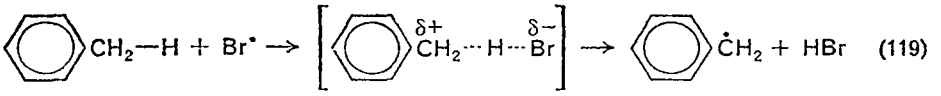


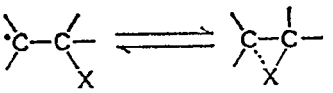
(119)

The ρ-values for benzylic hydrogen abstraction by bromine atoms from *meta*- and *para*-substituted toluenes depend significantly on the reaction conditions employed for the competition study. The ρ-value is lower at higher temperatures, as would be expected, but is also lower if the competition reaction is performed under conditions in which the ratio of Br_2 to HBr is low. When such a situation persists, there is appreciable reaction of the benzylic radicals produced with the hydrogen bromide rather than with bromine to yield the reaction product. Only at high Br_2 to HBr ratios do the

benzylic radicals react rapidly enough with bromine to provide a meaningful reaction rate ratio for the hydrogen abstraction reaction. High Br_2 to HBr ratios can be attained performing the competition reactions rapidly using relatively large amounts of bromine. If the reaction is performed slowly by addition of smaller quantities of bromine, a low Br_2 to HBr ratio develops. Some ρ-values that have been obtained are $-1{\cdot}07$ and $-1{\cdot}36$ at 80° and 19°, respectively, for reactions involving slow addition of bromine and $-1{\cdot}36$ and $-1{\cdot}76$ at 80° and 19°, respectively, for rapid reactions involving an excess of bromine[57].

C. Alkyl Halides

In some instances, monohaloalkanes are brominated in a free-radical chain reaction in which the halogen already present in the molecule plays a role in both the hydrogen atom abstraction and, owing to the character of the radical formed, in its reactions with molecular bromine. The peculiar behaviour noted in these reactions is ascribed to the ability of chlorine and bromine to bridge with the radical site positioned on a carbon atom adjacent to the atom to which it is bonded. The interaction of the unpaired



electron of the radical with the halogen atom may incorporate the energetically available *d*-orbitals of bromine and chlorine in the bridging process.

The involvement of a bridged radical can be observed in the relative rates of hydrogen abstraction from the various carbons of the alkyl halides by bromine atoms illustrated in Table 10. Abstractions of hydrogen atoms by both bromine atoms and chlorine atoms are listed in this table. The chlorinations of these alkyl halides appear to follow the expected behaviour in that the electrophilic chlorine atoms react faster at sites of higher electron density (see section III. C). Although bromination of the alkyl chlorides appears to involve some degree of selectivity based on electron density, the effect is far less pronounced. The product-like character in the transition states of the hydrogen atom abstractions by bromine atoms is evident to some degree in that abstraction from the carbon bonded to the chlorine occurs readily. In this case, the resulting radical is stabilized by delocalization of the unpaired electron by the chlorine.

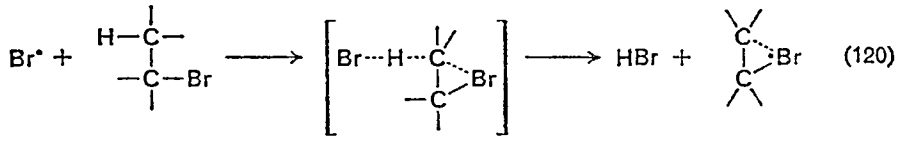
The most striking anomaly is the enhanced reactivity of the hydrogen atoms on the β-carbon relative to the bromine towards abstraction by bromine atoms. This effect is noted both in the reactions of 1-bromobutane

TABLE 10. Relative rates of hydrogen abstraction by bromine and chlorine atoms from butyl halides at 60° [58]

Butyl halide	Halogenating agent	Relative reactivities[a]
1-Chlorobutane	Chlorine	$\overset{0.397}{CH_3}-\overset{1.00}{CH_2}-\overset{0.478}{CH_2}-\overset{0.158}{CH_2}-Cl$
1-Chlorobutane	Bromine	$\overset{1.00}{CH_3}-\overset{0.488}{CH_2}-\overset{0.439}{CH_2}-Cl$
1-Bromobutane	Chlorine	$\overset{0.455}{CH_3}-\overset{1.00}{CH_2}-\overset{0.434}{CH_2}-\overset{0.093}{CH_2}-Br$
1-Bromobutane	Bromine	$\overset{1.00}{CH_3}-\overset{5.78}{CH_2}-\overset{0.62}{CH_2}-Br$
2-Chlorobutane	Bromine	$\overset{0.086}{CH_3}-\overset{1.00}{CH_2}-CHCl-CH_3$
2-Bromobutane	Bromine	$\overset{5.13}{CH_3}-\overset{1.00}{CH_2}-CHBr-CH_3$

[a] Statistically corrected.

and 2-bromobutane. The reactivities of these hydrogens towards abstraction by bromine atoms have been suggested to be augmented by participation of the bromine on the β-carbon in stabilizing the resulting radical by bridging with the radical site. If the contribution of the bridged species to the overall stability of the resulting radical is significant, this factor may lower the activation energy requirement for the hydrogen atom abstraction provided the transition state has product-like character. Such would be the case for hydrogen atom abstractions by bromine atoms, reactions that are endothermic, but not for the exothermic hydrogen atom abstractions by the more energetic chlorine atoms.



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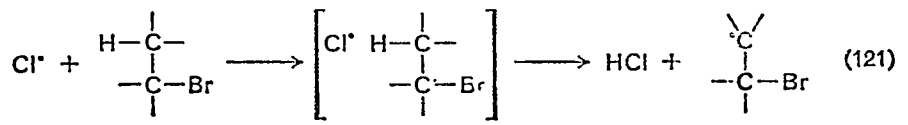
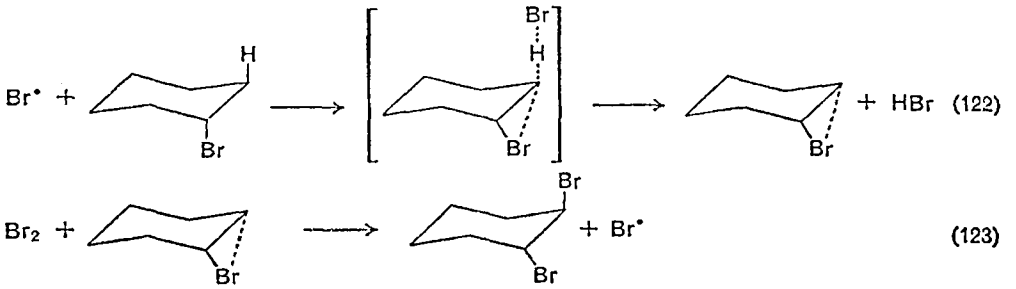


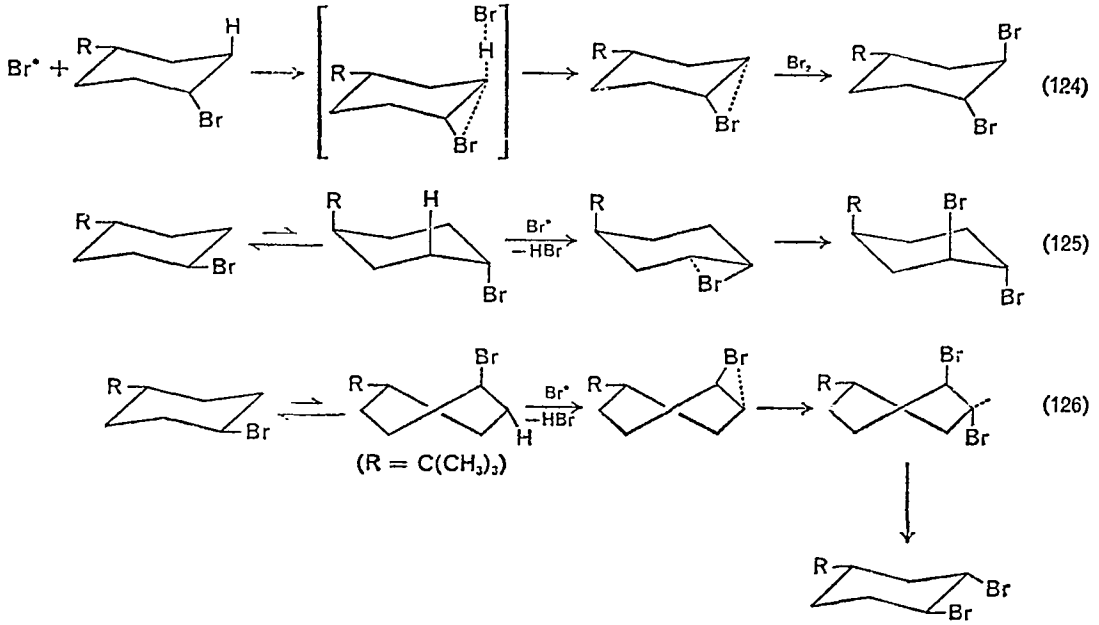
(121)

Evidence for the bridged radical is also found in the products resulting from its interaction with molecular bromine yielding the dibrominated alkane. For example, both bromocyclohexane and bromocyclopentane yield predominantly *trans*-1,2-dibromocycloalkanes on photobromination[59]. Not only is the site of hydrogen atom abstraction dictated by the participation of the bridged intermediate in the transition state, but the resulting free radical reacts in such a manner that the bromine molecule is attacked only from the unhindered side of the bridged radical.



Bromination of the isomeric 4-*t*-butylcyclohexyl bromides[60] illustrates both the anchimeric assistance of the bridged species in the hydrogen atom abstraction and the stereochemical control of the product formation dictated by the bridged intermediate. *cis*-4-*t*-Butylcyclohexyl bromide, with its axial bromine, is brominated 15 times more readily than the *trans*-isomer which has an equatorial bromine in its most stable conformer. In the case of the *cis*-isomer, anchimeric assistance of the bromine in the hydrogen atom abstraction reaction is readily attainable without the introduction of any severe conformational problems. The bridged radical formed reacts with molecular bromine yielding the expected *trans*-diaxial-1,2-dibromo-4-*t*-butylcyclohexane (equation 124). Participation of the equatorial bromine of the *trans*-isomer in the hydrogen atom abstraction process is not possible without a change in the cyclohexane ring system. Unless the ring flips to the other chair conformer in which the *t*-butyl group is in the axial position, so that the bromine may also be axial and participate in the same manner as encountered in the *cis*-isomer, anchimeric assistance can only be expected from the twist-boat conformer of the compound. In either case, the conformational strain would become part of the activation energy requirement for the hydrogen atom abstraction from the *trans*-isomer if the bridged radical is involved in the reaction. Consequently, bromination of the *trans*-isomer most likely does not involve any of the anchimeric effect in the hydrogen atom abstraction reaction as evidenced by its slower rate of bromination compared to the *cis*-isomer and

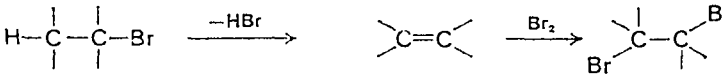
also by the fact that the *trans*-isomer yields a mixture of dibromides. The latter, of course, is the consequence of hydrogen atom abstraction from other sites on the cyclohexane ring.



The concept of the bridged free radical has been criticized and alternate explanations for the observations just outlined have been presented. There appears to be no marked enhancement in the rate of hydrogen atom abstraction from brominated alkanes relative to alkanes[61]. The argument for the bridged species in terms of its anchimeric effect in the transition state therefore, is one of relative rates of hydrogen abstraction at the different positions in the alkyl halides, the hydrogens in the β-position with respect to the halogen already present being favoured over the remaining hydrogens. If the anchimeric effect were indeed a significant factor, an alkyl bromide with β-hydrogens relative to either a chlorine or bromine might be expected to be more reactive than the corresponding alkane since bridging in the former would lower the activation energy requirement for the reaction.

The observed preference for formation of 1,2-dibromoalkanes in the bromination of bromoalkanes has been suggested to result from dehydrohalogenation of the alkyl bromide (in an ionic reaction catalysed by hydrogen bromide) yielding an alkene linkage which undergoes rapid addition of bromine to give the 1,2-dibromoalkane[61]. This mechanism not only explains the preference for formation of vicinal dibromides but also

accounts for the stereospecificity noted in both the reactivities of the isomeric *t*-butylcyclohexyl bromides and in the formation of the *trans*-diaxial bromides from the *cis*-isomer and from the bromocycloalkanes.



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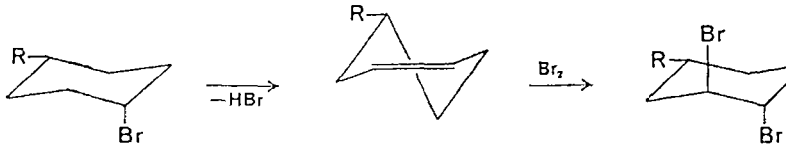
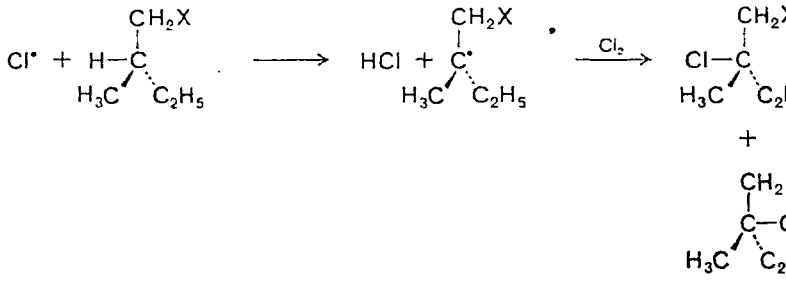
Dehydrohalogenation of the cycloalkyl bromides having the bromine in an axial position would be expected to occur more readily by an *E*2 mechanism than would the dehydrohalogenation of the cycloalkyl bromide having its bromine in the equatorial position in its most stable conformer. Ionic addition of molecular bromine to the unsaturated linkage would yield only the *trans*-diaxial vicinal dibromide.



(128)

Although the argument against the bridged radical is not without merit and at the time of the writing of this article is actively being investigated[62], there is evidence to support the existence of such species. Most compelling is the evidence that is observed in the halogenation reactions of (+)-2-bromo-2-methylbutane (active amyl bromide) and (+)-2-chloro-2-methylbutane (active amyl chloride)[63]. Hydrogen abstraction from the



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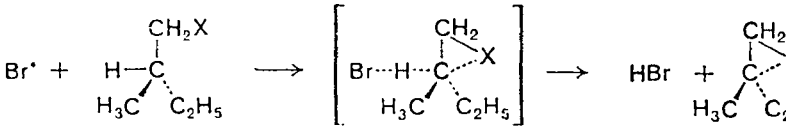

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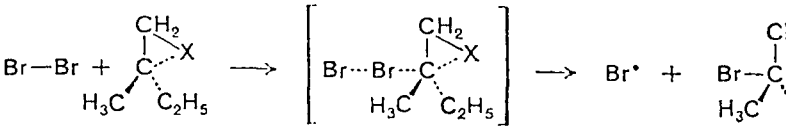


(131)

2-carbon of the active amyl halides by chlorine atoms yields planar, symmetrical radicals which on reaction with chlorine yield optically inactive products. On the other hand, bromination of the active amyl halides yields optically active reaction products. In the case of the bromination, hydrogen atom abstraction occurs less readily than it does in chlorination. As a consequence, the anchimeric effect of the halogen (either chlorine or bromine) on the β-carbon is significant and the product of the hydrogen atom abstraction is the bridged free radical which retains its asymmetry. Reaction of the asymmetrical free radical with bromine yields an asymmetric dihalide. The degree of optical purity of the product, particularly in the case of the amyl chloride, is smaller at low bromine concentrations, indicating a finite rate of conversion of the bridged asymmetrical radical to the non-bridged symmetrical radical.

D. Other Brominating Agents

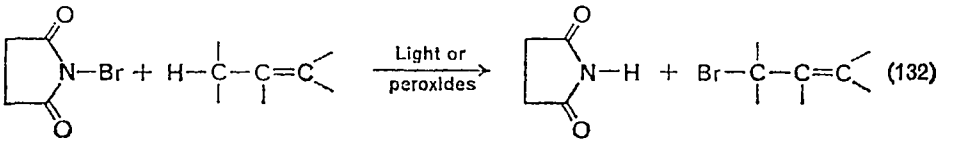
The lack of specificity of the chlorine atom as a hydrogen atom abstracting radical makes the search for chlorinating agents with more selective abstracting radicals of interest. The bromine atom, on the other hand, is selective in its role as a hydrogen abstractor and the use of brominating agents other than the element itself must be dictated by other factors. Some of these brominating agents, in particular the *N*-bromoamides, have been used extensively in organic synthesis because of their specificity in brominating the allylic position of compounds having unsaturated linkages. Most of the other brominating agents do not have any outstanding advantages over bromine as a brominating agent. They have been investigated mainly from the standpoint of determining the mechanistic and kinetic characteristics of the free-radical chain reactions in which they are involved. Some of these compounds will be discussed from this viewpoint.

1. *N*-Bromosuccinimide and related compounds

The bromination of an alkene in the allylic position by an *N*-bromoamide has been known as a valuable synthetic procedure for some time. The first report of such a reaction was made by Wohl in 1919[64]. The synthetic potential of the reaction was not appreciated until the 1940's when Ziegler and coworkers published their investigations[65]. The Wohl–Ziegler reaction has been used extensively for allylic brominations as well as for brominations of alkylaromatics and alkanes since that time. Several review articles are available which list the applications of the *N*-bromoamides as brominating agents[66].

N-Bromosuccinimide is generally employed in synthetic work for the allylic bromination reactions and serves well as a model for the reactions of

the *N*-bromoamides. The stoicheiometry of the reaction indicates a simple substitution of an allylic hydrogen of the unsaturated compound with the nitrogen-bonded bromine of the *N*-bromosuccinimide. A free-radical chain mechanism for this substitution seems plausible in view of the observations



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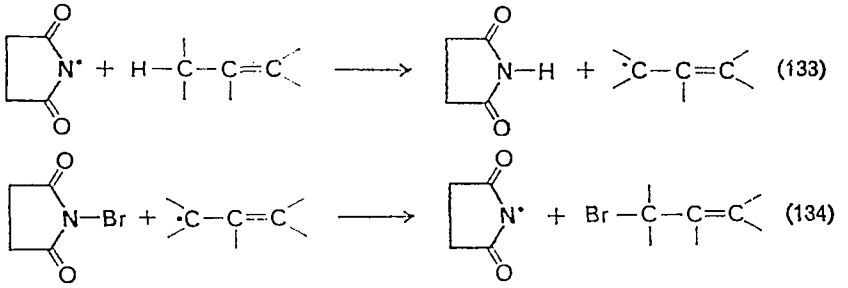
that the reaction rate is accelerated by free-radical initiation procedures such as decomposition of peroxides and illumination of the reaction mixture. The obvious mechanism for the reaction, namely that shown in the chain sequence below, involves abstraction of the allylic hydrogen atom by the *N*-succinimidyl radical followed by reaction of the resulting allylic radical with the brominating agent. This mechanism was first postulated by Hey[67] and Bloomfield[68] in 1944. Subsequent investigations showed,



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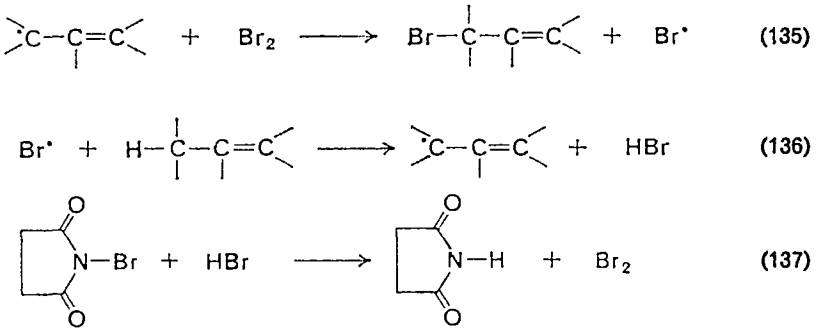
(134)

however, that this mechanism was not correct. The presently accepted mechanism for the reaction was suggested by Goldfinger in 1953[69], and invokes the formation of minute quantities of molecular bromine which serve as the brominating agent. The required bromine is generated by reaction of hydrogen bromide formed in the free-radical chain sequence



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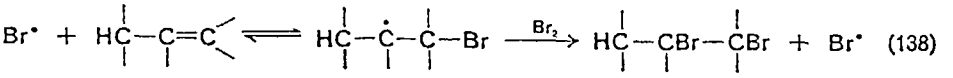
(137)

that produces the allylic bromide. The key features of this mechanism are the low concentration of bromine and the reversible addition of bromine atoms to the unsaturated linkage. The adduct radical formed in this addition process could react with bromine to form an addition product of bromine with the unsaturated compound. However, because of the low



(138)

concentration of bromine, the unimolecular decomposition of the adduct radical is faster than the bimolecular reaction with bromine. Abstraction of the allylic hydrogen by the bromine atom is also reversible but not to the same extent as the adduct radical fragmentation. Once formed, the allylic radical apparently reacts faster with bromine, although it may be present only in low concentrations, to form the allylic bromide than it does with the hydrogen bromide.

The most compelling evidence supporting the Goldfinger mechanism is the similarity observed in the relative rates of bromination of alkanes, alkylaromatics and substituted toluenes with bromine and with *N*-bromosuccinimide[70]. Both reagents require the bromine atom as the hydrogen atom abstracting radical. Other convincing evidence supporting this mechanism is the observation that alkenes are brominated in the allylic position under free-radical conditions if low bromine concentrations are maintained[71].

2. Polyhaloalkanes

Bromotrichloromethane reacts with alkylaromatics[72] and, to a lesser extent, with alkanes[73] in a free-radical chain process yielding the brominated substrate and chloroform. Hydrogen atom abstraction in this case is performed by the trichloromethyl radical, a species that has characteristics

$$RH + BrCCl_3 \longrightarrow RBr + HCCl_3 \qquad (139)$$

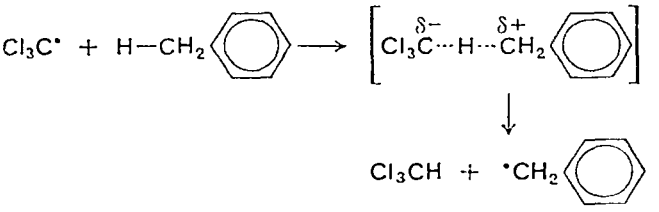
in this capacity similar to those of a bromine atom. While benzylic hydrogens are readily abstracted by both bromine atoms and trichloromethyl radicals, only alkanes with tertiary hydrogens are reactive enough

$$^{\bullet}CCl_3 + RH \longrightarrow HCCl_3 + R^{\bullet} \qquad (140)$$

$$R^{\bullet} + BrCCl_3 \longrightarrow RBr + {}^{\bullet}CCl_3 \qquad (141)$$

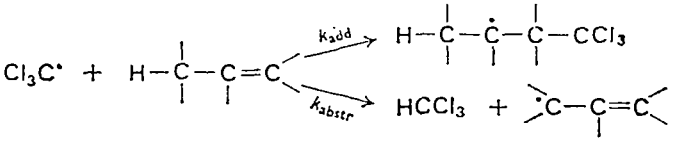
to participate readily in chain reactions with either bromine or bromotrichloromethane. Similarities are also observed in the reactivities of the benzylic hydrogens of substituted toluenes towards attack by bromine,

atoms and by trichloromethyl radicals. A better linear correlation is found if the log of the relative reactivities of substituted toluenes towards attack by the trichloromethyl radical is plotted against the σ^+-values of the substituents ($\rho = -1{\cdot}46$ at 50°) than when plotted against the σ-values[72]. Benzylic hydrogen abstractions by the trichloromethyl radical and by bromine atoms are similar in that cationic character at the site of the hydrogen atom abstraction is developed in the transition state of the reaction.



(142)

The trichloromethyl radical adds readily in a non-reversible process to unsaturated linkages and the resulting adduct radical on reaction with bromotrichloromethane yields an addition product. The trichloromethyl radical also shows a propensity for abstracting allylic hydrogens from alkenes. The latter reaction can lead to formation of an allylic substitution product. The relative amounts of addition product with respect to substitution product, measured by the ratio of the rate constants k_{add}/k_{abstr}



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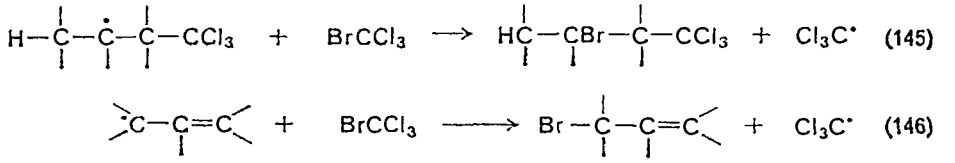

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depends on the structure of the alkene both in terms of the steric effects that may retard the rate of addition and resonance and polar effects that may enhance the rate of allylic hydrogen atom abstraction. Table 11 lists k_{add}/k_{abstr} ratios observed for simple alkenes. Note that terminal alkenes yield predominantly the addition product whereas substitution may account for as much as 40% of the reaction of bromotrichloromethane in reactions with cycloalkenes and alkenes with tertiary hydrogens in the allylic position.

TABLE 11. Relative rates of addition with respect to allylic hydrogen abstraction by trichloromethyl radicals[74]

Alkene	k_{add}/k_{abstr}		
	40°	77·8°	99°
1-Octene		44	
2-Pentene		5·7	
3-Heptene	5·0	3·5	
4-Methyl-2-pentene	1·68	1·26	
cis-2-Butene			34
trans-2-Butene			26
Cyclohexene		1·20	
Cyclopentene		5·4	
Cycloheptene		5·5	

1,2-Dibromo-1,1,2,2-tetrachloroethane brominates compounds having abstractable hydrogens via the following chain sequence of reactions:

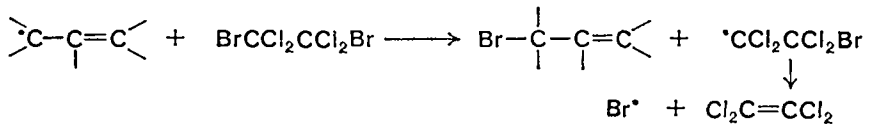
$$Br^{\bullet} + RH \longrightarrow HBr + R^{\bullet} \quad (147)$$

$$R^{\bullet} + BrCCl_2CCl_2Br \longrightarrow RBr + {}^{\bullet}CCl_2CCl_2Br \quad (148)$$

$${}^{\bullet}CCl_2CCl_2Br \longrightarrow Br^{\bullet} + Cl_2C{=}CCl_2 \quad (149)$$

Note that hydrogen abstraction is accomplished in this reaction sequence by a bromine atom. This material has been observed to brominate alkenes in the allylic position[75]. The bromine atom, as in the *N*-bromoamide reactions, may add to the unsaturated linkage yielding an adduct radical

(150)



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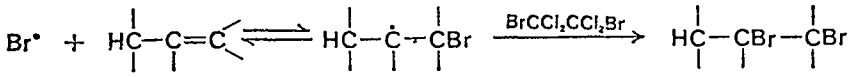
but reaction of the adduct radical with the polyhaloalkane is slower than its fragmentation. The allylic radical, on the other hand, apparently reacts



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with the dibromotetrachloroethane faster than it does with the hydrogen bromide that is present in the reaction mixture.

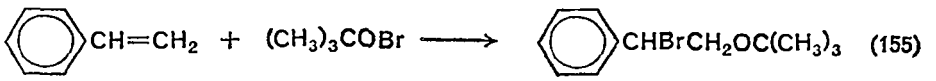
3. t-Butyl hypobromite

This reagent might be expected to behave in a manner similar to that of *t*-butyl hypochlorite in that the *t*-butoxy radical would be the hydrogen abstracting radical in a chain sequence resulting in substitution of a hydrogen for a bromine. However, little work has been reported on the use of this reagent as a brominating agent. Substitution of a propargyl hydrogen for bromine in 2-butyne using *t*-butyl hypobromite possibly proceeds by the expected chain sequence and is illustrative of the preference for hydrogen

$$(CH_3)_3CO^{\bullet} + CH_3C{\equiv}CCH_3 \longrightarrow (CH_3)_3COH + {}^{\bullet}CH_2C{\equiv}CCH_3 \quad (153)$$

$${}^{\bullet}CH_2C{\equiv}CCH_3 + (CH_3)_3COBr \longrightarrow BrCH_2C{\equiv}CCH_3 + (CH_3)_3CO^{\bullet} \quad (154)$$

abstraction by *t*-butoxy radicals relative to their addition to unsaturated linkages[76]. If no allylic, propargylic or benzylic hydrogens are available for abstraction, the *t*-butoxy radical may add to the unsaturated linkage that may be available. The result is the formation of an addition product of the brominating agent as shown with styrene[76].



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Brominations may be accomplished by the use of a mixture of *t*-butyl hypochlorite and bromotrichloromethane[77]. The procedure for the use of this mixture of reagents requires an excess of bromotrichloromethane relative to the hypochlorite. This is done by slowly adding the *t*-butyl hypochlorite to an illuminated solution of the substrate to be brominated and bromotrichloromethane. Note that the hydrogen abstraction is performed by the *t*-butoxy radical in this case although the polyhalomethane is the source of the bromine. Only reactive alkyl radicals react fast

$$(CH_3)_3CO^{\bullet} + RH \longrightarrow (CH_3)_3COH + R^{\bullet} \quad (156)$$

$$R^{\bullet} + BrCCl_3 \longrightarrow RBr + Cl_3C^{\bullet} \quad (157)$$

$$Cl_3C^{\bullet} + (CH_3)_3COCl \longrightarrow Cl_4C + (CH_3)_3CO^{\bullet} \quad (158)$$

enough with bromotrichloromethane to allow it to compete effectively with the *t*-butyl hypochlorite which, although present in small amounts, is very reactive towards attack by free radicals.

4. Bromochloride

Mixtures of molecular chlorine and bromine contain the mixed halogen bromochloride[78]. This mixed halogen can be used to brominate compounds

$$Cl_2 + Br_2 \rightleftharpoons 2\,BrCl \tag{159}$$

that are normally resistant to bromination. For example, methylene difluoride is brominated by bromochloride but does not react with bromine. It does, however, react with chlorine, suggesting that the mechanism for the

$$Cl^\bullet + CH_2F_2 \longrightarrow HCl + {}^\bullet CHF_2 \tag{160}$$

$${}^\bullet CHF_2 + BrCl \longrightarrow BrCHF_2 + Cl^\bullet \tag{161}$$

reaction involves hydrogen abstraction by the reactive chlorine atom. The selectivity of the reagent as a brominating agent would therefore be similar to that of molecular chlorine.

The attack on the bromochloride by the substrate radical occurs, interestingly, at the bromine end of the molecule. The larger size of the bromine may be responsible in part for this specificity. Another factor may be the greater polar contributions encountered in the transition state of the reaction in which the chlorine rather than bromine is the electron acceptor moiety.

$$R^\bullet + Br{-}Cl \longrightarrow [\overset{\delta+}{R}\cdots Br\cdots \overset{\delta-}{Cl}] \longrightarrow RBr + Cl^\bullet \tag{162}$$

5. Trichloromethanesulphonyl bromide

Trichloromethanesulphonyl bromide brominates alkanes and alkylaromatics in a reaction that stoicheiometrically resembles that of the corresponding sulphonyl chloride. Investigation has shown that the reaction

$$Cl_3CSO_2Br + RH \longrightarrow HCCl_3 + SO_2 + RBr \tag{163}$$

paths for the two reagents are different[79]. In the case of the sulphonyl chloride (see section III. E), much, if not all, of the hydrogen atom abstraction from the substrate is accomplished by the trichloromethanesulphonyl radical. Competition reactions indicate that the trichloromethyl radical is the sole hydrogen atom abstracting species in the reactions of the trichloromethanesulphonyl bromide. Under the influence of light or peroxides, the material has been observed to decompose yielding sulphur dioxide and bromotrichloromethane. The latter very likely is the actual brominating agent in the reactions of this material.

V. FLUORINATION

Reactions of alkanes with molecular fluorine are exothermic and often lead to complete oxidation of the alkane to carbon tetrafluoride if sufficient fluorine is present. The cleavage of carbon–carbon bonds in the fluorination of alkanes can be ascribed, at least in part, to the reactivity of the fluorine atom as a reaction intermediate. Whereas the reaction of a chlorine atom with ethane, for example, resulting in carbon–carbon cleavage, is endothermic, the same reaction with a fluorine atom is appreciably exothermic.

$$Cl^{\bullet} + CH_3{-}CH_3 \longrightarrow CH_3Cl + CH_3^{\bullet} \qquad (164)$$
$$(\Delta H = +4 \text{ kcal/mole})$$

It seems unlikely that displacement on carbon by fluorine atoms would

$$F^{\bullet} + CH_3{-}CH_3 \longrightarrow CH_3F + CH_3^{\bullet} \qquad (165)$$
$$(\Delta H = -20 \text{ kcal/mole})$$

compete with hydrogen atom abstraction since the latter is both more exothermic and sterically preferred. Carbon–carbon cleavage possibly occurs after all of the hydrogens have been substituted and are no longer

$$F^{\bullet} + CH_3{-}CH_3 \longrightarrow HF + CH_3CH_2^{\bullet} \qquad (166)$$
$$(\Delta H = -37{\cdot}8 \text{ kcal/mole})$$

available for reaction with fluorine atoms. The accessibility of the carbon to displacement, owing to the small size of the fluorines, as well as the

$$F^{\bullet} + CF_3{-}CF_3 \longrightarrow CF_4 + CF_3^{\bullet} \qquad (167)$$

exothermicity of the formation of the carbon–fluorine bond, are probably the most significant factors that lead to carbon attack in these reactions.

The fluorination of methane under carefully controlled reaction conditions reveals other interesting characteristics of fluorinations. Not only are the various fluorinated methanes observed as reaction products but appreciable amounts of hexafluoroethane (CF_3CF_3) and octafluoropropane ($CF_3CF_2CF_3$) are also found[80]. Furthermore, the reaction proceeds readily in the dark and at temperatures as low as $-80°$. The higher molecular weight fluorocarbons are probably formed in coupling reactions of radicals present in the reaction mixture (e.g. $2\ CF_3^{\bullet} \rightarrow CF_3CF_3$). In order for appreciable amounts of termination products such as these to be formed, some facile means of radical formation (initiation) must be available. The homolytic cleavage of fluorine, although energetically

$$F_2 \longrightarrow 2\ F^{\bullet} \qquad (168)$$
$$(\Delta H = +38 \text{ kcal/mole})$$

feasible at higher temperatures, would not be expected to account either for the initiation of an unusually large number of chains or for the reaction taking place at low temperatures. A bimolecular reaction of methane with fluorine, however, can occur at lower temperatures and may well be

$$CH_4 + F_2 \longrightarrow HF + CH_3^{\bullet} + F^{\bullet} \quad (169)$$
$$(\Delta H = +6{\cdot}2 \text{ kcal/mole})$$

responsible both for the rapid rates of fluorination at low temperatures and the formation of radical dimerization products in unexpectedly large amounts.

VI. IODINATION

Hydrogen atom abstraction by iodine atoms is an endothermic process with most organic compounds and consequently renders a severe limitation in the free-radical chain sequence between molecular iodine and most substrates (e.g. the reaction of methane with iodine). While the activation

$$I^{\bullet} + CH_4 \longrightarrow HI + CH_3^{\bullet} \quad (170)$$
$$(\Delta H = +33 \text{ kcal/mole})$$

$$CH_3^{\bullet} + I_2 \longrightarrow CH_3I + I^{\bullet} \quad (171)$$
$$(\Delta H = -20 \text{ kcal/mole})$$

energy requirements for hydrogen abstractions may be too high for reactions to occur at temperatures generally employed for halogenation reactions (room temperature $\pm 100°$), reactions might be possible at more elevated temperatures, particularly with substrates having readily abstractable hydrogens (e.g. the reaction with toluene). There are, however,

$$I^{\bullet} + C_6H_5CH_3 \longrightarrow HI + C_6H_5CH_2^{\bullet} \quad (172)$$
$$(\Delta H = +14 \text{ kcal/mole})$$

complicating features that would be encountered if the reaction does occur. One of these is the fact that the equilibrium favours reduction of alkyl iodides by hydrogen iodide. This reverse reaction becomes mechanistically

$$RH + I_2 \rightleftharpoons RI + HI \quad (173)$$

possible because of the facility of the reverse reactions of both steps in the chain sequence of the iodination reaction.

$$R^{\bullet} + HI \longrightarrow RH + I^{\bullet} \quad (174)$$

$$I^{\bullet} + RI \longrightarrow R^{\bullet} + I_2 \quad (175)$$

The alkyl iodide is labile to attack by iodine atoms both by attack on the iodine atom and also on the carbon to which the iodine is bonded. In the latter case, the process is an identity reaction but can be observed both in

$$I^{\bullet} + RI \longrightarrow IR + I^{\bullet} \qquad (176)$$

exchange reactions using radioactive iodine and in the racemization of optically active 2-iodobutane with iodine atoms[81].

It would appear that iodination with reagents that do not involve iodine atoms as the chain-carrying hydrogen abstracting species would be promising. Little work, however, has yet been done in this area. The reaction of iodine monochloride with alkanes apparently does effect the iodination of the alkane[82] but, unfortunately, the hydrogen chloride

$$Cl^{\bullet} + RH \longrightarrow HCl + R^{\bullet} \qquad (177)$$

$$R^{\bullet} + ICl \longrightarrow RI + Cl^{\bullet} \qquad (178)$$

formed in the chain reaction catalyses the dehydroiodination of the product.

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The Chemistry of The Carbon–Halogen Bond
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CHAPTER 9

Elimination reactions in solution

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I. INTRODUCTION

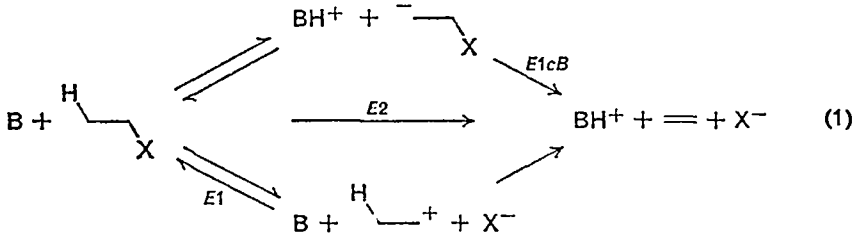
Base-initiated β-elimination is one of the most characteristic reactions of the carbon–halogen bond. The wide range of reactivity of the alkyl halides has meant that there are few features of β-elimination that they fail to illustrate, and the smooth variation of the factors contributing to their reactivity, the basicity, solvation energy, polarizability and steric requirements of the halogen leaving groups has made them, as a family, a useful foil in investigations of mechanism. However, β-eliminations are by no means confined to alkyl halides, and because it is the elimination process which has come to be recognized as chiefly defining the common characteristics of the reactions, no attempt will be made here to segregate related results solely on the basis of leaving group. From a practical standpoint it is now clear that the behaviour to be expected of an alkyl halide may often be inferred from measurements with, say, an alkyl arylsulphonate, and that an understanding of the halides in general may be increased by placing them in the context of a wider variety of leaving groups.

β-Eliminations have been well served by reviews, both of a general nature[1–8] and on restricted topics[9–13], and summaries of new work appear annually[14]. In this chapter older work will normally be presented only as a background to, or for reassessment in the light of, new results. The chapter reflects the nearly exclusive mechanistic emphasis of recent work and indeed is confined to the mechanistically homogeneous olefin-forming eliminations in which a hydrogen is lost from the β-carbon. Nonetheless it

should be emphasized that synthetic applications have not been lacking and the last five years have seen a useful expansion in the scope of stereoselective olefin syntheses[9,10,15-19].

II. MECHANISMS OF ELIMINATION

The three principal mechanisms now recognized for eliminations were first formulated by Ingold and Hughes in the course of their work on alkyl halides and 'onium ions[20,21]. As shown in Scheme 1, the bonds to the β-hydrogen and to the leaving group X may be broken in either a concerted or a stepwise manner. In the concerted mechanism the olefin is formed in a single reaction step, and in the stepwise mechanisms it is preceded by formation of an intermediate which may be either a carbonium ion or a carbanion, depending on whether it is the C—X or the C—H bond that is broken in the initial step.



(1)

The notation for the mechanisms, *E*1, *E*2 and *E*1*cB*, was also introduced by Hughes and Ingold[1,21,22] and had its origin in an operational distinction between mechanisms based on kinetic order. Strictly speaking the terms *E*1 and *E*1*cB* refer to kinetic modifications of the stepwise mechanisms in which formation of the carbonium ion and reaction of the carbanion respectively are rate-determining. Such a formulation is out of step with the modern view that the principal distinction between mechanisms lies in the presence or absence of a reactive intermediate, irrespective of the rate-determining step[23]. In so far as Hughes' and Ingold's notation is now firmly stamped on the literature, and indeed is a fitting reminder of their contributions to the field[1,24], in this chapter the sense of *E*1 and *E*1*cB* is simply extended to include both kinetic modifications of the mechanisms. With this small qualification Hughes' and Ingold's mechanistic classification is used as the framework for the discussion that follows.

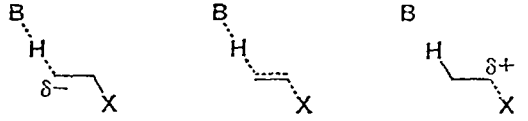
III. THE E2 MECHANISM

There has been a revival of interest both in experimental methods for distinguishing elimination mechanisms and in the factors that favour one

mechanism over another. These questions will be discussed in detail in connexion with the *E*1 and *E*1*cB* mechanisms and here it will suffice to note that the concerted mechanism is normally readily recognized by a combination of the kinetic necessity of a base and the kinetic sensitivity of the reaction to the chemical and isotopic nature of the leaving group. Except in borderline cases, the high rate of reaction rules out the possibility of carbanion formation. This does not cover all eventualities[25,26], but it is convenient at this point to take the concerted nature of reactions for granted and to return to the question of detailed corroboration later. For alkyl halides it will be true generally that primary and most secondary substrates reacting under basic conditions and lacking a very strongly activating β-substituent, such as RCO—, RSO_2—, NO_2—, will adopt a concerted mechanism.

A. The Transition State in E2 Eliminations

An important advance in the understanding of concerted eliminations came with the recognition that in the transition state there may be an imbalance in the degrees to which the C—H and C—X bonds are broken. This is illustrated in the now familiar[2-8] schematic diagrams **1**–**3** which further show that dominant C—X bond breaking leads to positive charge or 'carbonium ion character' at the α-carbon, while dominant C—H bond breaking leads to negative charge and 'carbanion character' at the β-carbon. Bartsch and Bunnett have called transition states **1** and **3** paenecarbanion and paenecarbonium ion respectively[15]. Transition state **2** is often described as 'central'.



(1) (2) (3)

Variability of structure for the *E*2 transition state was first seriously suggested by Cram, Greene and DePuy[27]. Subsequently, DePuy[28] and Saunders[29] and their collaborators demonstrated charge localization at the β-carbon in the elimination of ring-substituted β-phenethyl halides, tosylates and dimethylsulphonium ions, (**4**). Hammett plots gave values of

$$R{-}C_6H_4CH_2CH_2X$$

(4)

ρ in the range 2–3 with σ^- constants required for conjugating substituents.

By contrast a value of $\rho \nearrow 0{\cdot}2$ can be derived from the scattered plot of log K versus σ for the equilibrium dehydration of β-phenethyl alcohols[30].

$$R{-}C_6H_4CH_2CH_2OH \underset{}{\overset{H^+}{\rightleftharpoons}} R{-}C_6H_4CH{=}CH_2 + H_2O$$

In 1963 the factors affecting transition state structure were comprehensively reviewed by Bunnett[2], who promulgated the general principle that any substituent effect or change in reaction conditions favouring a particular element of the activation process, whether bond formation, bond breaking or charge development, increased its relative contribution in the transition state. This simple recipe makes qualitative predictions of changes in reactivity a simple matter. In the following sections the experimental methods for obtaining information about the transition state, especially measurements of linear free-energy relationships and isotope effects, are reviewed. At the same time the status of Bunnett's generalization in the light of recent experimental evidence is assessed.

I. Methods of determining transition state structure

a. Hammett ρ values. Values of ρ for reactions of β-phenethyl derivatives (**4**) in ethanolic sodium ethoxide[28,29,31] are listed for different leaving groups in Table 1. The magnitude of ρ depends on the leaving group, and

TABLE 1. *E*2 elimination of β-arylethyl derivatives at 30° C (**4**)

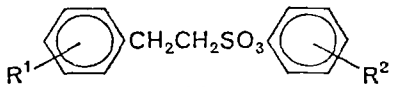
X	Relative rate (EtOH)	ρ (EtOH)	k_H/k_D (EtOH)	k_{OD^-}/k_{OH^-} [a]
I	26,600	2·07	—	—
Br	4100	2·14	7·1	1·30
OTs	392	2·27, 2·50	5·7	—
Cl	68	2·61	—	1·40
$\overset{+}{S}(CH_3)_2$	37,900	2·75	5·1	1·55
F	1	3·12	—	1·67
$\overset{+}{N}(CH_3)_3$	760	3·77[b]	3·0[c]	1·62

[a] *p*-$\overset{+}{N}(CH_3)_3$ derivative, 60°.
[b] Strongly temperature-dependent.
[c] 50°.

more reactive substrates are generally associated with smaller ρ values as may be seen from the halide family which follow their normal reactivity order, I > Br > Cl > F, with $k_{Br}/k_{Cl} = 60$. The sequence is broken if 'onium ions and halides are compared, but here the difference in charge type

renders reactivity comparisons of little significance; on the basis of the ρ values 'onium ions should be considered relatively poor leaving groups with $\overset{+}{N}(CH_3)_3$ inferior even to F. A broadly similar pattern is found for reactions in *t*-BuOH[28,31,32]; and in *t*-BuOH-DMSO at 50° β-phenethylmethylsulphoxide[33] with its exceptionally poor leaving group gives the large value of $\rho = 4{\cdot}4$.

A nice illustration of the correlation between ρ and the ease of displacing the leaving group has been found by Banger and Cockerill[34] in the elimination of β-phenethyl-*p*-benzenesulphonates substituted in both benzene rings (**5**). Electron-withdrawing substituents in the benzenesulphonate



(5)

ring both increase reactivity and decrease ρ for substitution in the β-phenyl ring. A plot of ρ for substitution at R^1 in **5** against σ for substitution at R^2 (or vice versa) gives a straight line of slope $\sim -0{\cdot}5$. If ρ for β-phenyl substitution is taken to reflect β-carbanion character in the transition state, these results and those of Table 1 imply that a poorer leaving group increases carbanion character and hence increases the ratio of C—H to C—X bond breaking in the transition state. This is consistent with Bunnett's dictum.

b. Brönsted exponents for base catalysis. The ρ value for β-phenyl substitution is sensitive to changes in the relative importance of C—H and C—X bond breaking in the transition state, not to changes in their absolute magnitudes. A more direct measure of the extent of C—H bond breaking is probably provided by the measurement of Brönsted exponents, β, for general base catalysis. For oxygen and nitrogen bases, values of β normally fall in the range 0–1 and may be considered to provide a rough measure of the order of the bond between the base and transferred hydrogen in the transition state[35,36]. Most of the available measurements for β-eliminations[37–39] are collected in Table 2. In some cases the use of thiolate ions may entail interaction between base and α-carbon in the transition state (section III. D). Nonetheless, comparisons between different substrates are in line with expectations based on Bunnett's principle and also with conclusions drawn from ρ values. Thus the smaller value of β for *t*-BuCl than *t*-Bu$\overset{+}{S}(CH_3)_2$ is consistent with less C—H bond breaking for the substrate with the better leaving group. Similarly, comparisons between bromoheptane, β-phenethyl bromide and *p*-nitrophenethyl bromide on the one hand, and between bromocyclohexane and 1,1-dibromocyclohexane

on the other, indicate that electron-withdrawing substituents at either the α- or β-carbons increase β; this is consistent with the increase in C—H bond breaking reasonably expected from the stabilization of β-carbanion character or inhibition of α-carbonium ion character in the transition state.

TABLE 2. Brönsted exponents for β-elimination in ethanol

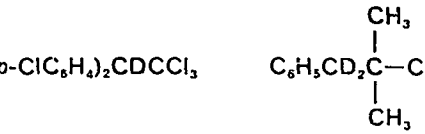
	β
t-Butyldimethylsulphonium ion	0·46[a]
t-Butyl chloride	0·17[a]
4-Bromoheptane	0·39
β-Phenethyl bromide	0·54
β-(*p*-Nitrophenethyl)bromide	0·67
Cyclohexyl tosylate	0·27[a]
Chlorocyclohexane	0·39[a]
Bromocyclohexane	0·36[a]
1,1-Dibromocyclohexane	0·51[a]

[a] Substituted benzenethiolate ions used as bases.

c. Isotope effects. Measurements of primary hydrogen isotope effects can be expected to reflect the relative strengths of the partial bonds to the β-hydrogen undergoing transfer in the transition state[40]. For simple hydrogen or proton transfer reactions both calculations[41] and experiments[42,43] suggest that the isotope effect should be maximized at a value of $k_H/k_D \sim 7$–10 for a transition state in which these bonds are of equal strength. For β-eliminations, Katz and Saunders have reported calculations which suggest that the concerted nature of the reaction should not alter the qualitative behaviour of the isotope effect[44]. This conclusion is supported by Cockerill's demonstration that β-deuterium isotope effects for elimination of β-phenethyl dimethylsulphonium bromide in mixtures of water and dimethylsulphoxide pass through a maximum value of $k_H/k_D = 6{\cdot}9$ as the composition of the solvent is varied[45]. Addition of dimethylsulphoxide greatly increases the basicity of the reacting hydroxide ion[46] so that a change in transition state structure is expected. The variation in k_H/k_D observed is matched by that of a straightforward proton transfer reaction in the same solvent mixture[43] and similar behaviour has been reported for the phenethyltrimethylammonium ion[47].

Table 1 lists primary isotope effects for phenethyl derivatives[49]. The large values for the bromide and tosylate suggest transition states close to symmetrical with respect to proton transfer. For the related eliminations of

2-aryl-1-propyl tosylates with potassium *t*-butoxide in *t*-butyl alcohol, similar values of k_H/k_D are observed which increase in magnitude with substitution of electron-withdrawing groups in the phenyl ring[32]. If electron-withdrawing substituents stabilize negative charge at the β-carbon and, as seems likely, increase the extent of C—H bond breaking in the transition state, the results imply a structure on the reactant side of symmetrical for the transition state. For the substrates with poorer leaving groups lower isotope effects, 3·2 for $\overset{+}{N}(CH_3)_3$ and 2·7 for $SOCH_3$[33], point to asymmetric transition states and the large ρ values and, more conclusively, the magnitudes of secondary solvent isotope effects considered below indicate a large rather than a small degree of C—H bond breaking. DDT, **6**, with electron-withdrawing substituents at α- and β-carbons favouring a large ratio of C—H to C—X bond breaking, also gives a small isotope effect[38]: $k_H/k_D = 3{\cdot}8$ in NaOEt/EtOH at 25°. For benzyldimethylcarbinyl chloride **7**, on the other hand, the moderate isotope effect, $k_H/k_D = 2{\cdot}6$ at 76° in CH_3OH, has been taken as indicating a small degree of hydrogen transfer[50]; this is consistent with the carbonium

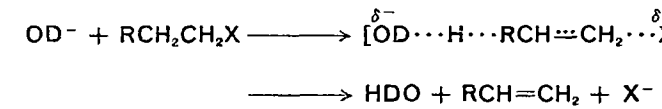


(6) **(7)**

ion character that might have been expected in the transition state[50] but the value of $\rho = +1{\cdot}0$ found for substitution in the β-phenyl ring[51] raises doubts as to the precise behaviour here.

Although the systematic investigation required to make primary isotope effects a really effective probe of transition state structure is lacking, available results appear to be generally consistent with expectations and independent measurements.

Further information on the extent of C—H bond breaking in the transition state comes from measurements of solvent isotope effects for elimination by hydroxide and deuteroxide ions in H_2O and D_2O [52, 53]. Here there is no primary isotope effect and a straightforward assumption is that the bond to the isotopically substituted hydrogen in the transition state is intermediate in character between the corresponding bonds in reactants



and products. If so, the kinetic isotope effects k_{OD^-}/k_{OH^-} may be expected to fall between the limits 1·0 and the equilibrium constant for the isotopic exchange reaction,

$$OD^- + H_2O \rightleftharpoons OH^- + HDO$$

which, at the temperature of the measurements, is ~1·90. Thus an increase in isotope effect may be taken as indicating an increase in the extent of C—H bond breaking in the transition state[52].

Results for different leaving groups are shown in Table 1; because of their solubility, substrates with a p-$\overset{+}{N}(CH_3)_3$ ring substituent were studied. All the measurements fall within the proper limits and they increase in magnitude as the leaving group becomes poorer, from 1·30 for X = Br to 1·62 for X = $\overset{+}{N}(CH_3)_3$. This is consistent with the trend in primary isotope effects and measurements of ρ, but unlike these results is subject to no ambiguity of interpretation[52].

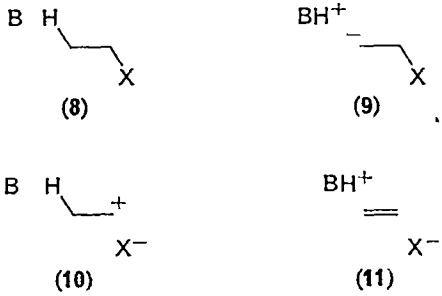
Secondary isotope effects have also been measured for deuterium substitution at the α- and β-carbons of the substrate[11,54–56]. Values fall in the range k_H/k_D = 1·02–1·52 and can probably be taken as indicative of transition state structure in much the same way as the secondary solvent isotope effects[55,56]; as yet no extensive correlation with changes in transition state structure has been reported. There have also been measurements of heavy atom isotope effects, for α- and β-carbons[57,58], and, with ammonium and sulphonium leaving groups, for nitrogen[59–62] and sulphur[63,64]. The latter are of interest in giving an index of leaving group bond breaking and some of the results are discussed below (section III. A. 3. b). It should be mentioned however, that, particularly with sulphur isotope effects, there have been some difficulties of interpretation[44,64]. Isotope effects for halogen leaving groups, although measurable, at least in the case of chlorine, do not appear to have been reported.

A comprehensive review of isotope effects in β-eliminations has been published[11].

2. Interpretations of structural changes in E2 transition states

In general the experimental data considered bear out well the principle that easing a bond-breaking process or the development of charge increases its contribution in the transition state. As noted by Bunnett, such behaviour is in apparent conflict with predictions based on existing treatments[36,65] of variations in transition state structure, including the Hammond postulate[66]. This may be appreciated by writing the $E2$ transition state as a hybrid of structures corresponding to reactants, products and the fully formed

carbanion and carbonium ion, as shown in **8–11**. Such a formulation is clearly related to that of structures **1**, **2** and **3**, and is also consistent with a representation[67] **12** commonly used for the S_N2 transition state and recently



(8) (9) (10) (11)

revived with new experimental evidence by Ko and Parker[68]. For S_N2 reactions, Ko and Parker point out that a contribution to the transition state from a carbonium ion structure $X^-\ R^+\ Y^-$ (in which X^- and Y^- denote the nucleophile and leaving group respectively) leads to a weakening

$$X^-\ R{-}Y \longleftrightarrow X^-R^+Y^- \longleftrightarrow X{-}R\ Y^-$$

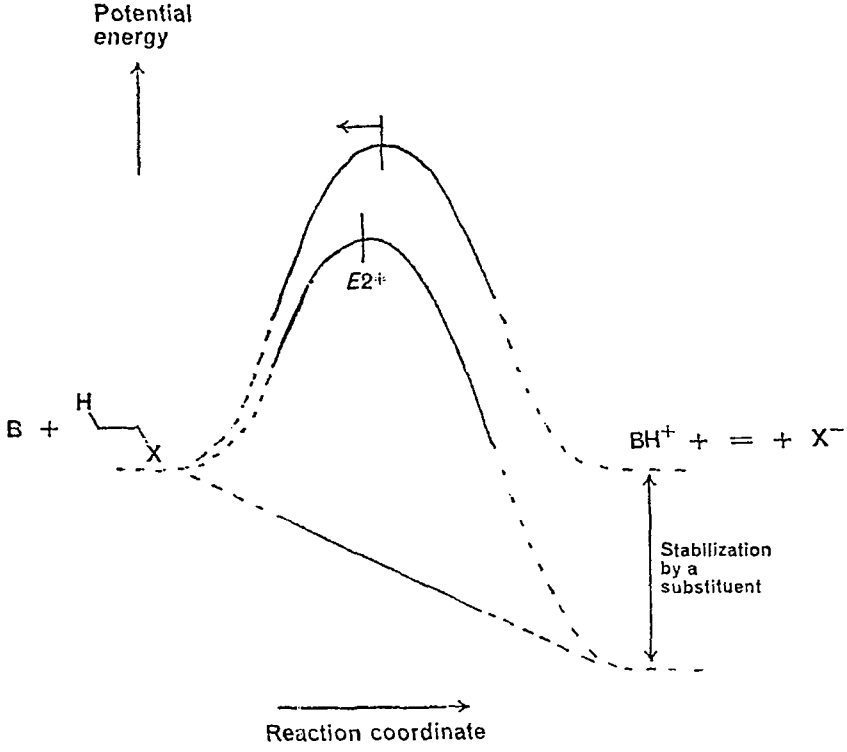
(12)

of the bonding to the central carbon, and they call such transition states 'loose', as opposed to 'tight'. Contributions of either carbanion or carbonium ion structures **9** or **10** could be regarded as leading to 'loose' *E*2 transition states.

Most interpretations of medium or substituent effects on transition state structure relate the effects to energy changes in reactants and products[65, 66]. An idealized representation of an effect which stabilizes products relative to reactants is illustrated by the potential energy–reaction coordinate curves of **13**; the energy of the transition state is decreased and its structure is moved closer to that of the reactants. Thornton[69] has provided a neat analytical model for this behaviour by superimposing a linear perturbing potential upon an inverted parabola in the manner shown by the full lines in **13**. It is found that the movement of the potential energy extremum is indeed in the direction shown.

Here stabilization of the product renders the transition state less product-like. This is contrary to the behaviour generally observed for *E*2 eliminations. However, energy changes are considered in the reactants and products only, whereas the *E*2 transition state is evidently sensitive to the stability of the carbanion and carbonium ion. Recently it has been shown that a potential energy surface may be formulated upon which all four

stable species **8–11** can be represented[70]. The C—X and C—H bond orders are taken as displacement coordinates and the potential energy is represented by contours. The form of the surface is determined by the necessity of locating the stable species at energy minima with C—X and C—H bond



(13)

orders of 0 or 1 and of interconnecting all species except the carbanion and carbonium ion by energy valleys and saddle points. The connexions between reactants and products and between the carbanion and carbonium ion are implied by the existence of *E*1 and *E*1*cB* mechanisms. The assumption is made that the π bond orders and developments of charge remain in step with C—H and C—X bond orders.

The surface is shown in Figure 1. *E*2 elimination is represented by the direct path from reactants to products and in this case involves a nice balance of C—H and C—X bond breaking, with a transition state similar to **2**. The surface may be used to examine the effect of energy changes in all the stable species **8–11** upon the energy and structure of the *E*2 transition state. This is done by extracting diagonal cross-sections, one

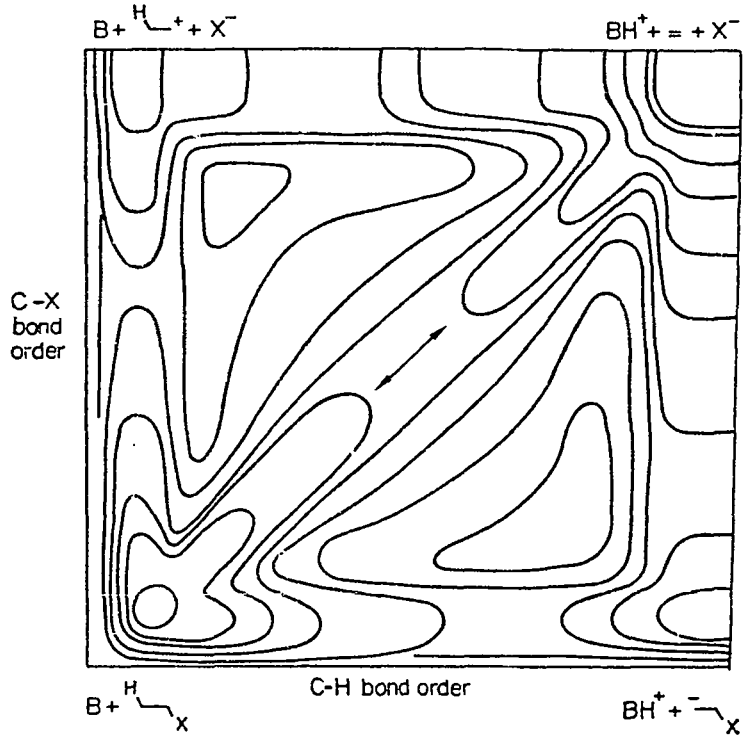
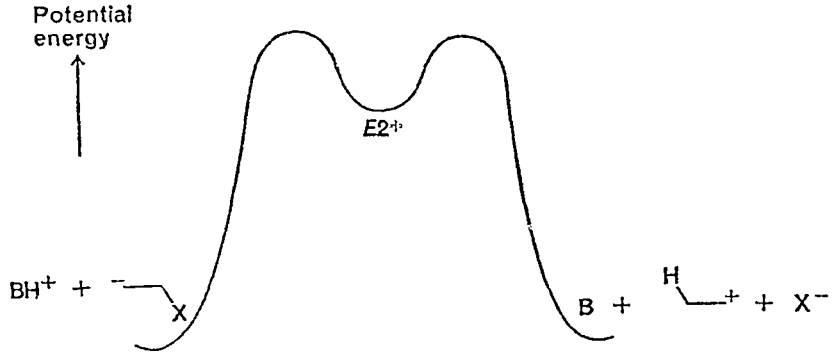


FIGURE 1. A potential energy surface encompassing concerted and stepwise β-elimination.

to include the transition state, reactants and products, which is fairly represented by the energy curves in **13**, the other to include the transition state, the carbanion and the carbonium ion, as is shown in **14**.



(14)

The effect of reactant and product stability is clearly in accord with normal, or Hammond postulate, behaviour. However, an essential difference in the effect of the carbanion and carbonium ion is that energy changes in these species are transmitted across the minimum rather than the maximum of the saddle point at which the *E*2 transition state lies. As pointed out by Thornton[69], application of the parabola model in this case leads to the expectation that the transition state will move *closer* in structure to the stabilizing influence. Thus for an extended potential energy model, carbanion and carbonium ion stabilizing substituents *increase* carbanion and carbonium ion character in the transition state.

The above model has strong affinities with an earlier treatment of substituent effects upon concerted reactions developed by Thornton[69]. Thornton considered the effects of substituents upon the ease of molecular displacements along the normal coordinates of the transition state. Effectively, attention was confined to the potential surface in the immediate vicinity of the *E*2 saddle point. The opposite signs for curvatures of the surface along the reaction coordinate and normal to it lead to changes in geometry respectively consistent with, and opposed to, the Hammond postulate in a manner complementary to that described above. No attempt will be made here to reproduce Thornton's treatment[52, 69, 71] or other[68, 72] approaches to the problem; these should be consulted directly. However, the practice already adopted of where possible adapting results to the potential energy model will be continued.

The predictions deriving from the simplest consideration of Figure 1 are that substituent and medium effects acting to stabilize structures **8**–**11** will lead to a smaller contribution of the reactant or product structures **8** and **11** and a larger contribution of the carbanion and carbonium ion structures **9** and **10**. This is consistent with Bunnett's rule when it is formulated as pertaining to the *relative* extents of C—H and C—X bond breaking in the transition state[6]. The rule then complements Hammond behaviour in much the same way as 'loose' transition states complement 'tight' transition states[68], and substituent effects exerted 'perpendicular' to the reaction coordinate complement those exerted 'parallel' to it[69, 70]. The importance of anti-Hammond behaviour in the *E*2 transition state stems from the charged character and hence sensitivity to substituent effects of the carbanion and carbonium ion.

3. Factors affecting transition state structure

With these points of interpretation in hand the following sections will illustrate the capability and limitations of the models in making predictions,

and also prepare the ground for the consideration of special features of *E*2 eliminations which follows (sections III. B. C. D).

a. The leaving group. A change to a poorer leaving group will stabilize reactant and carbanion structures **8** and **9** relative to carbonium ion and product structures **10** and **11**, since the latter incorporate the leaving group in ionized form, X^-. This will lead to both a more reactant-like transition state and an increase in carbanion character (or a decrease in carbonium ion character). There will also be an increase in C—H bond breaking; but because changes in contributions of **8** and **9** have opposite effects on C—X bond breaking it is not immediately clear whether C—X bond breaking will increase or decrease. Experimentally, as we have seen, the ρ values of Table 1 show that a poorer leaving group does increase carbanion character, while the primary and solvent isotope effects and changes in Brönsted exponent for base catalysis testify to an increase in C—H bond breaking. The effect on C—X bond breaking is not known.

b. Substituents at the β-carbon. For carbanion-like transition states β electron-withdrawing substituents should both increase the carbanion character and the degree of C—H bond breaking, and decrease the extent of C—X bond breaking; electron-donating substituents should have the opposite effect. In practice, carbanion stabilizing substituents such as phenyl are believed to promote carbanion-like transition states[6] and Table 2 shows that if Brönsted exponents are a reliable guide they also increase C—H bond breaking. Correspondingly an electron-donating β-methyl group leads to reduced ρ values (and hence less carbanion character) for elimination of β-arylethyl bromides and tosylates[32], as may be seen in Table 3 *.

Detailed measurements of β-hydrogen and leaving group isotope effects in the elimination of β-phenethyltrimethylammonium ions made by Smith and Bourns[60, 62, 73] show a different pattern. Table 4 shows that while electron-withdrawing substituents decrease the nitrogen isotope effects and hence, presumably, decrease the extent of C—X bond breaking, as would be expected, they lead to an *increase* in β-hydrogen isotope effects. Since transition states are here expected to involve a large degree of proton transfer (section III. A. 1. c) this must imply a decrease in C—H bond breaking, a conclusion that is corroborated by the decrease in solvent isotope effect[52, 53] also shown in Table 4.

This behaviour is clearly contrary to expectation and it may reflect a limitation in the substituent effect model. Re-examination of Figure 1

* The large effect of α-methyl substituents upon ρ in Table 3 is quite unexpected. It may signify interaction of the base with the α-carbon in the transition state.

indicates that simple predictions based on structures **8–11** apply only to a transition state centrally located on the potential surface. This case, in

TABLE 3. The effects of methyl substituents and solvent upon elimination of β-phenethyl derivatives ($PhCH_2CH_2X$) at 50°

X	Substituents	ρ EtOH/NaOEt	ρ *t*-BuOH/NaOBu-*t*
OTs	H	2·3	3·4
OTs	β-CH_3	1·8	2·2
OTs	α-CH_3	1·3	1·9
Br	H	2·1	2·1
Br	β-CH_3	2·1	1·8
Br	α-CH_3	1·8	1·4
$\overset{+}{N}(CH_3)_3$	H[a]	3·9	3·1

[a] 30°, *p*-MeO, *p*-Me and H substituents only.

which changes in carbanion stability are felt across the reaction coordinate, is usefully contrasted with that of elimination via a carbanion intermediate, in which, as may be seen from inspection of the *E1cB* reaction path in

TABLE 4. Substituent effects on isotope effects for β-phenylethyltrimethylammonium ions

p-Substituent	k^{14}/k^{15} [a] 40°, EtOH	k_H/k_D 40°, EtOH	k_{OD^-}/k_{OH^-} H_2O, D_2O, 80·45°
CH_3O	1·0137	2·64	
H	1·0133	3·23	1·79
Cl	1·0114	3·48	1·73
CF_3	1·0088	4·16	
NO_2		(6·0)[b]	
$\overset{+}{N}(CH_3)_3$			1·62[c]

[a] Nitrogen isotope effect for trimethylammonium leaving group.
[b] $(k_H/k_T)^{1/1·442}$ for $NaOCH_3/CH_3OH$ at 22°, references 57, 74.
[c] 60°. At 80·45° the value should be smaller.

Figure 1, changes in carbanion stability are felt along the reaction coordinate. It is apparent that a β-substituent increasing or decreasing carbanion character in a 'central' *E2* transition has the opposite effect on

carbanion character in an *E1cB* transition state. For a carbanion-like *E2* transition state, behaviour between these extremes may reasonably be expected, and for the reactions in Table 4 substituent effects could well be felt more strongly along the reaction coordinate than normal to it. This possibility has been considered in detail by Thornton[52] who points to the low curvature of the potential surface along the reaction coordinate as a factor magnifying substituent effects in this 'direction'[71]. On the other hand it seems likely that such behaviour is not normal and applies only to transition states of highly developed charge character.

c. The effect of base and solvent. Because it is a major factor affecting the orientation and stereochemistry of elimination, it is important to determine the influence of base strength upon the *E2* transition state. In practice a change in base is often associated with a change in solvent and, not surprisingly, the complication that this introduces has led to some differences in the interpretation of experimental results[6,31].

Focusing attention on the base B and its conjugate acid BH^+, consideration of structures **8–11** suggests that an increase in base strength will decrease the extent of C—X bond breaking and produce compensating effects on C—H bond breaking. With respect to the solvent, the predicted effects depend upon the nature of the leaving group. Normally an increase in base strength entails transfer to a poorer ion-solvating solvent. This will facilitate displacement of a positively charged leaving group, leading to a decrease in C—H bond breaking in the transition state, but will hinder displacement of an initially neutral group, causing an increase in C—H bond breaking. The net effects of base and solvent are tabulated below.

The combined effects of increased base strength and a poorer ion-solvating medium upon the *E2* transition state

	C—H bond breaking	C—X bond breaking	ρ
$R—X^+$	− −	− −	?
R—X	+	−	+ +

The predictions are in accord with those of Saunders and Cockerill[31,45] based largely on consideration of reactant and product stabilities. Bunnett's principle is also applicable[2,6] but should be confined to predicting relative and not absolute changes in bond breaking.

Experimentally, β-hydrogen isotope effects and values of ρ for β-phenyl substitution offer the best guides to actual behaviour. For a neutral leaving group an increase in carbanion character and an increase in ρ value is the expected effect of a stronger base and less polar solvent. The β-phenethyl tosylates in Table 3 offer examples of this[32]. In passing from NaOEt/EtOH to NaOBu-*t*/*t*-BuOH, ρ for β-phenethyl tosylate itself increases from 2·3–3·4, while k_H/k_D increases from 5·7–8·2. As discussed in section III. A. 1. c the change in isotope effect probably reflects the expected increase in C—H bond breaking.

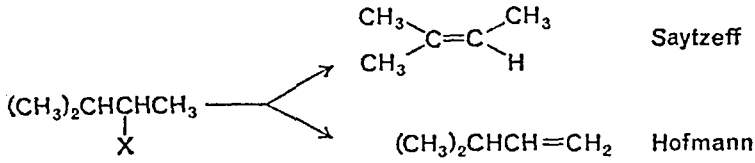
For 'onium ions the change in ρ cannot be firmly predicted because the solvent and base have opposing effects on carbanion character in the transition state. For the β-phenethyltrimethylammonium ion ρ decreases from 3·9 to 3·1 in passing from EtOH to *t*-BuOH (Table 3) suggesting that the solvent effect is dominant[31]. For the β-phenethyldimethylsulphonium ion addition of DMSO to water leads to a small increase in ρ[45]. In this case the relative insensitivity of ρ to solvent and the opposite direction of the change with respect to solvent polarity from that of the ammonium ion both suggest the operation of compensating effects. Measurements of changes in isotope effects for the ammonium ion in going from EtOH to *t*-BuOH show k_H/k_D increasing, from 3·0 to 7·0, and the nitrogen isotope effect decreasing[75], indicating a decrease in both C—H (cf. section III. A. 1. c) and C—X bond breaking. Broadly parallel behaviour for the dimethylsulphonium ion in H_2O—DMSO is found.

The consistency of this picture is marred by the behaviour of the phenethyl bromides. In a number of instances increasing the basicity of the medium[32,77], in going from EtOH to *t*-BuOH[32] or adding DMSO to *t*-BuOH[77], leaves k_H/k_D unchanged and actually causes ρ to decrease (cf. Table 3). This is particularly surprising insofar as simple alkyl halides appear to behave normally; for secondary butyl bromide, for example, k_H/k_D increases from 3·5 to 4·0 to 4·4 in going from EtOH to *s*-BuOH to *t*-BuOH, as would be expected of increased C—H bond breaking[78]. At present the behaviour cannot be fully understood; possibly, ion pairing plays a role[77].

B. The Hofmann and Saytzeff Rules

A touchstone of any theory of *E*2 eliminations is its ability to interpret the rules formulated by Saytzeff and Hofmann for predicting the orientation of elimination from substrates with β-hydrogens attached to different carbons. According to the Saytzeff rule[79], which was applied to elimination of alkyl halides (I, Br, Cl), reaction occurs preferentially at the most heavily substituted carbon; according to the Hofmann rule[80,81], which was applied

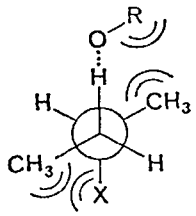
to alkyl ammonium ions, it occurs at the least substituted carbon. Nowadays, the rules are normally considered only in relation to alkyl substituents.



I. Interpretations

As pointed out by Ingold[1], a conflict between the rules became apparent when it was recognized that eliminations of alkyl halides and Hofmann degradations involve a common reaction mechanism. Once this was established the operation of two independent factors in determining the direction of alkyl substituent effects had to be accepted and explained. Hughes and Ingold proposed that in the elimination of alkyl halides the stabilizing effect of an alkyl substituent upon the olefinic product is felt by the incipient double bond in the transition state, but that in the 'onium ions, for which the acidity of the β-hydrogen was reckoned of overriding importance, this factor is more than counterbalanced by the adverse inductive effect of the methyl group[24,81].

Hughes' and Ingold's opposition of hyperconjugative and inductive effects was matched by an opposition of hyperconjugative and steric effects advocated by Brown and Moritani[82]. Brown made the important discovery that the Saytzeff orientation of halides was changed to Hofmann in passing from a primary alcohol–alkoxide solvent–base combination to a secondary or tertiary one. This is hardly consistent with an inductive interpretation of Hofmann behaviour and Brown suggested that the Hofmann orientation arises by default through steric hindrance, by a bulky leaving group or bulky base, to the attainment of an *anti*-periplanar conformation of the β-hydrogen and leaving group in the transition state for formation of Saytzeff olefin (**15**).



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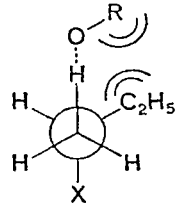

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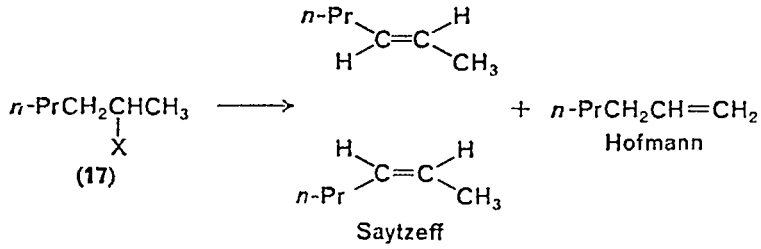
A weakness in both Brown's and Ingold's interpretations is that the factors determining orientation are unrelated to the large difference in reactivity between the common alkyl halides and the alkyl 'onium ions. This, on the other hand, provides the basis for an explanation in terms of variations in transition state structure[2,29]. In primary alcoholic solvents alkyl iodides, bromides and chlorides should react via 'central' or *E*1-like transition states (**2** or **3**) and the principal effect of the β-methyl group should indeed be its interaction with the incipient double bond, as Brown and Ingold suggest. For the 'onium ions, the poorer leaving group should induce greater C—H bond breaking and more carbanion character in the transition state so that the dominant effect of the alkyl group will be an unfavourable inductive interaction. This is similar to an updated interpretation of Banthorpe, Hughes and Ingold[83] save that they considered the inductive effect of the leaving group to be the factor-determining transition state structure.

2. Alkyl halides

a. Leaving group. With the advent of gas–liquid chromatography Saunders and coworkers[84] were able to show that previously undifferentiated olefin proportions from elimination of 2-pentyl iodide, bromide and chloride in fact showed an increase in the proportion of Hofmann olefin in the order I < Br < Cl, contrary to Brown's prediction. Although it could be argued[85] that here changes in steric requirements need not necessarily parallel changes in atomic radius[86], the subsequent finding of a much larger fraction of Hofmann olefin for 2-pentyl fluoride[87] appears to offer unassailable evidence against the generality of Brown's interpretation. The reactivity of the halides and hence the ease of displacing the halogen leaving group decreases with the atomic radius, I > Br > Cl > F, so that the observed behaviour is fully consistent with the explanation based on variations in transition state structure. These experiments provide a nice illustration of the mechanistic use that can be made of the halogens as a family.

The above results have been corroborated under kinetically controlled conditions[88] by Bartsch and Bunnett who have studied the elimination of 2-hexyl derivatives (**17**) for a wide variety of leaving groups and reaction conditions[15,88,89]. Rate constants and product fractions of 1- and 2-hexene for the hexyl halides in methanol[88] and *t*-butyl alcohol[15] are shown in Table 5. Also shown are the ratios of *trans*/*cis* 2-hexene. The variations of these with base and leaving group have been interpreted[84,87,88] as reflecting the extent of eclipsing and hence the degree of double-bond character in the transition state. The close correlation between changes in *cis–trans* and

Hofmann–Saytzeff olefin proportions supports such an interpretation, but for wider changes in solvent, base or leaving group other factors become important (sections III. C. 3 and III. D. 3). Significantly, the proportion of



Hofmann product shows no correlation with σ^* values for the leaving groups, arguing against the rather unlikely suggestion of inductive control of transition state geometry[88].

TABLE 5. Olefin compositions and rate constants for eliminations of 2-hexyl halides at 100°

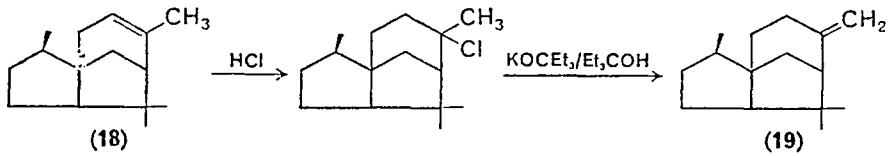
		$NaOCH_3/CH_3OH$		NaOBu-*t*/*t*-BuOH	
Leaving group	$k_2^a \times 10^5$	% 1-hexene	*trans*/*cis* 2-hexene	% 1-hexene	*trans*/*cis* 2-hexene
I	57,000	19	3·6	69	1·8
Br	14,400	28	3·0	80	1·4
Cl	380	33	2·9	88	1·1
F	0·55	70	2·3	97	1·2

[a] Rate constants for formation of 1-hexene in $NaOCH_3/CH_3OH$.

b. Base strength. In the light of the discussion in section III. A. 3. c the expected effect of a change to a stronger base and less polar solvent upon transition state geometry for reaction of a simple alkyl halide is that carbanion character should be increased[15]. This nicely explains the increase in Hofmann orientation between sodium methoxide and sodium *t*-butoxide seen in Table 5. In this instance, however, an explanation in terms of the steric requirements of the alkoxide base would also apply, and there have been attempts to complement the separation of steric and electronic effects of the leaving group with a similar separation for the base[16,76,90–94]. Curiously, a separation of changes in base strength from what could conceivably be construed as steric requirements of the base, especially if these are expanded to include solvating molecules[85], is quite difficult. For the commonly used alkoxide bases, for example, increases in basicity are

associated with homologation and, more strongly, with chain branching at the α-carbon atom. Perhaps the most straightforward demonstrations of the importance of base strength are provided by comparisons between substituted phenoxide ions[76,90] and between $C_2H_5O^-$ and $CF_3CH_2O^-$ ions[91]. In each case the predicted increase in Hofmann orientation with basicity was observed. Departures from the normal[16,82,85,89,92,94–96] effect of basicity on orientation of alkyl halides indeed seem to occur only for transfers from protic to dipolar aprotic solvents[89,92], in which case *E2C* elimination (section III. D) probably intrudes. However, the anomalous results for phenethyl bromides mentioned above (section III. A. 3. c) offer a reminder that not all is understood here[32,77].

Apart from its intrinsic interest the effect of base strength has some practical importance in that strongly basic media may be used for the efficient synthesis of thermodynamically unstable olefins[15,16]. An example of this has been given by Acharya and Brown[16] in the interconversion of α- and β-cedrene, **18** and **19**.



(18) (19)

3. Alkyl 'onium ions

A detailed consideration of orientation in alkyl 'onium ions adds little to the results obtained directly with halides and is beyond the scope of this chapter. It should be noted, however, that a number of results suggest that, especially for the trimethylammonium group, steric effects are important. For rigid cycloalkylammonium ions[97], particularly where heavily substituted, steric effects appear to weaken the C—N^+ bond[7,97–99] causing an increase in reaction rate; in acyclic alkyl ammonium ions, on the other hand, steric effects hinder the attainment of an *anti*-coplanar conformation of β-hydrogen and leaving group, in the manner discussed by Brown, and a retardation in rate results. Evidence of the latter effect comes from a comparison of the effect of β-alkyl substituents upon elimination of alkyl bromides and alkyltrimethylammonium ions[83], shown in Table 6. A *t*-butyl group slows elimination of the ethyltrimethylammonium ion in sodium *t*-butoxide/*t*-butyl alcohol by a factor of 40,000, a factor too large to be ascribed to an inductive effect alone[83]. The larger effect in *t*-BuOH than in EtOH is reasonably explained by the more reactant-like transition state for the poorer solvent and stronger base.

In retrospect Brown and Moritani's suggestion of a *gauche* interaction between β-substituents and leaving group[82a] appears more reasonable than that of the steric effect upon proton transfer to an alkoxide base. It is

TABLE 6. The effect of β-alkyl substituents on relative rates of elimination of alkyl bromides and trimethylammonium ions $RR'CHCH_2X$

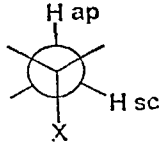
R, R′	X = Br NaOEt/EtOH, 55°	$X = \overset{+}{N}(CH_3)_3$ NaOEt/EtOH, 100°	$X = \overset{+}{N}(CH_3)_3$ NaOBu-*t*/*t*-BuOH, 73°
H, H	1·0	1·0	1·0
CH_3, H	3·3	0·07	0·012
Et, H	2·7	0·043	0·003
CH_3, CH_3	5·4	0·029	—
t-Bu, H	—	0·001	0·000024

possible that the implications of the *gauche* interaction for the rather complex behaviour of alkyl and cycloalkyl 'onium ions have not yet been fully worked out. An extension of the already fruitful comparison between fluorides and 'onium ions would be particularly welcome.

C. The Stereochemistry of E2 Elimination

1. Small rings

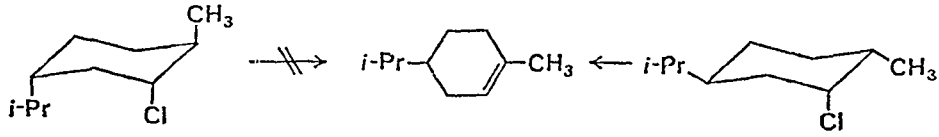
Until quite recently *E*2 eliminations were believed to show a strong preference for a transition state in which the β-hydrogen and leaving group bore an *anti*-periplanar (ap) relationship to each other (**20**). This belief was



(20)

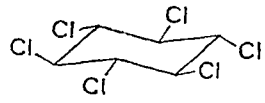
based in part upon early demonstrations[100] that under *E*2 conditions *trans*-1,2-cyclohexyl derivatives (e.g. **21**) appeared to undergo no elimination of the β-hydrogen unable to achieve an *anti*-periplanar conformation with respect to the leaving group, and in part upon the analogy drawn by Hughes and Ingold[24] between *E*2 elimination and S_N2 displacements, which could be taken to imply that the two reactions should show similarly rigid stereospecificities. The belief indeed seems to have been confirmed by the fact that early observations of *syn* elimination were confined to systems

in which either competing reactions were strongly inhibited, as, for example[101], with β-hexachlorocyclohexane (**22**), or *syn* elimination was



(21)

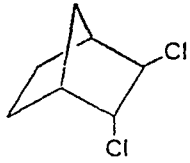
strongly activated[61, 101–5] as in the *trans*-1,2-phenylcyclohexyltrimethylammonium[61] ion (**23**). The deactivation implied for *syn* compared with *anti* elimination was sufficiently strong that observations of *syn* stereochemistry were taken as *prima facie* evidence for the formation of a carbanion intermediate[102, 106–109], this point has been well reviewed by McLennan[12].



(22)

(23)

Subsequently it was shown that *syn–anti* rate differences are much smaller in cyclopentyl than in cyclohexyl rings[103, 110, 111] and that in dihalobicycloheptanes, such as **24** and **25**, *syn* elimination from the *trans* isomer **24** is faster than *anti* elimination from the *exo* or *endo* (**25**) *cis isomers*[106, 112], a finding that complemented earlier measurements with



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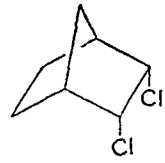
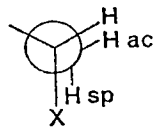


(25)

2,3-dibenzobicyclooctadiene dichlorides[107]. In 1962, DePuy and coworkers suggested that the coplanarity of the β-C—H and leaving group bonds might be a more important factor in determining stereochemistry than their *syn* or *anti* relationship[110]. On this basis, the preference for *syn* elimination of bicyclooctyl and bicycloheptyl derivatives comes from the close approach to a *syn* periplanar (sp) relationship between the *cis*-β-hydrogen and leaving group, and to an *anti*-clinal (ac) relationship between the *trans*-β-hydrogen and leaving group, as in **26**. In the cyclohexyl ring the preference for *anti* elimination of course tallies with the *anti*-periplanar relationship of leaving group and *trans*-β-hydrogen; indeed where *syn E*2

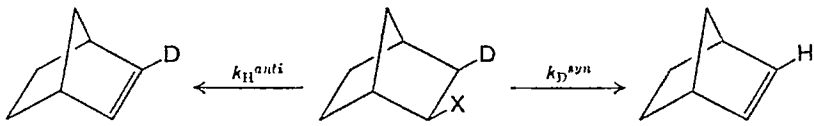
elimination in cyclohexyl rings does occur it may well do so through a skew-boat conformation[99]. In acyclic substrates *anti* elimination is still



(26)

expected to be favoured because *syn* elimination leads to unfavourable eclipsing effects in the transition state[12]. A stereoelectronic preference for *anti* elimination may also exist[5,24,113–115], but if so it is presumably either not very great, or readily relaxed or reversed[5,113] by changes in transition-state structure.

Measurements with norbornyl substrates labelled stereospecifically with deuterium *cis* or *trans* to the leaving group (27), from which the stereochemistry of elimination may be inferred by measurement of a kinetic isotope effect and the isotopic composition of the products[116], have shown that *exo–syn* elimination occurs very much more rapidly than *endo*[116,117] which suggests that an additional factor must be operating. However, where comparisons have been made the *endo syn–anti* ratio is still unusually high[118]. As shown in Table 7 a good qualitative correlation between



(27)

TABLE 7. *syn–anti* Rate ratios and values of ρ for elimination of phenylcycloalkyl tosylates at 50° in KOBu-*t*/*t*-BuOH

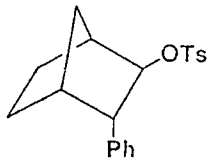
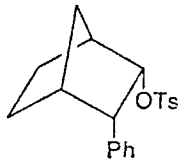
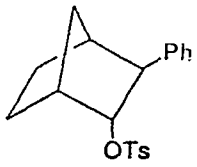
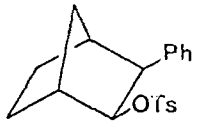
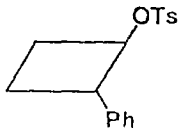
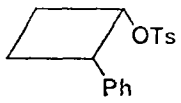
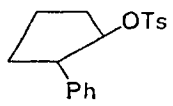
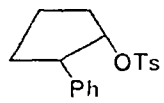
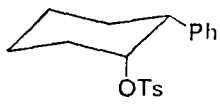
	Elimination mode	$k_2 \times 10^4$ $M^{-1}\,s^{-1}$	ρ	*syn–anti*
	*exo–syn*	15·7	3·1	30·7
	*exo–anti*	0·48	2·6	

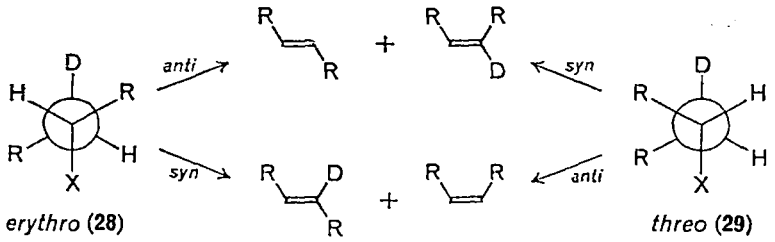
TABLE 7 (*cont.*)

	Elimination mode	$k_2 \times 10^4$ $M^{-1}\,s^{-1}$	ρ	*syn–anti*
	*endo–syn*	0·020	—	
				0·58
	*endo–anti*	0·033	—	
	*syn*	5·10	2·9	
				0·39
	*anti*	13·0	2·2	
	*syn*	2·9	2·8	
				0·10
	*anti*	29·1	1·5	
	*syn*	—	—	
				$< 10^{-4}$
	*anti*	1·92	—	

syn–anti ratios and the expected size of the dihedral angle between the leaving group and the *cis*-β-hydrogen is found. A broadly similar pattern has been found for Hofmann elimination of small ring-[119,120], bicyclooctyl- and bicycloheptyl-trimethylammonium ions[121], although in the bicycloheptyl case only *exo–syn* elimination was investigated.

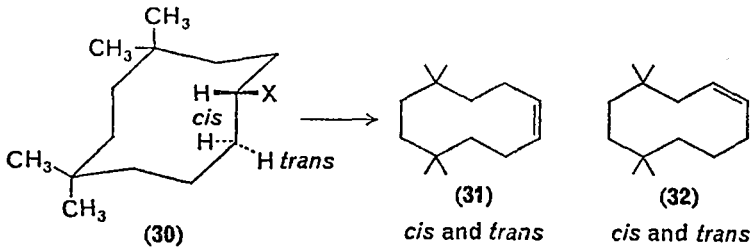
2. Medium rings

Stereospecific isotopic labelling has proved a powerful technique for investigating the stereochemistry of elimination from structurally simple non-cyclic and flexible-ring substrates. With stereospecifically deuterated *erythro* and *threo* diastereomers **28** and **29** as reactants the proportions of *syn* and *anti* elimination may be obtained either by combining product analyses for *cis* and *trans* olefins with determinations of the deuterium



contents of the separated olefin isomers or, when the protio and β-dideutero substrates are also available, by combining non-isotopic product analyses with measurements of kinetic isotope effects[48,122,123]. In favourable cases simplifying assumptions may also allow semiquantitative or qualitative conclusions to be drawn from more limited data[48].

Závada, Svoboda and Sicher[122] rigorously applied a stereospecific labelling method to elimination from the ten-membered ring substrate 1,1,4,4-tetramethylcyclodecyl-7-trimethylammonium chloride (**30**, $X = \overset{+}{N}(CH_3)_3$) in which the methyl substituents help to lock the ring in the favourable conformation[124] shown below. The cyclodecenes (**31** and **32**) formed as



products, like other monocyclic olefins of ring size greater than seven, may exist as *cis* and *trans* isomers, of which the *trans* isomer, although the less stable, is the major elimination product. As may be seen from Table 8 the remarkable result was obtained that both *cis* and *trans* olefins are formed stereospecifically, the *cis* isomer by *anti* elimination and the dominant *trans* isomer by *syn* elimination. The stereospecificity is directly revealed by the experimental results. While formation of both *cis* and *trans* cyclodec-7-enes

(**31**) from the 'onium ion (**30**) deuterated in the *trans*-8-*d* position is subject to a substantial isotope effect (k_H/k_D = 3·6 and 2·7 respectively), within experimental error formation of the same olefins from the isomeric *cis*-8-*d* 'onium ion (which has the stereochemistry of **28**, with the Rs representing ring residues) shows no isotope effect.

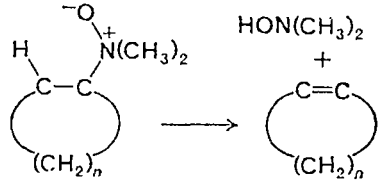
TABLE 8. Elimination of 1,1,4,4-tetramethylcyclodecyl-7-trimethylammonium chloride in $KOCH_3/CH_3OH$, at 130°

	% *trans* olefin[a]	k_H/k_D	% *cis* olefin[a]	k_H/k_D
7-$\overset{+}{N}Me_3$	49·3	—	5·6	—
cis-8-*d*-7-NMe_3^+	45·8	1·1	6·1	1·0
trans-8-*d*-7-NMe_3^+	28·7	2·7	2·2	3·6

[a] *cis*- and *trans*-1,1,4,4-tetramethyldec-7-enes (**31**). Percentages are of total olefin product **31** and **32**.

This result differs from that of *syn* eliminations in small or bicyclic rings in that *syn* elimination is not favoured by geometrical constraint in the reactants. Strong evidence that it is characteristic of elimination from medium rings in general comes from a comparison[125,126] of the kinetic dependence of 'onium ion eliminations upon ring size with that of the necessarily *syn* stereospecific thermal elimination of cycloalkyldimethylamine oxides[127] (**33**). From Figure 2 it can be seen that the two dependences are closely similar for formation of the *trans* olefin and substantially different for formation of the *cis* olefin.

The very strong preference for *syn* elimination is characteristic of alkylammonium ions in strongly basic media. Investigation of other leaving groups[128–130] and of a variety of solvent base systems[131,132] has revealed some of the factors upon which the stereochemistry of elimination depends. Generally speaking, a sharp inverse correlation between the fraction of *syn* elimination and the fraction of *cis*-olefin in the product prevails, with infractions of the *anti–cis* correlation occurring more readily than of the



(**33**)

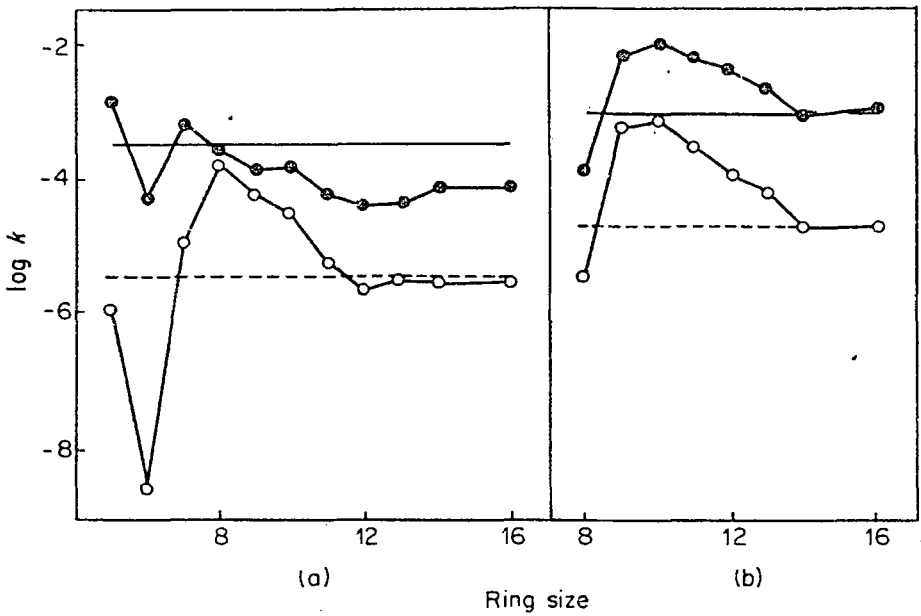


FIGURE 2. The ring-size dependence of eliminations; (a) *cis*-olefin formation, (b) *trans*-olefin formation; ●, cycloalkyltrimethylammonium ions in KOBu-*t*/*t*-BuOH at 55°; ○, cycloalkyldimethylamine oxides in *t*-BuOH at 70·6°; —, 5-nonyltrimethylammonium ion; ----, 5-nonyldimethylamine oxide.

syn–trans. The *syn–trans* mode is favoured by leaving groups in the order $\overset{+}{N}(CH_3)_3 > OTs \sim Br$[128] $\sim Cl$[130], which paralleis both steric requirements and ease of displacement. It is favoured by a strong base and a poor ion-solvating medium, typically KOBu-*t*/benzene > KOBu-*t*/*t*-BuOH > $KOCH_3$/CH_3OH, with behaviour in dipolar aprotic solvents depending on the nature of the leaving group. The effect of leaving group and medium, as reflected in the ratio of *cis–trans* olefin products from the cyclodecyl ring, is shown in Table 9. Figure 2 shows that the stereoselectivity also depends on ring size, being a maximum in the range 10–12.

Partial interpretations of the observed behaviour have been presented by Sicher and collaborators[10,131]. A feature of the medium rings expected to favour *syn* elimination is the distortion of normal C—C—C bond angles. As the ring size is increased from cyclohexane, angle distortions destroy the coplanarity of a leaving group and an *anti* C—H bond and improve coplanarity of a leaving group and a *syn* C—H bond. In the larger rings such as cyclodecyl a second factor is that substituents may occupy intra- or extra-annular positions in the ring. Preference of the leaving group,

particularly when bulky, as in the case of an 'onium ion, for the less sterically demanding extra-annular position will tend to place the *cis* β-hydrogen in an intra-annular position as in **30**. It is not hard to

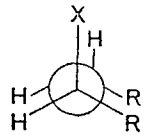
TABLE 9. The effect of base, solvent and leaving group upon *trans–cis* olefin ratios

	Cyclodecyl-X		5-Nonyl-X		
Base–solvent	X = $\overset{+}{N}(CH_3)_3$	Br	Br	OTs	$\overset{+}{N}(CH_3)_3$
t-BuOK/benzene	~200	8	0·8	1·0	9
t-BuOK/*t*-BuOH	65	7	1·5	0·5	2·8
i-PrOK/*i*-PrOH	24	1·4	2·3		0·9
EtOK/EtOH	4	0·18	3·3		0·3
t-BuOK/DMF	(65)[a]	0·06	7·0	3·1	(4·6)[a]

[a] *t*-BuOK/DMSO.

imagine that in this conformation the *cis* hydrogen is sterically 'shielded' from approach of a base. As expected, the preference for *syn* elimination decreases as the ring size becomes large and conformational behaviour approaches that of an open-chain substrate[128,129,131,132] (Figure 2).

The *trans* stereospecificity of *syn* elimination may be understood as a consequence of the extreme eclipsing that would occur in the transition state leading to *cis* olefin, **34**. Given the fact of predominant *syn* elimination this indeed provides an attractive explanation of the long-standing problem as to why elimination in medium rings gives preferentially the relatively strained *trans* olefin[131,133]. Significantly, there is a transgression

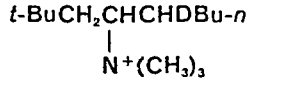


(34)

of the *syn–trans* rule for cyclooctene, for which the energy difference between *trans* and *cis* cycloolefins is maximized[134]. On the other hand, the relative stability of the *cis* olefin favours *cis*-stereoselectivity for the *anti* elimination mode. For larger rings this stereoselectivity is also relaxed.

3. Open-chain substrates

While comparisons between medium rings and the corresponding open-chain systems[122,128,130,135], for example between decyl and cyclodecyl dibromides and dichlorides[130], do indicate a greater proneness to *syn* elimination in the rings, *syn* elimination in acyclic substrates does occur. Indeed the tendency towards *syn* elimination shows qualitatively the same dependence upon medium and leaving group as for the rings[48,135,136], and for favourable structures, e.g. **35**, the same stereoselective *syn/trans–anti/cis* dichotomy is found[137]. In cases where *syn* elimination is probably



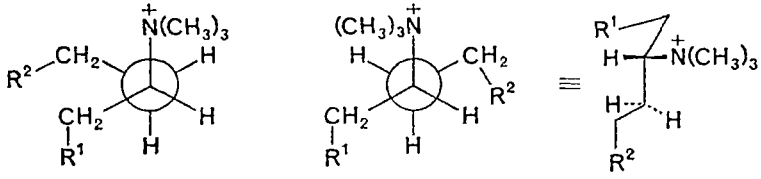
(35)

unimportant, strongly basic media can lead to predominant formation of the *cis*, and now thermodynamically unstable, olefin[76,135,136,138,139].

Saunders and collaborators have suggested that the open-chain substrates for which *syn* elimination is favoured may simulate some of the characteristics of the medium rings[48,136,139]. Product analyses for a range of alkyl tosylates[136] and 'onium ions[48,139,140] indicate that both the tendency towards *syn* elimination *and* the *cis* stereoselectivity of *anti* elimination are increased by bulky substituents at the α- and β-carbon atoms. In line with this, independent labelling measurements indicate very nearly exclusive *anti* elimination for the lightly substituted 2-butyl tosylate[141], 2-butyl bromide[78], and ethyl-[142] and β-phenylethyltrimethylammonium ions[143], as compared with the large fraction of *syn* elimination for **35**.

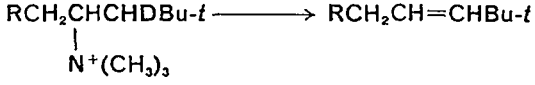
Bailey and Saunders[48] have pointed out that a bulky leaving group such as $\overset{+}{N}(CH_3)_3$, or to a lesser extent OTs, will cause alkyl substituents separated from the α- or β-carbons by a methylene group, as are R^1 and R^2 in **36** and **37**, to assume an arrangement in which, in the stable conformation leading to *trans* olefin, they shield the *trans* β-hydrogen from attack by base in a manner closely analogous to the intra-annular shielding surmised in the medium rings (compare **30** and **37**). By default, both the proportion of *syn* elimination, which normally leads to *trans* olefin, and the porportion of *anti* elimination occurring from the less stable but unshielded conformation **37** to give *cis* olefin will increase. Interestingly, a bulky substituent is more effective at R^1 than at R^2 in promoting *syn* elimination and *anti–cis* stereoselectivity. This is consistent with R^1 being principally responsible for the shielding[48].

Sicher has noted that the shielding may be enhanced by rotation from the perfectly staggered conformation under pressure of the *gauche* interactions[12,135]. However, he also points out that comparisons of cyclic and



(36) (37)

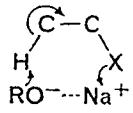
acyclic systems suggest that elimination is *accelerated* in the medium rings, and recently Závada[144a] has shown that an increase in the *syn/anti* elimination ratio in the open-chain 'onium ion **38**, brought about by bulky alkyl substituents at R^1, is due mainly to an *increase* in the rate of *syn* elimination. This is in contrast of course to the effect of alkyl substituents at the β-carbon which sharply retard elimination (Table 6). Clearly all aspects of the effect of alkyl structure are not yet understood.



(38)

For some time it was felt that the variable effect of a strong base and non-polar medium on *syn* elimination was associated with an increase in C—H bond breaking and greater carbanion character at the β-carbon in the transition state[131]. Saunders' measurements for phenethyl 'onium ions[31] make it more likely that for the trimethylammonium ions the main effect is to give a more reactant-like transition state with less double-bond character and less C—H bond breaking[31,76] (section III. A. 3. c). For a more reactant-like transition state any stereoelectronic constraint might well be relaxed and conformational factors in the reactants should assume greater importance[48], as seems to be implied by the results. There are indications, such as the observation of consistently small isotope effects[48,119,122,128,134], that a transition state with pronounced carbanion character does occur for *syn* elimination, but Saunders suggests that this reflects a discontinuity of structure between transition states for the *syn* and *anti* stereochemical modes[48,119]. In accord with this are the lower isotope effects, for both β-hydrogen and leaving group, for *syn* than for *anti* elimination in cases where direct comparisons have been made[61,119,134], and the larger positive ρ values for *syn* than for *anti* elimination of β-arylcycloalkyl tosylates (Table 7)[118].

A further factor is that *syn* elimination tends to occur in media favouring ion pairing. This has been emphasized in recent work[144], and in sufficiently non-polar media it has been found that substrates with leaving groups of steric requirements as different as $-\overset{+}{N}(CH_3)_3$ and —F can undergo *syn* elimination to similar extents[144b]. Ion pairing may readily be thought of as favouring *syn* elimination by promoting reaction via a cyclic transition state[131], as is shown for an anionic leaving group in **39**. If such is the case the cyclic nature of the transition state may influence the pattern of isotope and substituent effects in the manner discussed in sections III. D. 2 and 4 below. Ion pairing solvents also appear to favour formation of *trans* rather than *cis* olefin in the *anti* elimination mode[144c].

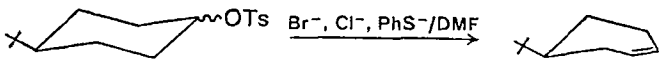


(39)

Much can now be done to predict reaction conditions and substrate structures favouring *syn* or *anti* elimination or *cis* or *trans* olefinic products, and although existing results pertain largely to 'onium ions and tosylates, which probably represent extreme behaviour as far as dependence on leaving group is concerned, a reasonable basis for attempting to predict the behaviour of alkyl halides is provided. On the other hand, interpretations evidently fall short of the observations and here further studies with alkyl halides would be welcome. The possibility of stereoselective synthesis of *cis* or *trans* isomers of medium ring cycloolefins by a proper choice of leaving group and solvent–base system has been noted[10, 19].

D. E2C Elimination

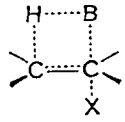
So far no reference has been made to a family of reactions which show an unusual sensitivity to the nucleophilicity of the reacting base. The first acknowledged example of this was provided by Winstein, Darwish and Holness[145], who found that with dimethylformamide as solvent elimination of *cis*- and *trans*-4-*t*-butylcyclohexyl tosylate (**40**) could be effected by



(40)

chloride, bromide or thiophenolate ions. A rather unlikely proposal of an intermediate common to substitution and elimination paths was quickly

disproved[146,147], but further extensive investigations, especially by Winstein and Parker[9,146–149], established the generality of the behaviour and led to the suggestion[148] that it arose from the capacity of a nucleophilic base to undergo what amounts to a neighbouring group interaction with positive charge developed at the α-carbon of favourable *E*2 transition states, i.e. as in **41**. Such transition states have been termed '*E*2*C*' to distinguish them from '*E*2*H*' transition states in which the base interacts only with the β-hydrogen[148].



(41)

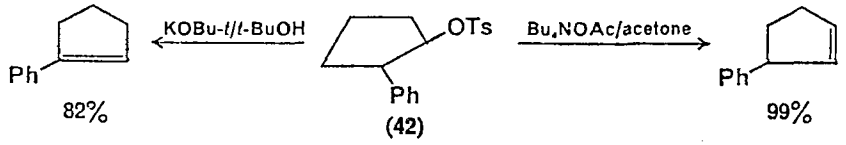
Empirically, the *E*2*C* character of a transition state has been judged by the relative effectiveness of nucleophilic and basic anions in promoting reaction[37,38,148–152], for example by the rate constant ratios $k_{Br^-}/k_{CH_3COO^-}$ or k_{RS^-}/k_{RO^-}. According to this criterion, *E*2*C* elimination is favoured by the alkyl structure of the substrate in the order tertiary > secondary > primary which is also the order of effectiveness of steric hindrance to competing substitution reactions[9,149]. It is also favoured by dipolar aprotic solvents such as acetone, DMSO, DMF or CH_3CN and by good leaving groups[9,152,153], especially arylsulphonates and the halogens, I, Br, Cl. Plainly the optimum conditions for *E*2*C* reactions stand in contrast to the alcoholic solvents and strongly basic alkoxide ions most commonly used for the *E*2 reactions considered so far.

In discussing the characteristics of *E*2*C* elimination it seems best tentatively to regard structure **41** as on a par with structures **1**–**3**. Parker and Winstein[9,149] have emphasized both an opposition between *E*2*C* and carbanion-like transition states, **41** and **1**, and a balance between *E*2*C* and the double-bond character of the transition state, as represented by structure **2**. Fewer references have been made to carbonium-ion-like transition states, **3**, but it seems likely that factors favouring **3** will also favour nucleophilic participation. An important point is that *E*2*C* character in the transition state appears to be *increased* by factors stabilizing structure **41**. This is contrary to expectations based on the Hammond postulate and in this respect *E*2*C* character is evidently analogous to carbonium ion–carbanion rather than reactant–product character.

Special features arising from the cyclic nature of the transition state may of course be expected.

1. Stereochemistry

Eliminations of secondary and tertiary halides and tosylates in dipolar aprotic solvents show a strong *anti* stereoselectivity with both basic and nucleophilic anions[9]; normally, as for **42**, the effect is greater than in hydroxylic solvents. This is clearly consistent with, if it does not require, interaction of the base with the α-carbon on the opposite face from the leaving group.



(42)

A characteristic of *E2C* elimination from cycloalkyl substrates, which, ironically, led to the formulation of the original 'merged' substitution–elimination mechanism[145] with a *syn* stereochemistry, is the rather small rate difference observed between isomers in which the leaving group and *trans* β-hydrogen are held respectively in diaxial and diequatorial conformations by a bulky 4-substituent; for example, for *cis*- and *trans*-4-*t*-butylcyclohexyl tosylate (**40**), $k_{cis}/k_{trans} \sim 14$. This cannot now be regarded as a consequence of *syn* elimination and the suggestion has been made that it reflects a product-like transition state[147]. This fits in with an interpretation given of other features of *E2C* elimination and the possibility is considered further below. Here, however, it seems fair to say that uncertainties in interpreting the kinetic effects of conformational differences in cyclohexyl rings make the deduction a less than certain one. Indeed, it appears to be in conflict with the relatively small changes in rates of *E2C* elimination of cyclohexyl substrates known to accompany a change in leaving group[153].

2. Substituent effects

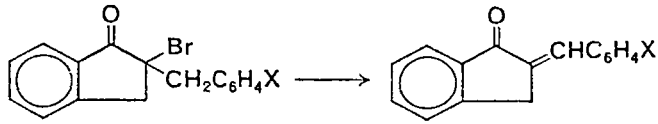
Electron-withdrawing substituents such as Ph, $COOCH_3$ or Br at the β-carbon favour carbanion-like transition states and reduce *E2C* character[149]. McLennan and Wong[154] have argued against nucleophilic participation on the grounds that ρ for elimination of the DDT derivatives (**43**) under *E2C* conditions is +1·23, indicating a carbanion-like transition

$$(XC_6H_4)_2CHCCl_3 \xrightarrow[\text{acetone, } 65^\circ]{Bu_4NCl} (XC_6H_4)_2C{=}CCl_2$$

(43)

state. However, the β-phenyl and α-chloro substituents of DDT strongly favour carbanion character in the transition state, and it is noteworthy that

ρ is less than the value of 2·46 observed for the corresponding reaction with EtO^- in ethanol. Values of ρ for β-phenethyl halides have also been found to be lower in aprotic than alcoholic solvents[17]; and for elimination of the β-phenyl-α-bromoketone[155] (**44**) with bromide ion in CH_3CN $\rho \sim -0{\cdot}2$. This would seem to be consistent with a spectrum of transition states involving *E2C* contributions to a greater or lesser degree.



(44)

For favourable substrates alkyl substituents at either α- or β-carbons commonly increase elimination rates under *E2C* conditions by factors of ~ 100. This is much larger than effects in hydroxylic solvents (Table 10)

TABLE 10. The effect of α-substituents on elimination rates of 1-bromopropanes $CH_3CH_2CRR'Br$

α-Substituents R	R′	$k \times 10^6$ M^{-1} s^{-1} Br^-/acetone[a]	$k \times 10^6$ M^{-1} s^{-1} KOBu-*t*/Bu-*t*OH[b]
H	H	1·2	15
CH_3	H	16	3·0
CH_3	CH_3	10,000	4·0
Ph	H	420	30
p-$O_2NC_6H_4$	H	260	

[a] 75°.
[b] 40°.

and has been interpreted as reflecting a large degree of double-bond character in the transition state[149]. However, the effect greatly exceeds the relative thermodynamic stabilities of the olefins, and it seems possible that the *gem*-dimethyl effect, well known in cyclization and neighbouring-group reactions[156], may also play a role. The effects show little dependence on the bulk of the substituent, and for *t*-butyl bromide **45** replacement of an α-methyl by a neopentyl group **46** actually leads to a small increase in rate[157]. Eck and Bunnett[157], indeed, have plausibly argued that the complete lack of steric hindrance here is inconsistent with the *E2C* formulation, but this may be pushing an analogy between participation and S_N2 substitution too far[149,158]. The effect of an α-phenyl group is also large and is practically unaffected by a *p*-nitro substituent (Table 10). This apparent lack of electronic effect is corroborated by the ready elimination of α-haloketones

under *E2C* conditions[155, 159–161] and has been noted as inconsistent with suggestions that the *E2C* syndrome may sometimes merely reflect

$(CH_3)_3CBr$ $\qquad$ $(CH_3)_2CCH_2C(CH_3)_3$ (Br)

(45) $\qquad$ (46)

$k_{45}/k_{46} = 1{\cdot}7$ with Bu_4NCl in acetone

carbonium ion character in a transition state[149]. However, it is possible that the behaviour of haloketones is linked with their still incompletely understood susceptibility to nucleophilic substitution[162] and, if experimentally accessible[150], more information on the purely electronic effects of α-substituents would be desirable[149].

3. Hofmann–Saytzeff and *cis–trans* olefin ratios

The large accelerating effect of β-alkyl substituents makes the orientation of *E2C* elimination strongly Saytzeff[9, 149, 163], to the point of being of synthetic utility[9]. Surprisingly, in view of the large and cumulative effect of alkyl substituents, the ratios of *trans* to *cis* olefin isomers are also large, suggesting appreciable eclipsing in the transition state. This has been taken as a further pointer to extensive double-bond character, but Bartsch and

TABLE 11. Orientation and *cis–trans* olefin ratios in elimination of 2-butyl halides $CH_3CH_2CHXCH_3$

X	Solvent/base	% 1-butene	*trans–cis* 2-butene
Cl	Bu-*t*OK/Bu-*t*OH	67	1·28
I	Bu-*t*OK/Bu-*t*OH	33·5	2·02
I	EtOK/EtOH	11·7	3·25
I	LiI/DMF	1·5	3·55
I	LiBr/DMSO	3·3	3·33
I	NaOAc/DMF	6·7	3·76
I	LiF/DMSO	19·4	3·23
Cl	LiF/DMSO	40·8	3·36

coworkers have found that[18, 92] for 2-butyl halides reacting in dipolar aprotic solvents the ratio of *cis*/*trans* 2-butene is practically independent of the nature of the solvent, base or leaving group (cf. references 164, 165). This is true despite considerable variations in the fraction of Hofmann olefin, and thus contrasts with the correlation between *cis–trans* ratios and the orientation of elimination that exists in hydroxylic solvents, and was

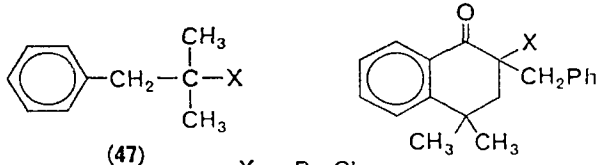
there taken as reflecting variations in double-bond development in the transition state[88]. Possibly this is a further manifestation of the cyclic nature of the transition state. The behaviour is illustrated in Table II.

4. Hydrogen isotope effects

A direct indication of the cyclic nature of the transition might have been expected from measurements of β-hydrogen isotope effects, insofar as non-linear transition states have generally been expected to exhibit low values of k_H/k_D[166]. In fact the largest of a number of isotope effect measurements[159,167], 3·6 at 75°, is significantly less than the values of 7–8, (usually measured at 30°) commonly found in hydroxylic solvents (section III. A. 1. c), and although alternative explanations of small isotope effects have not been excluded, an interpretation in favour of a cyclic transition state[167b] seems a reasonable one.

5. Changes in leaving group

No general discussion of the factors determining the relative reactivities of different leaving groups has been attempted in this chapter because data for the halides are limited and because the more numerous measurements of rate ratios for bromide and tosylate leaving groups indicate a comparatively complex behaviour[55,168–170]. Crudely, however, a large sensitivity to the nature of the leaving group may normally be taken as indicating a large degree of leaving group bond breaking in the transition state. In *E2C* eliminations, the very large ratio of 3400 has been found for the relative reactivities of benzyldimethylcarbinyl chloride and bromide (**47**) with chloride ions in acetone[171]. Comparable rate ratios (k_{Br}/k_{Cl} = 1160 and 1500) have been observed[159] only for elimination under *E2C* conditions of



(47) X = Br, Cl (48)

the 2-halotetralones **48** (cf. k_{Br}/k_{Cl} = 60 and 38 in Tables 1 and 5). These results have been offered as further evidence of product-like character in *E2C* transition states, but they cannot be generalized to secondary alkyl substrates because here the change in leaving group has a much smaller effect; for the reaction of cyclohexyl halides with chloride ions in dimethylformamide[153], for example, k_{Br}/k_{Cl} = 23. Probably the large ratio for the tertiary substrates does indicate extensive bond breaking in the transition

state, but it is possible that the natural increase in reactivity in going to a better leaving group is enhanced by the additional effect of increased participation. It may also be significant that large rate ratios, $k_{Br}/k_{Cl} \sim 500$, are observed for nucleophilic displacements[172].

For benzyldimethylcarbinyl derivatives it has also been found[171] that the relative effectiveness of mercaptide and alkoxide bases decreases as the leaving group becomes harder to displace. For **47** in methanol $k_{EtS^-}/k_{CH_3O^-} = 6{\cdot}5$, 0·8 and 0·05 for X = Cl, $\overset{+}{S}(CH_3)_2$ and SO_2CH_3 respectively. This parallels the expected increase in C—H bond breaking and carbanion character, and presumably decrease in *E2C* character, in the transition state. For cyclohexyl derivatives with different leaving groups there is evidence of a correlation between rates of elimination effected by chloride ions and the corresponding substitutions occurring under the same conditions. By contrast, no such correlation exists for alkoxide bases in alcoholic solvents[153].

6. The case against nucleophilic participation

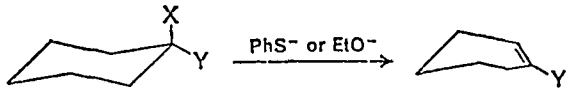
There have been criticisms of the *E2C* formulation for eliminations. The lack of sensitivity to steric effects[157] and the possibilities that *E2C* transition states simply show carbanion[154], carbonium ion[152] or product-like[152] characteristics have been referred to. Bunnett[152] and McLennan[37,38] have also argued that variations in the effectiveness of basic and nucleophilic ions may simply depend on the relative importance of ion desolvation and covalent bond making required of the base in the transition state. Measurements for cyclohexyl halides and tosylates (**49**) made by McLennan[37] and shown in Table 12 nicely illustrate the expected correlation between the

TABLE 12. Eliminations of cyclohexyl derivatives, **49**, with ethoxide and thiophenoxide ions in ethanol

X	Y	β	k_{PhS^-}/k_{EtO^-}
OTs	H	0·27	7·0
Br	H	0·36	1·6
Cl	H	0·39	0·73
Br	Br	0·51	0·63
Cl	Cl	0·58	0·21

extent of C—H bond breaking, as measured by the Brönsted exponent β for general base catalysis, and the rate constant ratio k_{PhS^-}/k_{EtO^-} for reaction

with thiophenolate and ethoxide ions. It may also be noted that a satisfactory formulation of a reaction coordinate leading to covalent bonding between atoms which are not joined by covalent bonds in either the reactants or products has yet to be made.



(49)

However, no explanation is offered of the relative importance of basic and nucleophilic properties of the reacting base in non-solvating media or in particular of the dependence of these upon the proneness of the substrate to react via carbanion or carbonium ion-like transition states. The remarkable pattern of α- and β-substituent effects and pronounced anti-stereoselectivity of elimination also point to a far-reaching difference from reactions in basic and protic media. At the time of writing, nucleophilic participation, though its interpretation and consequences are incompletely understood, appears to offer the most helpful formulation of the behaviour. It will be of some interest to see if, as Fraser and Hoffmann suggest[169], nucleophilic influences stretch to hydroxylic solvents and to those comparatively neglected *E*2 eliminations proceeding through transition states with strongly developed carbonium ion character.

IV. THE *E1cB* MECHANISM

The *E1cB* mechanism involves reaction via a carbanion intermediate and, as shown in Scheme 2, may exist in either of two kinetic modifications

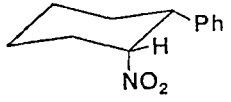
$$B + R_2CHCH_2X \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} BH^+ + R_2\bar{C}CH_2X \xrightarrow{k_2} R_2C{=}CH_2 + X^- \qquad (2)$$

depending upon whether formation or reaction of the carbanion is rate-determining ($k_2 \gg k_{-1}[BH^+]$ or $k_2 \ll k_{-1}[BH^+]$). In either case the kinetic dependence upon the concentration of base and substrate is the same as that for the *E*2 mechanism and, partly because of this and partly because the existence of carbanion character in the *E*2 transition state seems to imply a more subtle mechanistic relationship, experimental attempts at distinguishing the two mechanisms have been carried out with some care. At the outset, it is useful to consider how successful these attempts have been.

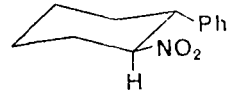
A. Methods of Diagnosing E1cB Mechanisms

1. The stereochemistry of elimination

As already noted (section III. C. 1), violations of *anti* stereochemistry in eliminations from cyclohexyl substrates have been cited as evidence for carbanion formation[12,102,106–109]. With the possibility of *syn* elimination and perhaps reaction via a non-chair conformation[99,173] now more widely acknowledged, significance should probably be attached only to the observation of a marked lack of stereoselectivity. In the case that carbanion formation is rate-determining, the likelihood that even this could be of diagnostic value is diminished by the finding[174] that rates of nitroanion formation from *cis*- and *trans*-1,2-phenylnitrocyclohexane, (**50**) and (**51**), differ by a factor of 350 : 1. Indeed, if, as suggested, this difference is due



(**50**)



(**51**)

largely to steric strain in the *trans* isomer[174,175], a similar factor could contribute to an enhanced rate for *syn* *E*2 elimination[25]. In the case that carbanion formation is not rate-determining, there is some evidence that configurationally stable carbanions[25], such as $RSO_2\bar{C}HR$, or ion-paired carbanions[176] may still lead to stereoselective reactions. For reactions other than of cyclohexyl derivatives the preference for *anti* elimination seems to be too weak to be of diagnostic value.

2. Isotope effects and isotope exchange

When the rate of elimination is significantly slower than that of formation of the carbanion the presence of the carbanion may be detected by the observation of β-hydrogen isotope exchange[176–184], as for example in the elimination of 1,1,1-trifluoro-2,2-dihaloethanes[177,178], such as **52**. This does not establish that the carbanion is an intermediate[177,185] but when exchange is sufficiently rapid the demonstration that reaction in a

$$CF_3CHCl_2 + CH_3O^- \longrightarrow CH_3OH + CF_2{=}CCl_2 + F^-$$

(**52**)

deuterated hydroxylic solvent occurs at a rate greater than or comparable with that in the light solvent affords evidence that it is. Such behaviour has been observed in the elimination of 4-methoxy-2-butanone (**53**)[179] and the β-phenoxyethylsulphonium ion (**54**)[180]; it is consistent with an *E*2 mechanism only in the rather unlikely event that the primary β-hydrogen isotope effect

($k_H/k_D > 1$) is too small to offset the weak inverse secondary isotope effects contributed by the base and solvent (cf. section III. A. 1. c.)

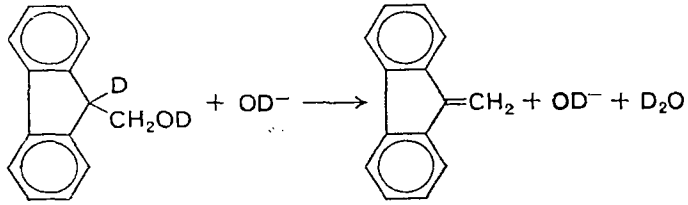
$$OD^- + CH_3\overset{O}{\overset{\|}{C}}CD_2CH_2OCH_3 \xrightarrow{k_{D_2O}/k_{H_2O} = 1{\cdot}15} CH_3\overset{O}{\overset{\|}{C}}CD{=}CH_2 + CH_3O^- + D_2O$$

(53)

$$OD^- + (CH_3)_2\overset{+}{S}CD_2CH_2OPh \xrightarrow{k_{D_2O}/k_{H_2O} = 1{\cdot}50} (CH_3)_2\overset{+}{S}CD{=}CH_2 + PhO^- + D_2O$$

(54)

The possibility of a small primary effect may also be ruled out when elimination and exchange occur at comparable rates[181]. In this case a primary isotope effect k_E^H/k_E^D, the significance of which depends upon the reaction mechanism, may be measured directly. When the mechanism is *E*2, k_E^H/k_E^D corresponds to the normal β-hydrogen isotope effect for concerted elimination, and when the mechanism is *E*1*cB* it is the isotope effect upon ionization to form the carbanion. For 9-fluorenylmethanol, (55), $k_E^H/k_E^D = 7{\cdot}2$, which is much too large for the small solvent isotope effect, $k_{H_2O}/k_{D_2O} = 0{\cdot}9$, to be consistent with an *E*2 mechanism[181].



(55)

3. Base catalysis

When carbanion formation occurs in a pre-equilibrium step *E*1*cB* elimination is subject to specific base catalysis and may in principle be distinguished from the general base-catalysed *E*2 mechanism. However, as pointed out by Fedor[179] in reporting specific catalysis for elimination of 4-methoxy-2-butanone the possibility of general catalysis with a Brönsted exponent close to unity is not excluded[186]. Indeed this situation seems likely to arise specifically for *E*2 elimination involving a carbanion-like transition state, which is likely to be the type of reaction from which *E*1*cB* elimination must be distinguished.

For a reactive substrate, the distinction can be made a rigorous one if a change in rate-determining step with changing pH can be found[187–191]. This is revealed by the appearance of a characteristic plateau connecting

regions of unit slope in a log k–pH rate profile, as shown in Figure 3a. The origin of such behaviour can be seen by expressing k, the pseudo first-order rate constant for the reaction, in terms of the molecular rate constants

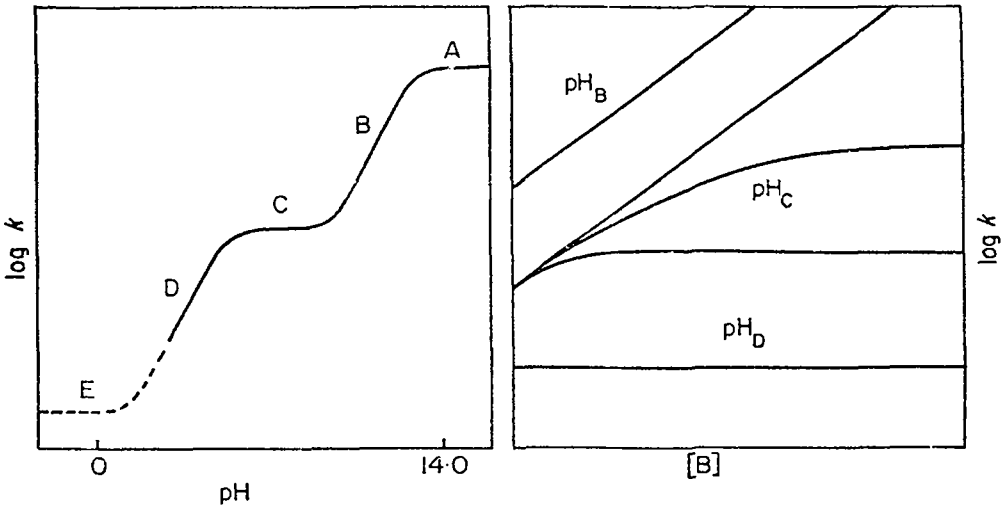


FIGURE 3. The base dependence of $E1cB$ elimination. (a) The dependence of log k upon pH. (b) The dependence of log k upon the concentration of general base at constant pH.

shown in equation (3), in which SH denotes the substrate and k_1' and k_{-1} are rate constants for reaction of the solvent with substrate and carbanion, respectively.

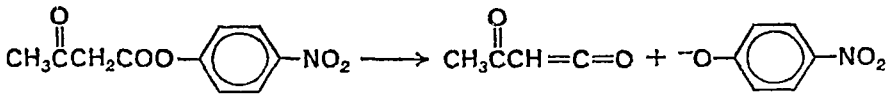
$$\mathrm{SH} \underset{k_{-1}+k'_{-1}[\mathrm{H_3O^+}]}{\overset{k_1[\mathrm{OH^-}]+k_1'}{\rightleftharpoons}} \mathrm{S^-} \xrightarrow{k_2} \text{olefin} \qquad (3)$$

$$k = \frac{k_2(k_1[\mathrm{OH^-}]+k_1')}{k_2+k_{-1}+k'_{-1}[\mathrm{H_3O^+}]} \qquad (k_2 \gg k_{-1} \text{ for a change in rate-determining step to be observed})$$

In Figure 3a the region of unit slope B corresponds to rate-determining carbanion formation or, most improbably, $E2$ elimination with $k = k_1[\mathrm{OH^-}]$. Over the plateau C, carbanion formation is still rate-determining but the pH is sufficiently low that $k = k_1'$. Here the reaction cannot involve $E2$ elimination because the drop in rate with a further decrease in pH over section D *must* entail a change in rate-determining step; i.e. $k'_{-1}[\mathrm{H_3O^+}]$ becomes $> k_2$ and $k = k_2 k_1'/k'_{-1}[\mathrm{H_3O^+}]$. In principle a change to an $E2$ mechanism with $\mathrm{H_2O}$ acting as base might now be revealed

by a further plateau E, but so far no example of this has been observed experimentally.

Textbook illustrations of this type of behaviour have been reported by Bruice[187,189,190] for some rather unusual β-eliminations in which ketenes, subsequently hydrolysed to acids, are formed from activated esters such as **56**. A further example[188] to be discussed in a later section has been found by



(56)

Crowell and coworkers for dehydrochlorination of *erythro*-4,4′-dichlorochalcone dichloride. Interestingly, for the esters, at higher pH's an additional plateau, A in Figure 3a, corresponding to a breakdown in the steady-state approximation and complete ionization of the substrate to form the carbanion, has been observed.

Apart from the pH profile, the addition of a general base B at constant buffer ratio, [B]/[BH$^+$], and hence constant pH, can also be diagnostic[187,188]. At a pH below that at which the change in rate-determining step occurs the reaction is subject to specific catalysis and the rate is independent of the concentration of general base, as is indicated by the line labelled pH_D in Figure 3b. At higher pH's general catalysis prevails and the rate increases linearly with [B], as at pH_B. At an intermediate pH close to, or just above, the point of change introduction of a term k''_{-1}[BH$^+$] into the denominator of the expression for k will tip the balance between k_2 being dominant and k_2 being insignificant in comparison with the net rate of protonation of the carbanion. This will lead to the tell-tale 'saturation' behaviour for added base, indicated at pH_C. Such behaviour has also been found[189] for **56** and for the *erythro*-4,4′-dichlorochalcone dichloride[188], as well as for elimination of 4-(*p*-chlorophenoxy)-2-butanone[192]. The additional lines shown in Figure 3b represent dependences on buffer concentration at pH's close to the limits of the plateau region C of Figure 3a.

These criteria apply only to hydroxylic solvents. In aprotic solvents specific catalysis may be indicated by a mass law rate depression upon adding the conjugate acid of the base[193] or by a Brönsted exponent of unity for reaction of a series of bases. Often, however, results in aprotic solvents are complicated by ion pairing, as described below.

4. The element effect

Except when the point of change in rate-determining step is directly observable, isotope effects and base catalysis do not distinguish an *E1cB*

mechanism in which formation of the carbanion is rate-determining from *E*2 elimination. In this case a lack of dependence of elimination rate upon the nature of the leaving group, or a comparison with the rate of hydrogen exchange of a related substrate incapable of undergoing elimination, offers the best hope of making a distinction[194]. Such comparisons have been made between exchange and elimination of various nitrocycloalkanes for a number of leaving groups[194], and also between fluorene and 9-fluorenylmethanol (**55**)[195]. Difficulties may arise in assessing electronic[25,109,196] or steric effects[194] of the leaving group upon ionization rates. These may sometimes be overcome either by measuring leaving group isotope effects[61] or by interpolating electronic effects with the aid of linear free-energy relationships[196,197].

A nice application of this criterion has been made by Fedor and Cavestri[197] in the general base-catalysed elimination of the β-ketoalcohol derivatives, **57**. The rates show a very mild dependence on the nature of the leaving group and when plotted as values of log *k* against the pK_as of the corresponding substituted acetic acids, **58**, give a straight line of slope close to unity (Figure 4) indicating that the dependence is consistent with an

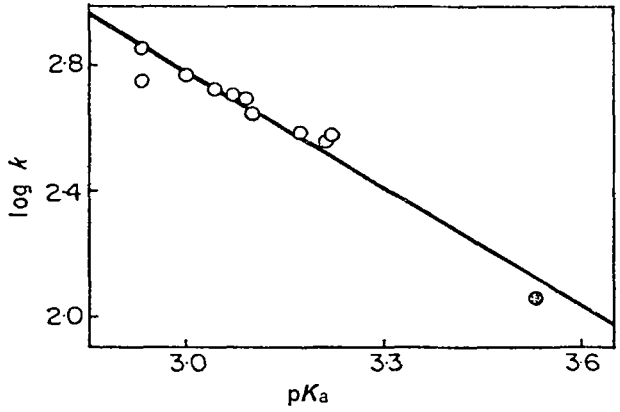
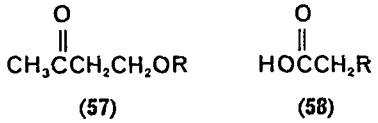


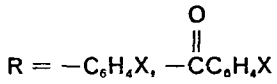
FIGURE 4. Plot of log *k* for elimination by hydroxide ion of aryl- and benzoyloxybutanones, $ROCH_2CH_2COCH_3$, against pK_as of the corresponding oxyacetic acids, $ROCH_2COOH$; for ⊛ log *k* refers to β-hydrogen exchange of $CH_3OCH_2CH_2COCH_3$[8].

ionization of the β-hydrogen subject only to an inductive effect from the leaving group. As shown in the figure the plot also correlates the *exchange* rate constant for 4-methoxy-2-butanone (**57**, R = CH_3) for which

elimination is subject to specific catalysis and occurs at a rate more than 200 times slower than that of exchange.

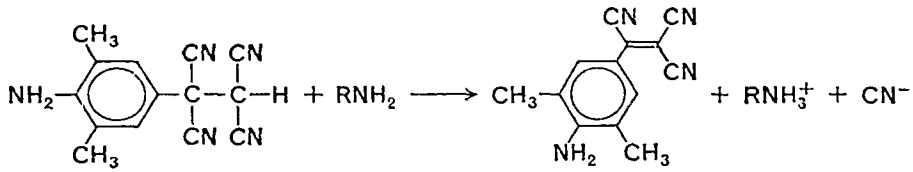


(57) (58)



5. The carbanion as reactant

For a number of relatively acidic substrates such as nitroalkanes the carbanion may constitute the reactant in elimination[194,198-201]. Technically the reaction no longer has the stoicheiometry of an elimination, but sensibly it must be considered a limiting modification ($k_1[B] \gg k_{-1}[BH^+]$ and k_2 in equation 2) of the *E*1*cB* scheme, and its observation as such for the ester **56** has already been noted[187,189]. The reaction has distinctive kinetic characteristics, which have been described by Rappoport[198], but these do not distinguish direct elimination from the now indirect '*E*2' mechanism[189,202]. If this kinetic form of elimination is the only one that can be observed, lack of general acid catalysis (*sic*) and of a significant primary isotope effect probably constitute the best evidence for a 'carbanion' mechanism, and have been demonstrated by Rappoport and Shohamy for the amine-catalysed elimination of 2,6-dimethyl-4-(1,1,2,2-tetracyanoethyl)aniline (**59**) in chloroform[200].



(59)

B. Factors Favouring an E1cB Mechanism

It would be expected that an *E*1*cB* mechanism should be favoured by an acidic β-proton and by a poor leaving group; the first factor should increase the rate of carbanion formation, and the second should slow *E*2 elimination to the point that carbanion formation competes. That this is so experimentally is illustrated by the examples already cited and, for the effect of acidifying β-substituents, by the relative reactivities of substrates

of the type XCH_2CH_2OPh reported by Crosby and Stirling[203] and shown in Table 13.

TABLE 13. Rate constants for elimination of phenyl ethers XCH_2CH_2OPh

X	k ($M^{-1}s^{-1}$) OH^-/H_2O	k ($M^{-1}s^{-1}$) $EtO^-/EtOH$
NO_2	320	1500
Ph_3P^+	1·98	6000
Me_2S^+	0·048	195
MeCO	3·12	31·5
$PhSO_2$		0·35
CN		0·094
COOEt	0·015	0·061
MeSO	$9·2\times10^{-6}$	$4·27\times10^{-4}$
$\overset{+}{N}(Me)_3$		$3·07\times10^{-7}$

For the most reactive substrates in Table 13, with $X = CH_3CO$ or NO_2, the results of Bordwell[194,199] and Fedor[197] indicate that carbanion formation is rate-determining. However, for $X = \overset{+}{S}(CH_3)_2$ and $SOCH_3$, inverse solvent isotope effects and, in the former case, a value of $\rho \sim 1·3$ for substitution in the phenoxy leaving group point to formation of the carbanion in a pre-equilibrium step. Since these groups nearly bracket the reactivity range shown in the remainder of Table 13 a pre-equilibrium *E1cB* mechanism probably applies in most cases[180]. The wide variation in reactivity observed testifies to the scope of the mechanism[204] and comparisons with other reactions involving carbanion intermediates show a close parallelism of substituent effects[205]. The effects of β and α alkyl and aryl substituents on *E1cB* elimination have also been reported[206].

The necessity for a poor leaving group in *E1cB* elimination is apparent from the leaving groups for which the reaction has been observed; e.g. CH_3O, HO, PhO, RCOO, CN. Among the halogens the poorest leaving group is F, and the strong activation of the β-hydrogen necessary to cause dehydrofluorination under mild conditions[207] makes it likely that an *E1cB* mechanism will most commonly be observed in this case; as for example with substrates such as **52** [177,178] (section IV. A. 2). On the other hand, for sufficiently strong β-activating substituents, and perhaps especially in the ion-pair forms of the reaction considered below, the more common halogens can also act as leaving groups. Because they are good leaving groups, however, except in cases where the base is very weak the

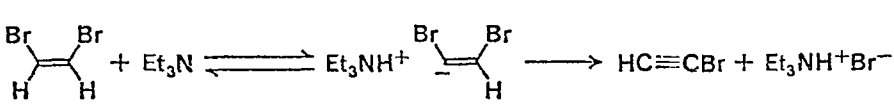
modification of the mechanism in which formation of the carbanion is rate-determining ($k_2 > k_{-1}[BH^+]$ in equation 2) can normally be expected to prevail.

An interesting inference to be drawn from the failure to observe a transition to an *E*2 mechanism in a number of studies of *E*1*cB* elimination carried out over a wide pH range[187–190] is that the strength of the base appears to be of little importance in determining the mechanism.

C. Ion Pairs in Carbanion Eliminations

1. Aprotic solvents

A further variation on the *E*1*cB* mechanism, a number of examples of which pertain to halogen leaving groups, involves rate-determining reaction of an ion pair. Such a mechanism was suggested by Miller and collaborators[208] for the elimination of *cis*-dibromoethylene (**60**) to bromoacetylene in dimethylformamide with triethylamine acting as base. The



(60)

reaction is not subject to common ion rate-depression and there is no deuterium exchange accompanying elimination. However, the very low deuterium isotope effect $k_H/k_D = 1{\cdot}0$ strongly suggests that complete transfer of the β-hydrogen occurs prior to the rate-determining step. Similar behaviour has been found in other instances[200, 209] and the proposed mechanism is consistent with the well-known observations of carbanion racemization within carbanion ammonium ion pairs in aprotic solvents[210]. Interestingly, for elimination of **59** in chloroform, when the amine base is the primary amine aniline there is still no common ion rate-depression but exchange *does* occur[200]. This is again consistent with measurements of carbanion racemization which suggest that for primary or secondary amines exchange within the ion pair is possible[210].

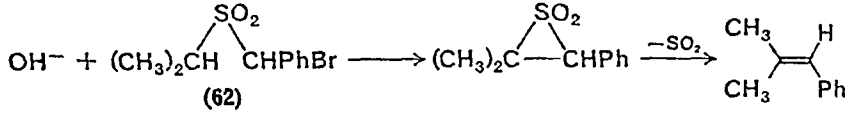
2. Hydroxylic solvents

Elimination from carbanion ion pairs in aprotic solvents is perhaps not surprising. More remarkable are demonstrations that ion pairs or specifically solvated carbanions can be of kinetic significance in hydroxylic media. A case where ion-pair formation in a hydroxylic medium appears to occur involves the elimination of *cis*- and *trans*-1,2-halo- and arylsulphonylcycloalkysulphones, (**61**), in 50% v/v aqueous acetone[25]. Reference to

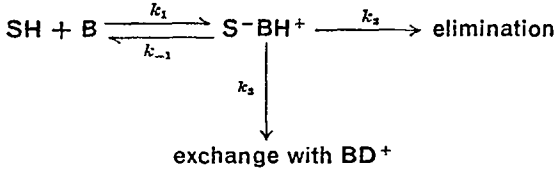
Table 13 suggests that the phenylsulphonyl group should favour a carbanion mechanism, and the combination of general base-catalysis[103] with a very low sensitivity to the nature of the leaving group[25] (e.g. $k_{Br}/k_{Cl} = 4{\cdot}2$) seems to indicate that carbanion formation occurs in the

(61) X = SO_3Ar, Br, Cl (X = F, reference 196)

rate-determining step, as indeed would be expected of the good leaving groups and strong bases that characterize the reactions. In apparent contradiction with this is the observation[211] that the rate of hydrogen exchange of cyclohexylphenyl sulphone is slower than that of the eliminations by a factor of $\sim 10^5$, a difference much too great to be put down to an inductive effect of the leaving groups. However, a comparable rate discrepancy, a factor of 560, is found between an exchange rate and the rate of 1,3-elimination of HBr in the Ramberg–Bäcklund reaction[212] of **62**.



Since it is most unlikely that a carbanion does not precede cyclization in this case, Bordwell and collaborators[25, 212] suggest that the isotope exchange reactions involve rate-determining diffusive separation of a carbanion and conjugate acid of the base, and that the elimination reactions represent the true (and faster) rate of carbanion formation (i.e. $k_2 > k_{-1} > k_3$ in equation 4). This is supported by the small isotope effect observed for the exchange reaction[196], and is consistent with the acknowledged configurational stability of sulphonyl carbanions[210, 213] (which may also imply a capacity for hydrogen bonding) as well as with increasing evidence of internal return in other reactions of carbanions in hydroxylic solvents[210, 212–214].



(4)

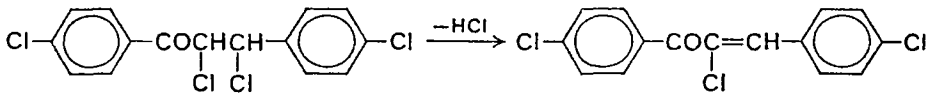
A puzzling feature of sulphone eliminations that remains is that with amine bases in aprotic solvents the rather unexpected combination of a small leaving group effect and a small isotope effect is observed[215]; e.g. for

63 reacting with $EtN(CH_2CH_2OH)_2$ in acetonitrile at 50° $k_{Br}/k_{Cl} = 7{\cdot}0$ and $k_H/k_D = 2{\cdot}0$ (**63**, X = OTs).

$C_6H_4SO_2CH_2CH_2X$

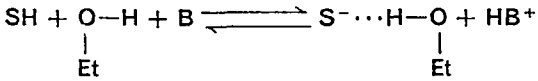
(63)

The finding that isotope exchange can take place at a slower rate than carbanion formation plainly implies that rate-determining reaction of a specifically solvated carbanion ($k_{-1} > k_2 > k_3$ in equation 4) can also occur. This indeed is the form of reaction for which the intervention of specifically solvated carbanions was originally suggested, by Crowell and collaborators[188], in the elimination of the dichlorochalcone (**64**). As already mentioned (section IV. A. 3) pre-equilibrium carbanion formation in the reaction of **64** with weak bases in ethanol was rigorously authenticated by the observation of both a kinetic 'saturation effect' with increasing concentration of general bases, and a rate retardation following addition of hydrogen ions. Nonetheless, no hydrogen exchange could be detected and no isomerization of *erythro* to *threo* chalcone occurred. Since the ionization step is subject to general base-catalysis, to account for the mass law



(64)

effect of added acids the involvement of a solvent molecule in addition to the base in the formation of the specifically solvated carbanion was suggested (equation 5). This is akin to the accepted mechanism for base-catalysed nucleophilic attack at a carbonyl group[40], although actual attack at a carbonyl carbon in **64** was considered improbable[188]. A stable solvated carbanion is particularly surprising for an α-keto carbanion because



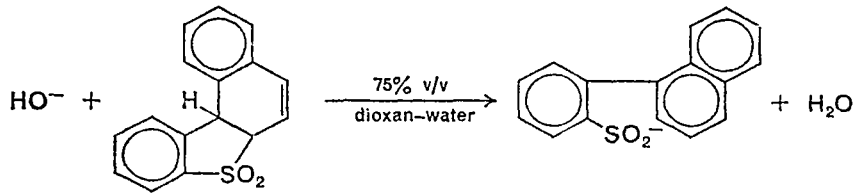
(5)

formation of the enol would appear to offer a diffusion-controlled pathway to racemization.

A recent observation[216] of specific catalysis for elimination of the sulphone $PhSO_2CH_2CHPh\overset{+}{N}(CH_3)_3$ probably provides a further example of this mechanism and suggests also that in elimination of other sulphones rates of internal return and elimination may be finely balanced.

D. Links between E2 and E1cB Mechanisms

The meticulous characterizations of the *E1cB* mechanism described above were in part prompted by doubts as to the generality and even existence of the mechanism. Ironically, they have now led to a questioning of the generality of the *E2* mechanism. As pointed out by Bordwell and collaborators, acceptance of the ion-pair modification of the mechanism means that one obvious criterion of an *E2* mechanism, the combination of an element effect on changing the leaving group with a lack of β-hydrogen exchange, no longer excludes a carbanion intermediate[25]. This complements the demonstration considered below that an ion-pair modification of elimination from a carbonium ion removes the simple distinction based on kinetic order between the *E2* and *E1* mechanisms (section V. D,)[26]. Bordwell, indeed, suggests that ion pair mechanisms may be offered as alternatives to a wide range of reactions now regarded as *E2*. In particular, he has shown that the cyclic sulphone **65** almost certainly reacts by a



(65)

carbanion mechanism[182]. In view of the exceptional stability of the aromatic double bond formed in the product it seems possible to ask: if the *E2* mechanism does not operate in this case when does it operate?

In fact, because the sulphone **65** contains an acidic β-hydrogen and a poor leaving group, as well as an unfavourable geometry for *E2* elimination, the observation of an *E1cB* mechanism for **65** may not be of general significance. Normally large β-hydrogen isotope effects preclude the intervention of ion pairs in exchange or elimination reactions, while for simple alkyl and aralkyl substrates the rate of elimination greatly exceeds any reasonable upper limit for the rate of carbanion formation. Except for substrates with β-substituents comparable with those of Table 13, or where unusually small isotope effects occur, it seems clear that the possibility of an *E1cB* mechanism for reaction of alkyl halides, RI, RBr or RCl, in the usual hydroxylic media may safely be disregarded.

A further question that arises is what is the nature of the borderline between the *E2* and *E1cB* mechanism? Factors that favour an *E1cB* mechanism, such as a poor leaving group and an acidic β-hydrogen, also favour carbanion character in an *E2* transition state. Does this imply an

'imperceptible merging'[217] of the two mechanisms? In an earlier section (III. A. 2), models for interpreting the common influence of a variety of factors, including the stability of the β-carbanion and difficulty of displacing the leaving group, upon the energy and structure of the transition states for concerted and stepwise mechanisms were considered. Since the models implied no necessity of a continuity between the transition states the only reason for doubting that at the borderline $E2$ and $E1cB$ mechanisms occur side by side along quite independent paths would appear to be removed. Further arguments and experimental evidence against a merging of mechanisms have been presented[70].

V. THE *E1* MECHANISM

$E1$ elimination proceeds by way of a carbonium ion intermediate, as shown in equation (6). It shares a common step with S_N1 substitution and in its microscopic reverse corresponds to electrophilic addition to an olefin. Both of these reactions throw considerable light on the $E1$ mechanism. They are, however, beyond the scope of the present chapter and here attention is confined mainly to the product-forming step and aspects of the mechanism important in the wider context of β-eliminations.

$$RX \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} R^+ + X^- \xrightarrow{k_2^E + k_2^S} \begin{cases} \text{olefin} \\ \text{substitution product} \end{cases} \qquad (6)$$

A. Diagnosis and Scope of the E1 Mechanism

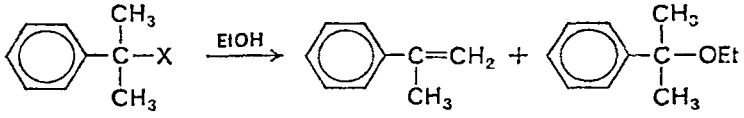
The traditional distinction between $E1$ and $E2$ mechanisms pointed out by Hughes and Ingold is that of kinetic order[218]. When the first step of the reaction is rate-determining $E1$ elimination may in principle be separated from $E2$ by extrapolating their combined rate coefficients, $k = k_{E1} + k_{E2}[B]$, to zero base concentration[6, 24, 50, 51, 218]. In practice the familiar difficulty arises of distinguishing a *bona fide* $E1$ mechanism from an $E2$ mechanism in which a solvent molecule acts as base. The following criteria for formation of a carbonium ion have been applied: mass law rate depression by the counter ion, trapping with a strong nucleophile[219], carbonium ion rearrangement, the formation of products in the same proportions with different leaving groups, and a break in structure reactivity correlations[220] spanning base-induced and solvolytic eliminations[1, 221].

These criteria are subject to well-known limitations[1], such as ion-pairing and complications from salt effects, some of which are dealt with below. Nevertheless the broad picture that emerges is of a mechanism favoured by polar solvents, a good leaving group and carbonium ion stabilizing

α-substituents[1–4]. The reaction is especially characteristic of the tertiary and secondary alkyl or aralkyl halides, iodide, bromide and chloride, although the poorer leaving group fluoride requires acid catalysis for reaction[222]. As befits a transition state with pronounced carbonium ion character the orientation of elimination is strongly Saytzeff, with violations normally occurring only when steric effects[223] reverse the usual relative thermodynamic stabilities of the olefins formed.

B. *Effects of Ion-pairing on the Products*

In strongly polar hydroxylic media the ratio of substitution to elimination products is independent of the leaving group involved in carbonium ion formation[1,224]. As the polarity of the solvent is reduced, this independence is lost and elimination appears to occur from a carbonium ion pair with the counter-ion acting as base[225–227]. This is illustrated by the increase in the proportion of olefinic product with increasing basicity of the leaving group in the solvolysis of the cumyl derivatives, **66**, in ethanol. The involvement of the counter-ion is also indicated by the variation in isotope effects on the product-forming step. In line with the reactant-like transition state expected of proton loss from a reactive carbonium ion the isotope effects are small[228] and decrease with increasing strength of the base.



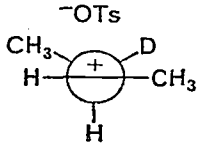
(66)

X^-	10^5k (s^{-1}, 50°)	% olefin	k_H/k_D
Cl^-	83	12	2·9
NO_2–C$_6$H$_4$–COO^-	0·0026	50	2·4
C$_6$H$_5$–COS^-	0·031	91	1·7

C. Stereochemistry of E1 Elimination

1. Open-chain substrates

Results obtained by Skell and Hall[229] for reaction of stereospecifically β-deuterated (cf. section III. C. 2) 2-butyl tosylate point to a commanding role for the counter-ion in determining the stereochemistry of elimination. In aqueous ethanol and in dimethylformamide dominant *anti* elimination together with some racemization is observed, but in non-polar poorly basic solvents elimination is very predominantly *syn*. The *syn* elimination is reasonably interpreted as a consequence of reaction with the counter-ion, as in **67**. The more surprising *anti* elimination may involve a preference for

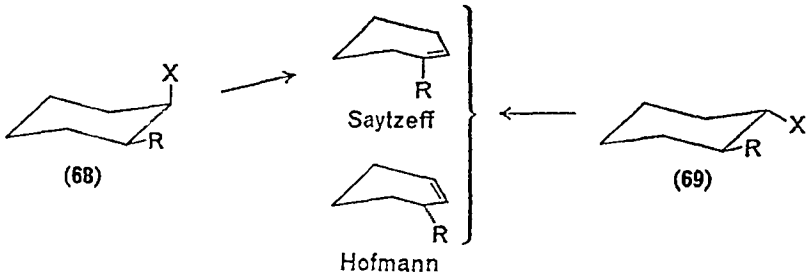


(67)

reaction on the 'unencumbered' face of the carbonium ion in cases where the solvent is a more effective base than the tosylate ion; it may also be due to the presence of solvent-mediated *E*2 elimination. The only other result available appears to be Cram's finding of dominant *anti* elimination for 3-phenyl-2-butyl tosylate in acetic acid[230].

2. Cyclohexyl rings

Early studies of the orientation and stereochemistry of elimination accompanying solvolysis of cycloalkyl halides[100,231] have recently been supplemented by detailed measurements with cycloalkyl tosylates[13,232,233]. Where old and new results can be compared no essential differences appear and it is sensible here to describe the more complete results for the tosylates. The outstanding feature of the results is a characteristic difference in products obtained from solvolyses of *cis* and *trans* isomers bearing 2-alkyl substituents. The *cis* isomer (**68**) gives more olefin than substitution



product and very preponderantly the 1-alkene or Saytzeff olefin; the *trans* isomer gives less olefin and affords 1- and 2-alkenes in comparable proportions. This is in conflict with the simple expectation that the two substrates should yield the same carbonium ion and hence the same products.

That the problem has a further ramification is shown by the dependence of the pattern of products not upon the conformation of the reactant but upon its configuration. This is nicely illustrated by the measurements of Pánková, Sicher, Tichý and Whiting[232] for acetolyses of the four isomeric 2-methyl-4-*t*-butyl tosylates (**70**–**73**) in which the conformation of the methyl and tosyl groups are maintained by the preference of the *t*-butyl group for an equatorial site of substitution. As shown in Table 14, the

TABLE 14. Rate constants and olefinic products from acetolyses of isomeric 2-methyl-4-*t*-butylcyclohexyl tosylates

	70 (*trans*)	**71** (*trans*)	**72** (*cis*)	**73** (*cis*)
$10^6 k$ (s^{-1}, 70°):	7·9	63	617	619
Olefin %[a]				
74—Saytzeff	35·0	41·4	54·7	58·9
75—Hofmann	16·1[b]	26·0[c]	0·8[c]	1·1[b]
76—rearranged	11·2	5·1	25·3	9·8

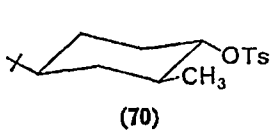
[a] Percentage of total products; olefins + methylcyclohexyl acetates.
[b] *cis*-Olefin.
[c] *trans*-Olefin.

formation of the Saytzeff olefin is just as strongly favoured for the conformation of the *cis* isomer in which the β-hydrogen and leaving group are diequatorial (**72**) as that in which they are diaxial (**73**).

Such results imply that the conformation of a carbonium ion intermediate cannot in all cases match the conformation of the reactants. If it did, the Saytzeff olefin (and also the products of hydride rearrangement) from tosylates **71** and **72** would be formed from an ion, **77**, in which the reacting β-C—H bond is held at an angle of nearly 90° to the *p*-orbital of the carbonium ion. The same conclusion may be drawn from the finding[234] that, as judged by infrared analysis, the products of solvolysis of *trans*-4-*t*-butylcyclohexyl tosylate stereospecifically deuterated in the *cis*-2-position (**78**) show no sign of *syn* elimination.

The explanation that has been offered[232, 234, 235] is that elimination occurs from a carbonium ion in a skew-boat conformation in which the *t*-butyl

group is in an equatorial position and the β-hydrogen is in an axial position, aligned nearly parallel to the carbonium-ion *p*-orbital (**79**). The driving force for forming so unfavourable a conformation is suggested as



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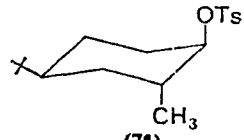

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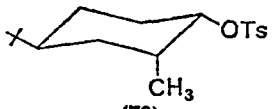

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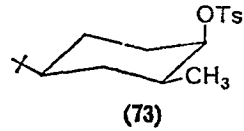

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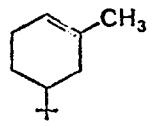

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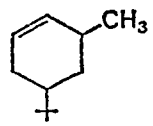

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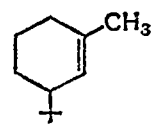

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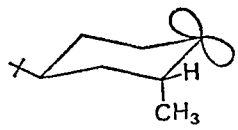

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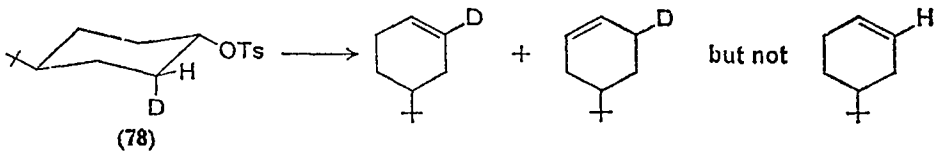

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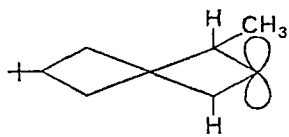


(79)

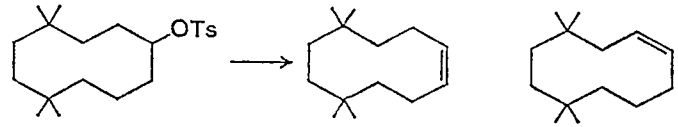
coming from the facilitation of ionization by 'β-hydrogen participation'. Participation by a neighbouring group in solvolysis reactions has been considered to occur when the leaving group and β-hydrogen bear an *anti* diaxial relationship to each other. When the leaving group occupies an equatorial position in a cyclohexyl ring, as in **70**, **72** and **78**, such a relationship cannot be achieved in the stable chair conformation and participation

is possible only in a skew-boat conformation. If, therefore, the stabilizing effect of participation more than offsets the unfavourable eclipsing interactions incurred, a skew-boat will be the preferred conformation of the transition state, and of the carbonium ion formed from it (at least until conformational equilibrium can be established). That participation in cyclohexyl substrates does occur is supported by measurements of non-cumulative secondary kinetic isotope effects, which show an anomalously large effect from a single β-deuterium *trans* to the leaving group[234–236].

The dependence of the above argument on β-hydrogen participation may, however, be a weakness. Although participation has long been favoured as an explanation of differences in cycloalkyl solvolysis rates[237], large differences between *cis* and *trans* cyclohexyl isomers have been found in reactions not involving carbonium ions[25,174], and it is possible that an interpretation in terms of steric interactions in reactants and transition state may be more appropriate[25,174,238]. In view of indications that ion-pair return may occur in solvolyses of secondary alkyl tosylates[239] the possibility that the olefin-forming step, which involves a primary hydrogen isotope effect, may be partially rate-determining can be considered as an alternative explanation of the non-cumulative isotope effects[240]. Also, a very marked control of stereochemistry of elimination and even of hydride rearrangement by the counter-ion would not be out of step with the limited experience available from open-chain substrates[229,230,241].

3. The cyclodecyl ring

Stereospecific deuteration shows that solvolysis of 7-tosyl-1,1,4,4-tetramethylcyclodecane, (**80**), yields isomeric tetramethyl decenes for which both *trans* and *cis* isomers are formed by *syn* elimination. Svoboda, Závada and Sicher[242] have suggested that both the *syn* stereochemistry and the relative

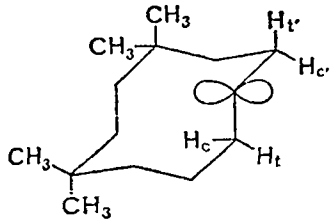


(**80**)
Solvent: CH_3COOH

proportions of isomeric olefins may reflect the degree of coplanarity between the β-C—H bonds and the carbonium ion *p*-orbital. For the expected conformation **81** the predicted order is $H_t > H_{c'} \sim H_{t'} > H_c$, which is broadly consistent with the olefin proportions found.

This result is in line with the general proneness of medium rings to *syn* elimination, but the *syn* mode to *cis*-olefin contrasts with the usual

stereochemistry of *E*2 eliminations. Probably the reduced severity of eclipsing effects in *E*1 as compared with *E*2 transition states is responsible. The *syn* elimination also contrasts with the elimination of cyclohexyl



(81)

tosylates. This is again expected but it may be significant that there is no indication that the counter-ion dictates an *anti* stereochemical course for reaction.

D. Rate-determining Attack upon an Ion Pair

For an *E*1 reaction occurring via an ion-pair intermediate (equation 7) the rate-determining step may involve either formation or reaction of the ion pair. When both processes occur at comparable rates a change in rate-determining step may follow from a change in base concentration. This may be detected by a change from first- to zero-order dependence on base concentration and the observation of a kinetic 'saturation' effect similar to that found for *E*1*cB* elimination (section IV. A. 3) as the concentration of the base is increased. Such behaviour has been reported by Sneen and Robbins[26] for elimination of α-phenethyl bromide (**82**) in ethanolic sodium ethoxide.

$$RX \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} R^+X^- \xrightarrow{k_2[B]} \text{olefin} \qquad (7)$$

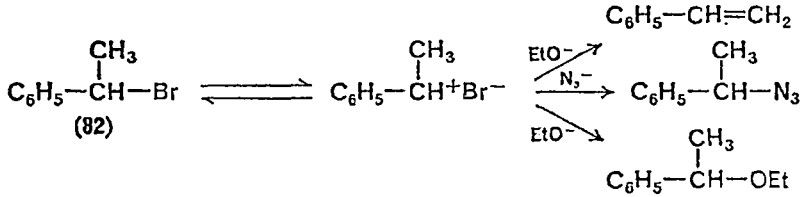
$$\text{Rate} = \frac{k_1 k_2[B][RX]}{k_2[B] + k_{-1}}$$

$$= \frac{k_1 k_2}{k_{-1}}[B][RX] \quad \text{at low base concentration}$$

$$= k_1[RX] \quad \text{at high base concentration}$$

α-Phenethyl bromide is subject to substitution as well as elimination and a change in the kinetic form from first- to zero-order can also be effected by addition of a strong nucleophile such as azide ion. This is nicely consistent

with the idea that the ion-pair intermediate should be common to both substitution and elimination paths. The change in rate-determining step in the case of ethoxide therefore may be attributed to the attack upon the ion



pair to yield both substitution and elimination products. Sneen and Robbins[26] showed that by combining analyses of the effect on the rate of added azide ion with the effect on the product proportions of added ethoxide ion it is possible to calculate the *kinetic* effect of added ethoxide. A comparison of the calculated and observed rates which includes additional data reported by McLennan[243] is shown in Figure 5. In view

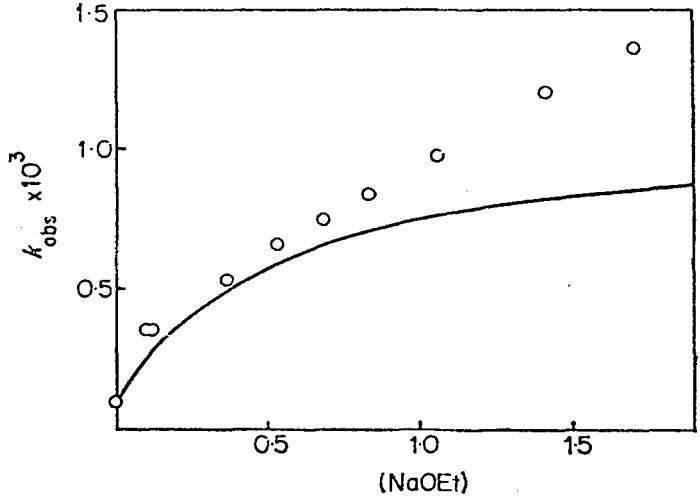


FIGURE 5. Calculated and observed dependences of the rate of reaction of α-phenethyl bromide upon the concentration of sodium ethoxide in ethanol.

of the neglect of salt effects and the large number of experimental variables involved the agreement is probably not unreasonable.

To be of diagnostic value the effects of added ethoxide upon the rate and products from an ion-pair mechanism have to be distinguished from the expected effect of contributions from $E2$ and S_N2 reactions. Provided that no unusual salt effects occur the distinction is a relatively clear one.

Unfortunately, salt effects of alkoxide ions appear to be quite complex[243, 244] and McLennan has been able to argue that they offer sufficient latitude to make possible an interpretation of the rate and product data in terms of competing $E1$–$E2$ and S_N1–S_N2 reactions not involving ion pairs[244].

Nonetheless Sneen's and Robbins' very neat analysis seems to be a perfectly reasonable one and, as they point out, has the interesting corollary that some of the simple criteria upon which distinctions between $E2$ and $E1$ mechanisms have been based may have to be discarded. Thus for rate-determining attack upon an ion pair, $E1$ elimination will have second-order kinetics, will be subject to a primary hydrogen isotope effect and will show no mass law rate depression by added halide ions, in each respect behaving as an $E2$ elimination. However, it does not follow that established examples of the $E2$ mechanism need to be widely reconsidered. The strong and well-documented (section III. A) dependence upon the nature of the leaving group of β-hydrogen isotope effects, the accelerating effect of β-substituents and the sensitivity of elimination rates to base catalysis points clearly to the operation of an authentic concerted mechanism in the majority of cases. We may conclude that although consideration of ion pair modifications of $E1$, and also of $E1cB$ (section IV. D) mechanisms, may lead to some encroachment on reactions hitherto regarded as $E2$ there is no question of so fundamental a modification of the mechanistic categories formulated by Hughes and Ingold[1] as a discarding of concerted elimination.

VI. ACKNOWLEDGMENTS

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The Chemistry of The Carbon–Halogen Bond
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CHAPTER 10

Pyrolysis reactions involving carbon–halogen bonds

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I. INTRODUCTION

As early as 1821 Faraday[1] reported the formation of perchloroethylene and chlorine on streaming perchloroethane down a heated tube, filled with porcelain chips. Later it was discovered that CCl_4 is also formed in this process[2], and today, over 150 years after the first report on the reversible reaction $C_2Cl_6 \rightleftarrows C_2Cl_4 + Cl_2$, the detailed kinetics and mechanism of this seemingly simple reaction are not known from a direct study of the system. This reaction already exemplified the mechanistic complexities generally inherent in pyrolysis reactions of haloalkanes. The initial thermolysis of organic halides can involve (i) a molecular homogeneous elimination process, (ii) a concerted elimination catalysed by the walls of the reactor, (iii) a halogen atom chain reaction, initiated by the homogeneous C—X bond breakage, (iv) a halogen atom chain, initiated and/or terminated on the walls of the reactors, or (v) a radical process initiated by a C—C bond cleavage.

In principle these are the important rate-controlling reactions encountered in the thermally initiated pyrolysis of organic molecules containing C—X bonds, but only the first four are within the scope of this review. In addition the overall pyrolysis might be self-catalysed (e.g. HX catalysed decomposition of RX) or self-inhibited (radical chain decompositions).

Kinetic data on the thermolysis of halogenated organic molecules accumulated since the early work of Faraday nevertheless do permit prediction of the activation parameters and relative rates for the homogeneous reaction paths outlined above. In contrast, today's knowledge of the mechanism and kinetics of heterogeneous reactions is very modest indeed, reflecting the complexities and diversities encountered in heterogeneous reactions.

The problems involved in reducing the multitude of competing reactions often encountered in pyrolysis studies of RX-molecules have limited the number of reactions accessible for detailed quantitative kinetic and mechanistic studies.

A. Background

1. Scope of review

The field of review is limited to unimolecular reactions involving C—X bond breakage in organic molecules. Essentially only studies reporting quantitative data are considered and the results are discussed applying the concepts of *thermochemical kinetics*[3]. Some important classes of reactions, for which only qualitative mechanistic information is available, have also been considered in an attempt to give as complete a mechanistic coverage as possible. The available kinetic data have been critically reviewed in terms of the internal consistency with data for similar reaction systems and compared with estimates based on the principles of transition state theory, bond dissociation energies and the appropriate detailed mechanism (outlined in section I. B) proposed for these reactions.

The pyrolyses of organic halogenated molecules involving the breaking of C—X bonds generally require temperatures $>200°C$. Obviously most studies are therefore limited to the *gas phase* and we have restricted our attention to gas-phase studies. Poly- or perhalogenated higher molecular weight materials, which would be suitable for liquid-phase studies, have attracted much less interest[2] as they are not expected to contribute novel mechanistic information and furthermore have not met any wide industrial or preparative applications. Moreover, where solvent participation can essentially be excluded, unimolecular reactions have been shown to proceed at closely the same rates in liquid and gas phase, the activation parameters being very similar[4]. The only liquid-phase study relevant to the topic of this review briefly reported the dehalogenations of some alkyl halides in acetonitrile solution[5]. A discussion of the products obtained from the thermal decompositions of polymers containing C—X— bonds is presented in reference 6.

The surface sensitivity of reactions involving the pyrolyses of C—X— bonds has long been recognized and has received considerable attention in recent years[7–9]. Practically all studies investigated the means to obviate heterogeneous components in homogeneous reactions rather than studying the scope and mechanism of heterogeneous reactions themselves. Quantitative data on wall-initiated reactions are thus lacking and this review will deal with essentially *homogeneous* data only.

The reliability and the reproducibility of kinetic data to be discussed are then primarily determined by the success of the authors in eliminating or correcting for competing reactions in their studies.

In cases where several experimental determinations of the same reaction system are available we have tried to assess their relative reliability and have indicated the set of 'preferred' data.

In this review we attempt to give a reasonably concise and critical evaluation of the relevant data and dominant reaction mechanisms in the field of thermal unimolecular reactions involving halohydrocarbons and related compounds from the viewpoint of the thermochemical kineticist. No claim can be made for the completeness of literature coverage, but all important kinetic data up to December 1971 should have been considered. Results from chemical activation studies have not been included as they fall outside the scope of this review.

2. Experimental methods

Most of the kinetic data available to date have been obtained using one of the conventional methods applicable to the study of relatively slow reactions in the gas phase. Some principal aspects and inherent errors of these methods are briefly indicated below. The major sources of errors introduced into rate constants originate from uncertainties in the measurements of temperature, concentration and time. Depending on the method and reaction conditions used, the relative importance of these errors is very different. For more details we refer to the comprehensive review by Batt[10] and to the original literature.

a. The static method. Static reaction systems are still most widely used in kinetic studies of the thermolysis of organic molecules. The most important inherent shortcoming of homogeneous static pyrolyses studies, particularly in the case of alkyl halides[7,11] is the problem of avoiding contributions from reactions taking place on the walls of the reaction vessel. Various methods for 'seasoning' the reactor walls have been used. Most common among them is the formation of carbonaceous coatings by pyrolysing allyl- (2 hr, 360°C) or alkyl- (24 hr, 480°C) bromides (~500 torr) in Pyrex glass reactors. The same effect is often achieved by repeated slow

decomposition of the reaction products in the reactor prior to its use in kinetic studies. Coating of the walls with KCl has also been used[12]. For temperatures up to ~310°C 'PTFE'-coated reactors probably provide the most inert surfaces[13].

Other sources of errors are the inadequate corrections of the contributions of the dead space reaction to the overall conversion and the problems relating to the establishment of the temperature equilibrium in the system. The chemical reaction should proceed much slower than temperature equilibration, which on average requires about 10 seconds after admission of the reactants, previously stored at room temperature.

Most of the kinetic studies concerned with the molecular mechanism in alkylchlorides, -bromides and -iodides have been carried out using static reaction systems.

b. The flow method. Flow systems have the advantage of minimizing surface effects through the use of higher reaction temperatures and shorter contact times. They allow studies at much lower overall conversions and they expand the practical pressure and temperature ranges for kinetic investigations. The main disadvantages are the ill-defined thermal and concentration gradients built up in flow systems, which increase with increasing pressures. The use of low pressures to minimize these problems may add further complications, especially in the case of simple molecules, due to the onset of unimolecular 'fall-off'. The use of stirred flow reactors[14] largely obviates concentration gradients and significantly reduces the uncertainties in determining the effective temperature of the reaction system, but the determination of the effective actual 'mean' temperature of the reactant gases still constitutes a major problem in obtaining reliable kinetic parameters. Accurate temperature calibration using test reactions with known activation parameters under comparable reaction conditions should minimize this error.

Tubular flow reactors have been widely used in connexion with the so-called toluene- or aniline-carrier technique[15], a method which was used to determine bond dissociation energies in many organic halides, by measuring the kinetics of bond fission reactions in the presence of free-radical scavengers. Unfortunately, in addition to the shortcomings inherent in 'non-stirred' laminar flow methods, this carrier technique is further complicated by side-reactions occurring contrary to the assumption that the primary radicals exclusively react with the carrier[16].

c. The shock-tube method. The advantages of the shock tube in the study of reaction rates lie in the fast and homogeneous heating of the reaction components, thus largely suppressing heterogeneous effects. In addition a much larger temperature range can usually be covered in shock-tube

experiments. The main disadvantages are the uncertainties associated with the temperature and time measurements, which are even larger than those in conventional flow systems, and reliable kinetic data from shock-tube studies have only recently been obtained.

Tsang[17–20] has developed a comparative single-pulse shock-tube technique in which a compound with known decomposition parameters is copyrolysed with the reactant, and he applied it successfully to studies of alkylchloride and alkylbromide pyrolyses. Alkylfluorides appear to be particularly sensitive towards surface catalysis and therefore studies in conventional static or flow systems are rendered very difficult. More recently, Tschuikow-Roux and coworkers[21] and Cadman and coworkers[22] investigated a series of pyrolysis reactions involving fluorinated hydrocarbons by a non-comparative shock technique. The poor agreement of the reported activation parameters (compare Table 5) reflects the experimental uncertainties of this method.

3. Literature

There have been several reviews published on the pyrolytic reactions of certain classes of organic halides. The reviews of Steacie[23] and Stroh[2] contain details of the early literature for decompositions of compounds containing C—X bonds. The elimination of hydrogen halides from alkyl halides has been exhaustively reviewed by Maccoll[24–31] and more recently by Smith and Kelly[32] who also present data for the thermal decomposition of chloroformates. These reviews give a comprehensive but essentially non-critical evaluation of the data available at the time, which did not include fluorinated halohydrocarbons.

Benson and O'Neal[16], in an extensive review of the Arrhenius parameters of unimolecular gas-phase reactions, have also critically examined the available data for many organic halides with special reference to transition state calculations.

B. Thermochemical Kinetics

1. General considerations

The *a priori* prediction of reaction products and the rates of their formation is one of the foremost objectives of chemistry in general. The state of knowledge achieved to date allows predictions of reaction products to be made with much more confidence and ease than predictions of reaction rates. However, over the last three decades a significant number of relatively reliable quantitative data on rates of individual *gas-phase* reactions and elementary reaction steps has become available,

particularly for unimolecular reactions[3,16,33]. On the basis of these data, methods for *a priori* prediction of rates have been derived for a limited number of reactions. The foremost work in this field has been presented by Benson and coworkers[3,16,34] who derived and 'demonstrated' the very useful concept of 'thermochemical kinetics' by applying the principles of thermodynamics and transition state theory to the available quantitative rate data. The principles of this method have been widely covered in the literature[3,16,33,34] and we can limit ourselves to the presentation and discussion of those aspects of 'thermochemical kinetics' that were used in critically evaluating the data covered in this review.

The Arrhenius activation parameters of a unimolecular decomposition reaction of the general type

$$A \underset{-a}{\overset{a}{\rightleftarrows}} B + C \tag{1}$$

which can also be formulated in terms of transition state theory as

$$A \underset{-x}{\overset{x}{\rightleftarrows}} [TS]^{\ddagger} \xrightarrow{\nu} B + C \tag{2}$$

can be related to the thermochemical parameters of reactants, products and transition state complex* by the relationships:

$$k_a = A \exp -(E_a/RT) = (kT/h)\, K^{\ddagger}_{x,-x} \tag{3}$$

where

$$K^{\ddagger}_{x,-x} = k_x/k_{-x}$$

Using the thermodynamic relationship

$$-RT \ln K_p = \Delta G^0_T = \Delta H^0_T - T\Delta S^0_T \tag{4}$$

yields the rate constants k_a in thermodynamic terms

$$k_a = A \exp -(E_a/RT) = (kT/h) \exp (\Delta S^{\ddagger}_{x,-x}/R) \exp (-\Delta H^{\ddagger}_{x,-x}/RT)$$

The pre-exponential A-factor can then be identified with

$$\log A = -\log (kT_m/h) + \log e\,(= 0{\cdot}434) + \Delta S^{\ddagger}_{x,-x}/2{\cdot}303\, R \tag{5}$$

and the activation energy E_a with $E_a = \Delta H^{\ddagger} + RT$, where T_m represents the mean reaction temperature. $kT/h = 10^{10.319} T\,(s^{-1})$ or $10^{13.0}$ at 500, $10^{13.2}$ at 700, $10^{13.3}$ at 900, and $10^{13.4}$ at 1100K.

* The transition state complex $[TS]^{\ddagger}$ is in effect regarded as an intermediate with definite thermodynamic properties (S^0, ΔH^0_f, C^0_p), dependent on a defined structure.

The above relationships only apply to unimolecular reactions at the high-pressure limit*.

2. Estimation of thermodynamic data

As was pointed out in the previous section, the equilibrium constant $K_{a,-a} = k_a[A]/k_{-a}[B][C]$ and the Van't Hoff equation (4) relate kinetic activation parameters with thermodynamic parameters for reactants and products.

The knowledge of accurate heats of formation, entropies and heat capacities of molecules is often a prerequisite for a complete interpretation of observed rate parameters with respect to forward and back reactions. Recent compilations of the available experimental data are to be found in the books of Cox and Pilcher[35] or Stull, Westrum and Sinke[36], as well as in the JANAF tables[37] or other sources[38,39]. Benson and coworkers[40] have derived a very useful concept involving the direct additivity of group-increments which allows estimation of ΔH_f^0- and S^0-values within 0·5 to 1·0 kcal mole^{-1} and 0·5 to 1·0 cal (K)$^{-1}$ mole^{-1} respectively for a large number of organic molecules for which direct data are still lacking. Using the same concept, additivity values have been generated for a variety of radical groups[41].

A detailed treatment of the thermodynamic aspects of halogenated organic molecules is given by Shaw in Chapter 16 of this book.

3. Activation parameters for gas-phase radical reactions

As mentioned earlier in section I. A. 1, this review deals primarily with the quantitative aspects of reactions involving $R_3C—X$ bond breakage. In terms of radical reactions our interest then concentrates on the Arrhenius parameters for the unimolecular bond fission as shown in reaction (6).

$$\begin{array}{c} | \quad | \\ RC—C—X \\ | \quad | \end{array} \underset{-1}{\overset{1}{\rightleftharpoons}} \begin{array}{c} | \quad | \\ RC—C^{\bullet} \\ | \quad | \end{array} + X^{\bullet} \qquad (6)$$

Accepting the assumption that the activation energy for recombination, E_{-1}, equals 0 (generally considered to be valid for most radicals) a simple

* At low pressures the collisional activation step in unimolecular reactions becomes increasingly important in determining the kinetics and the overall order of reaction changes from first to second. The pressure at which this so-called 'fall-off' occurs depends on the molecular complexity, being highest for the most simple molecules. For an account of the theories applicable to the 'fall-off' region see reference 34.

relationship between the observed activation energy for the bond-fission process and the corresponding bond dissociation energies can be derived.

For the unimolecular dissociation rate constant the Arrhenius relationship is given by $\log k_1 = \log A_1 - E_1/2{\cdot}303\ RT$, and the heat of the reaction at the average temperature of the rate data in pressure standard states[42] $(\Delta H^0_{1,-1})_T$ is directly equated to E_1 through:

$$(\Delta H^0_{1,-1})_T = E_1 - E_{-1(p)} \approx E_1$$

The applicability of the observed overall rate constants in a radical reaction to a quantitative interpretation in terms of the elementary initial bond-breaking step as outlined above depends on the complexity and knowledge of the detailed reaction mechanism involved.

Radical-induced reactions tend to be very complex due to the variety of fast secondary reactions involving decomposition, isomerization, addition and abstraction reactions of radicals. One of the methods widely used to suppress radical-chain reactions in order to obtain quantitative information about elementary steps is the addition of an excess of various free-radical scavengers such as toluene, aniline, propylene, cyclohexene, cyclohexane and nitric oxide. In static reaction systems additives were mostly used with halohydrocarbons to obtain 'maximum inhibited' rates assumed to represent predominantly molecular reaction paths only[24,32]. In flow systems toluene has been widely used as a radical trap, forming the very inert $PhCH_2^{\bullet}$ radical which was assumed to terminate exclusively[15]. In this case the 'maximum inhibited' rate would correspond to the bond-fission process. However, as discussed previously, the fact that the assumptions of total chain inhibition are not always strictly valid, and other shortcomings, limit the reliability of such data[16].

Where complex radical-chain reactions prevail, the analytical and kinetic evaluation of the system is often extremely difficult. Proper measurements of mass balances and overall product analysis with time, as well as the reliable analysis and identification of small amounts of materials are not easy to achieve, especially as the conversions should be kept low to avoid side-reactions. It is then not surprising that the detailed reaction schemes for only a few thermally initiated radical-chain decompositions involving molecules with C—X bonds have been reported. Further complication occurs if a reaction product can act as a radical initiator leading to a self-initiated radical-chain reaction, as is the case with HI or HBr produced by molecular elimination from alkyliodides or bromides.

Linear transition state complexes involved in bond-fission reactions would be expected to be 'loose' and in recent years it has become apparent that 'abnormally' high pre-exponential factors (10^{15}–10^{18}) observed in

simple bond-fission reactions are rather the rule than the exception[3]. A-factors of the order of 10^{13} s^{-1} that were considered 'normal' some years ago, due to their consistency with the Rice–Ramsperger–Kassel theory of unimolecular reactions[43], must now be viewed with suspicion. Recently, careful shock-tube data[17–20] gave A-factors for simple bond-fission reactions of 10^{14}–$10^{16.5}$, or about a factor of 10 lower than the values previously obtained. From such evidence for loose transition states, A-factors of $10^{15\pm1}$ would appear likely for the homolytic fission of C—X bonds.

a. Bond dissociation energies in molecules. Standard bond dissociation energies (BDE) are defined as the enthalpy change in a reaction of the type (6) where reactants and products are in their standard pressure states (1 atm at 25°C).

$$\begin{aligned}\mathrm{BDE}(R_3C{-}X) &= (\Delta H^0_{1,-1})_{298} \\ &= \Delta H^0_{f,298}(R_3C^{\cdot}) + \Delta H^0_{f,298}(X^{\cdot}) - \Delta H^0_{f,298}(R_3C{-}X) \qquad (7)\end{aligned}$$

Correcting the value for the activation energy observed at temperature T down to 298K via

$$E_{1(p)} = (\Delta H_{1,-1})_T = (\Delta H_{1,-1})_{298} + (\langle \Delta C^0_p \rangle_{(T+298)/2})(T-298) \qquad (8)$$

will directly yield BDE values with calculational uncertainties of $\sim \pm$ 1 kcal mole^{-1}. The $(T)\Delta C^0_p$ term usually amounts to less than 1 kcal mole^{-1} and can be neglected. The total uncertainties of BDE values are normally between 2 and 5 kcal mole^{-1}.

From equation (7) heats of formation of radicals such as $R_3C^{\cdot}$ can be obtained, if $\Delta H^0_f(X^{\cdot})$ and $\Delta H^0_f(R_3CX)$ are known or can be estimated. While data for molecules are usually known or can be generated, entropies and heat capacities of radicals are much more difficult to obtain. A method for estimating S^0 and C^0_p data of radicals has been outlined by O'Neal and Benson[41].

Based on the definition given in equation (7) and using the available thermochemical and kinetic data, critically selected 'best' bond dissociation energies have been derived and have been checked for overall consistency. These data are listed in Table 1.

Where no independent experimentally based data were available or where no reliable estimates could be derived, values for BDE's have not been incorporated in the table. Furuyama and coworkers[53] have summarized BDE values for unmixed halomethanes and heats of formation of halomethyl radicals and Kerr and Trotman-Dickenson[54] list selected BDE data for organic molecules and radicals.

TABLE 1. Carbon–X bond dissociation energies[a] (in kcal mole^{-1})

X	F	Cl	Br	I	H	Me
Bond						
CH_3—	108	84	70	56	104	88
RCH_2—	106	81	69	53	98	85
R_2CH—	105	81	68	53	95	85
R_3C—	[103]	79	63	50	92	82
Ph—	(125)[b]	95[b]	81[b]	64[b]	110[b]	100[b]
$PhCH_2$—	[94]	68	(54)	40	85	70
CH_2=$CHCH_2$—	[96]	71	57	44	88	76
CF_3—	(130)	(86)	71[g]	54	106	(100)
CCl_3—	106	73	54		96	
CBr_3—	[106]	[74]	56[c]		96[c]	
CI_2H—	121			55	103	
CIH_2—			70	52	103	91
$CH_3C(=O)$—	120	82	67	51	88	82
$PhC(=O)$—	[120]	81[d]	64[d]	(49)[d]	87[d]	81[d]
$CH_3CCH_2(=O)$—	[106]	[81]	64[f]	51[e]	98	85

[a] Unmarked values for bond-dissociation energies taken or calculated from thermochemical data in the following references: Kerr[44], Golden and Benson[45], U.S. National Bureau of Standards[46], Cox and Pilcher[35], Stull, Westrum and Sinke[36].
The values have been critically selected with special reference to consistency with the latest values for the heats of formation of the radicals and parent molecules and are probably accurate to ± 2 kcal mole^{-1} in general. Those values in parentheses are subject to larger uncertainty. Square brackets indicate interpolated values.

[b] ΔH_f Ph$^\bullet$ from Chamberlain and Whittle[47].

[c] King, Golden and Benson[48].

[d] ΔH_f PhC$^\bullet$O from Solly and Benson[49].

[e] King, Golden and Benson[50, 51].

[f] King, Golden and Benson[52].

[g] Reference 215.

b. Stabilization energies in delocalized radicals. As would be expected and can be seen from the data listed in Table 1 substituents on the carbon atom can drastically affect the strength of a C—X bond. If we exchange the C—H bonds in H_3CCl as an example, variations in the C—Cl bond dissociation energy between $+11$ and -16 kcal mole^{-1} are obtained, and even larger effects would be expected with other substituents, e.g. cyclopentadienyl. Unsaturation in general has a large effect. The strength of a

C—X bond in an olefinic position is significantly increased while benzyl- and allyl-type substituents lower the BDE of C—X bonds.

These effects usually exhibit a systematic trend with the nature of the halogen atom but do not appear to be constant. On the other hand, a reliable quantitative prediction of the effect of benzyl- or allyl-type substituents can be made, as the 'allylic'- or 'benzylic'-carbon radicals formed in the fission reaction always contain the same amount of 'extra' stabilization energy, attributed mainly to the delocalization of electrons, when compared with the parent hydrocarbon radicals.

TABLE 2. Stabilization energies (E_s) in kcal mole^{-1} in delocalized radicals

Radical	E_s[a]	Reference
Allyl	9·6	55, 56
Methallyl	12·6	57
Dimethallyl	13·1	58
Cyclopentenyl	12·6	59
Cyclopentadienyl	15–20[b]	60
Cyclohexadienyl	24·6	61
3-Methylenecyclohexenyl	23·4	62
Pentadienyl	18·5	63
Propargyl	4·1	64
Benzyl	12·5	65
$O{=}C\dot{H}\dot{C}R_2$[c]	0	50, 66
$CH_2{=}N\dot{C}R_2$	12·6	67

[a] The random uncertainties in these values are of the order of $\pm 1{\cdot}5$ kcal mole^{-1}.

[b] These values are probably too low by about 2 ± 1 kcal mole^{-1}. The activation energy for the back reaction in the iodine atom abstraction method used in these studies is probably in excess of the 'usual' 1·5 kcal mole^{-1} if the reaction is close to thermoneutrality.

[c] Small ring pyrolysis data give $E_s \approx 7$ kcal mole^{-1} (compare A. T. Cocks and K. W. Egger, *J. Chem. Soc., Perkin*, II, 199 (1973).

If we define the 'extra' stabilization energies (E_s) generated in hydrocarbon or related radicals as the difference in dissociation energies between the parent 'saturated' bond and the 'allylic- or benzyllic'-type bond, then

$$E_s = D(C{-}X)_{parent} - D(C{-}X)_{'allylic'}$$

Values for E_s, derived mainly from kinetic measurements, are listed in Table 2.

For a number of C—X bonds not listed in Table 1, values for the corresponding BDE's can then be estimated using the data given in Table 2.

It is of particular interest to note the absence of E_s both in the acetonyl- and in the methylacetonyl radicals[50, 66]. This has been explained by the large differences in π-bond strength in the canonical forms of the radicals $^{\bullet}C—C{=}O$ and $C{=}C—O^{\bullet}$ which makes the first of the two forms thermodynamically much more stable*.

4. Activation parameters for gas-phase molecular reactions

As outlined in section I. A. 1 we restrict our attention to unimolecular processes initiated thermally and homogeneously in the gas phase. This type of reaction may involve both isomerizations (observed, for example, with cyclopropylhalides) and decompositions (e.g. HX elimination from alkylhalides). Most of these reactions, which are discussed in sections II and III, appear to involve cyclic transition states. In an intramolecular C—X bond-breaking process, involving cyclic transition states, at least two 'old' bonds are broken and two 'new' ones made in a concerted manner. The estimation of activation parameters of such concerted reactions still depends largely on comparative predictions based on related reactions for which the detailed kinetics and activation parameters have been established.

In recent years molecular orbital theory has contributed considerable *qualitative* insight into the mechanisms of certain concerted reactions, particularly through the concept of conservation of orbital symmetry applied to electrocyclic reactions as presented by Woodward and Hoffmann[68] †. Methods to predict the activation parameters of concerted unimolecular reactions, however, are largely lacking. Methods for quantitative predictions of activation energies and entropies have been derived for a few classes of compounds by Benson and coworkers[3, 16] based on transition state theory combined with relatively simple valence bond and electrostatic semi-empirical concepts.

For multicentre unimolecular concerted reactions, O'Neal and Benson[69] derived a method for calculating $\Delta S^{\ddagger}_{x,-x}$ and thus predicting log A, by assigning bending, stretching and torsion frequencies to one- and three-electron bonds in the transition state.

For a four-centre process relatively small intrinsic entropies of activation have been calculated resulting in predicted A-factors between 10^{13} and

* See footnote [c] in Table 2.

† All future reference to Woodward and Hoffmann in the text refers to reference 68.

10^{14} depending primarily on the path degeneracy involved. For unimolecular reactions involving six-centre transition states the predicted A-factors range from about 10^{12} to 10^{13} depending on the valence bond structure of the transition complex. Benson and Haugen[70–72] derived a simple electrostatic model for calculating activation energies of four-centre reactions such as the elimination of HX from alkylhalides. The method involves the assumption of a quadrupolar semi-ion-pair type transition state complex, formed by the interaction of two longitudinal bond dipoles in the HX and the olefin moiety. Maccoll and Thomas[25], assuming the formation of quasi-ion pairs for the same type of reaction, proposed as a first approximation in estimating E_a the simple form $E_a = 0{\cdot}29D(R^+X^-)$, where $D(R^+X^-)$ is the heterolytic bond dissociation energy or the energy of the process $RX \rightarrow R^+ + X^-$. Further attention will be given to these models in sections II and III.

II. SURVEY OF UNIMOLECULAR THERMAL REACTIONS INVOLVING CLEAVAGE OF CARBON–HALOGEN BONDS

The contents of this section have essentially been grouped according to compound classes in an attempt to preserve the general concept of the carbon–halogen bond as an entity in different environments.

As was pointed out in section I, organic halides can decompose via molecular or radical reaction paths and the mode adopted largely depends on the nature of the halogen atom as well as the substituents in various positions of the molecule. It therefore appeared logical to subdivide the discussion within a given class of compounds according to the reaction pathway involved.

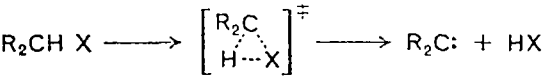
While the chosen method of division of the topic is intrinsically consistent, it is liable to underemphasize some unifying aspects within the bulk of these data, particularly the mechanistic features and kinetic parameters common to different classes of compounds. These similarities are discussed more fully in section III.

A. Saturated Halogenated Hydrocarbons

Thermal reactions of halomethanes are limited because of the structural simplicity of these compounds and it is therefore logical to discuss them separately from those of higher linear alkyl halides for which a wider range of routes is available. With the exception of cyclopropyl halides, which undergo unique thermal reactions and are therefore discussed separately, cycloalkyl halides appear to react in a manner analogous to linear alkyl halides.

i. Methane derivatives

a. Molecular hydrogen halide elimination. The only likely thermal molecular decomposition route open to halogenated methanes is elimination of hydrogen halide to give the carbene.



$$R_2CH\ X \longrightarrow \left[\begin{matrix} R_2C \\ H\cdots X \end{matrix}\right]^{\mp} \longrightarrow R_2C{:} + HX \qquad (9)$$

This has been shown to be the sole mode of decomposition of trifluoromethane[73,74], and difluorochloromethane[75,76], and a competitive pathway with carbon–bromine fission initiated radical reactions in the case of difluorobromomethane[77]. All these decompositions yield difluorocarbene which rapidly dimerizes. The α-elimination of HCl to give dichlorocarbene has been proposed in the pyrolysis of trichloromethane[78], but it is likely that this pathway is at best competitive with a radical route.

The Arrhenius parameters for α-eliminations from the difluorohalomethanes are given in Table 3. For the three-centre transition state

TABLE 3. α-Hydrogen halide eliminations from halomethanes

Reaction	Log A^a	E_a (kcal mole^{-1})	Reference
$CF_2HF \rightarrow :CF_2 + HF$	12·2[b]	59·6	73
	11·8	58·4	74
$CF_2HCl \rightarrow :CF_2 + HCl$	13·8	55·8	75
	12·6	52·8	76
$CF_2HBr \rightarrow :CF_2 + HBr$	14·3	55·6	77

[a] A in units of s^{-1}.
[b] Calculated from the Arrhenius plot of high pressure results in reference 73.

envisaged, A-factors between about 10^{13} and 10^{14} would be expected. Both studies of trifluoromethane were made using shock tubes and the results are undoubtedly low. For such simple molecules as the halomethanes, 'fall-off' would be expected to occur at relatively high pressures and this creates added difficulties in the interpretation of the data. The authors in reference 76 suggest that 'fall-off' accounts for their low parameters.

From the data in Table 3 it would appear that for three-centre eliminations there is little difference in the rates of elimination of hydrogen chloride and hydrogen bromide and that even allowing for 'fall-off' uncertainties, hydrogen fluoride elimination is a much slower process. The thermodynamic stability of difluorocarbene[44] would appear to account for

the occurrence of α-elimination in difluoromethyl halides. This mechanism has not been established for other types of halomethanes.

b. Radical reactions. Most halomethanes decompose by a radical pathway initiated by carbon–halogen bond fission. A comparison of the BDE values in Table 1 with the activation energies for the concerted process in Table 3 reveals the reason for the unimportance of radical processes in the pyrolysis of difluorochloromethane and trifluoromethane, in contrast to other halomethanes.

The range of reactions open to the simple radicals produced in the thermal reactions of halomethanes is limited, but very few reaction mechanisms have been thoroughly investigated. A careful study of the pyrolysis reactions of (i) carbontetrachloride[79] and (ii) methyl chloride[79] indicated that the following simple reaction schemes were operative:

(i)

$$CCl_4 \rightleftharpoons \dot{C}Cl_3 + Cl$$

$$Cl + CCl_4 \longrightarrow Cl_2 + \dot{C}Cl_3$$

$$2\,\dot{C}Cl_3 \longrightarrow C_2Cl_6$$

$$C_2Cl_6 \longrightarrow C_2Cl_4 + Cl_2$$

(ii)

$$CH_3Cl \longrightarrow \dot{C}H_3 + Cl$$

$$\dot{C}H_3 + CH_3Cl \longrightarrow CH_4 + \dot{C}H_2Cl$$

$$Cl + CH_3Cl \longrightarrow HCl + \dot{C}H_2Cl$$

$$\dot{C}H_2Cl + CH_3Cl \longrightarrow CH_2Cl_2 + \dot{C}H_3$$

$$2\,\dot{C}H_2Cl \longrightarrow C_2H_4Cl_2$$

$$C_2H_4Cl_2 \longrightarrow HCl + CH_2{=}CHCl$$

$$CH_2{=}CHCl \longrightarrow HCl + C_2H_2$$

A relatively simple scheme has also been proposed for the homogeneous pyrolysis of methyl iodide[80].

$$CH_3I \longrightarrow \dot{C}H_3 + I$$

$$I + CH_3I \longrightarrow \dot{C}H_3 + I_2$$

$$\dot{C}H_3 + CH_3I \longrightarrow CH_4 + \dot{C}H_2I$$

$$\dot{C}H_2I + I_2 \rightleftharpoons CH_2I_2 + I$$

$$2\,\dot{C}H_2I \longrightarrow (C_2H_4I_2)^* \longrightarrow C_2H_4 + I_2$$

Experimental studies[81], however, report the formation of large amounts of 'condensed' products and carbon. It is likely that heterogeneous reactions are responsible for the observed behaviour.

Attempts have been made to isolate the initial bond-breaking step for a number of halomethanes by the toluene carrier technique and reference 16 contains a compilation of the activation parameters obtained. The results do not appear to be reliable due to a combination of 'fall-off' difficulties and experimental artifacts. For initial bond breaking in halomethanes, *A*-factors of about $10^{14.5}$ and activation energies close to the bond dissociation energies (Table 1) would be expected.

2. Ethane and higher alkane derivatives

The homogeneous gas-phase pyrolyses of ethyl- and higher alkyl halides usually yield HX and the corresponding olefins as main products in a first-order process[24, 32]. While alkyl fluorides decompose exclusively via a concerted molecular elimination path, the decomposition of alkyl chlorides, bromides and iodides often involves a combination of molecular and radical reaction routes. This latter class can be divided further into (i) reactions with concurrent but essentially non-mixed individual radical and concerted paths and (ii) reactions with mixed concurrent radical and molecular paths. The preference for concurrent radical–molecular decompositions over a purely molecular reaction increases in parallel with the increased weakening of the C—X and H—X bonds.

The radical component of systems with mixed reaction kinetics has not been investigated independently in most cases and quantitative data for the radical paths are therefore scarce. On the other hand the addition of radical scavengers to systems of the type (ii) with individual concurrent radical and molecular decomposition routes yields 'maximum inhibited' rate constants which are usually equated with the molecular reaction path. A large number of activation parameters reported for HX eliminations from alkyl halides have been derived from kinetic studies in 'maximum inhibited systems'.

Some reactions of the type (ii) with mixed radical and molecular mechanisms, for example the iodine-atom-catalysed elimination of HX from alkyl halides[45], are not amenable to simple inhibition by radical scavengers.

a. The four-centre HX elimination from monohalo hydrocarbons. The *cis*-four-centre nature of the unimolecular elimination of HX from alkyl halides was recognized from the earliest studies of these processes, but the significant 'ionic character' of the reaction and its mechanistic importance

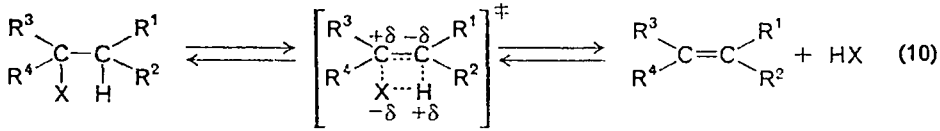
was not realized until Maccoll and Thomas[82] first proposed a quasi-heterolytic reaction path. The general concept of a highly polar or quasi-ionic four-centre transition complex involved in this (Woodward–Hoffmann non-allowed) *cis*-elimination process has generally been accepted and is substantiated by an ever-increasing amount of experimental data. The existence of a partial charge separation rather than the initially favoured but unreasonable concept of complete separation into gaseous ions has been established by a study of the pyrolysis of D-(+)-chlorooctane[83] in which no significant difference between rate constants based on optical rotation and pressure changes was observed.

Few classes of unimolecular decomposition reactions have been studied as extensively as the olefin 'eliminations' from alkyl halides. A dominant proportion of the available first-order activation parameters reported for the unimolecular decomposition of organic halogen compounds falls into this category and in Table 4 activation parameters observed for the concerted four-centre HX elimination for selected alkyl monohalides are listed.

Due to the stability of the product olefins and HX, secondary reactions can usually be disregarded. As has been discussed in section I. B. 4, the major problems involved in obtaining reliable activation parameters for the homogeneous molecular HX elimination originate from competing heterogeneous and radical reactions.

In view of the polar nature of the reaction the pronounced surface catalysis, generally observed in HX elimination from alkyl halides, is not surprising and has been quantitatively studied in a number of cases[7,115]. The reported activation parameters for most of the alkyl monohalides can be considered to be essentially unperturbed by heterogeneous reactions. Contributions from heterogeneous components amounting to a few per cent of the total conversions observed must, however, be taken into consideration.

While surface sensitivity is common to all these reactions, complications from radical decompositions are particularly noticeable where weak C—X and H—X bonds are involved, and are therefore more pronounced with tertiary alkyl halides than with secondary or primary derivatives. The available literature data for molecular reactions indicate a large stabilizing effect of alkyl groups in the α-position and a smaller effect in



(10)

TABLE 4. Arrhenius parameters for the unimolecular four-centre elimination of HX from alkyl monohalides[a]

	F			Cl			Br			I		
RX	log A	E_a	Ref.	log A	E_a	Ref.	log A	E_a	Ref.	log A	E_a	Ref.
X—(Et)				13·3	56·6	19, 20	13·0	52·2	87	14·1	52·8	90
				14·0	58·4	84	12·9	52·0	88	13·2	49·3	91
							13·3	53·9	19, 20	14·1	51·6	7
Preferred	*13·4*	*59·9*	22	*13·5*	*56·6*	85, 86	*13·5*	*53·9*	89	*13·4*	*50·0*	92
X—(*n*-Pr)				13·5	55·0	93	13·0	50·7	94			
							12·9	50·7	95			
Preferred	*13·3*	*58·3*	22	*13·5*	55·1	86	*13·2*	*51·9*	96	(*13·3*)	*49·0*	97
X—$CH_2CH(CH_3)_2$				14·0	56·9	99						
Preferred	*13·3*	*58·6*	98	*12·9*	*53·2*	98	*13·1*	*50·4*	100			
X—(*i*-Pr)				13·7	51·2	19, 20	13·6	47·7	93	14·5	48·0	104
				13·4	50·5	101	13·6	47·8	103	13·0	43·5	105
				13·4	50·5	102				12·9	42·9	106
										13·7	45·9	7
Preferred	*13·4*	*53·9*	98	*13·6*	*50·8*	22	*13·7*	*47·6*	20	*13·8*	*45·3*	19, 20
X—(*t*-Bu)				13·8	44·9	17	14·0	42·0	109			
				13·7	44·9	107						
Preferred	*13·4*	*51·5*	98	*13·8*	*45·0*	108	*14·0*	*41·7*	17, 20	*13·8*	*38·1*	20, 93
X—(*s*-Bu) (total)[b]				13·6	49·6	110	13·1	45·5	113	14·9	47·9	104
				14·0	50·8	111						
				14·0	50·8	112	13·5	46·5	114			
Preferred				*13·8*	*50·0*	16	*13·7*	*47·0*	16	(*13·7*)	(*44·7*)	16
→ But-1-ene				13·6	51·7	111	13·3	47·8	16			
→ But-2-ene *cis*				13·3	52·7	111	13·1	45·8	16			
→ But-2-ene *trans*				13·6	51·8	111						

[a] E_a in kcal mole^{-1}, A in s^{-1}. Data in parentheses refer to estimated values.
[b] *s*-Butyl halides have three independent elimination routes. 'Total' refers to the overall rate constants.

β-position and also show that methyl and higher *n*-alkyl substituents bonded tc the reactive carbon atoms have essentially the same effect. The large α-substituent effect can only be satisfactorily explained by a polar transition state in which the α-carbon is positive. Any difference in effective stabilization energies of alkyl groups would on this basis be predicted to be small (less than 1 kcal mole^{-1}) and, therefore, completely hidden by the uncertainties inherent in the data.

All the available literature data have been considered, but we have incorporated only data for 'prototype' reactants such as EtX, *n*-PrX, *i*-PrX, . . ., etc. in Table 4. Higher alkyl halides do not contribute basically novel information and additional data for such compounds can be found in the review articles of Maccoll[24-31] and of Smith and Kelly[32].

Based on the criteria outlined in the introduction section the available data have been critically selected and the activation parameters considered to be most reliable have been entered as 'preferred' values in Table 4. These 'preferred' literature data do not always coincide exactly with our estimates of the best values derived from considerations of the overall consistency of the data for olefin formation from RX. In most instances, however, experimental and estimated data agree within about 0·2 in log A and 1 kcal mole^{-1} in E_a. Where larger discrepancies have been observed, corrected data based on our estimates for the pre-exponential factor have also been incorporated, in parentheses, in Table 4.

Apart from studies of chemical activation[24,116] relatively reliable data on the elimination reactions of *alkyl fluorides* were not available until recently, when the comparative single-pulse shock-tube method was applied to these systems[22,98]. The experimental difficulties, particularly the heterogeneous effects, made reliable studies in conventional flow or static systems very difficult[11]. Due to the higher reaction temperature and the absence of surface effects the comparative shock-tube technique[17-20] appears to be particularly suited for studies of alkyl fluoride pyrolyses and more data are to be expected from such studies.

Like the fluorides, most of the *alkyl chlorides* pyrolyse via a concerted mechanism which is essentially free of radical components. The rates appear to be unaffected by the addition of 'classical' radical scavengers and there is no indication of induction periods. The activation parameters for alkyl chlorides are probably the most reliable data reported in this review and these compounds have been used as standards in the comparative shock-tube technique[22,98].

With *alkyl bromides*, first-order reaction kinetics, equated with the molecular reaction path, are only observed in 'maximum inhibited' systems.

In contrast to the other alkyl halides, *alkyl iodides* yield alkanes, alkenes and iodine as stable pyrolysis products. The details of the overall mechanism of the decomposition, involving mixed radical and molecular kinetics, have been treated comprehensively by Benson and coworkers[45,80]. Essentially two pathways are operative, with one of two rate-determining steps: (i) the 'normal' four-centre molecular elimination of HI and (ii) the concerted iodine atom catalysed elimination of HI, which might also be regarded as a concerted iodine atom abstraction reaction. The HI eliminations are followed by fast secondary atom and radical reactions in the overall system $RI + HI \rightleftarrows RH + I_2$, yielding alkane and iodine as observable major products.

The thermally initiated molecular four-centre elimination of HX appears to be rate-controlling in the pyrolysis of EtI, *i*-PrI and *t*-BuI, while the I-atom catalysed elimination of HI is the major pathway for *n*-PrI, *n*-BuI, *i*-BuI and possibly *s*-BuI[45]. The data listed in Table 4 refer to the non-catalysed elimination step. The value listed for *n*-PrI has only recently become available[97] from *v*ery *l*ow *p*ressure ($\sim 10^{-4}$torr) *p*yrolysis studies, using an effusion flow system technique and mass spectroscopic identification[117]. This *vlpp*-technique minimizes bimolecular reactions, as the gas is essentially heated through wall collisions only. The experimental activation parameters for *s*-BuI[16] appear to be too high and they have been scaled down, using a reasonable *A*-factor and mid-temperature rate constants, resulting in an activation energy consistent with the data for *s*-BuCl and *s*-BuBr.

The assumption of a common mechanism for all the reactions listed in Table 4 is substantiated by the rather impressive consistency of the experimental data. The systematic incremental differences in the activation parameters and the observed pre-exponential factors are in agreement with predictions for a mechanism involving a polar four-centre transition complex, based on considerations of thermochemical kinetics. The pronounced alkyl-substituent effects corroborate the polar nature of the transition state. The quantitative aspects of these stabilization energies and activation parameters will be discussed in section III together with the observations on HX eliminations from unsaturated and oxygenated haloalkanes with particular reference to the structure of the transition state.

b. The four-centre HX eliminations from α,α- and α,β-polyhalohydrocarbons. Substitution of halogen atoms for hydrogens in α- and β-positions of alkyl halides may affect not only the activation parameters for the concerted molecular four-centre HX elimination, but also the overall mechanistics of the reaction. As might be expected, the surface sensitivity

generally observed for HX eliminations from alkyl halides appears to be increased by additional polar substituents in the molecule and contributions from radical reactions also tend to become more pronounced. For example, both ethyl chloride and 1,2-dichloroethane can eliminate HCl in a homogeneous first-order process yielding ethylene and vinyl chloride respectively, but only EtX decomposes via a 'clean' four-centre mechanism (Table 4). The pyrolysis of 1,2-dichloroethane is complicated by contributions from heterogeneous and particularly radical reactions[118,119]. The system exhibits induction periods and the rate is decreased by addition of propene. Reliable 'maximum inhibited' rate data are still lacking.

The available kinetic data for the molecular elimination of HX from polyhaloalkanes are summarized in Table 5.

When compared with the data for alkyl halides listed in Table 4, it is readily apparent that the data for α- and β-polyhalogenated alkanes are subject to much larger uncertainties. The reliability of these data can best be judged from the rate constants, calculated for a temperature of 1000K and listed in Table 5. These data have been incorporated primarily to allow

TABLE 5. Arrhenius parameters for the four-centre unimolecular elimination of HX and XX from alkyl polyhalides

Reaction	Mean temp. (K)	Method[a]	k_{1000}[b] (s^{-1})	log A[c]	E_a[c] (kcal $mole^{-1}$)	Ref.
HF elimination						
FCH_2CH_3		ST	2·1	13·4	59·9	22
F_2CHCH_3	1300	SPST	2·4	13·9	61·9	120
	1000	F	0·61	13·3	61·9	121
Preferred	1620	ST	0·20	13·5	65·0	122
F_3CCH_3	1000	F	0·20	12·1	61·4	121
	1200	SPST	0·10	14·0	68·7	21
Preferred	1700	ST	0·0053	13·8	73·6	122
FCH_2CH_2Cl	730	S	0·79	13·0	60·0	122
	1600	ST	0·42	12·9	60·8	122
F_2CHCF_2H	1300	SPST	0·014	13·4	70·1	123
	1300	SPST	0·014	13·3	69·4	124
F_3CCF_2H	1300	SPST	0·0082	13·7	72·3	123
FCH_2CH_2F					(62)[e]	125
HCl elimination						
$ClCH_2CH_3$	720	S	13·9	13·5	56·6	122
Cl_2CHCH_3	700	S	20	12·1	49·5	126
	700	S	14	11·7	48·3	100
Preferred	700	S	69	13·5	53·4	127

TABLE 5. (*cont.*)

Reaction	Mean temp. (K)	Method[a]	k_{1000}[b] (s^{-1})	log A[c]	E_a[c] (kcal $mole^{-1}$)	Ref.
Cl_3CCH_3	700	S	147	14·0	54·2	128
	1000	F	162	14·0	54·0	16
$ClCF_2CH_3$	1000	F	37	14·8	60·6	121
Cl_2CFCH_3	1000	F	21	(11·6)	(47)	121
$ClCH_2CH_2Cl$	650	S	[41]	[12·8]	[51·2]	118, 119
	700	S	[1·29]	[11·9]	[54]	115
$ClCH_2CH_2F$	730	S	1·0	13·6	62·3	122
	1600	ST	0·37	13·5	63·8	121
$ClCH_2CH_2CH_3$	700	S	20	13·5	55·1	86
$ClCH_2CHCH_3$ (total)[f]	700	S	66	13·8	54·9	101
|	700	F	26	13·0	53·1	129
Cl	700	S	68	13·8	54·8	130
→ 2-Chloroprop-1-ene	700	F	0·80	(11·5)	(53·1)	129
			0·65	(13·4)[d]	(62·2)[d]	
→ 3-Chloroprop-1-ene	700	F	13	(12·7)	(53·1)	129
	700	S	41	13·4	54	130
→ 1-Chloro-prop-1-ene	700	F	8·1	(12·5)	(53·1)	129
trans	700	S	11	13·3	56·1	130
cis	700	S	15	13·1	54·5	130
$Cl_2CH(CH_3)_2$	650	S	207	(11·9)	(43·9)	131
$Cl_2CHCH_2CH_3$	700	S	42	12·8	51·2	131
	700	S	83	14·3	56·7	132
$Cl_2CHCH_2CH_2CH_3$	700	S	85	13·7	53·9	132
HBr eliminations						
$BrCH_2CH_3$	700	S	53	13·5	53·9	89
$BrCH_2CH_2Br$	700	S	14	13·6[d]	56·3	133
Br_2CHCH_3	700	S	179	13·3	50·6	133
I_2 elimination						
ICH_2CH_2I	500	S		[13·0]	[36·6]	134

[a] ST = shock tube, SPST = single-pulse shock tube, F = flow system, S = static system.

[b] Rate constants calculated for a temperature of 1000K. Where the mean experimental temperature differs by more than ~100°, the extrapolation introduces an additional uncertainty due to the temperature dependence of the Arrhenius parameters, which, however, is usually masked by the experimental error itself.

[c] Data in square brackets are considered unreliable. Values in parentheses are considered to be too low, and the Arrhenius parameters should be scaled up, based on the rate constants at the mean reaction temperature. A in units of s^{-1}.

[d] Estimated preferred value.

[e] Values estimated from chemical activation studies, expected to be reliable to ±3 kcal $mole^{-1}$.

[f] Multiple paths. 'total' refers to the overall rate constants.

for intrinsic comparison of the results and do not represent average rate constants for the mean experimental temperatures $\langle T \rangle$. Where $\langle T \rangle$ differs by more than about 100K from the chosen standard of 1000K, the extrapolation introduces additional uncertainty due to the temperature dependence of the Arrhenius parameters.

The experimental problems are reflected in the fact that rate constants obtained in different laboratories using similar techniques are found to differ in some cases by more than a factor of 20. The largest differences are observed for fluoroalkanes which have mostly been studied using the shock-tube method. The rate constants for 1,1-dichloroethane however, studied in static reaction systems only, also differ by a factor of 3·5. Good agreement between two independent results obtained by using different techniques has been observed for 1,1,1-trichloroethane.

The only case of a four-centre X_2 elimination from an α,β-dihaloalkane was reported for the elimination of iodine from 1,2-diiodoethane[45]. As can be seen from Table 5, the activation energy observed for this process is particularly low.

Polyhaloalkanes have not attracted nearly as much attention as monohalides and it is not possible to present reliable critically selected activation parameters or even preferred rate data in most cases. Where several experimental data have been reported, we have nevertheless indicated preferred values in an attempt to provide internally compatible and comparable data, which, however, do not necessarily agree with our estimates of the most probable values.

The unexpectedly large discrepancies in the rate constants reported for the HF eliminations from 1,1-difluoroethane and 1,1,1-trifluoroethane using either a comparative shock-tube technique[122] or a direct single-pulse shock-tube method[21] cannot be satisfactorily rationalized. Such a large difference would correspond to an apparent error in the temperature measurement, the major problem in these methods, of 250K, which is clearly outside the error limits usually inherent in shock-tube data. Preference has been given to the data based on the comparative shock-tube method, primarily because of the expected reduction of systematic errors in comparative rate studies compared to absolute rate measurements. It should be pointed out, however, that the non-comparative shock-tube method applied to the essentially non-problematic EtCl decomposition[21] yielded data in close agreement with the preferred values for this system, listed in Table 4. While the absolute rate constants and activation parameters are open to question, the relative differences in rates and activation parameters for $C_2F_2H_4$ and $C_2F_3H_3$ obtained from the two methods are in good agreement.

For most reactants only one set of experimental data is available and quantitative comparative deductions must therefore be viewed with caution.

It is interesting to note that there is no experimental evidence for α,α-HX-eliminations even in the most favourable situations such as the pyrolysis of HCF_2CH_3. This pathway has been estimated to involve about 10 kcal mole^{-1} more activation energy than the corresponding four-centre elimination process[135] *.

The concept of a polar four-centre transition state as outlined in the previous section and shown in equation (10) also applies to the related HX eliminations from substituted alkyl halides. In principle α,α-, or α,β-polyhaloalkanes have additional potential secondary reactions involving the C—X bond of the substituted vinyl halide products. If radical reactions initiated by C—X bond fissions can be ruled out in the starting polyhaloalkanes, they are also unimportant in secondary reactions involving the vinyl halides, as the C=C—X bonds are stronger than C—C—X bonds.

Depending on the reactant and the reaction conditions used, however, secondary concerted HX eliminations forming acetylene derivatives may take place. This class of reactions is discussed in section II. B. 1.

Despite the relatively large uncertainties in the data, the entries in Table 5 allow several interesting conclusions to be drawn with regard to the α- and β-halogen substituent effect. For better comparison the pertinent data for the corresponding alkyl halides have also been incorporated in Table 5.

(1) Chlorine, bromine and probably also iodine (for which few data are available) show similar substituent effects, while fluorine substituents affect the rate of HX elimination in a different manner.

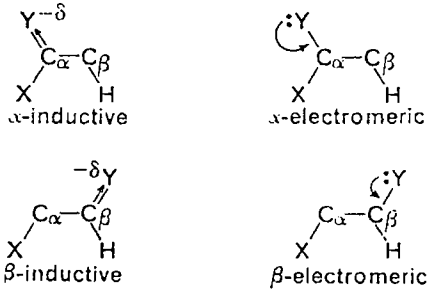
(2) It appears that fluorine atoms bonded to the α-carbon atom significantly lower the rate of elimination, while fluorine in the β-position exercises a similar, but smaller effect.

(3) Chlorine and bromine bonded to the α-carbon increase the rate of elimination with respect to the alkyl halides while β-substitution (as in 1,2-dichloropropane[130] or 1,2-dibromoethane[133]) apparently lowers the reaction rate by about the same amount.

Considering the established heteropolar nature of the reaction it appears reasonable to evaluate the consistency of these conclusions within the well-known concepts of substituent effects derived from liquid-phase studies for ionic reactions. Halogen substituent effects may therefore

* Note added in proof: α,α-HCl elimination has recently been observed[216] from CF_3CH_2Cl (E_a = 65·5, log A = 13·3) competitively with the slower α,β-HF elimination (E_a = 67·6, log A = 12·7).

essentially be divided into: effects on the bond dissociation energy, electromeric or conjugation effects, and electronic or inductive effects. The relative importance of these effects on substituting hydrogens on the α- or β-carbon atom (C_α, C_β) of alkyl halides by halogen atoms (Y) would then be responsible for the observed changes in the rates of HX elimination.



For a highly polar reaction mechanism, electromeric and inductive substituent effects are much more important than effects on the homopolar bond dissociation energy, which to a first approximation can be neglected.

The partial conjugation of the substituents with the positively induced carbon centre (C_α) in the transition state, i.e. the *α-electromeric* effect, is expected to be different for the different halogens. Chlorine, bromine and iodine should support the accommodation of a positive charge on the α-carbon atom through the electromeric release of electrons while no effect is expected for a negative charge. Vicinal α-electromeric effects, i.e. the conjugative effect of a vicinal halogen substituent on a positive charge adjacent to the bonded carbon, are negligible. Fluorine substituents, on the other hand, would be expected to be essentially non-effective in conjugative stabilization of negative or positive charges on adjacent carbon atoms.

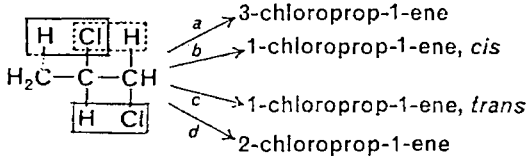
As the electron-affinity of the substituent increases the *α-inductive* effects will become increasingly more positive, i.e. the trend to induce a positive charge on the bonded carbon atom and thereby increase the energy required to break (fully or partially) a C—X bond heterolytically will be promoted. On the basis of the inductive effect only, halogen atoms and in particular fluorine should in general raise the energy required to eliminate HX from α,α-polyhalides.

The effects of halogen substituents (Y) bonded to the negatively induced β-carbon atom are more difficult to visualize. Two *a priori* possibilities are that they might exercise a relatively small stabilizing β-inductive effect on the bonded negative centre, thereby enhancing the rate of elimination, or they might act in the opposite manner via a destabilizing 'secondary' inductive effect on the positive α-carbon centre. For this latter effect to

prevail, the negatively induced charge on the β-carbon atom bonded to the halogen substituent must be inductively non-effective, i.e. essentially small.

Based on the outlined concept of inductive and electromeric effects, the general conclusions drawn from the data listed in Table 5 can be rationalized as follows. Fluorine substituents bonded to the α- or β-carbon atom can essentially only exercise an inductive effect, resulting in a much more pronounced lowering of the rate of elimination in α,α-fluoroalkanes compared to α,β-fluoroalkanes. When chlorine, bromine or iodine is bonded to the α-carbon atom, the enhancement of the rate of HX elimination due to the electromeric effect overrules the inhibitive inductive effect. With halogen substituents bonded to the β-carbon atom (rendering an electromeric effect onto the positively induced charge on the α-carbon atom unlikely), a secondary inductive effect would explain the observed decrease in rates. Fluorine substituents bonded to the β-carbon (in 1-fluoro-2-chloroethane) appear to reduce the rate of HX elimination more significantly than do either chlorine or bromine (1,2-dichloropropane and 1,2-dibromoethane). This again is consistent with fluorine being a more effective positive inductive substituent.

The most reliable information concerning the relative size of these substituent effects is to be expected from intrinsically competitive rates as is the case with 1,2-dichloropropane:



(11)

The relative amounts of 3-chloroprop-1-ene and 1-chloroprop-1-ene at the average reaction temperature of the study[130] have been reported to be 63·6 and 35·6% respectively, or fairly close to the statistical ratio of 3:2. Very little 2-chloro-prop-1-ene is formed.

This can be interpreted in terms of the substituent effects as follows, where C^+ indicates the positively induced and C^- the negatively induced carbon atom in the transition state. In route *a* of equation (11) a stabilizing $ClCH_2—C^+$ and a destabilizing inductive β-Cl—C^+ effect are operative, compared to routes *b* and *c* in which a $CH_3—C^+$ stabilization and a stabilizing but small inductive α-Cl—C^- effect are expected. The fact that the reaction rates for routes *a* and *b* + *c* are approximately equal indicates that the stabilization of the positively induced carbon centre by alkyl substituents dominates the overall substituent effect. In path *d* forming 2-chloroprop-1-ene the combined stabilizing α-Cl—C^+ and $CH_3—C^-$

effects are obviously not as large as the stabilizing effect of a methyl group on a positive charge, $CH_3—C^+$. The quantitative aspects of these stabilization energies will be pursued further in the last section of this review.

c. Radical reactions. The reaction products and mechanistic information obtained from *non-inhibited*, thermal decompositions of alkyl halides initiated homogeneously by C—X or H—X bond fission show all the characteristics of radical-chain reactions in general[34]. Some reaction systems show self-inhibitive or autocatalytic behaviour and induction periods have been observed.

The overall reaction mechanism and the individual steps of the radical-chain decomposition are different for different reactants. The reaction conditions used and, in certain cases, the presence of products from the concurrent molecular reaction path play an important role.

Despite the fact that practically every reaction system may be expected to follow different detailed and overall reaction kinetics, some general features, outlined below, are common to all of these reactions.

(1) For most reactants the radical path is in direct competition with the four-centre molecular elimination step, leading often to the same major products, HX + olefin. In obtaining quantitative information about the radical path, the contribution from the molecular route must be known.

(2) Halogen atoms are practically always the chain-carrying species.

(3) The main product-forming propagation steps involve radical decompositions which are in general governed by the preference for fission of C—Y bonds, where Y = C, H or halogen in β-position to the radical site, to the practical exclusion of all other processes[33]. The relative β-bond dissociation energies in the radicals parallel those observed for the parent molecules listed in Table 1, i.e. the preference for bond breakage decreases in the series C—I > C—Br > C—Cl > C—C > C—H > C—F.

The rate of homogeneous initiation yielding the chain-carrying halogen atoms is determined by the C—X or H—X bond dissociation energies. In the presence of HX, the system may become autocatalytic.

In general C—X bond energies are significantly affected only by substituents in the α-position to the halogen atom. β-Substitution is only effective in cases where extra 'resonance' stabilization is produced in the emergent carbon radical as is the case for allyl- or benzyl-halides (Table 2). In α-alkylpolychlorides, bromides or iodides the C—X bond dissociation energies are about 10 ± 5 kcal mole^{-1} lower than those in the parent alkyl halides, while in the case of polyfluorides, fluorine substitution raises the BDE by about the same amount. The stepwise replacement of α-hydrogens by halogen atoms does not appear to affect the BDE in a similarly consistent manner, as do alkyl- or allyl-substituents (Table 1).

The C—F bond in ethyl- and higher *alkyl fluorides* is the strongest bond in these molecules and homogeneous bond fission of C—C and C—H bonds is more favoured. Hexafluoroethane, for example, breaks thermally into two CF_3 radicals[136]. For alkyl fluorides however, in which four-centre HF elimination is possible, the molecular route is followed[21, 22, 120, 124] to the exclusion of homolytic bond breaking, despite the relatively high activation energies of ~ 73 kcal mole^{-1}. The weakest bond in these compounds is the C—C bond, which is strengthened with respect to the corresponding paraffins by the presence of fluorine.

Contrary to the fluorides, alkyl chlorides, bromides and iodides are, in principle, capable of initiating radical chain decompositions by primary C—X bond fission. In *alkyl chlorides*, both the molecular and radical decompositions usually lead to the dehydrochlorination of the reactant in an overall first-order process yielding the corresponding olefinic products. The molecular reaction path is generally preferred over the radical route in the concurrent non-mixed competitive reaction scheme.

A general scheme for the non-inhibited radical-chain decomposition of alkyl chlorides has been proposed by Barton and coworkers[137]. This is shown below and is discussed in reference 3.

$$CR^1R^2HCR^3R^4Cl \xrightarrow{a} CR^1R^2H\dot{C}R^3R^4 + Cl$$

$$Cl + CR^1R^2HCR^3R^4Cl \xrightarrow{b} {}^{\bullet}CR^1R^2CR^3R^4Cl + HCl$$

$${}^{\bullet}CR^1R^2CR^3R^4Cl \xrightarrow{c} R^1R^2C{=}CR^3R^4 + Cl$$

$$Cl + {}^{\bullet}CR^1R^2CR^3R^4Cl \xrightarrow{d} CR^1R^2ClCR^3R^4Cl$$

The precise course of this mechanism is dependent on the nature of R. If either R^3 or R^4 is hydrogen and R^1 and R^2 do not weaken the C_β—H bond, then radical attack will occur mainly at the α-carbon site and step *c* will not occur[3].

In primary and secondary monochloroalkanes the radical pathway is disfavoured with respect to the molecular elimination of HCl. In tertiary monochloroalkanes, radical routes are competitive.

The product olefins are inhibitors while the addition of chlorine, oxygen or HCl [115] enhances the rate. In general, however, HCl does not appear to undergo further reaction, in contrast to HBr, which leads to autocatalytic behaviour in the case of alkyl bromides. Due to the fact that β-chlorine substituents lower the rate of the concerted HCl elimination, and favour β-abstraction, the radical decomposition path becomes more important in 1,2-dichloroalkanes[115] compared to monochloroalkanes (Table 4) or 1,1-dichloroalkanes[132].

Holbrook and coworkers[115] in a careful study of the surface effects in the radical decomposition of 1,2-dichloroethane observed for low surface to volume ratios ($\sim 1{\cdot}3$) a much higher overall *initial* reaction order (2·4–2·8) than earlier studies, which reported overall first-order behaviour[126] for *maximum* rates of pyrolysis. The activation energy observed using static reactors (coated with pyrolytic carbon films) with high surface to volume ratios (~ 37) was only 33 kcal mole^{-1} compared to 73 kcal mole^{-1} in a low surface to volume vessel. The above chain mechanism was extended to include heterogeneous reaction paths.

The radical pathways in *alkyl bromide* pyrolyses well illustrate the complexities of radical reactions. In general it would appear that C—Br fission is not an important initiation step in these systems, but that HBr formed in the molecular four-centre elimination reaction is the source of the chain-carrying bromine atoms.

The variety of behaviour in alkyl bromide pyrolyses is best illustrated with a few selected specific examples of reaction schemes.

Ethyl bromide, in contrast to ethyl chloride, decomposes by a concurrent *mixed* radical-chain and molecular reaction path. Earlier reports of the uninhibited pyrolysis claimed first-order behaviour with $\log A = 11{\cdot}8$ and $E_a = 46{\cdot}4$ kcal mole^{-1}[88] while later studies[85] revealed an order of 3/2. Ethylene and HBr are the major reaction products and the following overall reaction scheme has been proposed[88]:

$$C_2H_5Br \xrightarrow{a} C_2H_4 + HBr$$

$$C_2H_5Br + HBr\,(wall) \xrightarrow{b} C_2H_6 + Br_2$$

$$Br_2 + M \rightleftarrows 2\,Br + M$$

$$Br + C_2H_5Br \xrightarrow{c} {}^{\bullet}CH_2CH_2Br$$

$${}^{\bullet}CH_2CH_2Br \xrightarrow{d} C_2H_4 + Br$$

$$Br + C_2H_4 \xrightarrow{e} C_2H_3^{\bullet} + HBr$$

$$Br + C_2H_6 \xrightarrow{f} C_2H_5^{\bullet} + HBr$$

$$C_2H_3^{\bullet} + wall \xrightarrow{g} C + CH_3^{\bullet}$$

$$CH_3^{\bullet} + C_2H_5^{\bullet} \xrightarrow{h} C_3H_8$$

$$2\,C_2H_5^{\bullet} \xrightarrow{i} C_4H_{10}$$

It should be pointed out that reaction step *c* involves the formation of the β-carbon radical. Considering that the α-C—H bond is weaker than the β-C—H bond this step can only prevail because of the high endothermicity (~35 kcal mole^{-1}) for the step *j*, involving the preferred α-carbon radical.

$$CH_3\dot{C}HBr \xrightarrow{j} CH_2{=}CHBr + H^{\bullet}$$

Reaction steps *e* and *g* are likely to occur on the walls. The actual mechanism is expected to be even more complicated if reactions such as:

$$C_2H_5^{\bullet} + Br \longrightarrow HBr + C_2H_4$$

$$C_2H_5^{\bullet} + C_2H_5Br \longrightarrow C_2H_6 + \dot{C}H_2CH_2Br$$

$$2\,C_2H_5^{\bullet} \longrightarrow C_2H_4 + C_2H_6$$

etc. are incorporated.

For *n*-propyl bromide the initial reaction was reported to follow second-order overall kinetics[96] with $A = 10^{15.1}$ (l mole^{-1} s^{-1}) and $E_a = 49{\cdot}3$ kcal mole^{-1}. The following reaction scheme was proposed:

$$CH_3CH_2CH_2Br \xrightarrow{a} CH_3CH{=}CH_2 + HBr$$

$$CH_3CH_2CH_2Br + HBr \xrightarrow{b} C_3H_8 + 2\,Br$$

$$Br + CH_3CH_2CH_2Br \xrightarrow{c} CH_3CH_2\dot{C}HBr + HBr$$

$$CH_3CH_2\dot{C}HBr + CH_3CH_2CH_2Br \xrightarrow{d} CH_3CH_2CH_2Br + CH_3\dot{C}HCH_2Br$$

$$CH_3\dot{C}HCH_2Br \xrightarrow{e} CH_3CH{=}CH_2 + Br$$

$$Br + CH_3CH{=}CH_2 \xrightarrow{f} HBr + {}^{\bullet}CH_2CH{=}CH_2$$

$$Br + {}^{\bullet}CH_2CH{=}CH_2 \longrightarrow BrCH_2CH{=}CH_2$$

$$Br + Br + M \rightleftharpoons Br_2 + M$$

The reaction mechanism *b* has not been specified, and the relative significance of various steps depends on the conditions and stage of reaction[3]. With large amounts of HBr, the reaction was first-order in $CH_3CH_2CH_2Br$ and about half-order in HBr.

1-Bromo-2-chloroethane decomposes via a radical-chain mechanism[138] outlined below, with little or no contribution from a molecular reaction path, which is disfavoured by the β-Cl substituent.

$$CH_2BrCH_2Cl \xrightarrow{a} {}^{\bullet}CH_2CH_2Cl + Br$$

$$Br + CH_2BrCH_2Cl \xrightarrow{b} CH_2Br\dot{C}HCl + HBr$$

$$Br + CH_2BrCH_2Cl \xrightarrow{c} {}^{\bullet}CHBrCH_2Cl + HBr$$

$$CH_2Br\dot{C}HCl \xrightarrow{d} CH_2{=}CHCl + Br$$

$$CH_2Cl\dot{C}HBr \xrightarrow{e} CH_2{=}CHBr + Cl$$

$$Br + {}^{\bullet}CHBrCH_2Cl \xrightarrow{f} \text{termination products}$$

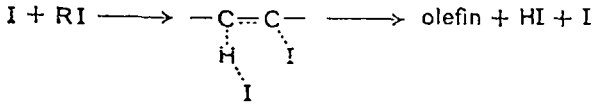
$$Br + Br + M \underset{}{\overset{g}{\rightleftharpoons}} Br_2 + M$$

$$2\,CH_2Br\dot{C}HCl \xrightarrow{h} \text{termination products}$$

Reaction step b is slightly faster than c and $d \gg e$. In the early stages of the reaction ${}^{\bullet}CHBrCH_2Cl$ is accumulated favouring termination via f and the initial overall rate law is predicted to show first-order kinetics in reactant and half-order in HBr. At high concentrations of HBr, which is apparently stable under the conditions of the study, the reaction has been observed to follow half-order kinetics in reactant and zero-order in HBr. The concentration of the ${}^{\bullet}CHBrCH_2Cl$ radical is depressed by the reverse reaction $-c$ and termination via h obviously becomes important, as this is the only termination step leading to the observed half-order in reactant and zero-order in HBr. For the half-order reaction the observed overall rate constants yielded $A = 9{\cdot}3 \times 10^9$ mole$^{-\frac{1}{2}}$ l$^{\frac{1}{2}}$ s^{-1} and $E_a = 40{\cdot}8$ kcal mole^{-1}. The insertion of the appropriate kinetic parameters for the basic reaction steps a–h gives poor agreement between observed (k_{obs}) and predicted (k_{pred}) rate constants, with $k_{pred} \approx 10^3 k_{obs}$. The precise mechanism still remains unclear and surface effects may play an important role.

Radical reactions *initiated* by fission of the relatively weak C—I bond are unimportant in the non-inhibited pyrolysis of *alkyl iodides*, which have been comprehensively treated by Benson and coworkers[80]. The addition of iodine atoms to olefins is endothermic by about 6 kcal mole^{-1} and therefore a radical mechanism has been considered unlikely. As mentioned in Chapter 2, section A. 2. b, dealing with the molecular reaction paths, the pyrolysis of alkyl iodides is effectively rate-controlled by the elimination of HI either via a direct four-centre route (1) or via an iodine-atom-catalysed

path (2). The I-catalysed path has been suggested to prevail for *n*-PrI, *n*-BuI and *i*-BuI, while *s*-BuI, 1,2-diiodoethylene and 1,2-diiodoethane appear to involve reaction paths (1) and (2) concurrently. For the iodine-atom-catalysed route a concerted mechanism as shown in equation (12) has been proposed rather than a two-step abstraction reaction.



(12)

Whether an alkyl iodide decomposes according to the molecular route or the iodine-atom-catalysed path can essentially be rationalized on the basis of the strength of the attacked C—H bond. The dehydroiodination of alkyl halides is followed by the rapid overall reaction

$$RI + HI \rightleftharpoons RH + I_2$$

resulting from the simple mechanism

$$RI + I \rightleftharpoons R^{\bullet} + I_2$$

$$R^{\bullet} + HI \rightleftharpoons RH + I$$

with the equilibrium

$$I_2 + M \rightleftharpoons 2I + M$$

superimposed, whereby it is assumed that the reaction steps

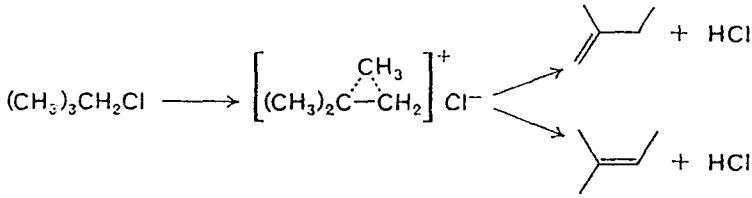
$$RI \longrightarrow R^{\bullet} + I$$

$$R^{\bullet} + RI \longrightarrow RH + R^{\bullet}I$$

can be neglected. The contribution from a competing initiation via C—I bond breakage is expected to be significant only with substituents introducing extra 'resonance' stabilization in the hydrocarbon radical (Table 1) but small contributions from C—I fission cannot be ruled out. Evidence has been presented for C—I bond cleavage, concurrent with the molecular elimination, in the pyrolysis of ethyl iodide using a toluene carrier technique[90].

d. Neopentylchloride. The unique structural feature of neopentyl halides from a mechanistic point of view is the absence of C—H bonds in β-position to the halogen atom, making a four-centre HX elimination impossible. Neopentyl chloride decomposes by an apparently homogeneous process, yielding methylbutenes and HCl as major products, for which both

a molecular[139] and a radical[140] pathway have been suggested. A Wagner–Meerwein shift involving the prior formation of an intermediate ion pair as shown in equation (13) was proposed[139] to account for the molecular elimination of HCl, yielding methylbutenes.



(13)

The most complete study of this system was reported by Shapiro and Swinbourne[141,142] who suggested a complex overall mechanism involving concurrent concerted unimolecular and radical chain paths, the former amounting to between 30 and 40% of the overall conversion observed. The authors claim that the molecular reaction path[141] produces only 2-methylbut-1-ene and 2-methylbut-2-ene, while 3-methylbut-1-ene is assumed to be a secondary product from the HCl-catalysed isomerization of the other isomers. 1,1-Dimethylcyclopropane, another important product of the reaction, was not considered to be formed by a direct molecular elimination of HCl despite the fact that inhibitors did not suppress its formation completely. HCl was observed to accelerate the formation of all products.

For the presumably molecular first-order process, reasonable Arrhenius parameters (log $A = 13{\cdot}26$, $E_a = 60{\cdot}0$ kcal mole^{-1}) were reported. The major products observed from the *radical-chain* reaction were HCl, methane, isobutene, methylchloride, 1-chloro-2-methylpropene and apparently 1,1-dimethylcyclopropane. 3-Chloro-2-methylpropene, another likely product, was not detected as it polymerizes under the reaction conditions used. The overall order of the proposed complex 10-step radical-chain reaction is 3/2 with log $A = 13{\cdot}6$ and $E_a = 56{\cdot}3$ kcal mole^{-1}. Surface problems were apparent, but pyrolytic coatings were claimed to have little effect on the primary step.

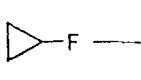
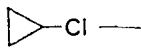
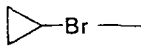
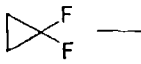
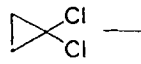
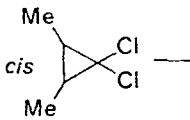
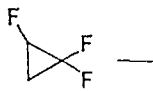
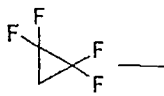
The question of the origin of 1,1-dimethylcyclopropane is of crucial mechanistic importance. Accepting the authors' claim, that a molecular homogeneous route is operative and that nearly all of the 1,1-dimethyl-cyclopropane is formed in a radical-chain process, then it would appear necessary to invoke a methyl shift to explain the products from the concerted reaction. While the formation of truly ionic species in the gas phase is considered highly unlikely a Wagner–Meerwein shift might be possible in an incipient ion pair.

3. Cycloalkane derivatives

a. Cyclopropyl halides. The pyrolysis of cyclopropyl halides has been the subject of several recent kinetic and mechanistic studies and the kinetic data are summarized in Table 6.

Perfluorocyclopropane[148] has been shown to undergo exclusive expulsion of difluorocarbene on pyrolysis. An attempt has been made to rationalize

TABLE 6. Arrhenius parameters for the unimolecular isomerization of cyclopropyl halides to alkene halides

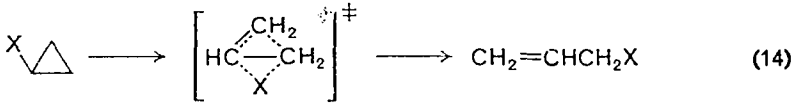
Reaction	log A^a	E_a (kcal mole^{-1})	Reference
 → $FCH{=}CHCH_3$ (79%), $CH_2{=}CFCH_3$ (9%), $CH_2{=}CHCH_2F$ (11%)	14·6	61	143
 → $CH_2{=}CHCH_2Cl$	14·8	56·2	144
 → $CH_2{=}CHCH_2Br$ ↓ $BrCH{=}CHCH_3$	13·5	47·3	144
 → Difluoropropenes	14·1	56·4	145
 → $CH_2{=}CClCH_2Cl$	15·1	57·8	146
 → $CH_3CHClCCl{=}CHCH_3$ (*trans only*)	13·7	44·6	147
 → Trifluoropropenes	14·4	50·5	145
 → Tetrafluoropropenes	15·3	48·5	145

[a] A in units of s^{-1}.

the results for the other fluorinated cyclopropanes on the basis of a biradical mechanism[149] identical to that involved in the isomerizations of alkylcyclopropanes. The differences in activation energy were attributed to the increase in ring strain by fluorine substitution.

The validity of the results for polyfluorinated cyclopropanes has been questioned[146] on the basis of results from chemical activation studies[150] which indicate that the expulsion of difluorocarbene with consequent formation of ethylene compounds should be at least competitive with the proposed biradical reactions. Calculations based on the carbene pathway agree equally well with the experimental parameters. In conclusion it appears unlikely that the thermal reactions of fluorinated cyclopropanes involve a carbon–halogen bond cleavage.

The decompositions of chloro- and bromocyclopropanes, which yield exclusively 3-halopropene as primary product, have been rationalized in terms of a process involving a 1–2-halogen transfer with simultaneous cleavage of the C—C bond opposite to the halogen-substituted carbon atom.



(14)

This concept is further substantiated by the fact that 2,3-dichloropropene is the sole product from the pyrolysis of 1,1-dichlorocyclopropane, and by the product specificity in the thermal reactions of several substituted 1,1-dichlorocyclopropanes[151]. The large increase in the rate of thermal isomerization of *cis*-2,3-dimethyl-1,1-dichlorocyclopropane[147] compared to 1,1-dichlorocyclopropane itself and the stereospecificity of the former reaction have been rationalized on the basis of an ion-pair transition state in which the cyclopropyl cation isomerizes to the allyl cation by a Woodward–Hoffmann allowed disrotatory process. A similar mechanism for 1,1-dichlorocyclopropanes was postulated on the basis of pyrolysis studies over calcium oxide[152] but complete separation into an ion pair was not proposed. While a complete heterolytic bond cleavage in the gas phase at these temperatures can be ruled out, the assumption of the formation and isomerization of an *emergent* cyclopropyl cation may be a valid concept.

It is almost certain that the chlorine- and bromine-substituted cyclopropanes react by the same mechanism but the *A*-factors in Table 6 vary from $10^{13.5}$–$10^{15.3}$. Such a wide variation is difficult to rationalize on the basis of the proposed four-centre polar pathway. *A*-factors of about $10^{14.5}$ would appear to be reasonable for the proposed transition state and

experimental artifacts may account for some of the observed differences. However, the precise pathway of the transformation cannot be regarded as established.

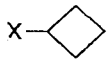
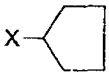
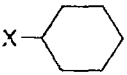
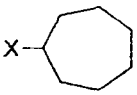
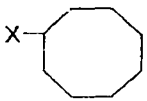
b. Higher cycloalkyl halides. While there is no evidence for hydrogen halide elimination as a primary reaction in the pyrolysis of cyclopropyl halides, this reaction is the sole molecular process involving carbon–halogen bond breakage in the higher cycloalkyl halides, and a list of gas-phase Arrhenius parameters is presented in Table 7.

Cyclobutyl chloride reacts by two pathways[155], one a normal cyclobutane fission process into ethylene and vinyl chloride and the other an elimination of hydrogen chloride to yield butadiene as the observed product. There are two possible mechanisms for the hydrogen chloride elimination, a direct Woodward–Hoffmann allowed process and a polar four-centre elimination to form cyclobutene, which at the temperatures of the study isomerizes immediately to butadiene. The Arrhenius parameters appear to be more in accord with the latter mechanism in which increased bond distortion and ring strain in the transition state can account for the high activation energy. (Such a preference for a polar route over a non-polar Woodward–Hoffmann allowed process is also evident in the reactions of ketene with dienes[68,164].)

The thermal decomposition products of the other monocycloalkyl halides are cycloalkenes. The rates of elimination for the cyclopentyl[154–157] and cyclohexyl[154,155,158] halides are very close to those expected for 3-halopentanes whereas the rates for cycloheptyl-[159,155] and cyclooctyl-[159,155] halides are significantly faster. The preferred parameters for all these reactions are compatible with a polar four-centre transition state and the rates for the chloro-compounds correlate with the differences in ring strain between the cycloalkenes and cycloalkanes[155]. The magnitudes of these differences are just sufficient to account for the observed rate variation, but it is unlikely that the full strain energy effects are realized in the transition state. It is, therefore, likely that other factors affecting the motions necessary to bring the hydrogen and chlorine atoms to the transition state configuration also contribute to the differences in energetics observed in the cycloalkyl halide series.

The Arrhenius parameters for the hydrogen chloride eliminations from menthyl chloride[160,161] and neomenthyl chloride[160] are too low. The observed mid-temperature rate constants could, however, be rationalized with a polar four-centre transition state. The formation of *p*-menth-3-ene in addition to *p*-menth-2-ene from neomenthyl chloride requires a *trans*-elimination and the presence of a greatly extended carbon–chlorine bond has been suggested to account for this[160]. However, a heterogeneous

TABLE 7. The four-centre unimolecular elimination of HX from cycloalkyl monohalides[a]

	Chlorides			Bromides		
	log A	E_a	Ref.	log A	E_a	Ref.
	13·6	55·2	153			
	13·5	48·3	154	11·9	41·4	156
Preferred	*13·4*	*48·6*	155	*12·8*	*43·7*	157
	13·9	50·3	155			
Preferred	*13·5*	*49·2*	154	*13·5*	*46·1*	158
	12·0	43·6	159			
Preferred	*13·9*	*47·3*	155			
	11·9	42·4	159			
Preferred	*12·0*	*42·6*	155			
Menthyl-X[b]	11·8	42·1	160			
	12·6	45·0	161			
Neomenthyl-X[c]	10·7	40·1	160			
Bornyl-X[d]	14·0	50·6	162			
Isobornyl-X[e]	14·8	49·7	163			

[a] E_a in kcal mole^{-1}, A in s^{-1}.
[b] Products are *p*-menth-2-ene and *p*-menth-3-ene in the ratio 1 : 3.
[c] Products are as in *b* with the ratio 5·7 : 1.
[d] Products are tricyclene, camphene and bornene.
[e] Products are camphene and bornene.

component of the primary reaction or heterogeneous product rearrangement appears to be a more likely explanation. The 2- and 3-menthenes formed in the pyrolysis of (−)menthyl chloride were essentially unracemized, indicating that a complete ionic separation did not occur.

The presence of tricyclene and camphene as products in the pyrolysis of bornyl[162] and isobornyl[163] chlorides, in addition to the expected 2-bornene, has been rationalized on the basis of rearrangements in a carbonium ion intermediate. While the presence of carbonium ions in the gas phase is unlikely at the temperatures of these studies, emergent carbonium ions as an extreme form of highly polar transition state complexes may be a possibility. It is again possible that heterogeneous processes are responsible for the additional products.

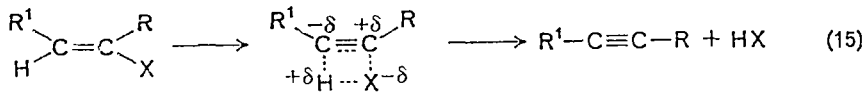
Doubt has also been cast on the validity of this work by the reported rapid retrodiene decomposition of bornene at the temperature of the HCl elimination studies[165].

B. Vinyl, Allyl, Benzyl and Aryl Halides

Grouping according to the character of C—X bonds logically leads to a division of unsaturated halohydrocarbons into vinyl halides, allyl and benzyl halides and aromatic halides. As observed for saturated haloalkanes, the pyrolysis of unsaturated halogenated hydrocarbons may involve both radical or molecular reaction paths, depending on the C—X bond strength and the availability of feasible concerted reaction routes for these systems. The particular structure of olefinic compounds, however, opens new routes involving the π-electrons in multicentre delocalized transition state complexes.

1. Vinyl halides

Only a few studies on the thermal decomposition of vinyl halides have been reported and these indicate a preference for molecular reaction paths to the exclusion of radical reactions. This is a logical consequence of the large increase in the C=C—X bond strength in vinyl compounds compared to C—C—X in the parent alkyl, while at the same time the activation energies for the four-centre elimination, shown in equation (15), are much less affected when compared with those observed for the alkyl halides.



(15)

The rates of eliminating HX from vinyl halides are usually much slower than those observed for the corresponding saturated alkyl halides. Vinyl halides formed in the four-centre elimination process from α,α- or α,β-polyhaloalkanes are therefore, in general, thermally stable under the reaction conditions used. In the pyrolysis of 1,1,1-trifluoroethane[21], the

second step, the elimination of HF from 1,1-difluoroethylene, is indeed not competitive, while in the case of 1,1-difluoroethane[120] the secondary elimination products, acetylene and HF, were observed. These differences can readily be rationalized on the basis of the large inductive effects exercised by fluorine substituents and outlined in section II. A. 2. b.

Reliable experimentally based C=C—X bond dissociation energies cannot be derived from available literature data, and therefore no data have been entered in Table 1. The (C=C—X) BDE can be estimated from the corresponding bond dissociation energies in the phenyl compounds listed in Table 1, reducing the values by about 3 kcal mole^{-1}. For vinyl iodide this would result in BDE(C=C—I) $\approx 64-3=61$. The quantitative data observed for the decomposition of vinyl halides are summarized in Table 8.

TABLE 8. Thermal decomposition of vinyl halides

Reaction	log A	E_a (kcal mole^{-1})	Reference
$CH_2CHF \rightarrow C_2H_2 + HF$	14·0[a]	70·8	166
$CH_2CF_2 \rightarrow C_2HF + HF$	14·4[a]	86·0	167
$CHICHI \rightarrow C_2H_2 + I_2$ (molecular)	12·6[a]	46·0	168
$CHICHI \rightarrow C_2H_2 + I_2$ (I-atom-catalysed second-order)	11·8[b]	23·0	168

[a] A in units of s^{-1}.
[b] A in units of 1 mole^{-1} s^{-1}.

The data for vinyl fluoride have been obtained using the single-pulse shock-tube method, while the pyrolysis of 1,2-diiodoethylene was studied spectrophotometrically using a static reaction system. The thermal decomposition of $C_2H_2I_2$ yielding I_2+ acetylene has been rationalized with a concurrent 'normal' four-centre unimolecular I_2 elimination and an iodine-atom-catalysed I_2 elimination, similar to that postulated for 1,2-diiodoethane[45]. The kinetics are further complicated by the fact that the 'normal' homogeneous concerted route, shown in Table 8, must be separated from a heterogeneous component. It has been suggested that the iodine-atom-catalysed path involves a π complex.

2. Allyl and benzyl halides and related compounds

a. Four-centre HX eliminations. Substituted allyl or benzyl halides undergo 'normal' four-centre HX elimination reactions if a β-hydrogen atom attached to a saturated carbon centre is available. In Table 9

TABLE 9. Arrhenius parameters for the unimolecular four-centre elimination of HX from unsaturated, allyl and substituted benzyl halides[a]

RX	Cl			Br		
	log A	E_a	Ref.	log A	E_a	Ref.
$X-CH_2CH_2CH=CH_2$	13·7	55·0	169			
$X-\underset{\displaystyle CH_3}{\underset{\vert}{C}}HCH_2CH=CH_2$				12·9 13·7[b]	44·7 47·0[b]	89 16
$X-\underset{\displaystyle CH_3}{\underset{\vert}{C}}HCH=CH_2$	13·4	48·5	170			
$X-\underset{\displaystyle H_3C\quad CH_3}{\underset{\diagup\quad\diagdown}{C}}CH=CH_2$	13·3	42·6	171			
$X-\underset{\displaystyle CH_3}{\underset{\vert}{C}}HC_6H_5$	12·6	44·9	172	12·2	38·8	173

[a] E_a in kcal mole^{-1}, A in s^{-1}.
[b] Estimated values.

Arrhenius parameters are listed for the unimolecular concerted HX elimination observed for chlorides and bromides. Data for substituted allyl or benzyl iodides or fluorides have not been reported.

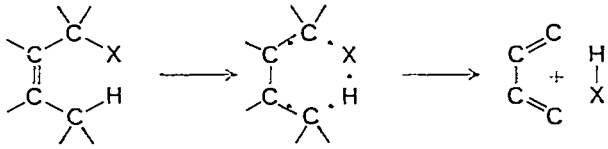
Compared with the data listed in Table 4 it becomes apparent that allyl substituents attached to the carbon centre carrying a positively induced charge in the transition state (compare equation 10) lower the activation energy for the elimination step more than alkyl substituents. When bonded to the carbon atom carrying the negatively induced charge in the transition state, about the same stabilizing effect is observed as with alkyl substituents.

The reported A-factor for 4-bromo-but-1-ene appears to be too low compared with the values for the other allyl halides and the estimated values based on a transition-state calculation of the pre-exponential factor are to be preferred. The low A-factor observed for 1-chloro-1-phenylethane is reasonable if 'stiffening' of the benzyl rotor is assumed. The A-factor for the bromo-compound should be identical and, making this correction, a value of 39·8 kcal mole^{-1} is obtained for the activation energy. From these results, it would appear that the effect of a phenyl group is more marked in the case of the bromo-compound. For both chloro- and bromo-compounds, the stabilizing effect of phenyl on a positive centre is greater than

that of allyl. This is in agreement with observations of substituent effects in liquid-phase carbonium ion chemistry.

The quantitative aspects of these stabilization energies will be pursued further in section III.

b. Six-centre eliminations of HX. Cisoid allyl halide structures of the type shown in equation (16) eliminate HX via a six-centre transition state



(16)

complex. This type of reaction has been reported[171] for the systems discussed below.

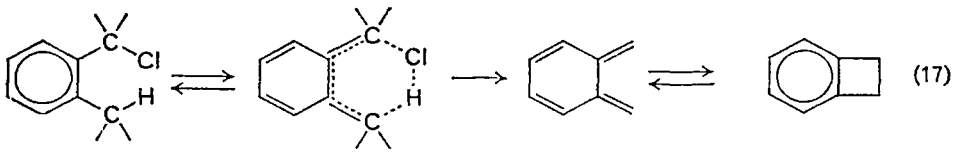
1-*chloro*-3-*methylbut*-2-*ene* yields isoprene in a first-order process, for which a pre-exponential factor of 10^{12} and an activation energy of 38·3 kcal mole^{-1} have been reported. The low value for the *A*-factor is in line with predictions[69] based on the loss of rotational entropy in forming the cyclic transition state complex. The interconversion of 1-chloro-3-methyl-but-2-ene and 3-chloro-3-methyl-but-1-ene, presumably proceeding via a 1,3-chlorine shift, has also been observed in this system. The isomerization proceeds, however, at a slower rate than the six-centre HX elimination process.

Cis-1-*chlorobut*-2-*ene* undergoes a six-centre HX elimination at a rate about 10 times faster than that observed for the corresponding four-centre HX elimination from 3-chloro-but-1-ene.

For *cis*-2-*chloropent*-3-*ene*, another example in this series, the same authors reported the six-centre HX elimination, forming penta-1,3-diene, to be about 100 times faster than was observed for 2-chloro-pent-3-ene, which involves a four-centre mechanism.

The elimination of HI from *cis*-1-*iodobut*-2-*ene* has also been observed[174] to follow a six-centre reaction path.

From a mechanistic point of view, another particularly interesting reaction following the general scheme outlined in equation (16) is the formation of benzocyclobutene from α-chloro-*o*-xylene[175] (= *o*-xylyl-chloride) shown in equation (17).



(17)

The reported first-order activation parameters[175] (log $A = 11{\cdot}5$ and $E_a = 47$ kcal mole^{-1}) are consistent with a six-centre mechanism. The activation energy is about 10 kcal mole^{-1} higher than for the substituted allyl chlorides[171]. It is most interesting to note that the corresponding α-bromo-*o*-xylene[176] undergoes C—Br bond fission into radicals with an activation energy of 54 kcal mole^{-1} rather than the intramolecular elimination via (17). Assuming the same molecular activation parameters for the bromo- and chloro-compounds, the differences in pre-exponential factors between the concerted and the radical routes would be expected to compensate for the activation energies. A lower activation energy would be expected, however, for the six-centre elimination of HBr. This casts some doubts on the proposed[176] exclusive radical path for *o*-xylyl-bromide.

c. Radical reactions. As discussed in the introductory section and apparent from the entries in Tables 1 and 2, the homopolar dissociation energies of allyl—X and benzyl—X bonds are about 13 kcal mole^{-1} lower than those for the corresponding alkyl—X and cycloalkyl—X bonds. In principle this would facilitate radical-chain decompositions initiated homogeneously by the fission of C—X bonds, were it not for the fact that alkyl and benzyl substituents also enhance the competitive four-centre HX elimination rate. Substituted allyl and benzyl halides generally prefer molecular decomposition routes over radical pathways. In the case of the *parent* allyl and benzyl halides however, neither the four- nor the six-centre HX-elimination paths are structurally possible. These reactants then decompose via complex radical-chain mechanisms, involving the lethargic allyl or benzyl radicals. A variety of products are formed, including carbonaceous or tar deposits.

In the pyrolysis of *allyl chloride*[177], biallyl is the major product observed at temperatures from 540–580°C. Within a middle temperature range of 600–630°C cyclohexa-1,3-diene is dominant and at temperatures > 630°C benzene is the main product[177]. The following mechanism has been proposed[177,178].

$$C_3H_5Cl \xrightarrow{a} C_3H_5^{\bullet} + Cl$$

$$Cl + C_3H_5Cl \xrightarrow{b} C_3H_4Cl^{\bullet} + HCl$$

$$2\,C_3H_5^{\bullet} \rightleftharpoons (C_3H_5)_2$$

$$2\,C_3H_4Cl^{\bullet} \xrightarrow{d} C_6H_6 + HCl$$

$$C_3H_5^{\bullet} + C_3H_4Cl^{\bullet} \xrightarrow{e} C_6H_8 + HCl$$

$$C_6H_8 \xrightarrow{f} C_6H_6 + H_2$$

$$C_3H_5^{\bullet} + RH \xrightarrow{g} C_3H_6 + R^{\bullet}$$

The actual mechanism is probably more complicated. Reaction step *f* is a radical-chain rather than a molecular process[179], which is substantiated by the observation of cyclohexene as product. Earlier suggestions[180] that the primary reaction involves the elimination of HCl yielding allene are only valid for heterogeneous reactions.

A similar mechanism applies to the pyrolysis of *allyl bromide*[181], for which an overall first-order activation energy of 45·5 kcal mole^{-1} and an *A*-factor of $10^{12\cdot3}$ were reported. Both these values are too low to be equated with the initial bond-breaking step.

For *allyl iodide*, which yields I_2, biallyl and cyclohexene, an iodine-atom-catalysed decomposition has been suggested[80].

$$I + C_3H_5I \longrightarrow C_3H_5^{\bullet} + I_2 \quad \text{(equilibrium)}$$

$$C_3H_5^{\bullet} + C_3H_5I \longrightarrow (C_3H_5)_2 + I \quad \text{(slow)}$$

$$2\,C_3H_5^{\bullet} \longrightarrow (C_3H_5)_2 \quad \text{(slow)}$$

$$I_2 + (C_3H_5)_2 \longrightarrow \text{cyclohexene} + I_2$$

Due to the particularly stable benzyl radical, benzyliodide gives bibenzyl and I_2 in a simple iodine-atom-catalysed process[80].

$$I + C_6H_5CH_2I \longrightarrow I_2 + C_6H_5CH_2^{\bullet} \quad \text{(equilibrium)}$$

$$2\,C_6H_5CH_2^{\bullet} \longrightarrow (C_6H_5CH_2)_2 \quad \text{(slow)}$$

Under kinetically controlled conditions, *benzotrifluoride* breaks exclusively the C—C bond[182], with a dissociation energy of about 104 kcal mole^{-1}, even though the $C_6H_5CF_2$—F bond is about 13 kcal mole^{-1} weaker than the parent CH_3CF_2—F bond. The C—F bond dissociation energy in benzotrifluoride is not known, but for benzylfluoride $C_6H_5CH_2$—F has been estimated at 94 kcal mole^{-1} (Table 1). This then implies a destabilizing effect of the two additional α-fluorine substituents onto the $C_6H_5CF_2$—F bond of > 10 kcal mole^{-1}.

The toluene-carrier technique has been used to obtain activation parameters for the initial C—X bond fission process for a number of benzyl chlorides and benzyl bromides. These data are summarized in Table 10.

The reported Arrhenius parameters are certainly too low, due to the experimental shortcomings inherent in the toluene-carrier technique discussed in the introductory section. The rates observed for the middle temperature of the study are, however, considered reliable. The activation energies listed in Table 10 have been calculated from these mid-temperature rates, assuming 'reasonable' *A*-factors. These 'corrected' activation energies are in reasonable agreement with the bond-dissociation energies

TABLE 10. Homolytic C—X bond fission in benzylhalides

Compound	log A^a	$E_a{}^a$	Relative rate at 800K	Reference
Benzylchloride	14·8	68·0	$1{\cdot}1 \times 10^{-3}$	183
Benzylbromide	14·5	56·1	1·0	184
o-Chlorobenzylbromide	14·5	54·5	2·3	176
m-Chlorobenzylbromide	14·5	55·9	1·1	176
p-Chlorobenzylbromide	14·5	55·7	1·3	176
m-Bromobenzylbromide	14·5	54·5	2·3	176
p-Bromobenzylbromide	14·5	54·5	2·3	176
o-Xylylbromide	14·5	53·9	4·0	176
m-Xylylbromide	14·5	56·0	1·1	176
p-Xylylbromide	14·5	55·9	1·1	185
ω,ω'-Dibromo-*p*-xylene	14·8	55·9	2·2	185
m-Nitrosobenzylbromide	14·5	53·8	4·2	176
p-Nitrosobenzylbromide	14·5	54·9	2·1	176
m-Cyanobenzylbromide	14·5	54·5	2·3	176
p-Cyanobenzylbromide	14·5	55·2	1·8	176

[a] Arrhenius parameters reported in references 176, 183–185 are low due to experimental artifacts. Rates in the middle of the temperature ranges studied are probably reliable. As reaction enthalpies are subject to large uncertainties, 'reasonable' *A*-factors have been assumed and activation energies calculated from mid-temperature rates.

listed in Table 1. The observed increase in rates for the *ortho*-compounds is probably due to steric factors. With electron-donating substituents one would also expect a slight increase in rates with *ortho*- and *para*-substitution due to the electromeric effect. The increase in rate with *meta*-substitution however, appears to be more difficult to rationalize. A small steric effect may be involved.

3. Aromatic halides

The predominant mode of thermal decomposition of aromatic halides appears to involve a chain mechanism initiated by carbon–halogen bond cleavage. For chlorobenzene, a minor pathway involving the four-centre elimination of hydrogen chloride with the formation of benzyne has been proposed[186]. The heat of formation of benzyne as determined from ionization potential studies[187] is 118 kcal mole^{-1}. From this value, the heat of reaction for the formation of benzyne from chloro- and bromobenzene is calculated to be about 84 kcal mole^{-1} in both cases. This also corresponds to the minimum value for the activation energy and comparison of this figure with the BDE values in Table 1 indicates that while this pathway

may occur to some extent in chlorobenzene pyrolysis, it is most unlikely to occur in the pyrolysis reactions of aromatic bromides.

The overall radical reaction mechanisms in the pyrolyses of aromatic halides have not been extensively investigated. The radical decomposition of chlorobenzene[188] yields hydrogen chloride, hydrogen, *p,p'*-dichlorodiphenyl and polymer. The rate constants observed showed a discontinuity in the Arrhenius plot and the authors postulated that two mechanisms were operative but could not establish the chemical process involved. The reaction is obviously very complex and probably has a large heterogeneous component.

The initial bond-fission step in the pyrolysis of a number of aromatic bromides has been studied by Szwarc and coworkers using the toluene-carrier technique[189,190]. The reported Arrhenius parameters are certainly too low, due to experimental artifacts, but the rates in the middle of the temperature range are probably reliable. Based on these mid-temperature rates and the known bond dissociation energy of bromobenzene (Table 1), corrected Arrhenius parameters have been calculated, and are presented in Table 11.

It can be seen from the data listed in Table 11 that the C—Br bond energy is not very sensitive to substitution. Only electron-donating substituents such as hydroxyl and aromatic rings have a marked effect. *Ortho* substitution appears to have the greatest effect and this is most noticeable for 9-bromoanthracene in which two benzene rings are fused at the *o*-positions.

C. Oxygenated Compounds Containing Carbon–Halogen Bonds

The pyrolysis reactions of organic compounds containing both oxygen and halogen depend not only on the relative positions of these groups (i.e. the class of compound) but also on the position and nature of alkyl substituents. An oxygen-containing group may act merely as a substituent in a 'normal' organic halide reaction (compare section II. A) or may involve the carbon–halogen bond in new types of reaction. There are also examples of reactions in which halogens (particularly fluorine) act only as substituents in typical reactions of oxygenated hydrocarbons, but these are outside the scope of this review. The various classes of oxyhalo compounds form convenient groupings for discussion of the reactions involving carbon–halogen bonds.

1. Acyl halides

There has been little reliable work reported on the pyrolysis of acyl halides. It has been claimed that *formyl fluoride* undergoes homogeneous

TABLE 11. Homolytic C—Br bond fission in aromatic bromides

Compound	log A^a	$E_a{}^a$ (kcal mole^{-1})	Rate relative to bromobenzene at 1050K	Reference
Bromobenzene	15·3	80·8	≡1·0	189
p-Fluorobromobenzene	15·3	80·2	1·3	190
p-Chlorobromobenzene	15·3	80·2	1·3	190
m-Chlorobromobenzene	15·3	79·7	1·7	190
o-Chlorobromobenzene	15·3	79·6	1·8	190
p-Dibromobenzene	15·6	80·5	2·3	190
o-Dibromobenzene	15·6	78·9	5·0	190
p-Bromotoluene	15·3	80·5	1·2	190
m-Bromotoluene	15·3	80·5	1·2	190
o-Bromotoluene	15·3	79·9	1·5	190
p-Bromobiphenyl	15·3	80·5	1·2	190
m-Bromobiphenyl	15·3	80·0	1·5	190
o-Bromobiphenyl	15·3	77·9	4·0	190
p-Cyanobromobenzene	15·3	80·4	1·2	190
m-Cyanobromobenzene	15·3	79·8	1·6	190
o-Cyanobromobenzene	15·3	80·1	1·4	190
p-Bromophenol	15·3	76·7	7·1	190
o-Bromophenol	15·3	76·5	7·9	190
1-Bromonaphthalene	15·5	80·7	1·2	189
2-Bromonaphthalene	15·2	79·8	1·3	189
9-Bromoanthracene	15·2	74·9	13·4	189
9-Bromophenanthrene	15·0	77·4	2·6	189
2-Bromopyridine	15·3	81·4	0·8	190
3-Bromopyridine	15·3	86·9	0·05	190
2-Bromothiophene	15·3	78·2	3·5	190

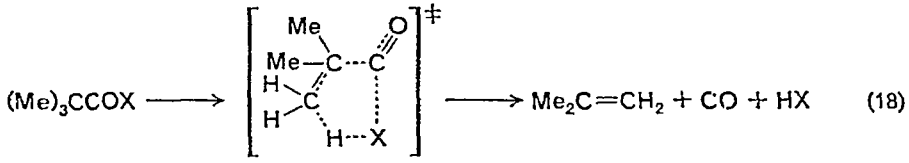
[a] The Arrhenius parameters reported in references 189 and 190 are certainly too low due to experimental artifacts but rates at the middle of the temperature range are probably reliable[16]. The *A*-factor for bromobenzene has been corrected using the known enthalpy of reaction and the other *A*-factors have been scaled up accordingly. Activation energies have been calculated using corrected *A*-factors and mid-temperature rates. *A*-factors are given in units of s^{-1}.

elimination of HF to yield carbon monoxide[191]. The abnormally low Arrhenius parameters ($\log A = 2{\cdot}3$, $E_a = 10$ kcal mole^{-1}) obtained in a Teflon reactor were rationalized on the basis of an electronic-state crossover path. In view of the susceptibility of formyl fluoride to heterogeneous decomposition[191], however, this explanation remains open to question.

The decomposition of *carbonyl fluoride* has been studied in shock waves[192] and involves an initial carbon–fluorine bond fission followed by

rapid elimination of the second fluorine atom to yield carbon monoxide. The reaction was studied in the pressure-dependent region and the high-pressure Arrhenius parameters for the initial fission were obtained by application of the Rice–Ramsperger–Kassel[34,43] theory of unimolecular reactions to the data. The values were calculated to be $\log A = 11{\cdot}8$, $E_a = 91{\cdot}9$. The A-factor is certainly too low for a bond-fission process, due probably to a combination of experimental error and uncertainties in the extrapolation to the high-pressure limit.

Trimethyl acetyl halides furnish an example of novel reactions resulting from the presence of both oxygen and halogen in a molecule. Leanon and Stimson have studied the kinetics of the thermal decompositions of the chloro-[193] and bromo-[194] compounds and in both cases the reaction products are 2-methylpropene, carbon monoxide and hydrogen halide. These reactions appear to be genuine unimolecular processes and the Arrhenius parameters are: $\log A = 14{\cdot}4$, $E_a = 55{\cdot}2$ kcal mole^{-1} for the chloride and $\log A = 14{\cdot}1$, $E_a = 48{\cdot}9$ kcal mole^{-1} for the bromide. The most reasonable transition state would appear to be a five-membered cyclic complex. As fission of three bonds is involved, this complex is 'loose' and could account for the observed A-factors. The five-centre molecular reaction is a Woodward–Hoffmann allowed process and is more likely than an alternative mechanism involving a linear polar transition state.



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2. Benzoyl halides

There are no feasible thermal molecular routes open to benzoyl halides. Both benzoyl chloride[183] and benzoyl bromide[195] undergo radical reactions initiated by carbon–halogen bond fission followed by rapid elimination of carbon monoxide from the benzoyl radical. The kinetics of the primary reactions have been studied by the toluene-carrier technique[183,195], but both the bond dissociation energies *and* reaction rates are in poor agreement with the latest estimates of the thermochemistry of the bond-fission reactions. It would appear, therefore, that these studies of the pyrolysis of benzoyl halides were affected by experimental uncertainties additional to the normal shortcomings of the toluene-carrier technique discussed in the introductory section.

3. Halogenated ketones

In the thermal reactions of halogenated ketones studied to date[196, 197] the ketone group has acted only as a substituent in a typical four-centre alkyl halide reaction. The Arrhenius parameters obtained from these studies are shown in Table 12. The rates of elimination from 3-chlorobutan-2-one and

TABLE 12. Hydrogen halide eliminations from halogenated ketones

Compound	log A^c	E_a (kcal mole^{-1})	Reference
$CH_3\overset{\overset{O}{\|}}{C}CHClCH_3$	11·74 (13·0)[b]	49·1 (52·9)[b]	196
$CH_3\overset{\overset{O}{\|}}{C}CHClCH_2CH_3$	12·8	50·8	196
$CH_3\overset{\overset{O}{\|}}{C}CH_2CHClCH_3$[a]	12·2 (12·8)[b]	44·5 (46·3)[b]	196
$CH_3\overset{\overset{O}{\|}}{C}CHICH_3$	13·4	41·9	197

[a] Sole product pent-2-ene-4-one.
[b] Figures in parentheses are preferred parameters obtained from 'reasonable' A-factor and scaling of E_a to fit mid-temperature rates.
[c] A in units of s^{-1}.

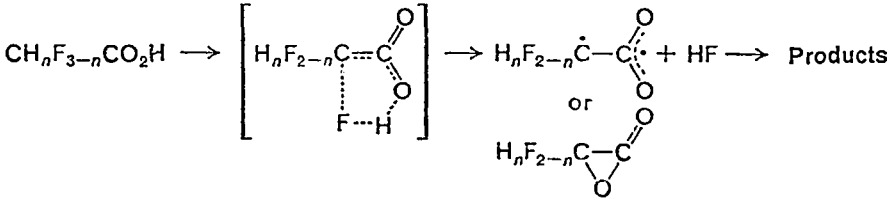
4-chloropentan-2-one are probably reliable around the mid-temperatures of the studies, but the Arrhenius parameters appear to be low. We have, therefore, corrected these values by using a 'reasonable' A-factor and scaling the activation energy to fit the mid-temperature reaction rates. The corrected results are shown in parentheses.

From the data for chloro-compounds it would appear that the MeCO group stabilizes an adjacent positive charge in the transition state slightly less than an adjacent negative charge. The stabilizing effect of MeCO is less than alkyl with respect to positive charges but greater with respect to negative charges. These effects agree qualitatively with predictions. In the case of the iodoketone, however, the apparent stabilizing effect of MeCO on a positive centre is about 8 kcal mole^{-1} which is greater than the effect of alkyl substitution. This observation is difficult to rationalize on the basis of a simple electronic effect. It has been argued[197] that in haloketones the

destabilization of the ground-state molecule by the halogen atom may play an important role in the energetics of the reaction. If this effect is more important with iodine than with chlorine substitution, the enhanced rate of decomposition of 3-iodobutan-2-one can be rationalized.

4. Fluoroacetic acids

The thermal decompositions of mono-[198], di-[199] and trifluoroacetic[200] acids have been studied in silica reaction vessels. These reactions are complex and probably involve wall reactions but it is claimed that the initial step for all three compounds is the elimination of HF, via a five-centre transition state to yield the biradical or ring-closed lactone intermediate. The overall decomposition rates for all three acids are very similar.



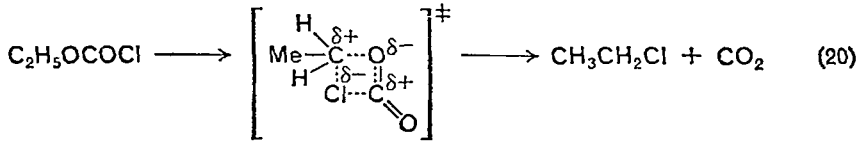
(19)

In the case of the mono- and difluoroacids it is postulated that the biradical or lactone reacts further to yield carbon monoxide and the aldehyde, whereas in the case of trifluoroacetic acid the formation of difluorocarbene and carbon dioxide is suggested to explain the observed reaction pattern. Unfortunately, there is insufficient thermochemical data available to check the feasibility of the proposed mechanism.

5. Chloroformates

Most of the quantitative studies of the molecular decompositions of chloroformates have been complicated by surface and/or radical components and many of the reported Arrhenius parameters are obviously in error.

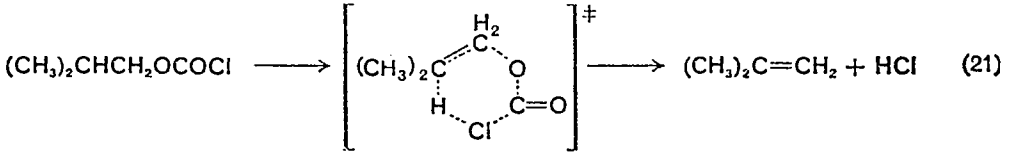
The mode of decomposition of chloroformates depends on the nature of the substituents. The thermal decomposition of *ethyl chloroformate*[201, 202] yields ethyl chloride and carbon dioxide. This may be envisaged as occurring through a four-centre transition state involving an energetically unfavourable pentacoordinated carbon atom.



(20)

A similar path has been proposed for the decomposition of *methyl chloroformate*[202]. This process is Woodward–Hoffmann forbidden and would have to involve polar character in the transition state. However, the large discrepancy in rates ($\sim 10^3$) reported for ethyl chloroformate from independent studies in static[201] and stirred-flow[202] systems indicates that the reaction may involve a radical-chain or heterogeneous mechanism and the low Arrhenius parameters obtained tend to support this interpretation.

The products from the thermal decomposition of *isobutyl chloroformate*[203] are 2-methylpropene, carbon dioxide and hydrogen chloride and the reported Arrhenius parameters[204] are $\log A = 13{\cdot}0$, $E_a = 40{\cdot}0$ kcal mole^{-1}. This reaction probably proceeds directly via a Woodward–Hoffmann

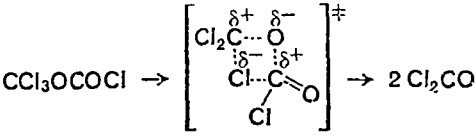


(21)

allowed six-centre transition state. The A-factor is higher than that of typical six-centre reactions but is not unreasonable as the reaction involves eventual decomposition into three fragments and should consequently involve a particularly 'loose' transition state. *Isopropyl*-[202, 204] *2-butyl*-[202] and *neopentyl*-[205] *chloroformates* appear to decompose thermally by two pathways: one to give alkene, carbon dioxide and hydrogen chloride, analogous to the isobutylchloroformate reaction, and the other to give alkyl chloride and carbon dioxide, similar to the ethylchloroformate reaction. Again, the quantitative results from static and stirred-flow studies are radically different and the true nature of the reaction, particularly the alkyl chloride pathway, is in doubt. However, if it is assumed that the data obtained in the stirred-flow system, which yielded the lower rate constants, are approximately correct, the relative rates of the four-centre routes for methyl-, ethyl-, isopropyl-, 2-butyl- and neopentyl chloroformates at 240°C are 1, 2·2, 220, 640 and 3·4 respectively[202]. The Arrhenius parameters for the six-centre elimination of isopropyl and 2-butyl chloroformates[206] obtained from these studies have reasonable values. For the isopropyl compound, $\log A = 13{\cdot}2$, $E_a = 38{\cdot}2$ kcal mole^{-1} and for the 2-butyl compound, $\log A = 12{\cdot}8$, $E_a = 36{\cdot}9$ kcal mole^{-1}. Studies of deuterium-substituted 2-butylchloroformates indicate that the olefin formation involves a *cis* elimination which substantiates the postulated six-centre transition state.

The pyrolysis of *trichloromethyl chloroformate*[207] yields phosgene as the sole product. The reported Arrhenius parameters, $\log A = 13{\cdot}2$,

$E_a = 41{\cdot}5$ kcal mole^{-1}, indicate that a four-centre polar transition state is involved. It is interesting to note that, in this case, chlorine is transferred to the carbonyl group, thereby avoiding the intermediacy of pentavalent



(22)

carbon whereas in the postulated transition state for ethyl chloroformate, a transfer can only occur in the opposite sense.

6. Chloroethers

The introduction of the ether linkage into a chlorohydrocarbon does not appear to cause any change in the mechanism of decomposition. Only 1-chloro-1-methoxyethane[208] and 1-chloro-1-ethoxyethane[209] have been studied quantitatively and both eliminate hydrogen chloride to give the unsaturated ether. The reported Arrhenius parameters for the methoxyl compound are $\log A = 11{\cdot}5$, $E_a = 33{\cdot}3$ kcal mole^{-1}, and for the ethoxyl compound $\log A = 10{\cdot}5$, $E_a = 30{\cdot}3$ kcal mole^{-1}. Both sets of parameters appear to be too low for the four-centre process proposed. The following corrected parameters, obtained from mid-temperature rates and A-factors based on transition state estimates[16], are preferred: chloromethoxyethane, $\log A = 13{\cdot}1$, $E_a = 36{\cdot}9$ kcal mole^{-1}, chloroethoxyethane, $\log A = 13{\cdot}2$, $E_a = 36{\cdot}0$ kcal mole^{-1}. The effect of the ether group on the rate of elimination is dramatic. The chloroethers eliminate hydrogen chloride at about 10^9 times the rate observed for ethyl chloride and 10^3 times that for tertiary butyl chloride. Both studies report a heterogeneous component of about 20% and it appears that the fast rates observed are indeed those of the homogeneous unimolecular process. This would imply that the ether group can stabilize an adjacent positive centre in the transition state by about 20 kcal mole^{-1}. Although this value is remarkably high it is not unreasonable in view of the fact that the ether compounds undergo S_N1 solvolysis at about 10^7 times the rate of t-butyl chloride[210].

III. SUMMARY AND CONCLUSIONS

A. General

The homolytic carbon–halogen bond-breaking process in which the transition state is energetically, but not entropically, equivalent to the association of one electron in the rupturing bond with each centre is easily

visualized, and the effects of substituents on the activation energy are readily rationalized. The aspects of radical decompositions pertaining to the C—X bonds have been comprehensively covered in the survey section and further details can be found in reference 3. The summary and conclusions are therefore restricted to the molecular reaction routes.

In the case of molecular reactions in which more than two centres are involved, the electronic structure of the transition state is not so readily pictured.

The principle of the conservation of orbital symmetry can indicate the preferred geometry for a reaction process involving essentially synchronous and balanced electron rearrangement but is not capable of yielding quantitative results with respect to the energy or entropy involved or the effect of substituents. It is also difficult to estimate the degree of non-synchroneity or electron inbalance (i.e. polar nature) which can be accommodated before predictions based on an essentially synchronous and neutral reaction path become invalid.

The four-centre *cis*-elimination reaction is certainly forbidden on an orbital symmetry basis. The experimental evidence suggests that both non-synchronous bond breaking and polar nature are operative and this combination perturbs the system sufficiently to invalidate any conclusions based on simple orbital symmetry considerations. However, the extent to which each contributes to this process is not known.

B. The Molecular Reaction Path

1. Three-centre mechanisms

Three-centre mechanisms involving carbon–halogen bond cleavage have been confirmed only in cases where difluorocarbene is the product* (section II. A. 1). If the activation energies in Table 3 are scaled to fit a common *A*-factor, 13·8, using mid-temperature rates, the following activation energies in kcal mole^{-1} are obtained: $CHF_3 = 75{\cdot}8$, $CHF_2Cl = 55{\cdot}8$ and $CHF_2Br = 53{\cdot}9$. The simple 'least-motion' three-centre process is Woodward–Hoffmann forbidden and there is insufficient data to establish the structure and charge distribution in the transition state. The large difference in effective activation energy (20 kcal) between the fluoro- and chloro-derivatives and the small difference between chloro- and bromo-compounds ($\sim$2 kcal) can be rationalized by consideration of the partial cleavage of the carbon–halogen bond in either a polar or non-polar transition state.

* Compare footnote on page 701 and reference 216.

2. Four-centre mechanisms

The four-centre mechanism is by far the most dominant molecular reaction route in the thermally initiated decompositions of organic halocompounds. Irrespective of the variety of substituents, all compounds reviewed which incorporate the structural element

$$\begin{array}{cc} C_\alpha & -C_\beta \\ | & | \\ X & H \end{array}$$

undergo a four-centre concerted HX elimination to the exclusion of other multicentre molecular reaction paths. The preference for the four-centre route may only be sacrificed in molecules with particular structures, such as the chloroformates, enabling the competitive formation of a six-centre transition complex, or in molecules with very weak C—X bonds, preferring a radical decomposition path, e.g. 3-iodo-but-1-ene.

While substituents on both the α- and β-carbon atoms do not alter the basic simplicity of the reaction yielding HX and olefinic products, they have a very pronounced effect on the rate of the HX elimination. For a simple *homo*polar four-centre process a much smaller effect would be expected, and the observed unusually large α- and β-substituent effects lead to the recognition of the pronounced polar character of these reactions. Similar substituent effects are observed for the reverse reaction, the addition of HX to a substituted olefinic moiety. From the available data, summarized in section II, it is apparent that substituents bonded to the α-carbon atom carrying a partial positive charge in the transition state in general affect the rate of elimination more than substituents on the 'negative' β-carbon. This is in agreement with the observations from solution chemistry, where the effects of substituents on carbonium ions are usually more pronounced than on carbanions.

The four-centre nature of the process and the polar character of the transition state involved in HX eliminations have been adequately established in section II. As can be seen from the data listed in Tables 4, 5, 7 and 9, the preferred *pre-exponential factors* for the same type of halides usually agree within a factor of $10^{0.4}$, and these values are essentially in agreement with predicted data, based on the concept of O'Neal and Benson[41], and shown below in parentheses: EtX 13·4 (13·2), *i*-PrX 13·7 (13·5), *t*-BuX 14·0 (13·8).

For the alkyl halide series, for which the most reliable and complete data are available, the incremental differences in *activation energies* are summarized in Table 13, where EtCl has arbitrarily been used as a comparative standard.

The data listed in Table 13 show directly additive constant incremental differences between the various halides for the six different alkyl groups listed. Furthermore, within a given alkyl halide, for example EtX, the activation energies increase by an apparently almost constant value of

TABLE 13. Differences in activation energies[a] (ΔE_a)[b] for the four-centre elimination of HX from alkyl halides[b]

	ΔE_a			E_a[c]
Alkyl—X	F	Br	I	Cl
Et—	+ 3·3	− 2·7	− 6·6	56·6
n-Pr—	+ 3·2	− 3·2	− 6·1	55·1
i-Pr—	+ 3·1	− 3·2	− 5·5	50·8
s-Bu—	—	− 3·0	− 5·9	50·0
i-Bu—	+ 5·4	− 2·8	—	53·2
t-Bu—	+ 6·5	− 3·3	− 6·9	45·0

[a] In kcal mole^{-1}.
[b] Based on the data listed in Table 5, using the activation energies for alkyl chlorides[c] as standards.
[c] Activation energies for HX elimination from alkyl chlorides.

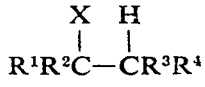
3·1 ± 0·5 kcal mole^{-1} in the series I < Br < Cl < F. The only exceptions are *t*-BuF and *i*-BuF, for which increments of about 6 kcal mole^{-1} are calculated.

The same incremental difference is expected for a given set of halides, as for example ΔE_a(EtCl—EtBr) ≈ ΔE_a(*t*-BuCl—*t*-BuBr), but there is no apparent reason to expect *a priori* the same increments *within* the series of halogens, i.e. ΔE_a(EtCl—EtBr) ≈ ΔE_a(EtBr—EtI). Considerations of the differences in homopolar or heteropolar bond dissociation energies, longitudinal polarizabilities or polarities do not lead to the expectation of constant increments between the halogens in the series I, Br, Cl, F. The observed surprising consistency is then considered to result from a fortuitous combination of effects of the halogen atoms on the rate-controlling factors involved in generating the polar transition state complex.

The observed α- and β-substituent effects on the activation energies for the four-centre HX elimination from the various classes of organic halocompounds are summarized in Table 14.

The stabilizing and destabilizing effects derived in Table 14 evidently result from the interactions of the substituents with the partially developed charges in the transition state complex. To a first approximation, electron-donating groups such as alkoxy, phenyl, allyl and alkyl groups might be

TABLE 14. Substituent[a] effects on the activation energy for the four-centre elimination of hydrogen halides



Positive (α)-centre		Negative (β)-centre		ΔE_a[b]			
R^1	R^2	R^3	R^4	X = F	Cl	Br	I
H	H	H	H	0	0	0	0
H	H	H	Me	−1·6	−1·5	−2·0	−1·0
H	Me	H	H	−6·0	−5·8	−6·3	−4·7
H	Me	H	Me		−6·6	−8·1	−5·3
H	H	Me	Me	−1·3	−3·4	−3·5	
Me	Me	H	H	−8·4	−11·6	−12·2	−11·9
H	H	H	Vinyl		−1·6	−1·4	
H	Vinyl	H	H		−7·9		
Me	Vinyl	H	H		−14·0		
H	Ph	H	H		−11·7	−14·1	
F	H	H	H	+5·1			
Cl	H	H	H		−1·0		
Br	H	H	H			−3·3	
F	F	H	H	+13·7	+4·0		
Cl	Cl	H	H		−2·6		
H	H	F	H		+7·2		
H	H	Cl	H		+2·9		
H	H	Br	H			+2·4	
F	H	F	F	+10·2			
F	F	F	F	+12·4			
$CH_3C(=O)-$	H	H	H		−4·0		−8·1
Me	H	H	$CH_3C(=O)-$		−10·3		
MeO	H	H	H		−19·7		
EtO	H	H	H		−20·6		

[a] α- and β-positions with respect to the eliminating halogen atom.
[b] Activation energy differences in kcal $mole^{-1}$ based on the ethyl halides as reference compounds.

expected to stabilize preferentially a positively charged centre, having relatively little effect on negative charges. On the other hand, carbonyl, cyano or nitro groups as electron-withdrawing entities might be expected to stabilize negative charges preferentially. The available data listed in Table 14 are in general agreement with these expectations.

It is seen that irrespective of the halogen atom, alkyl substituents stabilize the positively induced centre by about 5·5 and the negative centre by about 1·5 kcal mole^{-1}. Quantitative information about the effects of the other substituents can only be derived from a much more reduced set of data, and in most cases values can be obtained only from the elimination of HCl from chlorine compounds. Nevertheless, the concept of direct additivity and the incremental nature of the effects evident for alkyl groups is apparently also valid for the other substituents.

In Table 15 more reliable mean substituent effects, extracted from the data given in Table 14, are presented. The values for the alkyl and vinyl

TABLE 15. Stabilizing effects on polar centres in the four-centre elimination of hydrogen halides (in kcal mole^{-1})

Substituent	Alkyl	Vinyl	Phenyl	Alkoxy	MeCO	Cl
+ Centre	5·5 ± 0·9	8·2 ± 0·3	12·9 ± 1·2	20·2 ± 0·4	6·0 ± 2·0	1·2 ± 0·1
− Centre	1·5 ± 0·4	1·5 ± 0·1			4·8	(−2·9)

substituents appear to be well established, but the error limits quoted for the other substituents do not necessarily reflect the reliability of these data as they mostly represent the consistency between two available sets of experimental data only. While there may be some question as to the accurate value of the stabilizing and destabilizing effects of these substituents, the order of magnitude and the general trend reflected in these data are clear.

The value of ~20 kcal mole^{-1} observed for alkoxy groups appears to be surprisingly large in relation to the other substituent effects, even considering the pronounced electron-donating capacity. For the keto group a larger stabilizing effect on a negative charge than that observed might be expected.

The fact that the stabilizing effect of a benzyl-type conjugation with the positively induced centre, $C_6H_5—C^{\delta+}$, is about 5 kcal mole^{-1} larger than that for an allyl-type $C=C—C^{\delta+}$ structure, which again is 2·7 kcal mole^{-1} more effective than $C—C—C^{\delta+}$, is perfectly in line with expectation based on inductive effects and the mesomeric release of electrons by the substituents. The small effect of these substituents when bonded to the negative centre is also expected from these considerations.

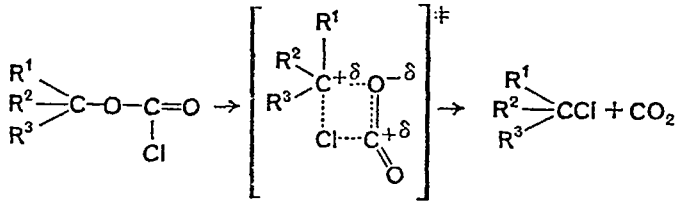
The assumption that the homopolar bond dissociation energies essentially do not affect the activation energy for the polar HX elimination process is also substantiated by the observed differences in the stabilizing effects of vinyl and phenyl substituents. Based on homopolar considerations, both substituents would be expected to have the same effect, as the

'resonance' stabilization energies generated in delocalized allyl-type and benzyl-type radicals are the same (13 kcal mole^{-1}).

The effects of halogen substituents on the rate of HX elimination, discussed in section II. A. 2. b, are far from established. Undoubtedly, fluorine bonded to the emerging positive carbon centre inhibits the generation of a positive charge at this site, and the *destabilizing* effect, when compared with the parent alkyl fluoride, appears to be of the order of 6 kcal mole^{-1} per fluorine atom. In the β-position, i.e. bonded to the negatively induced carbon centre, no consistency in the effect of fluorine substituents can be derived from the data listed in Table 14. In part the data appear to indicate the absence of any effect, which is considered to be the more likely alternative. Some of the data suggest, however, a destabilizing effect amounting to 7·2 kcal mole^{-1} for fluorine in a β-position, which is not readily explicable.

Chlorine and bromine substituents stabilize the positive carbon centre and a value of 2 ± 1 kcal mole^{-1} appears to best represent the data. The effect is expectedly significantly less than that observed with alkyl substituents. When bonded to the β-carbon atom, chlorine and bromine exercise the opposite effect. The data would indicate that the destabilizing β-chlorine and β-bromine effects are about 2·5 kcal mole^{-1}, approximately the same magnitude as the stabilizing effects in the α-position. This is in agreement with liquid-phase data for ionic reactions[30].

The extensive applicability and quantitative as well as qualitative consistency of the outlined four-centre HX elimination from organic halocompounds are exemplified by the data for the thermal decomposition of chloroformates shown in equation (23). Accepting the observed relative



(23)

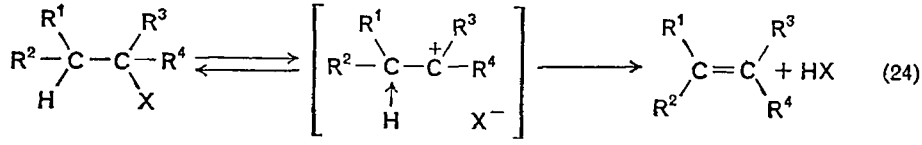
rates as reliable, the following decreases in E_a (in kcal mole^{-1}) for the CO_2 elimination compared with the parent compound ($R^1 = R^2 = R^3 = H$) as standard, have been calculated:

$R^1 = R^2 = H$, $R^3 = Me$	0·8
$R^1 = R^2 = H$, $R^3 = t$-Bu	1·2
$R^1 = H$, $R^2 = R^3 = Me$	5·5
$R^1 = H$, $R^2 = Me$, $R^3 = Et$	6·6

The results for methyl chloroformate appear to disagree with the quantitative prediction, but the difference between mono- and dialkyl-substitution on the positive centre is ~ 5 kcal mole^{-1}, about the same as that observed for the alkyl halides. Furthermore from the rates at 240°C for the closely related decomposition of trichloromethylchloroformate shown in equation (22) (which involves the stabilization effect of three halogen atoms on positive charges), an activation energy 1·9 kcal mole^{-1} lower than that for methyl chloroformate is calculated. This implies that the positive stabilization by three chlorines is equal to that of an alkyl group and is in approximate agreement with the findings from the alkyl halide series.

While the concept of a four-centre partially ionic transition-state complex involved in all these elimination reactions has met with general agreement, there appears to be still some disagreement, apart from purely verbal differences, as to the true nature and the amount of the charge separation in the transition state. Essentially two types of transition-state complexes have been suggested and were used as a basis for semi-empirical quantitative predictions of activation energies.

Maccoll and coworkers[24–31], since their early suggestion of a 'quasi-heterolytic' mechanism involving a very polar, intimate, ion-pair transition-state complex as symbolized in equation (24), favoured a picture in which

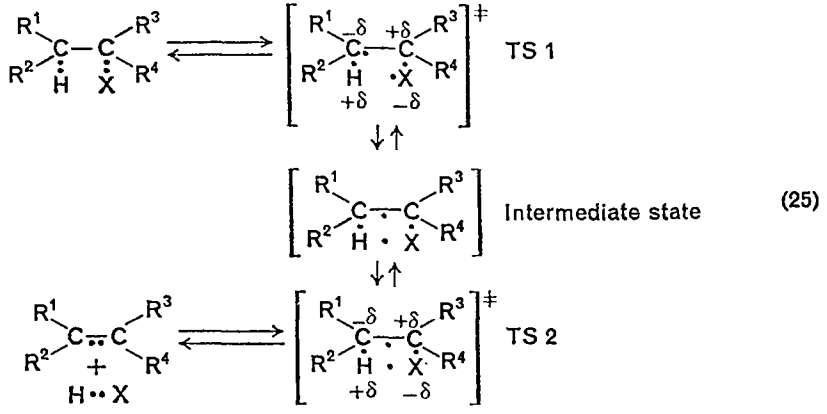


(24)

the polar character of the reaction is essentially restricted to the C—X bond. Consequently the observed activation energies for elimination were expected to be linearly related to the heterolytic bond dissociation energies and the relationship proposed was $E_a = 0{\cdot}29D(C^+X^-)$. From this model substituent effects are then essentially only operative on the positive charge. As more experimental data became available, it was apparent that the nature of the reaction was only moderately polar and certainly did not necessitate the assumption of the presence of carbonium ions.

The ready reversibility of the elimination reaction and considerations of the back reactions, the addition of HX to the olefinic moieties, led Benson and coworkers[70,72] to the assumption of a quadrupolar transition state, depicted in equation (25). In this model the transition state is represented by an intimate association of two semi-ion pairs into a four-centre quadrupole with the formal charge separation of $\frac{1}{2}$ electron on each centre. The

quantitative electrostatic analysis based on this model assumes point dipoles and point aggregates of polarizable matter. The intermediate state essentially only reflects the asymmetry of the transition state.



(25)

The four-centre elimination reactions of alkyl halides are all from 10–20 kcal mole^{-1} endothermic and the overall rate-determining transition state would then be expected to be product-like, as symbolized in TS 2. For other classes of non-halogenated compounds for which this mechanism also appears to hold (for example, X may stand for H, OH, SH, etc.) the potential energy surface may be skewed towards the side of the reactants, and TS 1 may become overall rate-controlling. Based on this semi-ion-pair model, the activation energy for the addition of HX to olefins can be calculated from the energies required to polarize the olefinic bond (ΔE_{olef}) and the HX bond (ΔE_{HX}) and from the interactions of these dipoles in the quadrupolar transition state (E_{int}), corrected by the dipole present in the ground-state molecules (E_{gs}). $E_a = \Delta E_{\text{olef}} + \Delta E_{\text{HX}} - E_{\text{int}} - E_{\text{gs}}$. Distances, dipoles and longitudinal polarizabilities of the bonds in the ground-state and transition-state complex must be known or estimated to calculate these activation energies.

This semi-ion-pair model takes its justification primarily from the fact that it is capable of accurately and consistently predicting the activation energies for a large number of reactions. For the addition of HX, H_2, X_2, H_2O, H_2S, H_3N and H_3P to olefins and acetylenes, Benson and Haugen[70–72] calculated activation energies that generally agreed with the available experimental data within ± 2 kcal mole^{-1}. This model also yields a consistent quantitative description of the Markovnikov rule[211]. More recently, however, larger discrepancies between predicted and observed

data were reported for the elimination of HF from 1,1-difluoroethane[120], 1,1-difluoroethylene[120], 1,1,1-trifluoroethane[21] and for the addition of HI to 1,1-difluoroethylene[212].

In conclusion, it appears that the quadrupolar semi-ion concept in general adequately represents the nature of the transition complex, but that complications may arise in the quantitative analysis of systems with a pronounced tendency for asymmetric charge distribution in the transition state. Even the presence of emergent carbonium ions as an extreme form of highly polar transition-state complexes cannot be ruled out. The neopentyl chloride rearrangement via a true Wagner–Meerwein shift would constitute such an example involving an almost complete charge separation into an ion pair. Practically all the other multicentre rearrangements involving haloalkanes and related compounds reported to date can mechanistically be explained on the basis of a polar concept involving charge separation in the transition state, without an apparent necessity for the assumption of an ion-pair intermediate. It is, however, to be expected that the amount and the symmetry of the charge separation in the transition state varies considerably between the various classes of compounds, which may be reflected in the apparent failure of the semi-ion-pair model to predict accurately the activation energies for HX elimination from polyfluoroalkanes.

As has been shown in section II. B. 1, the four-centre elimination of HX across a double bond is a feasible but slower process when compared to the elimination from a saturated C—C bond. It has been argued[72] that the ground states of olefins and acetylenes contain about equal amounts of 'ionic' character and that the addition of HX to acetylenes, i.e. the reverse reaction in equation (15), involves about 1·5 kcal mole^{-1} less activation energy than the corresponding addition to the olefin. This would imply that the activation energy for eliminating HX from vinyl halides (E_{vinyl}) would be given by

$$E_{(\text{vinyl})} = E_{(\text{alk})} - 1{\cdot}5 + \Delta\Delta H_r \tag{26}$$

where $E_{(\text{alk})}$ is the activation energy for eliminating HX from the corresponding alkyl halides and $\Delta\Delta H_r$ is the difference in the heats of the two reaction systems calculated as the heat of reaction for the acetylene formation reduced by the heat of reaction for the olefin formation. For EtCl and EtBr $\Delta\Delta H_r$ equals about 7 kcal mole^{-1} [35–37] yielding $E_{(\text{vinyl})} \approx E_{(\text{alk})} + 5{\cdot}5$. This prediction is qualitatively borne out by the experimental observations and it is in fortuitously good quantitative agreement with the observed difference of 5·8 kcal mole^{-1} between the activation energies for ethylfluoride and vinylfluoride.

3. Five-centre mechanisms

Although five-centre transition states have been proposed for the pyrolysis of cyclopropylmethyliodide[213] and the HBr-catalysed decomposition of methyl formate[214], *trimethylacetyl* halides (section II. C. 1) provide the only quantitative data for a probable five-centre process. The difference in activation energy between the chloro- and bromo-compounds is 6·3 kcal mole^{-1} which is higher than that observed for the corresponding four-centre HX eliminations in the alkyl halide series ($\sim$3 kcal mole^{-1}) in contrast to the results for the three-centre mechanism ($\sim$2 kcal mole^{-1}). As the five-centre mechanism is an 'allowed' process, it may be reasonable to assume that it has a less polar transition state than the 'non-allowed' four-centre reactions. This would imply that halogen differences are more marked in non-polar reactions and that the three-centre elimination of hydrogen halide in difluorohalomethanes probably involves a polar transition state. However, the probable non-synchronous nature of the three-component fragmentation from the five-centre transition state may affect the charge distribution and work on other substituted acetyl halides is required to clarify the exact nature of the transition state.

The relative rates of five-centre elimination in the *fluoroacetic acids* (section III. C. 4) should be governed by the carbon–fluorine homolytic bond strengths. These are unknown, but the carbon–hydrogen bond strengths in mono- and difluoromethane[44] are equal and slightly less than the bond strength in methane. The report of similar reaction rates for the fluoroacetic acids, therefore, appears reasonable.

4. Six-centre mechanisms

Six-centre transition-state complexes appear to have been established for reactions involving both unsaturated halohydrocarbons (section II. B. 2) and oxygenated compounds (section II. C. 5).

The six-centre HCl elimination from α-chloro-*o*-xylene is much faster than the rate of decomposition of ethyl chloride. This is surprising in view of the fact that the six-centre transition state involves at least partial destruction of the benzene resonance energy. The unique nature of this reaction, however, precludes its inclusion in the general analysis of six-centre reactions.

From the data for four- and six-centre eliminations in *allyl halides* presented in section II. B. 2, and the substituent effects discussed in section III. B. 2, it is possible to estimate the difference in activation energy between the four- and six-centre reaction for the hypothetical case in which substituent effects are the same for both processes. Using 'reasonable'

A-factors, this difference is calculated to be between 5 and 7·5 kcal mole^{-1}, favouring the six-centre path. The stabilizing effect of a methyl group in the α-position in the six-centre transition state can also be calculated and is found to be 2·5 kcal mole^{-1}, indicating a reduced polar character in the transition state when compared to the four-centre elimination. Again this would be expected as the six-centre process is Woodward–Hoffmann allowed.

From the data for the six-centre *chloroformate* decompositions, however (section II. C. 5), the stabilizing effect of monoalkyl substitution on the α-carbon atom adjacent to the oxygen can be estimated to be ~4·4 kcal mole^{-1} and that of an alkyl substituent on the β-position to be about 1·3 kcal mole^{-1}. These values indicate that the polar nature of the transition state (with the α-carbon atom positive and the β-carbon negative) is greater than that in the allyl halide series and approaches that of the four-centre eliminations. This is not unreasonable, as, in the case of the chloroformates, the degree of polarity is governed by the cleavage of a carbon–oxygen bond.

The apparently small differences in transition state polarity between Woodward–Hoffmann allowed and non-allowed processes is worthy of note. This may be a result of the non-synchronous nature of the three-component fragmentation in the case of the chloroformate decompositions, or it may indicate a very narrow boundary between the charge requirements of allowed and non-allowed processes.

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The Chemistry of The Carbon–Halogen Bond
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CHAPTER 11

Photochemistry of the C—X group

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I. INTRODUCTION

The photochemistry of simple alkyl halides has been extensively studied by spectroscopists, physical chemists and organic chemists and several reviews on these works have been published[1,2,3]. By contrast the photochemistry of aromatic halides and more complex, substituted systems has only recently attracted attention[4]. The application of the photochemical reactions of organic halides to synthetic problems is in an even more nascent state and it is therefore on this aspect that the current chapter will concentrate.

Since the numerous textbooks recently published adequately describe fundamental principles of photochemistry[5–11], these will be assumed.

Photohalogenations are also excluded. Furthermore, because of the sheer bulk of literature on the photochemical reactions of organic halides, this chapter is not intended as an exhaustive survey of that area of chemistry. Throughout, the main emphasis is on the chemical transformations which can be brought about as a consequence of photochemical reactions and the discussion concentrates on reactions carried out in solution. Such reactions do not necessarily involve direct excitation of the carbon–halogen bond. In fact, the carbon–fluorine and many carbon–chlorine bonds absorb ultraviolet light in a region often inaccessible to direct photolysis and these bonds are often cleaved only as a secondary process in the reaction. The u.v. properties of some representative examples of carbon–halogen-containing compounds are surveyed below.

II. ULTRAVIOLET PROPERTIES OF ORGANIC HALIDES

Light absorption by simple alkyl halides principally occurs by means of an $n \rightarrow \sigma^*$ transition. For fluorinated and chlorinated hydrocarbons such absorptions occur at less than 200 nm and are hence outside the u.v. region generally accessible in photochemical work. Because of the high bond strength of the carbon–fluorine bond fluorinated solvents are particularly useful as reaction media in photochemical work. End absorptions for chlorinated hydrocarbons do, however, extend into regions of wavelength greater than 200 nm and hence photochemical reactions involving chlorinated compounds are observed. Since the $n \rightarrow \sigma^*$ transition is formally forbidden, the intensities of absorption for alkyl halides are generally low, with extinction coefficients in the region 100–500.

Bromides absorb at longer wavelengths than chlorides and iodides at even longer wavelengths. In the case of iodoform the absorption tails into the visible region, hence its yellow colour. As a consequence of halogen–halogen interactions, polyhalogenated compounds generally show more than one absorption band and there is a bathochromic shift with increased halogen substitution. Some typical absorption maxima are recorded in Table 1.

Substitution of halogen for hydrogen in vinylic systems generally results in a bathochromic shift of the $\pi \rightarrow \pi^*$ absorption, assigned to interaction between the lone-pair electrons on the halogen atom with the olefinic π orbitals[2]. Relatively little work has been attempted on the photochemistry of vinylic halides. In contrast, both the u.v. absorption properties and, lately, the photochemistry of aromatic halides are receiving increased attention. Monosubstitution of benzene by the halogens has relatively little effect on the absorption pattern (see Table 2). A slight bathochromic shift

TABLE 1. U.v. absorption properties of alkyl halides

Compound	λ_{max} (ϵ)	Comments	Reference
CH_3F, CH_2F_2, CHF_3, CF_4, CH_3Cl		No maxima > 200 nm	
CH_3Br	202 (260)	Heptane	12
CH_3I	257 (760)	Heptane	12
CH_2Cl_2	173 (–)	Vapour	13
$CHCl_3$	175 (–)	Vapour	13
CCl_4	175 (–)	Vapour	13
CH_2Br_2	220 (1100)	Heptane	12
$CHBr_3$	205 (2140) 224 (2130)	Heptane	12
CH_2I_2	212 (1580) 240 (600) 290 (1300)	Heptane	12
CHI_3	274 (1300) 307 (1860) 349 (2170)	Heptane	12
CF_3Br	208 (–)	Vapour	14
CF_2Br_2	227 (–)	Vapour	14
CF_3I	270 (360)	Vapour	15

TABLE 2. U.v. absorption properties of monosubstituted halogenobenzenes

Compound	λ_{max} (ϵ)	Comments	Reference
Benzene	203 (7400) 254 (204)	Water; fine structure	17
Fluorobenzene	204 (6200) 254 (900)	Alcohol; fine structure	18
Chlorobenzene	210 (7500) 263 (190)	Alcohol; fine structure	17
Bromobenzene	210 (7900) 267 (190)	Alcohol; little fine structure	17
Iodobenzene	226 (13000) 256 (800)	Alcohol; no fine structure	18

is experienced by the principal short wavelength band whilst the longer absorption band hardly alters. It has been suggested for iodobenzene that the longer wavelength absorption, which shows no vibrational fine structure, is due to absorption by the carbon–iodine bond or iodine non-bonding electrons, leading to direct loss of iodine[16]. Quantum yield studies on the photolysis of simple alkyl iodides show that the primary photochemical step is extremely efficient (see section III. A) and that homolysis of iodine–carbon bonds may always be an important process following absorption of light.

More significant absorption changes are associated with disubstitution of the benzene nucleus. *p*-Disubstituted halobenzenes are of interest since their inductive and mesomeric effects are in opposition. It is found that the bathochromic shift increases in the order F < Cl < Br < I, i.e. polarizability governs electron transfer in the conjugated system.

Some examples of the absorption maxima of halogenated ketones are given in Table 3, with cyclohexanone and acetone for comparison. The

TABLE 3. U.v. absorption properties of halogenated ketones

Compound	λ_{max} (ϵ)	Solvent	Reference
Cyclohexanone	283 (16)	Ethanol	19
2-Fluorocyclohexanone	280 (5)	Methanol	20
or	296 (18)	Isooctane	20
2-Chlorocyclohexanone	295 (24)	Ethanol	20[a]
2-Bromocyclohexanone	312 (44)	Methanol	21
Acetone	279 (16)	Hexane	22
α,α-Dichloroacetone	294 (63)	Dioxan	23
α,α′-Dichloroacetone	299 (41)	Ethanol	24
α,α,α-Trifluoroacetone	278 (40)	Heptane	25
α-Bromoacetone	215 (400) 299 (80)	Hexane	26
α-Chloroacetone	292 (31)	Ethanol	24
1,3-Dichloro-1,1,3,3-tetrafluoropropan-2-one	300 (80)	No solvent given	27
2,2,4,4-Tetrabromocyclobutanone	241 (1100) 336 (55) 345 (54)	Cyclohexane	28

[a] For cyclohexanones the α-halogen effect varies with its conformation. For α-bromo derivatives an axial substituent causes a bathochromic shift of 23 nm, equatorial bromine causes a hypsochromic shift of 5 nm[29]; for chlorine the shifts are in the order 11 nm (axial, bathochromic) and 4 nm (equatorial, hypsochromic)[30].

near-u.v. absorption for fluoro-, chloro- and bromoketones is probably due to an $n \rightarrow \pi^*$ transition. α-Halogen substitution leads to an increase in the extinction coefficient and to a bathochromic shift in the absorption maximum.

III. ALIPHATIC HALIDES

A. Alkyl Halides

The chemical consequence of absorption of light by the simple alkyl halides is generally carbon–halogen cleavage. The ease of bond homolysis is paralleled by the strength of the bond to be broken (see Table 4). Thus,

TABLE 4[36]. Carbon–halogen bond strengths (Kj mole^{-1})

C—F:	CF_4 485 [32], C_6H_5F 481 [34]
C—Cl:	CH_3Cl 326 [32], $CH_2{=}CHCH_2Cl$ 251 [35]
C—Br:	CH_3Br 280 [33], $CH_2{=}CHCH_2Br$ 201 [35], C_6H_5Br 297 [33]
C—I:	CH_3I 213 [32], $CH_2{=}CHCH_2I$ 142 [35], $CH_2{=}CHI$ 276 [37]
C—H:	CH_4 414 [32]

the fragmentation of carbon–iodine bonds is well documented, while the direct photochemical cleavage of the carbon–fluorine bond is extremely rare. Absorption of light by alkyl iodides leads to efficient carbon–iodine homolysis, probably with unit quantum efficiency[31]. However, because the recombination process (reaction 3) is also generally efficient, the overall quantum yield of such photochemical conversions is often low. A common sequence of reactions is

$$RI + h\nu \longrightarrow R^{*\bullet} + I^{\bullet} \quad \text{(primary step)} \tag{1}$$

$$R^{*\bullet} + RI \longrightarrow [RI\cdots R]^{\bullet} \longrightarrow RI + R^{\bullet} \tag{2}$$

$$R^{\bullet} + I^{\bullet} \longrightarrow RI \tag{3}$$

$$R^{\bullet} + R^{\bullet} \longrightarrow R{-}R \tag{4}$$

$$I^{\bullet} + I^{\bullet} \longrightarrow I_2 \tag{5}$$

For light of wavelength 253·7 nm (a component of the light from a low-pressure mercury lamp), which is equivalent to 460 Kj per Einstein, an excess of energy will remain after absorption and carbon–iodine dissociation. For alkyl iodides the excess of energy will be in the order of 230 Kj mole^{-1} and a large proportion of it will reside in the alkyl radical as vibrational and translational energy. These 'hot' radicals will rapidly lose

their translational energy in solution but retain their vibrational energy for longer periods. Such 'hot' radicals can react with substrate alkyl iodide (reaction 2), via an activated complex, in which the excess of vibrational energy has time to be redistributed[38–40]. Reaction (4) leads to the principal reaction product, that of alkyl coupling. Ethane is also produced from methyl iodide by a further reaction of 'hot' methyl radicals (step 6)[41].

$$CH_3^{*\bullet} + CH_3I \longrightarrow C_2H_6 + I^{\bullet} \qquad (6)$$

Alternatively, the hot methyl radicals can also participate in a reaction with methyl iodide which leads to the formation of methane and iodomethyl radicals (reaction 7)[42]. It is possible that reaction (7) can proceed by an

$$CH_3^{*\bullet} + CH_3I \longrightarrow CH_4 + {}^{\bullet}CH_2I \qquad (7)$$

alternative decomposition mode of the activated complex produced in step (2)[38,43].

Further intricacies of such photochemical reactions include the expected reaction of hot (i.e. excited) iodine radicals with the substrate (step 8)[31].

$$I^{*\bullet} + CH_3I \longrightarrow I_2 + CH_3^{\bullet} \qquad (8)$$

Homologues of methyl iodide appear to behave in a similar manner upon photolysis. Interest in the higher alkyl iodides has largely centred on whether the alternative primary process (reaction 9) can occur[44–46]. This reaction involves a concerted elimination of hydrogen iodide with formation of an olefin. Under normal photolytic conditions, using light of wavelength >200 nm, no evidence for a true concerted reaction has been

$$\begin{array}{l} H \quad I \\ | \quad | \\ RCH-CH_2 \end{array} \xrightarrow{h\nu} \begin{array}{l} H\cdots\cdots I \\ \vdots \quad \vdots \\ RCH=CH_2 \end{array} \longrightarrow RCH=CH_2 + HI \qquad (9)$$

forthcoming—even for *t*-butyl iodide, which decomposes to give large quantities of hydrogen iodide, a radical process is favoured[47]. In the latter case it appears that the radical pair initially produced is held in a solvent cage and that subsequent reaction, to give isobutylene and hydrogen iodide, is rapid.

Under flash photolytic conditions irradiation of ethyl iodide gave no detectable quantity of ethyl radicals and only hydrogen iodide formation was observed[48]. This implies a concerted elimination reaction although a different mechanism, one not involving the normal $n \rightarrow \sigma^*$ excitation, might be involved.

A related reaction, for which two primary processes have been considered, is the photochemical decomposition of geminal diiodoalkanes. The two

processes (reactions 10 and 11) lead to a radical or a carbene. Step (11) was originally proposed for diiodomethane by Gregory and Style[49] and

$$RCHI_2 \longrightarrow RCHI^{\bullet\bullet} + I^{\bullet} \quad (10)$$

$$RCHI_2 \longrightarrow RCH: + I_2 \quad (11)$$

$$RCHI^{\bullet\bullet} \longrightarrow RCH: + I^{\bullet} \quad (12)$$

carbene formation was indicated by subsequent trapping experiments with olefins to give cyclopropanes[50]. However, on the basis of product distributions and stereochemical studies, it was concluded that the main product-forming intermediate was probably an excited state iodomethylene radical rather than free methylene. The latter species is probably a major product from irradiations in the far u.v. region[51]. Homologues of diiodomethane did not give carbene-like products[52].

Chemical evidence for alkyl radical formation after photolysis of alkyl halides is manifested by trapping reactions. These can be with itself (cf. reactions 4 and 6) or with added trapping reagents, which are often free-radical species such as nitric oxide. A common free-radical trap is oxygen[53]; thus methyl iodide yields a variety of oxidation products, including methanol, formaldehyde and water[54]. The secondary reactions that can occur are complex[55], oxidation proceeding through the participation of methylhydroperoxy radicals. Ethyl iodide[56], isopropyl iodide[57] and *t*-butyl iodide[47] react similarly.

The use of metals, such as silver or mercury, to quench the iodine radicals, also diverts the normal reactions and enhances coupling and reduction. For example, isopropyl iodide normally produces more propene than propane on irradiation, but in the presence of mercury equimolar amounts are produced[58] and in this case no coupling of the isopropyl radicals occurs. By contrast, the photolysis of polyhalogenated iodides in the presence of an iodine radical scavenger results in efficient coupling and this process is important for the preparation of polyfluorinated alkanes[59].

Reduction of alkyl radicals derived from alkyl iodides is also well established, for example with hydrogen iodide. Recently, an interesting method for reducing carbon–halogen bonds using trichlorosilane has been studied[60]. A radical chain reaction has been established for the gas-phase reaction[55]. Both alkyl bromides and chlorides could be reduced.

The reduction of fluorinated alkyl halides to the corresponding fluorinated alkane has also been studied. The reduction is carried out in the presence of primary or secondary alcohols as reductant. For example, photolysis of 1,1,2-trifluoro-2-chloro-1-bromo-1-iodoethane (**1**) in ethanol results in reduction of the carbon–iodine bond[61]. Remarkably selective

reductions of carbon–chlorine bonds in some fluorinated chloro-alcohols have also been observed, again with alcohols as reductant[62]. Thus the

$$R{-}X \xrightarrow{h\nu} R^{\bullet} + X^{\bullet} \quad (13)$$

$$R^{\bullet} + H{-}SiCl_3 \longrightarrow R{-}H + {}^{\bullet}SiCl_3 \quad (14)$$

$$R{-}X + {}^{\bullet}SiCl_3 \longrightarrow R^{\bullet} + X{-}SiCl_3 \quad (15)$$

$$X^{\bullet} + H{-}SiCl_3 \longrightarrow H{-}X + {}^{\bullet}SiCl_3 \quad (16)$$

$$R^{\bullet} + H{-}X \longrightarrow R{-}H + X^{\bullet} \quad (17)$$

alcohol **2** gives the alcohol **3** upon irradiation in isopropanol. No reduction of the terminal chlorine atom occurred. From a detailed study of a range of such alcohols it was concluded that only the carbon–chlorine bonds of the part structure **4** are reduced by isopropanol on photolysis.

$CF_2BrCFClI$ (1)

$CHFClCF_2CFClCF_2CH_2OH$ (2)

$CHFClCF_2CHFCF_2CH_2OH$ (3)

$-CF_2CFClCF_2-$ (4)

Photolysis of polyhalogenated alkanes often leads to a polyhalogenoalkyl radical. An important reaction of the halogenoalkyl radical (R_X) so produced is its addition across olefinic bonds[63]. The principal reactions occurring are (18)–(24). Such additions are chain reactions and do not

$$R_XX \longrightarrow R_X^{\bullet} + X^{\bullet} \quad \text{(initiation)} \quad (18)$$

$$X^{\bullet} + R_2C{=}CR_2 \longrightarrow R_2CX{-}CR_2^{\bullet} \quad \text{(propagation)} \quad (19)$$

$$R_X^{\bullet} + R_2C{=}CR_2 \longrightarrow R_XCR_2{-}CR_2^{\bullet} \quad \text{(propagation)} \quad (20)$$

$$R_XCR_2{-}CR_2^{\bullet} + R_XX \longrightarrow R_XCR_2CR_2X + R_X^{\bullet} \quad \text{(propagation)} \quad (21)$$

$$R_XCR_2{-}CR_2^{\bullet} + R_X^{\bullet} \longrightarrow R_XCR_2CR_2R_X \quad \text{(termination)} \quad (22)$$

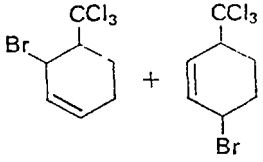
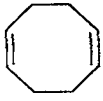
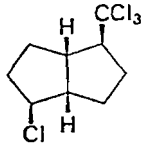
$$R_XCR_2{-}CR_2^{\bullet} + X^{\bullet} \longrightarrow R_XCR_2CR_2X \quad \text{(termination)} \quad (23)$$

$$2\,R_XCR_2{-}CR_2^{\bullet} \longrightarrow R_XCR_2CR_2CR_2CR_2R_X \quad \text{(termination)} \quad (24)$$

need large amounts of light. Although such reactions can often be initiated thermally in the presence of radical sources, such as benzoyl peroxide, the photo-initiated reactions often have advantages in that the reactions are frequently cleaner. Furthermore, since the number of initiating species is dependent on the amount of light used, reactions with relatively short propagation sequences can be effected. The kinetic requirements of the

addition reaction have been delineated[63]. Polar effects are of importance, polyhalogenoalkanes adding across electron-rich olefins such as vinyl ethers more efficiently than across electron-deficient olefins. Some examples of the addition of polyhalogenoalkanes across double bonds are listed in Table 5 (for more extensive lists see reference 63). From the table it can

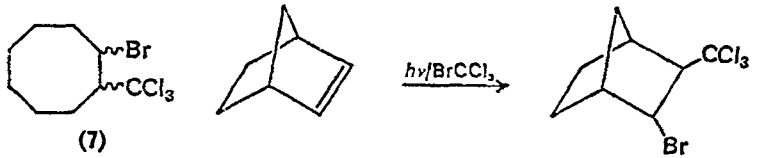
TABLE 5. Some examples of the photoaddition of halogenoalkanes to olefins

Olefin	Halogeno-alkane	Adduct	Yield (%)	Ref.
$CH_2=CHCH(OEt)_2$	CCl_4	$CCl_3CH_2CHClCH(OEt)_2$	(Good)	64
$(CH_3)_2C=CHCH_3$	$BrCCl_3$	$CCl_3CH(CH_3)CBr(CH_3)_2$	77	65
$CH_2=CHCH_3$	CF_3I	$CF_3CH_2CHICH_3$	50	66
$CH_2=CHCF_3$	CCl_3I	$CCl_3CH_2CHICF_3$	57	67
$HC\equiv CCF_3$	CCl_3I	$CCl_3CH=CICF_3$	74	67
1-Octene	CBr_4	$CBr_3CH_2CHBr(CH_2)_5CH_3$	96	68
1-Octyne	$BrCCl_3$	$CCl_3CH=CHBr(CH_2)_5CH_3$	20	69
	$BrCCl_3$		—	70
	CCl_4		—	71
$CH_2=CHCN$	CF_3I	CF_3CH_2CHICN	—	72
$CH_2=C(CH_3)$– 	$BrCCl_3$	$CCl_3CH_2C(CH_3)=CHCH_2CH_2Br$	—	73

be seen that acetylenes preferentially form 1 : 1 adducts. The direction of addition to terminal olefins is exclusively at the methylene group, leading to the more substituted radical[74] and the eventual formation of unbranched homologues. Addition to 1,2-disubstituted olefins is not as selective, for example bromotrichloromethane addition across substituted stilbenes is not grossly affected by varying the substituents. Thus, addition to 4-nitro-stilbene followed acid hydrolysis and elimination of hydrogen bromide gave only a 40 : 60 ratio of the cinnamic acids **5** and **6** respectively[75].

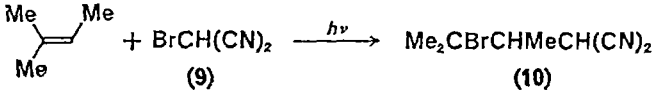
p-$O_2NC_6H_4CH=C(Ph)CO_2H$ (**5**) p-$O_2NC_6H_4C(CO_2H)=CHPh$ (**6**)

The stereochemistry of addition across double bonds by halogenoalkanes has also been investigated. Addition of bromotrichloromethane to *cis*-cyclooctene produced a 1 : 1 mixture of the *cis*- and *trans*-adducts **7** as major products[76]. Addition of the same substrate to cyclohexene yielded a 45 : 55 ratio of the *cis*- to *trans*-adducts, whilst cyclopentene only gave the *trans*-adduct[77]. Norbornene also gave a *trans*-adduct **8**, indicating that steric effects are important in rigid ring systems.

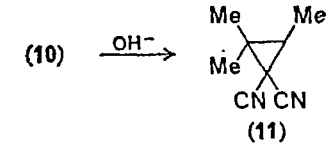


(7) (8) (25)

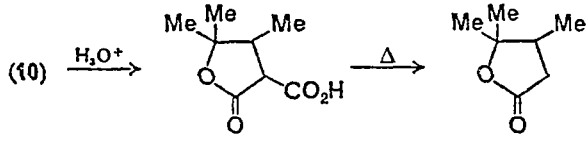
α-Haloesters and α-halonitriles can also be made to participate in free-radical additions across olefins although these substrates are more often used in conjunction with a chemical free-radical initiator[78] rather than with light. Some photo-initiated processes, however, are of importance. An example which highlights the synthetic utility of this reaction is the photo-induced addition of bromomalononitrile (**9**) across an olefin to yield a 1-bromo-3,3-dinitrile (e.g. **10**) in high yields. With base the adduct **10** produces the cyclopropane **11**[79], whilst acid hydrolysis, followed by decarboxylation (reaction 28) produces a γ-lactone **12**, again in high yield (> 60%)[80].



(9) (10) (26)



(11) (27)



(12) (28)

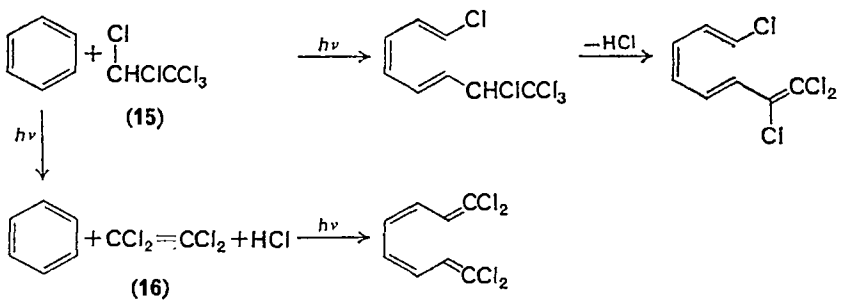
A further important use of polyhalogenoalkanes is as a *source* of halogen. 1,2-Dibromotetrachloroethane (**13**), for example, is an excellent brominating agent[81]. On irradiation homolysis occurs with formation of a bromine atom. The residual fragment, the 2-bromotetrachloroethyl radical (**14**)

rapidly collapses with formation of tetrachloroethylene and a second atom of bromine. Thus, the dibromide yields bromine atoms of synthetic use in radical brominations and allylic bromides can be readily prepared. It is cheaper than *N*-bromosuccinimide and the yields of products are generally as good. Since it is soluble in organic solvents and the side-product, tetrachloroethylene, is easily removed, reactions involving this reagent require simple work-up procedures.

$$\underset{\textbf{(13)}}{CCl_2BrCCl_2Br} \longrightarrow CCl_2BrCCl_2^{\bullet} + Br^{\bullet} \qquad (29)$$

$$\underset{\textbf{(14)}}{CCl_2BrCCl_2^{\bullet}} \longrightarrow CCl_2{=}CCl_2 + Br^{\bullet} \qquad (30)$$

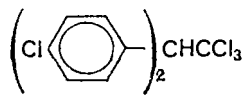
As mentioned above, carbon–chlorine bonds are often more inert towards direct photochemical cleavage than carbon–bromine or carbon–iodine bonds and this is partly because the simple alkyl chlorides absorb outside the normally accessible u.v. region (< 200 nm). One possible method of overcoming this difficulty is to employ sensitizers[82]. A complication of such processes is the expected reaction between the sensitizer itself and the radicals derived from the chloride[83]. The gas-phase photolysis of trifluoromethyl chloride at 254 nm, using mercury as sensitizer, leads to mercurous chloride and hexafluoroethane; in the absence of mercury no cleavage occurs[84]. Benzene could also be acting as a photosensitizer in a reaction with pentachloroethane. Whereas hexachloroethane had no effect on the normal photochemical reactions of benzene, pentachloroethane adds to it[85]. The photochemical cleavage of a carbon–chlorine bond was assumed (reaction 31), a postulate inconsistent with the failure of hexachloroethane to react. Possibly, hydrogen chloride is initially eliminated from the pentachloroethane (**15**) to give tetrachloroethylene (**16**), followed by its addition to benzene in a precedented manner (reaction 32)[86]. The product from this reaction was only identified by its spectroscopic properties and it has not been isolated.



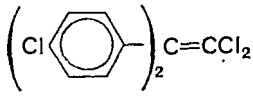
(31)

(32)

The elimination of hydrogen chloride from a chlorocompound during photolysis was also observed with DDT (**17**), which first yields the ethene, DDE (**18**) before undergoing photochemical oxidation to 4,4′-dichlorobenzophenone and other products[87].



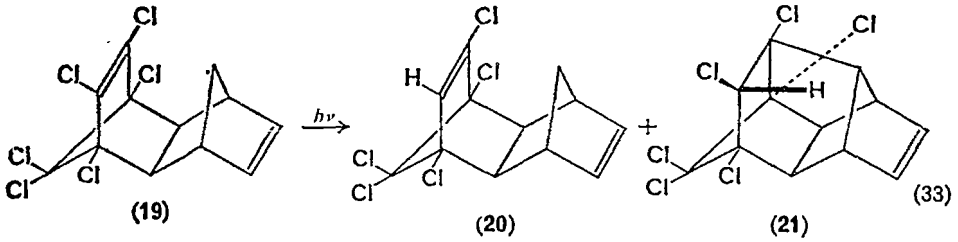
(**17**)



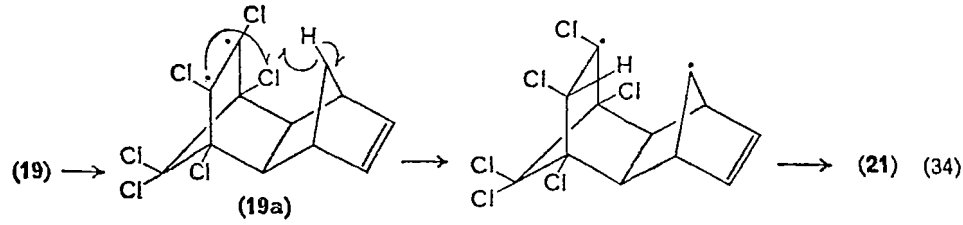
(**18**)

B. Vinylic Halides

The photochemical properties of commercial insecticides of the polychlorinated type are of interest for ecological as well as for chemical reasons. Such insecticides are known to be sensitive to light and air[88]. Irradiation of aldrin **19** in ethyl acetate afforded two principal products, the dechlorinated species **20** together with smaller quantities of the bridged compound **21**[88]. By contrast, dieldrin **22**, in which there is a greater steric compression between the bridging carbons, does not lose chlorine on photolysis, bond formation being preferred[89]. Bridging occurs by internal hydrogen abstraction via a six-membered transition state **19a** (e.g. reaction 34).



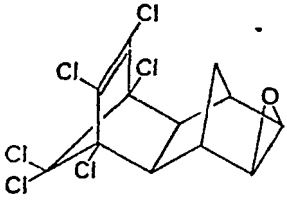
(**19**) (**20**) (**21**) (33)



(**19**) (**19a**) (**21**) (34)

Dechlorination must occur via carbon–chlorine bond homolysis, followed by hydrogen abstraction from the solvent. Dechlorinations analogous to the conversion **19** to **20** have also been observed for endosulphan (**23**) (in dioxan–water, but not in hexane)[90] and the chlordanes, e.g. *trans*-chlordane (**24**)[91]. In the above insecticides only reduction of the

vinylic chlorine atoms was observed. Few studies have been made with simpler vinylic chlorides[2]. Wijnen has investigated the gas-phase photolysis



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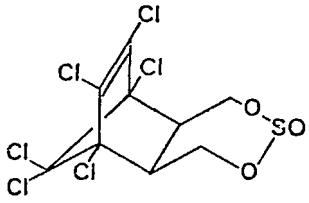

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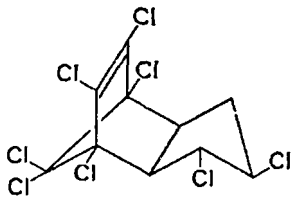


(24)

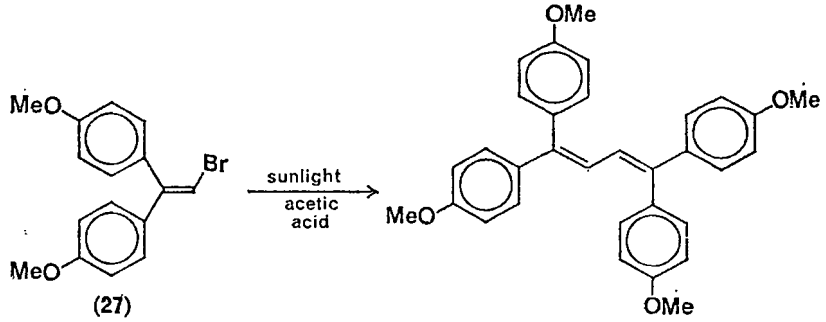
of *cis*-dichloroethylene. In this case acetylene and monochloroacetylene were produced. With unfiltered u.v. light a ratio of 9 : 1, respectively, of the two acetylenes was formed but the ratio changed to 3 : 1 with light of wavelength <220 nm, which suggested a wavelength dependence for the two products, a fact explained in terms of the products originating from two different excited states[92].

Vinylic iodides are far more sensitive to light than the corresponding chlorides. Vinyl iodide (**25**) has been photolysed in carbontetrachloride solution to give hydrogen iodide, iodine, ethylene, acetylene and vinyl chloride as principal products[93]. Dissociation to a radical pair (**26**) precedes loss of hydrogen in the formation of acetylene and ethylene is produced by reduction of the radical pair **26** with hydrogen iodide. Vinyl chloride is obtained by abstraction of chlorine from the solvent (reaction 36). In this particular reaction little dimerization of the vinyl radical was

$$\underset{\textbf{(25)}}{CH_2{=}CHI} \longrightarrow \underset{\textbf{(26)}}{CH_2{=}CH^{\bullet}\cdots I^{\bullet}} \qquad (35)$$

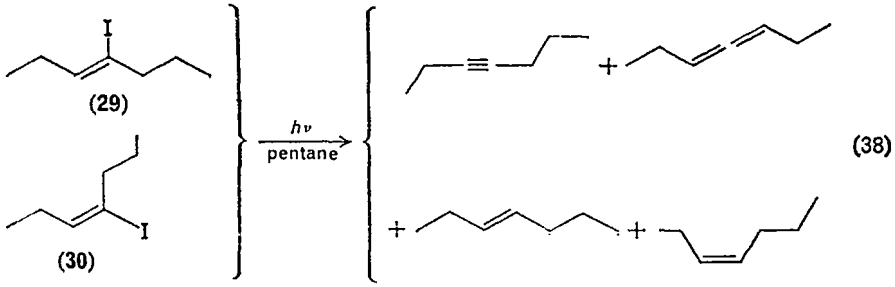
$$CH_2{=}CH^{\bullet} + CCl_4 \longrightarrow CH_2{=}CHCl + CCl_3^{\bullet} \qquad (36)$$

observed. However, for the vinylic bromide **27** the major product, after irradiating it in sunlight, was the dimer **28**[94].



(27) (28) (37)

Alkyl-substituted vinylic iodides have been examined in order to determine whether the vinylic radicals formed retain their stereochemical integrity. Photolysis of (Z)- or (E)-4-iodohept-3-ene (**29** and **30** respectively) gave the indicated products (reaction 38)[95]. The product ratios were isomer dependent, indicating some degree of retention of stereochemical character in the isomeric radicals produced upon carbon–iodine homolysis. Unfortunately, the results were complicated by competing *cis–trans* isomerization of both the starting materials and the product olefins. *cis*- and *trans*-1-iodopropenes both gave the same yields of acetylene, methylacetylene and propylene upon irradiation[96].

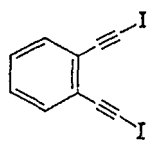


(38)

Acetylenic radicals are produced by irradiation of acetylenic iodides. Thus, photolysis of 1-iodo-2-phenylacetylene (**31**) in benzene gives good yields of 1,2-diphenylacetylene[97]. Radical attack onto the solvent occurs to give the product (see section V. A). The coupling of the acetylenic radicals with alkyl-substituted benzenes appears to be more efficient than with benzene itself[98]. Self-coupling of the acetylenic radicals can be favoured either by irradiation of concentrated solutions of the iodo-acetylene or by use of thin films of the neat material. In this manner, the iodo-acetylene (**31**) afforded the diphenyldiacetylene (**32**) in an optimum yield of 23%[99]. In an attempt to induce dimeric self-coupling, *o*-bisiodoethynylbenzene (**33**) was irradiated as a thin film. No cyclic poly-ynes were isolated, mainly polymers and a small quantity of the tetra-iodonaphthalene (**34**) being obtained.

PhC≡CI
(31)

PhC≡C—C≡CPh
(32)



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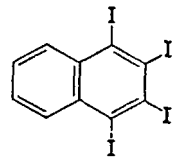
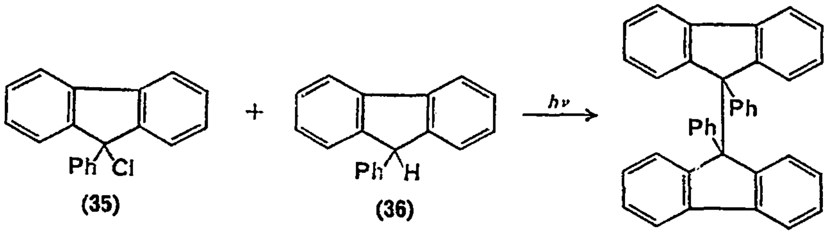


(34)

C. Allylic Halides

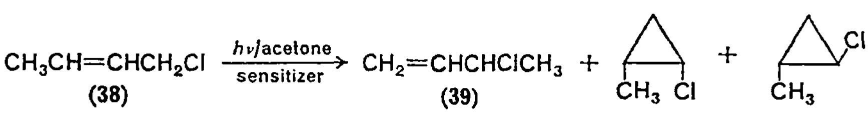
Benzylic halides are homolytically cleaved by photolysis[100]. Thus the fluorene derivative **35** reacts with 9-phenylfluorene (**36**) on irradiation to produce the dimer **37**[101].



(35) (36) (37) (39)

Allyl iodide readily gives iodine in light but the fate of the allyl radicals thus formed has not been carefully determined[102]. Similarly, the photolysis of allyl chloride in the presence of mercury rapidly produces mercury salts and a solid described as a polymer[103]. Recently a more detailed study was reported on the unsensitized photolysis of allyl chloride, both as a liquid and, at low temperatures, as a solid[104]. The primary reaction at 254 nm is homolysis of the carbon–chlorine bond (reaction 40) and no evidence for the elimination of hydrogen chloride in a primary reaction could be found. Examination of the reaction products revealed at least sixteen volatile components, the principal constituents being dimers. No cyclopropyl products were found from the photolysis carried out in the liquid phase. Furthermore, all the products could be explained in terms of homolytic reactions. In contrast, the sensitized photolysis of allylic chlorides gives completely different products, the principal compound being cyclopropyl chloride[105]. Thus, photolysis of crotyl chloride **38** with acetone as the sensitizer gave the cyclopropyl chlorides **40** and **41**. The cyclization was preceded by a fast equilibrium of the crotyl chloride with its isomer **39**.

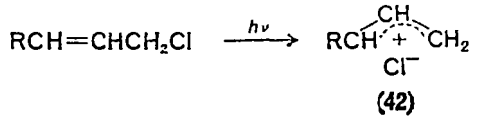
$$CH_2{=}CHCH_2Cl \xrightarrow{h\nu/254\ nm} CH_2{=}CHCH_2^{\bullet} + Cl^{\bullet} \qquad (40)$$



(38) (39) (40) (41) (41)

Under similar conditions allyl chloride gave cyclopropyl chloride (19% in 24 hours); allyl bromide behaved similarly. No *free* chlorine radicals are produced in the sensitized process since no chloroacetone could be detected. Two possible mechanisms for the latter reactions can be considered. The

more interesting mechanism involves the formation of a vibrationally excited carbonium ion–halide ion pair (**42**) which then recombines to give either the thermodynamically stable products (e.g. **38** and **39**) or unstable products (e.g. **40** and **41**). Although there is precedent for such an 'ionic' mechanism[106], a corresponding triplet-state diradical mechanism could also explain the observed result. The diradical **43** could rearrange by either a 1,2- or a 1,3-chlorine shift (reaction 43). Excited states with ionic character would be favoured by dipolar or protic solvents, whilst the diradical pair mechanism would be preferred in non-polar solvents. Ion-pair formation (e.g. **42**) in polar solvents could take place by rapid electron transfer from initially produced diradical pairs (e.g. **43**).



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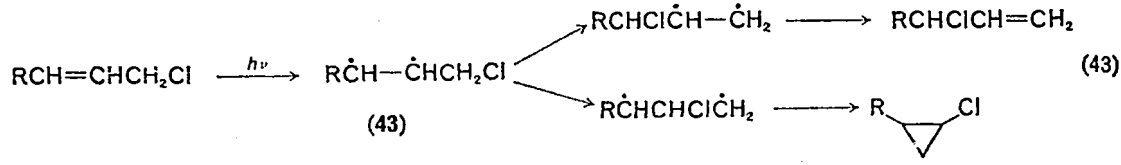
(42)



(43)

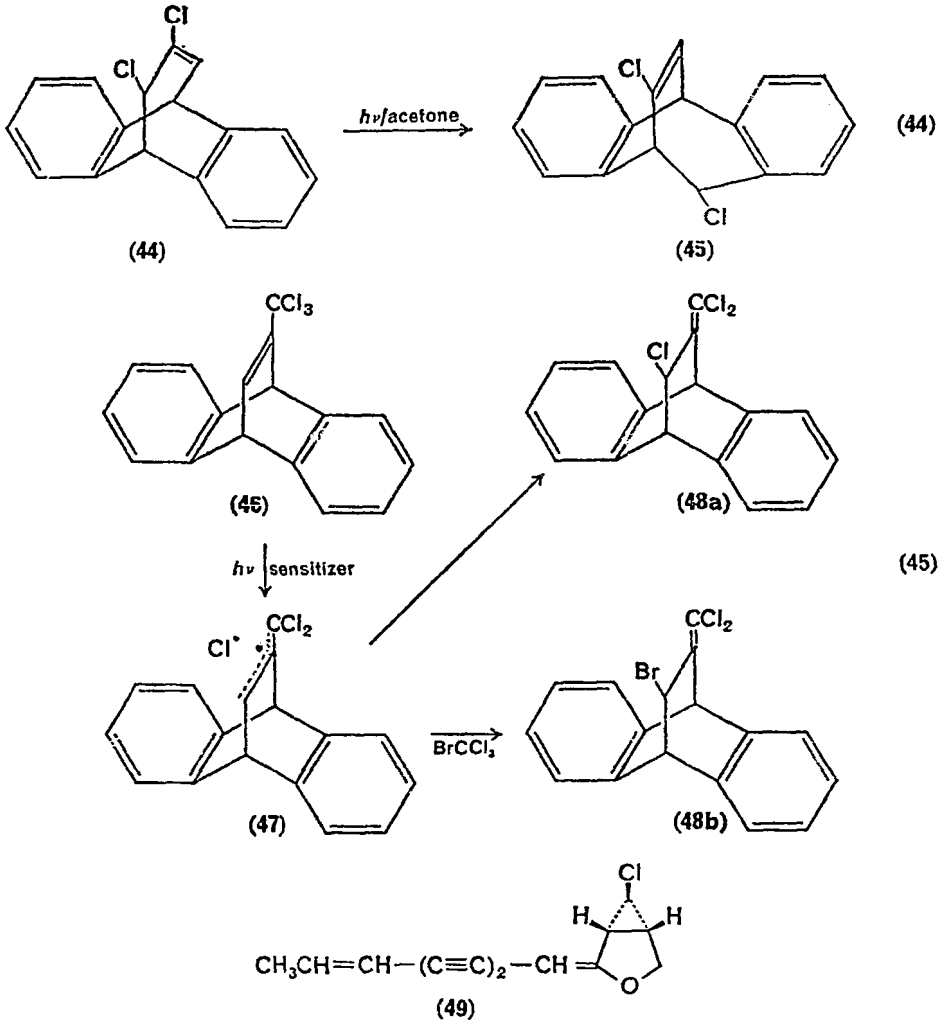
(43)

A similar, sensitized reaction was also observed for the isomerization of the dibenzobicylic chloride **44** to the compound **45**[107]. However, when the α,β-unsaturated trichloromethyl derivative **46** was irradiated in the presence of both a sensitizer and bromotrichloromethane[108], the brominated product **48b** was obtained, along with the normal photoproduct **48a**. The bromotrichloromethane must react with the activated intermediate **47**, which implies that under these reaction conditions it has a great deal of radical character. The absence of chloroacetone when acetone is used as a sensitizer implies that the activated diradical (e.g. **47**) does not readily dissociate into free chlorine atoms and alkyl radicals. Exchange of the chlorine with a bromine from bromotrichloromethane, however, can occur since the bromine–carbon bond energy in this compound is relatively weak. The association of the chlorine radical with the substrate species attenuates its normal hydrogen-abstracting properties.

The polyacetylene derivative **49**, isolated from *Centaura ruthemia* Lam, has been synthesized by photolysis of an appropriate allylic chloride precursor[109].

Very little work has been carried out on the photolysis of propargylic halides. In one study, propargyl bromide was irradiated in the liquid

phase to give methylacetylene and a polymer. The sensitized photolysis of such systems has not been reported[110].

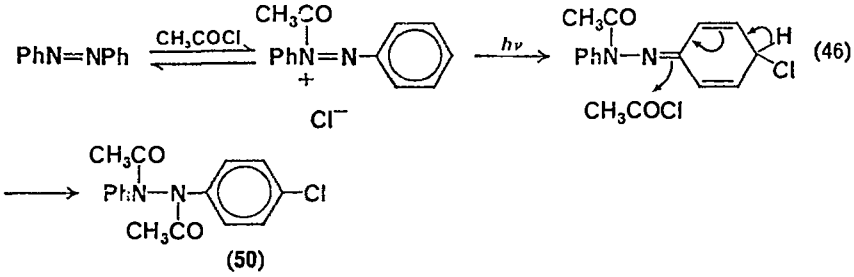


IV. HALOCARBONYL COMPOUNDS

A. Acyl Halides

Diverse reports on the photochemical behaviour of carboxylic acid halides have appeared[110a]. For example, the photoreaction of azobenzene with acetyl chloride gives *N,N'*-diacetyl-4-chlorohydrazobenzene (**50**). No reaction occurs between azobenzene and acetyl chloride in the dark, even at reflux[111]. This reaction probably does not constitute a radical process,

since only the mono-*p*-substituted chloride is formed, as expected for an ionic mechanism. The reaction is probably an example of a photo-induced nucleophilic substitution reaction (reaction 46).



α-Cleavage of acyl halides by photolysis has been observed, particularly for acyl bromides[112], producing acyl radicals. Besides the possible loss of carbon monoxide, such radicals can abstract hydrogen from suitable donors such as ethers (reaction 48) to produce an aldehyde. With acyl bromides the ether radical so produced adds on bromine (reaction 49). With acyl chlorides a different sequence of events has been observed. Initial hydrogen abstraction from an ether is effected by the chlorine

$$CH_3COBr \xrightarrow{h\nu} CH_3CO^{\bullet} + Br^{\bullet} \quad (47)$$

$$CH_3CO^{\bullet} + CH_3CH_2OCH_2CH_3 \longrightarrow CH_3CHO + CH_3\dot{C}HOCH_2CH_3 \quad (48)$$

$$CH_3\dot{C}HOCH_2CH_3 + CH_3COBr \longrightarrow CH_3CO^{\bullet} + CH_3CHBrOCH_2CH_3 \quad (49)$$

$$CH_3COCl + CH_3CH_2OCH_2CH_3 \xrightarrow{h\nu} HCl + CH_3CH(COCH_3)OCH_2CH_3 \quad (50)$$

radicals, the resulting acetyl and ether radicals coupling to form a new carbon–carbon bond (reaction 50).

The photolysis of perfluoroacyl halides has also been studied. For such acyl fluorides bond cleavage occurs towards the alkyl chain and *not* across the carbonyl–fluorine link, the resulting perfluoroalkyl radicals (R_f) coupling (reaction 51). The perfluoroalkyl chloride and bromide behave as expected, with α-cleavage occurring across the relatively weaker carbonyl–halogen bond, followed by loss of carbon monoxide and recoupling to form the lower polyfluoroalkyl chloride or bromide as the major reaction product[113].

$$R_fCOF \xrightarrow{h\nu} R_f^{\bullet} + COF^{\bullet}; \quad 2\,R_f^{\bullet} \longrightarrow R_f{-}R_f \quad (51)$$

In contrast to carboxylic acid chlorides, oxalyl chloride is extremely photolabile (reactions 52–57) and readily yields chlorocarbonyl radicals[114].

Two primary cleavage reactions have been detected, which appear to be wavelength dependent. The first (reaction 52) is initiated by light of wavelength 254 nm and the second by light at 366 nm (reaction 53). Both processes lead to the formation of chlorine and chlorocarbonyl radicals. Hydrogen abstraction from a substrate solvent followed by coupling with

$$ClCOCOCl \xrightarrow{h\nu/254\ nm} 2\ COCl^{\bullet} \quad (52)$$

$$ClCOCOCl \xrightarrow{h\nu/365\ nm} Cl^{\bullet} + {}^{\bullet}COCOCl \quad (53)$$

$${}^{\bullet}COCOCl \longrightarrow CO + {}^{\bullet}COCl \quad (54)$$

$$COCl^{\bullet} \longrightarrow CO + Cl^{\bullet} \quad (55)$$

$$Cl^{\bullet} + R{-}H \longrightarrow R^{\bullet} + HCl \quad (56)$$

$$R^{\bullet} + COCl^{\bullet} \longrightarrow RCOCl \quad (57)$$

the chlorocarbonyl radicals yields acid chlorides. Cyclohexane is readily attacked and the reaction appears to be general for aliphatic hydrocarbons[115]. In contrast alkylated aromatic substrates such as toluene tend to self-couple and chlorinate rather than add the chloroformyl group[116]. Ethyl chloroformate has also been used to substitute aliphatic compounds with ethoxycarbonyl groups[117].

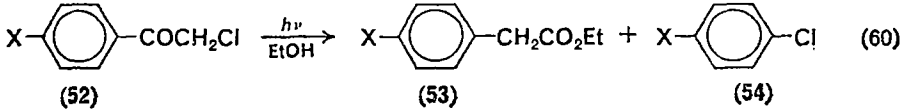
B. α-Haloketones

The first definitive work on the photochemistry of α-haloketones was carried out by Strachan and Blacet[118] who found that two competing primary processes occur. These were the α-cleavage reaction (58) and carbon–chlorine fission (reaction 59). The acetonyl radical **51** can either

$$ClCH_2COCH_3 \xrightarrow{h\nu} {}^{\bullet}CH_2Cl + CH_3CO^{\bullet} \quad (58)$$

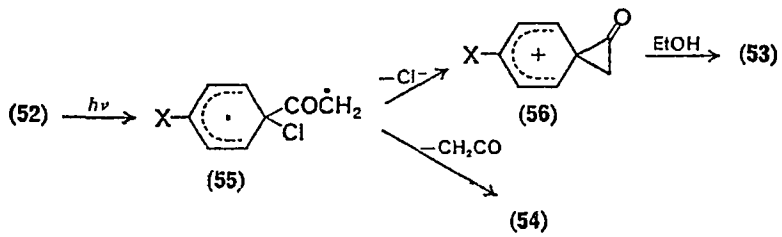
$$ClCH_2COCH_3 \xrightarrow{h\nu} Cl^{\bullet} + \underset{(51)}{{}^{\bullet}CH_2COCH_3} \quad (59)$$

abstract hydrogen, to form acetone, or dimerize. Details of the excited states involved were not established. Extension of such photochemical studies to substituted phenacyl chlorides also revealed the occurrence of a novel rearrangement reaction. Thus, whereas phenacyl chloride could be photolysed in alcoholic solution to give, mainly, acetophenone, derivatives substituted with electron rich *o*- or *p*-groups (e.g. **52**) mainly produced the rearranged ester **53** along with smaller amounts of the aryl chloride **54**[119]. A radical process was favoured which involved the intermediate



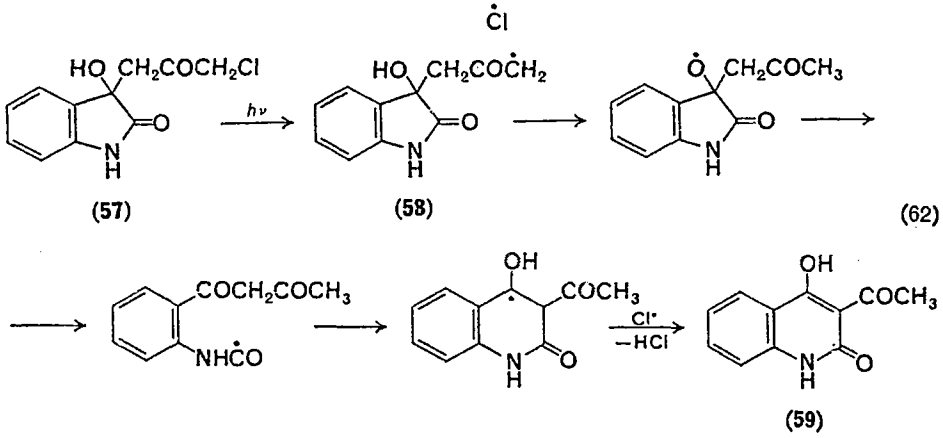
(52) (53) (54) (60)

55. Loss of chloride from 55 leads to the intermediate 56, which can be attacked by solvent to produce the ester 53. Alternatively, ketene loss can occur to give the chloride 54.



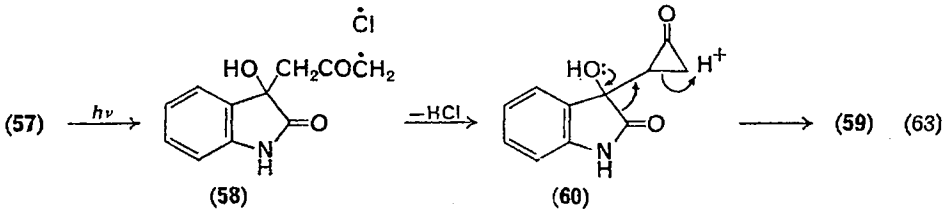
(61)

A more deep-seated rearrangement occurs in the photolysis of the chloroketone (57), obtained by the addition of chloroacetone to isatin. The principal product was 3-acetyl-4-hydroxycarbostyril (59). A mechanism involving initial homolysis of the carbon–chlorine bond, to produce the radical 58, was proposed, followed by a hydrogen atom transfer from the



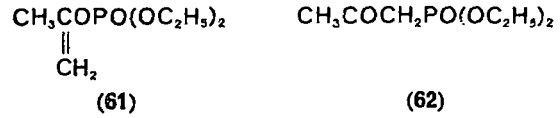
(62)

hydroxyl group—an energetically unfavourable process—and ring expansion (reaction 63)[120]. A preferable mechanism would involve collapse of the diradical 58 or its equivalent, to a cyclopropanone 60, followed by ring expansion to the product 59:



(63)

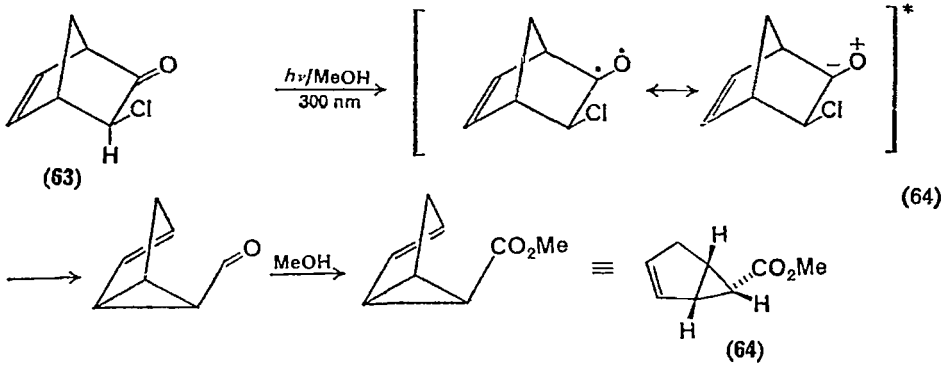
Initial carbon–chlorine homolysis probably follows excitation of the carbonyl group, representing one route for the collapse of the excited state. The addition of radical-quenching agents tends to alter the course of the reactions, thus supporting the evidence for an initial homolytic step. For example, in the presence of triethyl phosphite, photolysis of chloroacetone affords vinyl phosphate **61** and the ketophosphonate **62**, together with ethyl chloride, triethyl phosphate, diethyl ethylphosphonate and biacetonyl. A dual mechanism leading to the principal products **61** and **62** must



(61) **(62)**

operate since formation of the vinyl phosphate **61** was not inhibited by radical scavengers, whilst formation of the phosphonate **62** was inhibited. The former product arises by an ionic reaction and the latter by a free-radical reaction[121].

A detailed study on the photolysis of the *exo*-chlorobicyclo[2.2.1]-heptenone (**63**) in methanol showed that the reaction could be neither sensitized nor quenched, indicating an excited singlet-state reaction for formation of the product **64** (reaction 64) Because of the lack of typical free-radical produced side-products an ionic mechanism was favoured[122].

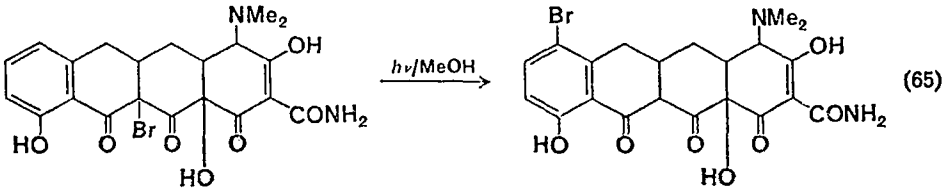


(63) **(64)** **(64)**

Fewer photoreactions with α-bromoketones have been recorded but a novel reaction of the tetracycline derivative **65**, which afforded the isomer **66**, has been examined[123].

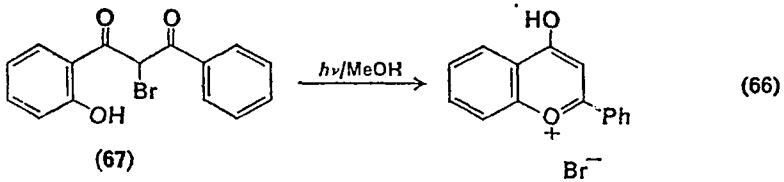
In the presence of α-naphthol, as competitor, little of the 7-bromo-derivative (**66**) formed, overall debromination occurring. This indicated debromination of the starting material with formation of free bromine or, in methanol, methyl hypobromite. Of the mechanisms considered, the results were best explained in terms of initial loss of hydrogen bromide

followed by a redox reaction between the starting material and the hydrogen bromide to produce the 'free' bromine. The bromine liberated then reacts with the reduced substrate at position 7, the known site of electrophilic



(65) (66) (65)

attack, to give the observed product **66**. With the related model compound **67**, reduction followed by cyclization to the flavone salt **68** occurred, and no bromination of the phenolic ring was noted (reaction 66)[124].



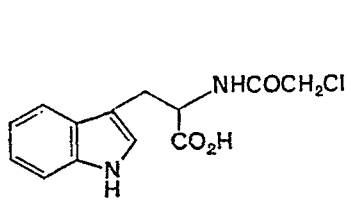
(67) (68) (66)

C. Chloroacetamides

A series of *N*-chloroacetyl derivatives of some pharmacodynamic amines have been photolysed. The amines used were generally derivatives of tryptophan and tyrosine. Thus, the tryptophan derivative **69** gave, after photolysis in methanol, the tricyclic derivative **70** in which a new carbon–carbon bond formed at position 4, a position not normally very reactive[125]. The 5-methoxytryptamine amide **71** behaved similarly, to produce dehydromelatonine **72**[126,127].

Mechanistic studies of these reactions have been made. It was shown that chloroacetamide and methyl chloroacetate are efficient quenchers of the excited *singlet* state of electron-rich aromatic compounds, i.e. via intermolecular energy transfer. In contrast, methyl acetate and acetamide gave little quenching. Also, although the u.v. absorption spectra of *N*-acetyltryptamine and *N*-chloroacetyltryptamine are very similar, the former fluoresces at least fifteen times more efficiently than the latter, indicating intramolecular energy transfer in the latter case[128]. Examination

of the products from irradiation of chloroacetamide with anisole in water showed the major products to be the corresponding methoxyphenylacetamides[129] and methyl chloroacetate behaved similarly[128]. As the polarity of the solvent was decreased far less of the substitution products



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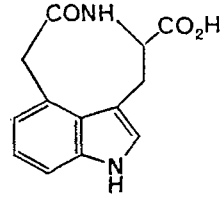

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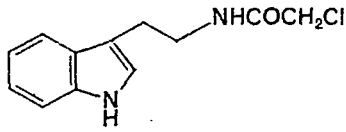

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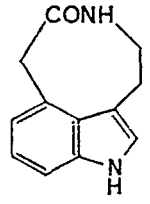
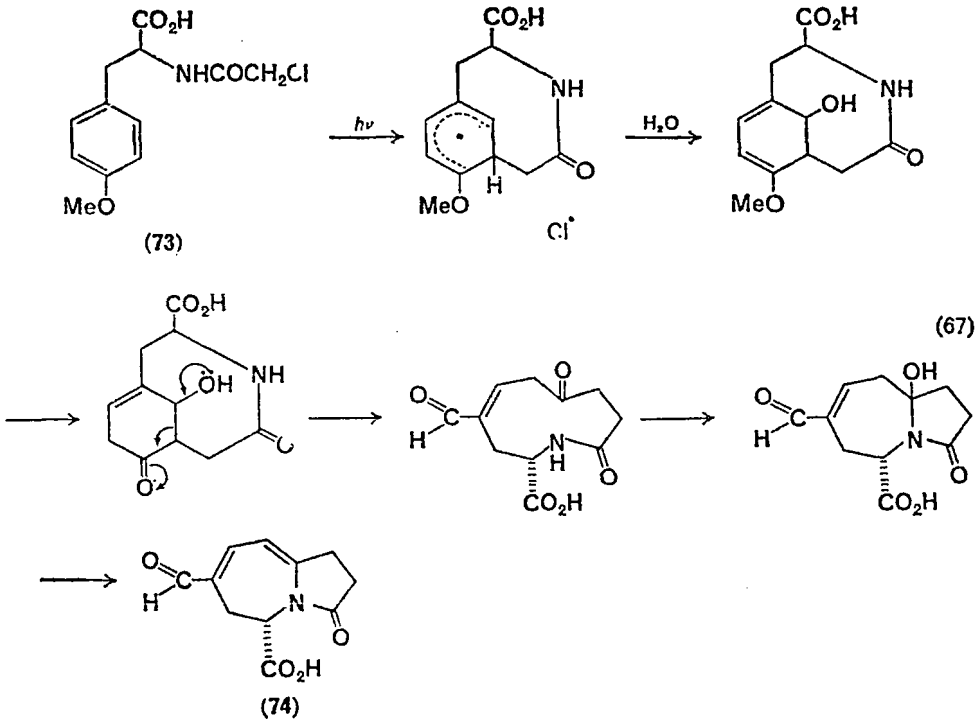


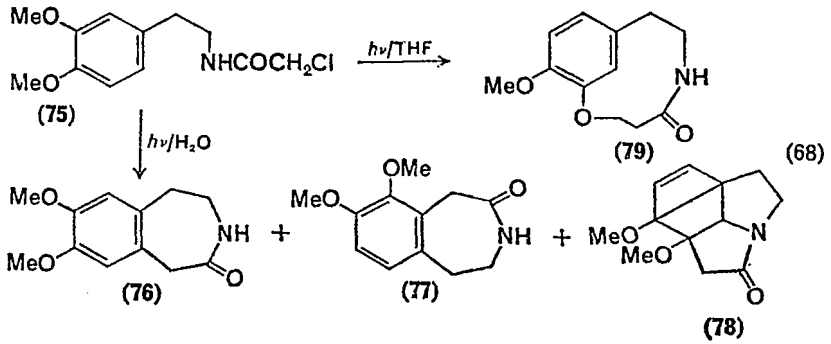
(72)

formed. It was shown that the ratio of the methoxyphenyl acetamide isomers was characteristic of a free-radical reaction[130].

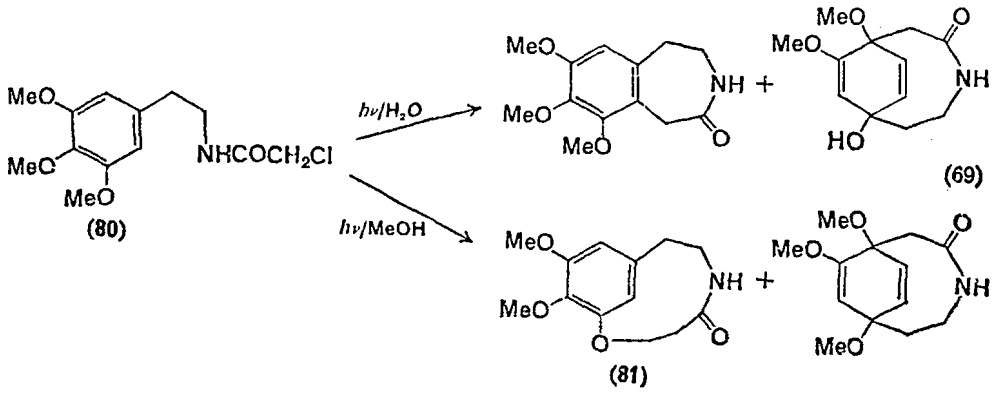
Such photocyclization reactions have been extended to produce benzazepinones (e.g. **76**) and azaazulenes (e.g. **74**). Photolysis of *O*-methyl-*N*-chloroacetyl-L-tyrosine (**73**) in water rapidly afforded the azaazulene (**74**) (reaction 67)[126]. Such photochemical reactions are extremely sensitive to the nature of the substituents on the aromatic ring. The introduction of an extra methoxyl group into the aromatic nucleus **75** gave no products analogous to the azaazulene **74** but, instead, a complex mixture (reaction 68)[131, 132]. In tetrahydrofuran the same three products (**76–78**) were formed together with the medium ring compound **79**, produced by radical attack on the methoxyl group. All the products can be rationalized in terms of initial carbon–chlorine homolysis. *N*-Chloroacetylmescaline (**80**) gave products analogous to those from compound **75**. In water some hydrolysis was observed but, in methanol, attack onto a methoxyl group was again noted (reaction 69) to give the product **81**. During these reactions hydrogen chloride is liberated and this was titrated to monitor the extent of reaction[133]. Presumably such photocyclization reactions are general for electron-rich aromatic substrates. The naphthalene derivative **82** gave the cyclized product **83** on irradiation[134].

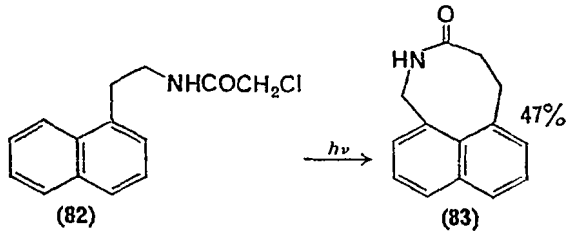


Phenolic derivatives appear to react more simply than their methyl ethers and the principal reaction products are the corresponding cyclized derivatives. *N*-Chloroacetyl-*m*-tyramine (**84**) in aqueous ethanol affords



70% of the cyclic products **85** and **86** (ratio 10 : 1) upon photolysis. Analogous products were obtained by the photolysis of more substituted phenols[135].





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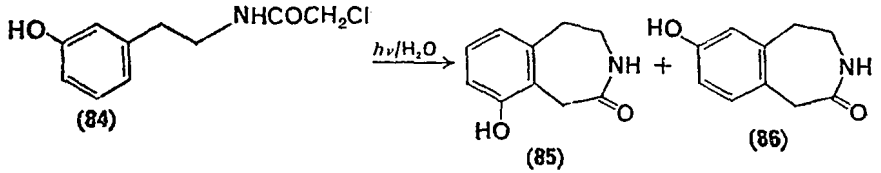
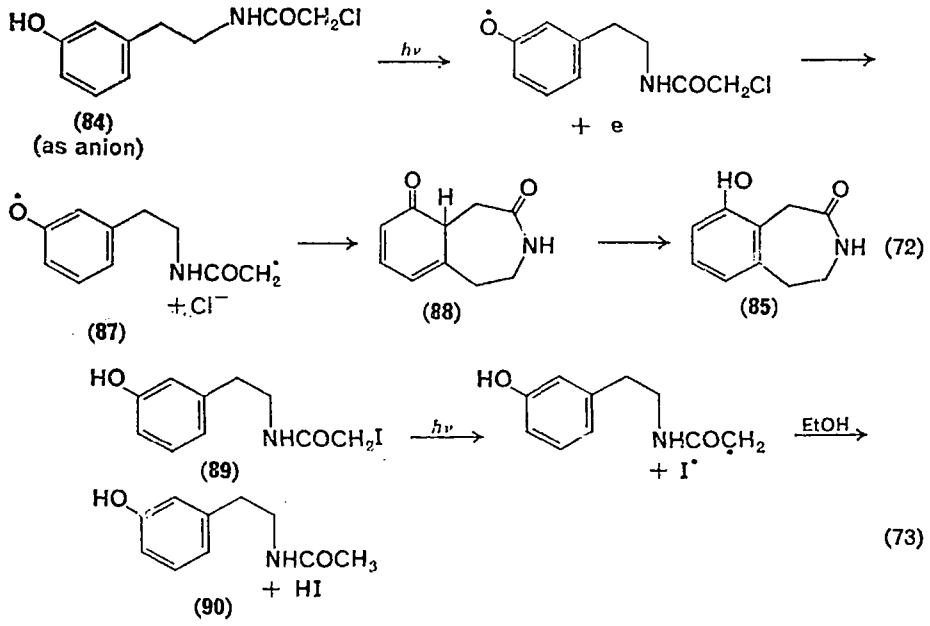


(71)

A flash photolysis examination of reaction (71) in aqueous solution showed that the first step was formation of a phenoxy radical, either by loss of a hydrogen atom from the phenol or by loss of an electron from the corresponding phenolate anion. It would be expected that the latter step might be preferred. The electron can be transferred either to the solvent or to the electronegative amide group, followed by reductive cleavage of the carbon–chlorine bond. Coupling of the diradical species **87** so generated affords a cyclohexadienone species **88**, which was also detected before its collapse to the phenol **85**. The reaction involves only one photon[136]. The mechanism outlined for the amide **84** is corroborated by the fact that photolysis of *N*-iodoacetyl *m*-tyramine (**89**) in aqueous ethanol gives much *less* cyclization (11%) than the *N*-chloroacetyl derivative, reductive elimination of hydrogen iodide predominating to give the acetamide **90**. In this instance the major photochemical reaction is *initial* carbon–halogen cleavage[135], reduction competing successfully with intramolecular cyclization (reaction 73).



V. AROMATIC HALIDES

A. Arylation Reactions

A recent review[4] on the photolysis of iodo-aromatic compounds stresses the ease with which iodine–aryl bonds are broken upon photolysis. This ease of bond breaking reflects the relatively weak nature of this type of bond, with bond energy in the order of 230 Kj mole^{-1}. The free-radical nature of the bond cleavage was early recognized and it was also realized that such a process was a useful method for the preparation of aryl radicals[137]. Phenyl and aryl radicals are valuable in synthetic work and optimum conditions for their preparation from iodo-aromatics by photolysis are now clearly delineated. The reactions (74–80) can occur:

$$\mathrm{Ar{-}I} \xrightarrow{h\nu} \mathrm{Ar^{\bullet} + I^{\bullet}} \quad (74)$$

$$\mathrm{Ar^{\bullet} + I^{\bullet}} \longrightarrow \mathrm{Ar{-}I} \quad (75)$$

$$\mathrm{Ar^{\bullet} + I_2} \longrightarrow \mathrm{Ar{-}I + I^{\bullet}} \quad (76)$$

$$\mathrm{Ar^{\bullet} + R{-}H} \longrightarrow \mathrm{Ar{-}H + R^{\bullet}} \quad (77)$$

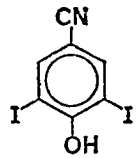
$$\mathrm{Ar^{\bullet} + ArH} \longrightarrow \mathrm{[Ar{-}ArH]^{\bullet}} \quad (78)$$

$$\mathrm{Ar^{\bullet} + [Ar{-}ArH]^{\bullet}} \longrightarrow \mathrm{Ar{-}Ar + ArH} \quad (79)$$

$$\mathrm{I^{\bullet} + [Ar{-}ArH]^{\bullet}} \longrightarrow \mathrm{Ar{-}Ar + HI} \quad (80)$$

The homolysis of aromatic iodides can also be sensitized. For example, 1-iodonaphthalene is relatively stable towards light of wavelength 360 nm but it readily dissociates at this wavelength upon the addition of benzophenone[138]. Iodine exchange has also been noted in the photolysis of aryl iodides (reaction 76)[139]. Hydrogen abstraction (reaction 77) by phenyl radicals is also known[140], as well as abstraction of chlorine from carbon tetrachloride[141,142] and of bromine from bromoform[4]. However, one of the most important reactions of an aryl radical involves its coupling with aromatic substrates (reaction 78) and this section will concentrate on the utility of this process.

In benzene aryl radicals undergo phenylation in preparative amounts[140]. For example, following the observation that the diiodocyanophenol (ionoxyl; **91**), a herbicide and molluscicide, is more toxic in the presence of light than in the dark, its photochemistry in benzene solution was explored[143]. The diphenyl-substituted product **92** was isolated in 71% yield. The bromo-analogue, the dibromocyanophenol (**93**) behaved similarly, giving **92**, but in lower yield. Some heteroaromatic iodides can



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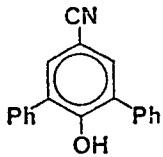

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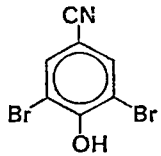
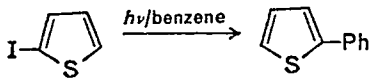


(93)

also be arylated by photolysis in aromatic solvents, for example 2-iodothiophen (**94**) gives 2-phenylthiophen (**95**) in benzene solution[144]. Some further examples are tabulated (Table 6). Of particular note is the selectivity of aromatic radicals produced in this way, arylation being the preferred fate. Hydrogen abstraction from both phenols and from aldehydes is a relatively inefficient side-reaction. Alkyl substituted iodo-phenols, however, seem to give lower yields of the arylated derivatives.

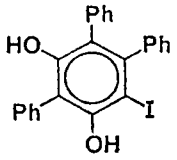
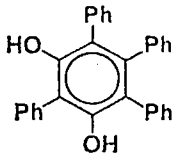
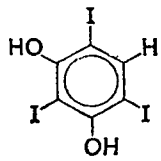
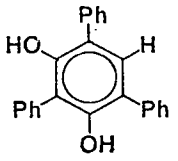
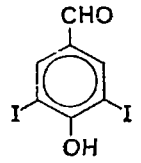
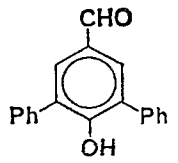
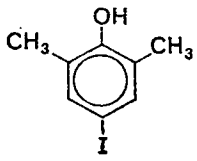
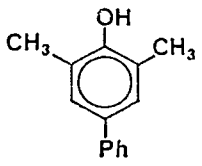
Self-coupling of aryl radicals is aided by carrying out the reaction in an inert solvent or with the neat iodo-aromatic compound and using a metal, such as silver, to scavenge the iodine radicals formed[150].



(94) (95) (81)

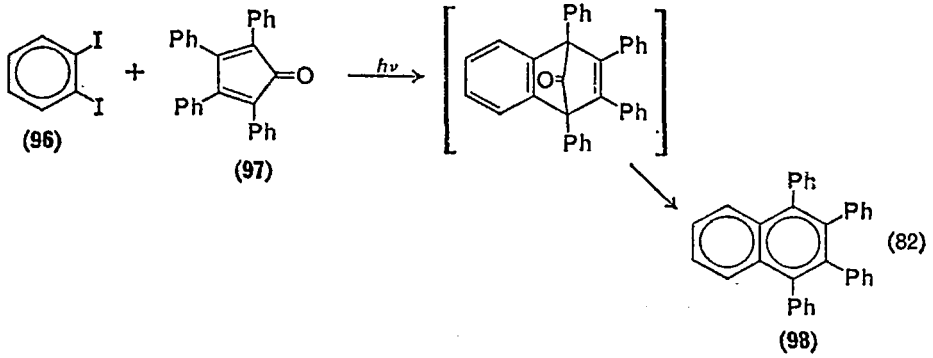
Polyiodobenzenes have also been photolysed (see Table 6). The intriguing possibility that *o*-diiodobenzene **96** would give benzyne upon photolysis has been confirmed. Photolysis of the diiodide **96** in the presence of

TABLE 6. Phenylation of iodoaromatic substrates and related compounds

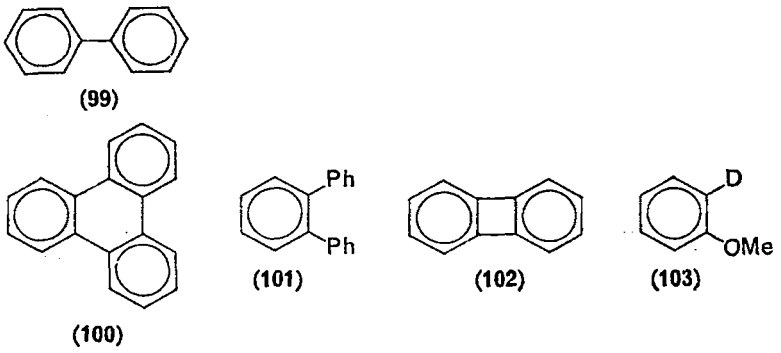
Starting material	Product	Yield	Reference
1-Iodo-2-phenyl-acetylene	Tolane	50	145
Benzoyl iodide	Benzophenone	12	145
2-Iodobenzaldehyde	2-Phenylbenzaldehyde	95	145
4-Iodobenzaldehyde	4-Phenylbenzaldehyde	90	145
Iodoacetic acid	Phenylacetic acid	67	145
Cyanogen iodide	Benzonitrile	50	145
2,4,6-Triiodophenol	2,4,6-Triphenylphenol	45	146
		53	147
		12	147
		20	148
		10	149

tetracyclone **97** gave the expected naphthalene derivative **98**[151]. However, in the absence of a trapping agent the iodide **96** only gave 2-iodobiphenyl and small amounts of biphenyl **99** and triphenylene **100**, the latter arising from further cyclodehydrogenation of *o*-terphenyl **101**[152]. No biphenylene **102**, as expected from benzyne, was formed. Since the tetracyclone derivative **98** could have been formed by a two-step radical process, rather than by a trapping reaction of benzyne, *o*-diiodobenzene **96** was photolysed in deuteriomethanol. Mass spectral analysis of the anisole produced showed that it was principally monodeuterated (i.e. **103**),

as required for the intermediacy of benzyne[4]. Neither *m*- nor *p*-diiodobenzene gave significant quantities of anisole upon photolysis in methanol. The absence of even traces of biphenylene from the photolysis of **96** in

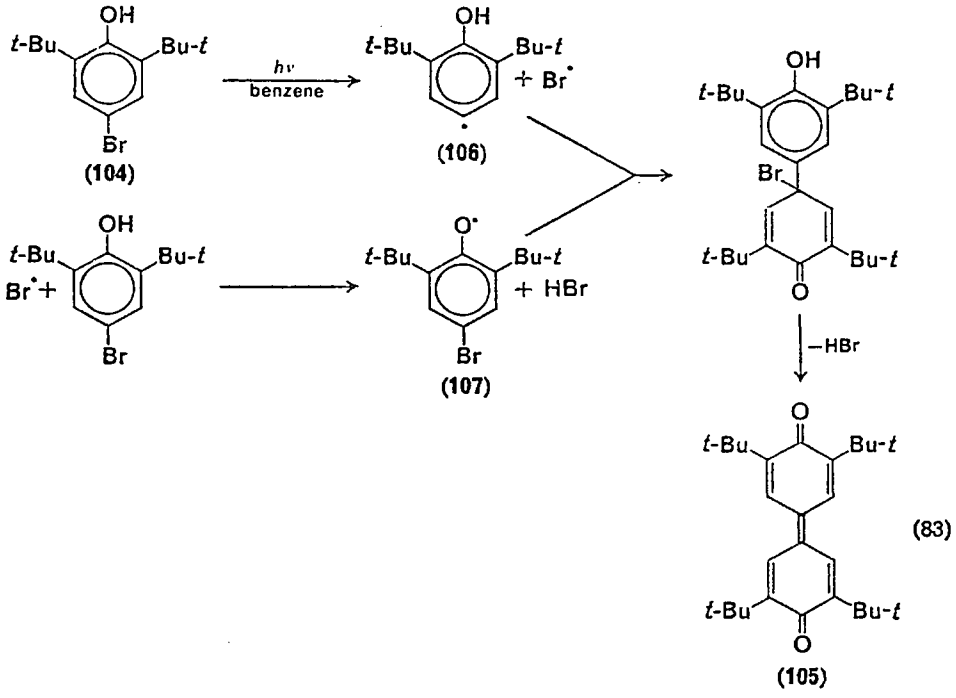


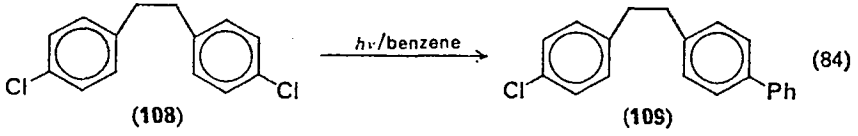
benzene[153] can only be explained by a reversible reaction of the benzyne with the iodine liberated, i.e. the concentration of free benzyne is always exceptionally low.



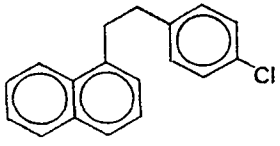
Bromobenzenes also undergo photochemical bond cleavage and arylation with aromatic solvents but not so efficiently as for the corresponding iodides[154,155]. Whereas iodophenols arylate in benzene (see Table 6), the bromophenol **104** does so only poorly[156]. The major product was the diphenoquinone **105**, which must arise by formation of the corresponding phenoxy radical **106**. Since 4-bromo-2,6-xylenol also gave a poor yield of phenylated product it is presumed that the bromine radicals initially produced react preferentially with starting phenol to produce the phenoxy radical **107** and hydrogen bromide. Coupling of the radicals **106** and **107**, followed by loss of hydrogen bromide, gives the quinone **105** (reaction 83).

Aromatic chlorides are also photolabile[157] and can be arylated. In benzene phenylation occurs with formation of the corresponding biphenyl. Interestingly, only one chlorine atom could be replaced by phenyl with 4,4′-dichlorobibenzyl (**108**), the product **109** being photostable.





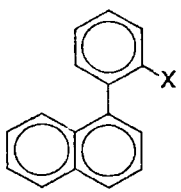
To account for this stability intramolecular quenching of the excited phenyl chloride ring by the biphenyl group was invoked. Thus the biphenyl group acts as a photochemical moderator, quenching further substitution. Likewise, the α-naphthyl derivative **110** was also found to be photochemically stable to further phenylation in benzene.



(110)

B. Photocyclizations

Intramolecular arylation reactions via photolysis of carbon–halogen bonds are useful for the preparation of cyclized products. In this context the 1-(*o*-halogenophenyl)-naphthalenes (**111**) gave highly informative results. Whereas the chloro-compound (**111**, X = Cl) mainly gave fluoroanthene **112**, the iodine derivative (**111**, X = I) gave little fluoranthene and mainly 2-(α-naphthyl)-biphenyl (**113**) and its further cyclized product benzo[g]chrysene (**114**), whilst the bromine derivative (**111**, X = Br) exhibited intermediate behaviour. Fluoranthene **112** was not formed from 1-phenylnaphthalene even after extended photolysis times. The iodo-derivative must react via homolysis of the carbon–iodine bond followed by the preferred arylation reaction with the solvent benzene. In this case the reaction can be sensitized with benzophenone[158] although neither the bromine nor the chlorine derivatives gave detectable quantities of products on sensitization, implying, in these cases, reaction via an excited singlet state. However, since similar products are formed from all three halides, albeit in different ratios, a common intermediate is implicated and this can only arise via initial homolysis of the carbon–halogen bond. Of interest is the observed photoreaction (scheme 85) of the 1-halogeno-8-phenylnaphthalenes (**115**) into the corresponding 1-(*o*-halogenophenyl)-naphthalenes (**111**)—a result again consistent with homolytic cleavage reactions. A kinetic explanation for the variation in product yields was formulated. Thus, a *rapid* equilibration of the radical **116** with the radical **117** should occur by intramolecular arylation. Since the radical **117** is strained the equilibrium will lie largely in favour of the radical **116**,



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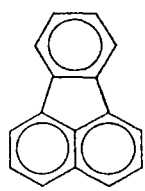

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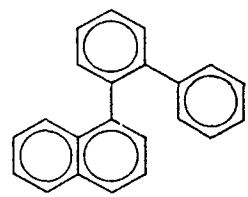

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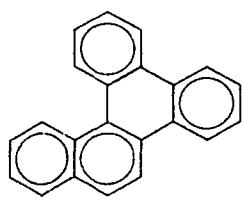
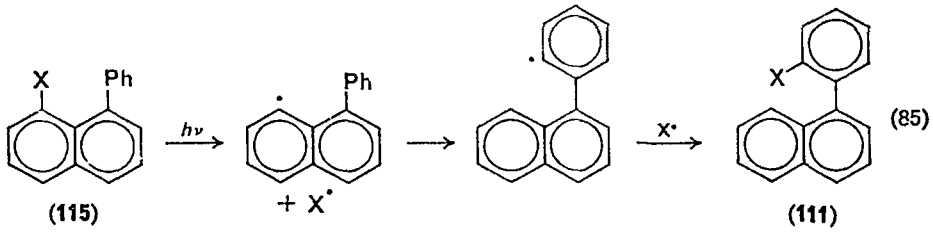


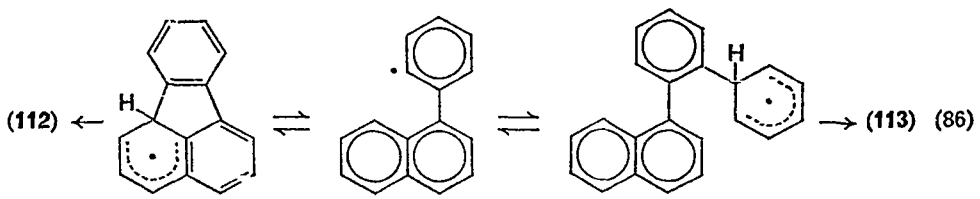
(114)

which can also undergo a much slower equilibration with solvent benzene to form the radical **118**. Chlorine coradical, which are extremely reactive, will immediately quench the radical **117** to give fluoranthene **112**, whilst iodine radicals are much poorer hydrogen atom abstractors and hence will allow formation of the radical **118**, from which hydrogen abstraction yields 1-(α-naphthyl)biphenyl (**113**)[159].

The preferred cyclization path of the phenyl ether **119** was to give the five-membered furan derivative **120** and not the xanthene **121**[160].

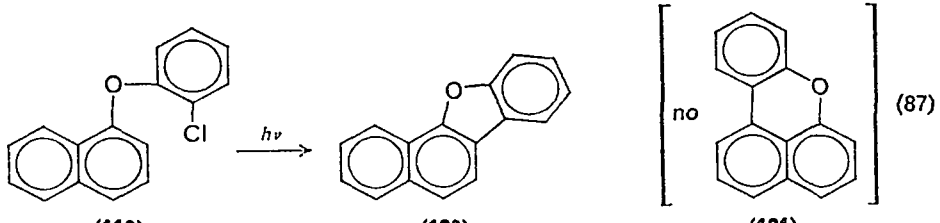


(115) (111)



(117) (116) (118)

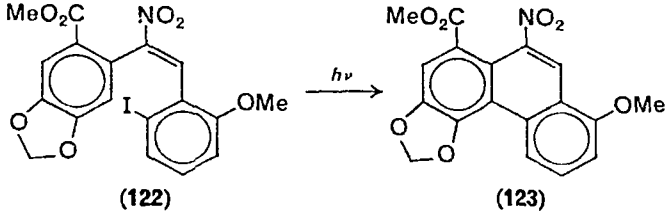
Intramolecular photocyclization reactions can be extremely efficient. The substituted stilbene **122** gave the methyl ester of aristolochic acid **123**, a tumour inhibitor, in 54% yield; normal chemical methods for the synthesis failed[161]. This reaction again proceeds via homolysis of the carbon iodine bond, since neither the corresponding 3′- nor 4′-iodo-isomers photocyclized, thus ruling out the possibility of dihydrophenanthrene intermediates[162].



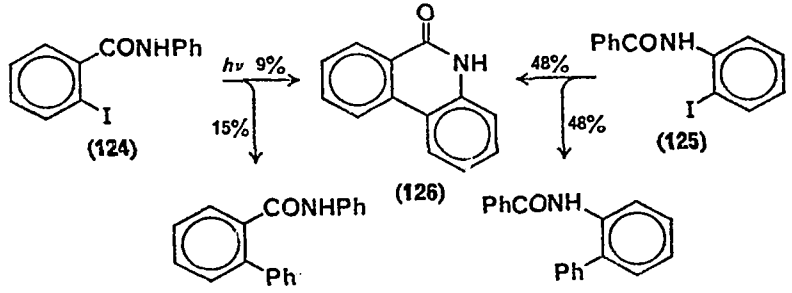
(119) (120) (121)

The iodobenzanilides **124** and **125** also cyclize with ease upon irradiation in benzene to give phenanthridone **116**, but with considerable amounts of phenylation also occurring[163]. The former iodide **124** gave a

rather low yield of phenanthridone (see reaction 89). In contrast, the *N*-methyl analogue **127** gave a reasonable yield of the corresponding phenanthridine **128**, together with the spirodienes **129** and **130**[164].

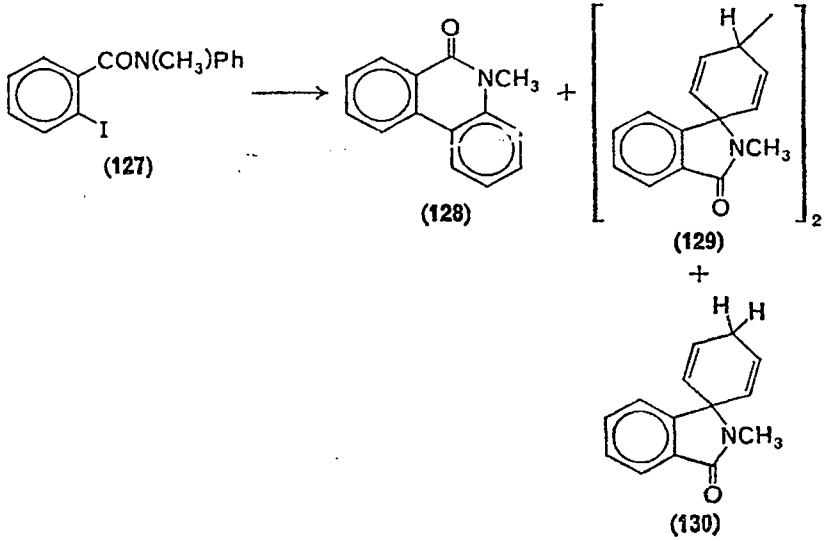


(88)



(89)

These trends can be rationalized in terms of the preferred conformations of the amide bond. For the amide **124** this would be with a *trans*-arrangement, from which intramolecular arylation can only occur after rotation about the amide bond. With the *N*-methyl-analogue **127** either conformation about the amide bond is possible, spectral evidence indicating a preponderance of the *cis*-isomer (9 : 1) at 0°C, hence allowing easier

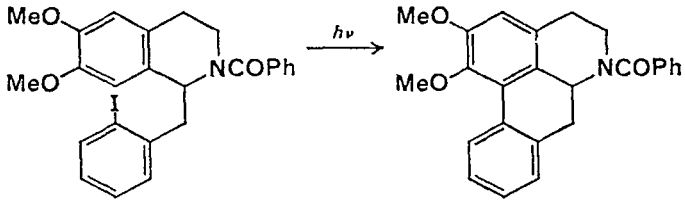


(90)

approach for intramolecular arylation. Presumably, for the iodoaniline derivative **125**, spirodienone formation does not compete well with the intra- and intermolecular arylation reactions.

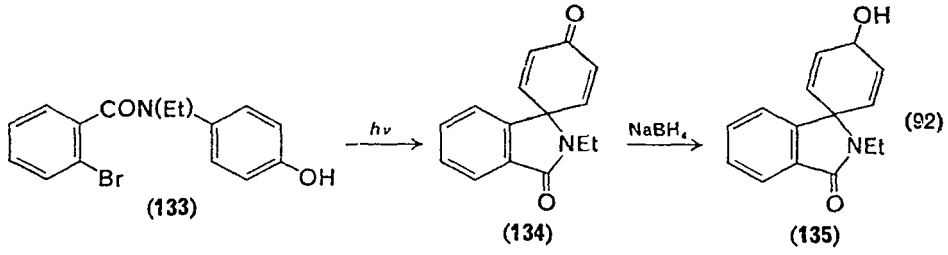
C. Alkaloid Synthesis

Photocyclizations of the type outlined in section V. B, have been used extensively for the preparation of alkaloids, particularly for those of the aporphine type[165]. For example, photolysis of the precursor **131** gave *N*-benzoyl-*nor*-nuciferine (**132**) in 38% yield. The intramolecular coupling

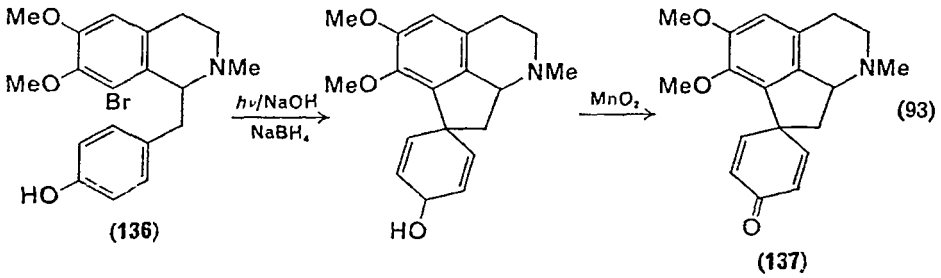


(131) (132) (91)

of some bromophenols has also been demonstrated. Thus the phenol **133** cyclized to the spirodienone **134** as one of the products. When the reaction was carried out in the presence of sodium borohydride the photosensitive dienone **134** was reduced to the corresponding dienol

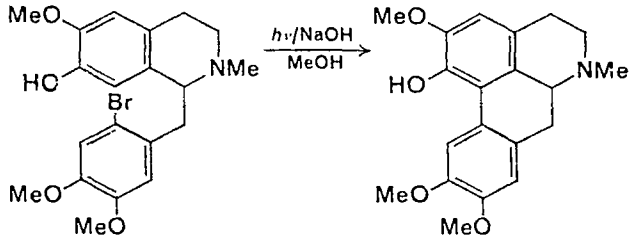


(133) (134) (135) (92)



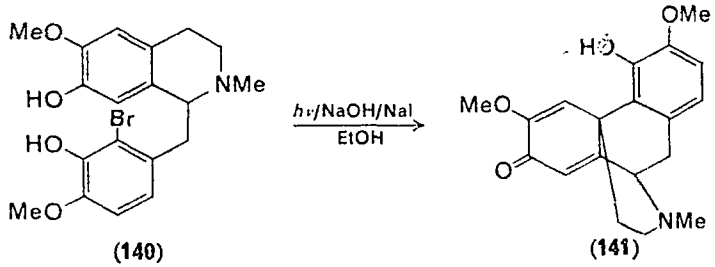
(136) (137) (93)

135 (reaction 92)[166]. This sequence of reactions has been adapted to the cyclization of benzyl-tetrahydroquinolines. In the synthesis of pronuciferine **137**, for instance, a 20% yield was obtained from the precursor **136**[167]. In the absence of sodium borohydride yields are poor since the dienone itself is extremely photolabile[168].



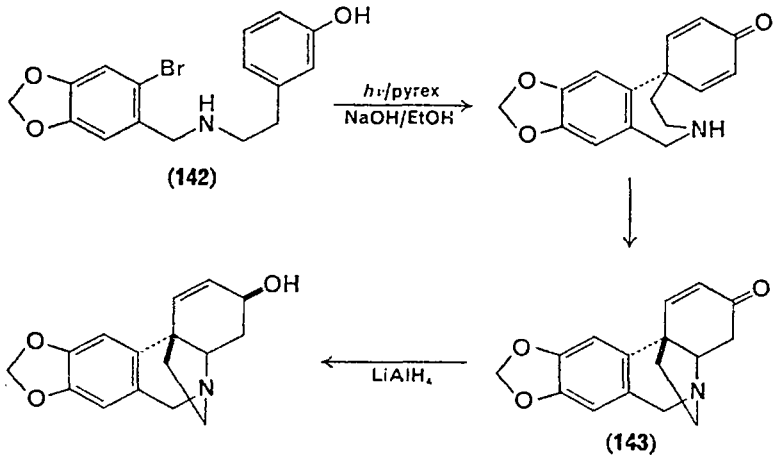
(138) (139) (94)

The site of the phenolic hydroxyl group tends to control the point of cyclization, which is either *ortho-* or *para-* to it. The bromophenol **138** is cyclized *ortho-* to the phenolic group, yielding the aporphine skeleton **139**[169] in high yield (52%). In contrast, the more hindered bromine derivatives, such as compound **140**, also yield some *para*-coupled product, leading to the morphinandienone alkaloids[170], in this case giving small quantities of salutaridine **141**[171] (reaction 95).



(140) (141) (95)

By the appropriate modification of the above reaction the crinine skeleton can be synthesized[172,173]. The precursor (**142**) after photolysis in aqueous base, followed by reduction, gave (±)-epicrinine (**143**) (reaction 96). Although yields of these reactions are often low, the simplicity of such a direct entry into the bridged alkaloid systems will be of increasing significance[172]. It is tempting to suggest that these phenolic bromides react by a mechanism similar to that established for aryl substituted chloroacetamides (see section IV. C).



VI. AROMATIC SUBSTITUTION REACTIONS

A. Homolytic Substitution Reactions

Aryl radicals, besides addition to aromatic substrates, as described in section V, can interact with a variety of reactants. Halogen exchange reactions have already been referred to (section V. A). Reduction of aryl radicals is also possible[140]. An example is the formation of aryl ketones from bromoaryl ketones upon photolysis in toluene. Intramolecular energy transfer from the $n \rightarrow \pi^*$ excited state of the carbonyl group is implicated, the excited state lying some $330 K_j\,mole^{-1}$ above the ground state. This excess of energy is sufficient to allow cleavage of the carbon–bromine bond but not sufficient for homolysis of the related aryl chlorides (bond strength ca. $370 K_j\,mole^{-1}$) which were not reduced under similar reaction conditions[174]. Subsequently, it has been found that chlorobenzene itself, which has excited state energies over $370 K_j\,mole^{-1}$ above the ground state, *can* be photoreduced. The reduction also proceeds at a similar rate for bromo- and iodobenzene and requires the presence of a hydrogen donor such as isopropanol[175]. High yields of benzene and the coproduct, pinacol, are formed. The reaction proceeds by carbon–chlorine bond homolysis. The stability often attributed to some aromatic chlorides must therefore occasionally reflect the availability of excited states of energy lower than that required to break the carbon–halogen bond (*vide supra*). Alternative reduction mechanisms can also operate. Charge-transfer donation of an electron to the aromatic halide nucleus from an electron-rich donor can occur after photolysis. The radical anion so formed

can then lose a halide ion to form an aryl radical (reaction 97). Dimethylaniline has been used to reduce chlorobenzene in this way, the hydrogen being abstracted from the solvent methanol[176].

$$Me_2NPh + PhCl \xrightarrow{h\nu} [Me_2NPh]^{+\cdot}[PhCl]^{-\cdot}$$

$$\longrightarrow Me_2\overset{+\cdot}{N}Ph + Cl^- + Ph^\cdot;\quad Ph^\cdot \xrightarrow{MeOH} PhH \qquad (97)$$

Hydrogen sources such as trialkyltin hydrides are also efficient reducing agents, especially for iodo- and bromo-benzenes. Triethyltin hydride reacts with 2,6-dichlorobromobenzene at 254 nm to give 1,3-dichlorobenzene in 97% yield[177].

Trivalent phosphorus compounds are also efficient aryl radical traps, trialkyl phosphites giving dialkyl arylphosphonates (reaction 98). Under

$$ArI + P(OR)_3 \longrightarrow ArPO(OR)_2 + RI \qquad (98)$$

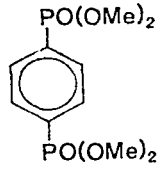
carefully controlled conditions the further reaction of the alkyl iodide produced with more trialkyl phosphite, via a normal Michaelis–Arbusov reaction, can be minimized[178]. The proposed mechanism is shown in reactions (99–101). Aryl bromides behaved similarly although fluoro- and

$$ArI \xrightarrow{h\nu} Ar^\cdot + I^\cdot \qquad (99)$$

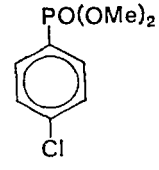
$$P(OR)_3 + Ph^\cdot \longrightarrow Ph\dot{P}O(OR)_3 \qquad (100)$$

$$I^\cdot + Ph\dot{P}(OR)_3 \longrightarrow Ph\overset{+}{P}(OR)_3I^- \longrightarrow PhPO(OR)_2 + RI \qquad (101)$$

chloro-benzenes appeared to be inert. In contrast, an investigation of a variety of dihalogenobenzenes showed that both *p*-iodochlorobenzene and *p*-bromofluorobenzene reacted with trimethylphosphite on photolysis to give appreciable quantities of the *bis*-phosphonate **144**. A more detailed



(144)



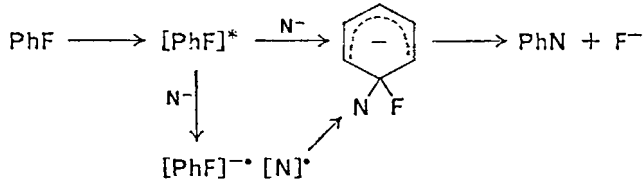
(145)

examination of the reaction showed that the monophosphonate (e.g. **145**) was first formed, this phosphorus substituent then activating the aromatic ring towards further substitution, leading to displacement of the second, normally inert, halogen atom[179].

Iodobenzene also reacts with phosphorus tribromide but the reaction may proceed by initial homolysis of the phosphorus tribromide[180]. Boron halides behave similarly with aryl iodides, hydrolysis of the product forming arylboronic acids.

B. *'Nucleophilic' Substitution Reactions*

Enhancement of nucleophilic aromatic substitution rates in excited states was first exploited by Havinga and coworkers[181] and has since been reviewed[182,183]. Aromatic halogen compounds can also be activated in this manner. Despite the resistance of the carbon–fluorine bond in fluorobenzene to dissociate homolytically, the excited state of the phenyl ring can add a nucleophile, followed by displacement of a fluoride ion. Piperidine can react with fluorobenzene in this manner, to give *N*-phenylpiperidine, whilst cyanide ion leads to benzonitrile[184]. Two mechanisms can operate. Nucleophilic attack on an electron-deficient excited state would lead to a σ-complex, which can then eliminate an anion. Alternatively, and perhaps more commonly, electron transfer from the nucleophile to the excited state of the aromatic substrate to form a charge-transfer complex could precede collapse of the σ-complex. Chlorobenzene behaves similarly to fluorobenzene with nucleophiles, but less efficiently because of the competing direct homolysis (at 254 nm). A similar photonucleophilic displacement of fluoride ion is observed with substituted benzotrifluorides[185] and with trifluoromethylnaphthols[186].



(102)

It was found that *m*-hydroxyl- and *m*-aminobenzotrifluorides are extremely susceptible to photohydrolysis, giving high yields of the corresponding benzoic acids, thus correlating with the excited state electronic distribution. In the ground state these trifluorides are very stable towards hydrolysis.

1-Bromonaphthalene is also photolysed under hydrolytic conditions to give, besides naphthalene, the hydrolysis product 1-naphthol. At low pH (<8), water is the nucleophile, whilst at greater pH hydroxide ion attacks[187].

The formation of charge-transfer complexes, in the excited state, between halogenobenzenes and donors is enhanced with electron availability

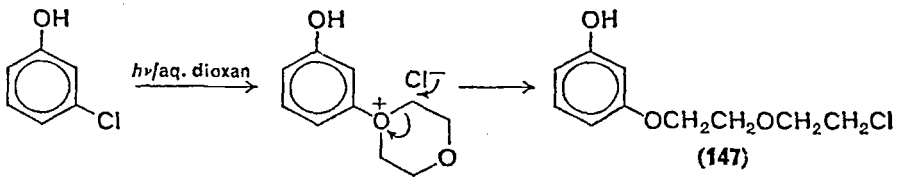
in the donor (see section VI. A)[176]. For example, chlorobenzene is normally inert to irradiation at 310 nm, but reacts with dimethylaniline at this wavelength to produce chloride ions. Electron donation from the dimethylaniline to the aromatic substrate precedes loss of a chloride ion and formation of a phenyl radical. In the *absence* of a reducing agent the phenyl radicals can couple with the donating species[188]. Even aliphatic chlorides can react in this way, dichloromethane giving the adduct **146** (scheme 103)[189].

$$Me_2NPh + CH_2Cl_2 \longrightarrow Me_2\overset{+\cdot}{N}Ph + \dot{C}H_2Cl + Cl^-$$

$$\dot{C}H_2Cl + Me_2\overset{+\cdot}{N}Ph_3 \longrightarrow CH_2{=}\langle\rangle{=}\overset{+}{N}Me_2\ Cl^- \qquad (103)$$

(146)

The sensitivity of halogenophenols towards photolysis is well documented. In dilute aqueous alkali, bromo- and chlorophenols lead to the corresponding dihydroxybenzenes together with some of the corresponding reduction product (phenol)[190]. A more recent study on the photolysis of phenols under neutral conditions showed that whereas *o*- and *p*-chlorophenols underwent reduction[175], the *m*-isomer gave predominantly photosubstitution[191]; *m*-halogenoamides behaved similarly and so did chlorophenylesters[192]. The very high reactivity of *m*-chlorophenol with nucleophiles, on photolysis, was demonstrated by irradiation in aqueous dioxan. Besides phenol, the principal product was the ether **147**. That little dihydroxybenzene was formed implies a charge-transfer process. By comparison with *m*-chlorophenol the bromo-analogue gave far more of the reduction product, phenol, whilst *m*-iodophenol gave only the reduction product.



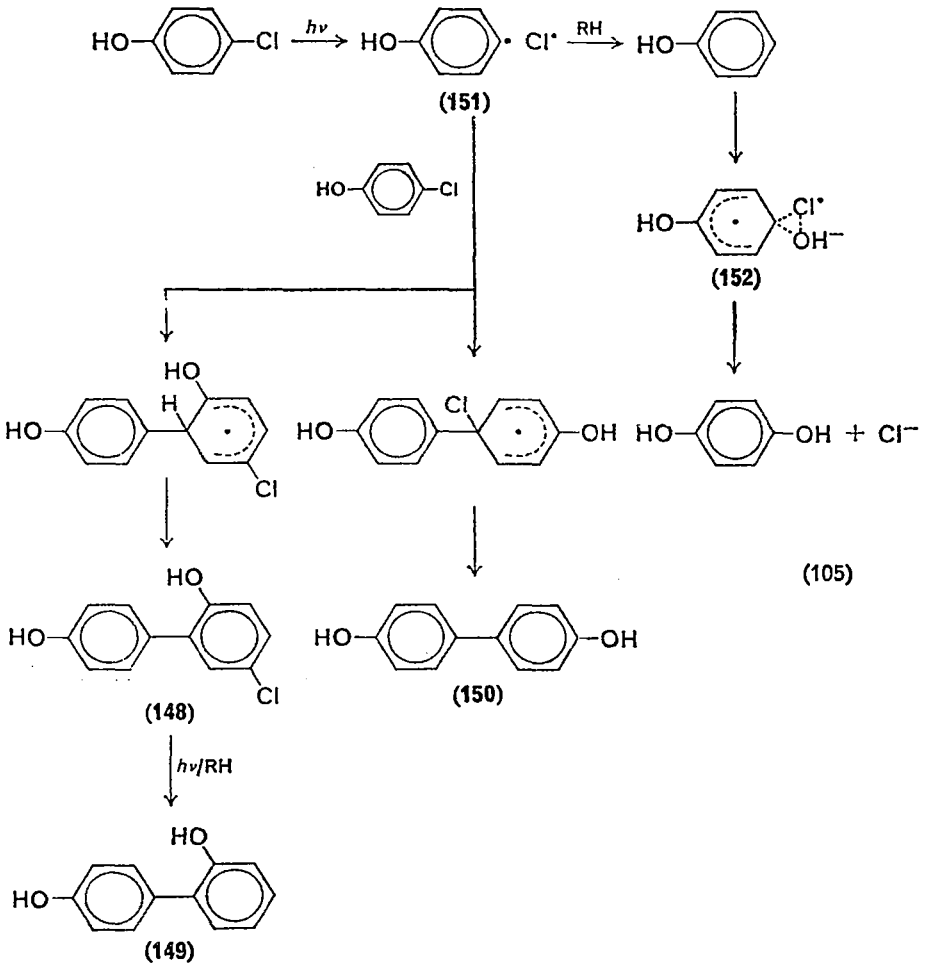
(104)

(147)

Under basic aqueous conditions solvolysis of *p*-chlorophenol gave coupled products such as **148–150**, besides hydroquinone and a little phenol. The yield of hydroquinone again increased in the order I < Br < Cl whilst that of the phenol and the biphenyl **150** increased in the order Cl < Br < I. Hydroquinone formation also increased with hydroxide concentration. The *m*-isomer mainly gave resorcinol. In the presence of

cyanide ion the *p*-isomer gave *p*-hydroxybenzonitrile, but the *m*-isomer again gave mainly resorcinol[193].

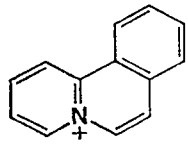
In order to explain these results, for the *p*-isomer, an initial carbon–halogen dissociation was again postulated (scheme 105). Coupling of the initial radical **151** to the starting phenol leads to the biphenyls **148**, **149** and **150**. Hydrogen abstraction gives the phenol and attack by hydroxide ion gives hydroquinone. Hydroxide attack probably takes place with electron transfer to the departing halogen atom **152**. Self-coupling of the phenyl radicals was discounted since their encounter rate would be too low. The increased amount of nucleophilic substitution of the *m*-isomer probably reflects the stronger electrophilic character of this position in the excited state, the substitution at this point being mainly ionic in character.



C. Heteroaromatic Halides

Scattered studies on the reactivity of halogenated heteroaromatic systems have been reported. A brief survey of some trends in this area is presented.

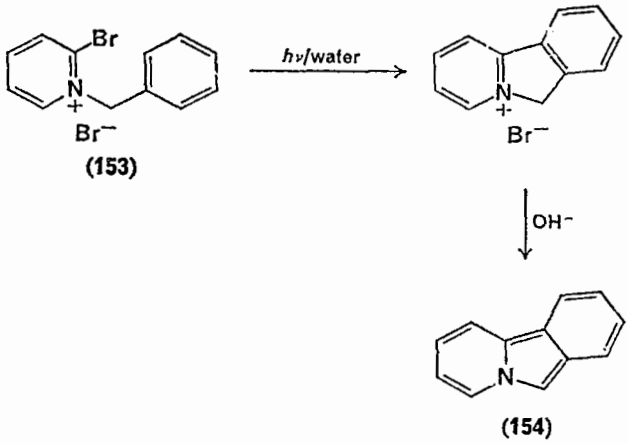
Intramolecular cyclization takes place when 2-bromo-*N*-benzylpyridinium bromide (**153**) is photolysed[194]. Treatment of the salt produced with one equivalent of base gave the indolizine **154**. 2-Bromophenacylpyridinium salts also cyclize on irradiation to form 7-hydroxybenzo[a]quinolizinium salts (e.g. **155**); both reactions proceed in high yield. In contrast, neither *N*-methyl-2-bromopyridinium bromide nor *N*-(4-nitrobenzyl)-2-bromopyridinium bromide reacted under similar photolysis conditions, using water as solvent. In the former case a rapid back-reaction predominates, whilst in the latter case intramolecular deactivation of the excited state might be responsible.

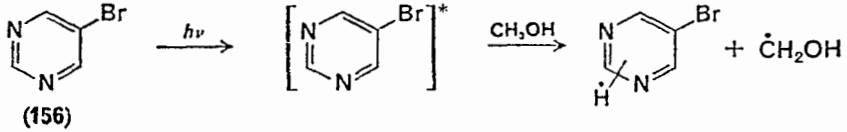


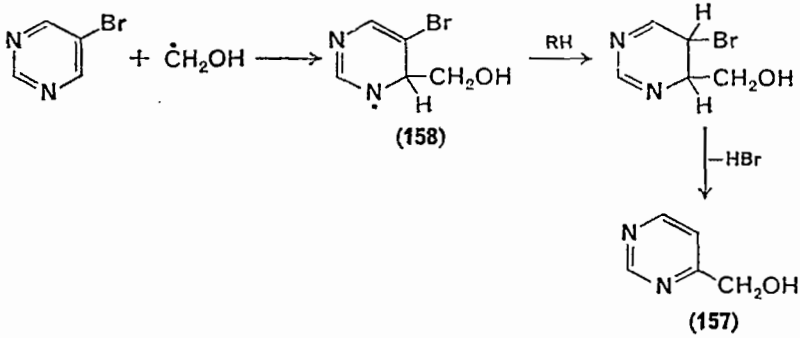
(155)

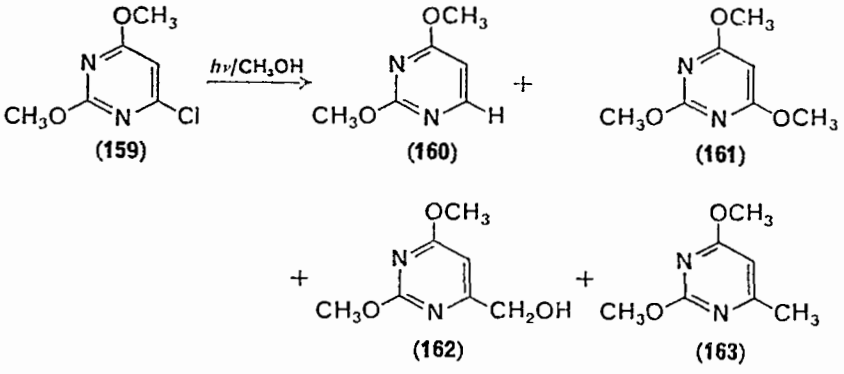
Many of the reactions of heteroaromatic halides should be analogous to those of the parent benzene analogues, such as the phenylation observed for the thiophen iodides[144] (reaction 81). With some heteroaromatic substrates such reactions have to compete with those characteristic of the heterocyclic substrate. Photochemical reactions of pyrimidines fall into this class, both additions to the azomethine link and apparent substitution of the halogen atom occurring. 5-Bromopyrimidine (**156**) gave 4-hydroxymethylpyrimidine (**157**) upon irradiation in methanol (reaction 107)[195]. Reaction proceeds by initial abstraction of hydrogen from a solvent molecule by an excited pyrimidine species. The hydroxymethyl radicals so formed then alkylate the starting pyrimidine to give the radical **158**. Hydrogen transfer to **158** completes the addition of the solvent and this is followed by loss of hydrogen bromide to give the observed product **157**. In this case *no* direct involvement of the bromide substituent occurs in the photochemical step.

2,4-Dimethoxy-6-chloropyrimidine (**159**) gave several photochemical products by reaction in methanol[196]. Direct reduction of the carbon–chlorine bond, via homolysis, produced the pyrimidine **160**. Photonucleophilic substitution also occurred, to form the methoxyl ether **161**,


Br
hν/water
Br⁻
(153)
OH⁻
(106)
(154)

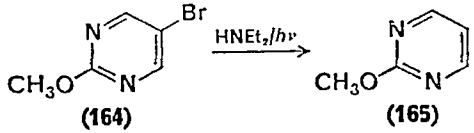

Br
hν
CH₃OH
+ ĊH₂OH
(156)


Br
+ ĊH₂OH
CH₂OH
RH
(107)
(158)
–HBr
(157)


OCH₃
hν/CH₃OH
CH₃O
Cl
H
OCH₃
(159)
(160)
(161)
CH₂OH
CH₃
(162)
(163)

as well as photoalkylation with methanol, followed by loss of hydrogen chloride, leading to the pyrimidines **162** and **163**.

Reduction of bromopyrimidines is aided by the presence of an electron donor. Thus diethylamine reacts with the excited substrate **164** to give, mainly, the reduced compound **165**[197]. Because of the relatively high concentration of diethylamine required for the reduction a short-lived excited species was suggested, probably an excited singlet state.



(164) (165) (109)

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The Chemistry of The Carbon–Halogen Bond
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CHAPTER 12

Radiation chemistry of the carbon–halogen bond

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I. INTRODUCTION

Halocarbons have acquired a fundamental importance in radiation chemistry, primarily through their often high electron affinities. They are widely used as electron scavengers and preferentially interfere with ionic reactions. As a result halocarbons are used in a vast number of studies, making it difficult to reach an overall view of the subject. This is reflected by the number of papers which report applications of organic halides: well over two thousand for the period of the last six years. In spite of this fact, no review has yet been written to cover the radiation chemistry of halocarbons exclusively. Rather, many aspects are treated under widely scattered headings. It is obvious that a proper choice of papers, pertinent to the present chapter, is not an easy task. Studies which use halocarbons merely as a tool to scavenge electrons or ionic species without particular reference to the basic process involved, will not be discussed here. Further, the discussion will be limited to systematic studies of the molecular processes, the elementary reactions and transient particles involved (sections II–VI). By far the most information is available for reactions with thermal electrons (section III). During recent years the knowledge of non-thermal electron reactions has rapidly increased, and the techniques of electron-swarms and near-monoenergetic electron-beams have made available extensive data on electron-attachment cross-sections as a function of the electron energy (section II). Radical reactions are not clearly separable from reactions in photochemistry, but a number of radiation chemical aspects will be treated in section VI. Only little specific information about ionic processes (section IV) and excited states (section V) is available. In the latter case many more facts are derived by photochemical methods.

The selected papers for sections II–VI happen to be mostly from the last three to four years. This is surprising since halocarbons have always been of interest to radiation chemists, but the development of techniques and

methods in recent years, such as the nanosecond or picosecond pulse radiolysis, the electron spin resonance of transients in liquid systems, the near-monoenergetic electron beam technique, etc., are obviously responsible for this accelerated activity.

Quite clearly many very interesting papers, particularly those about the radiolysis of pure halocarbons, their mixtures with non-halogen compounds and others are lost by such a selection on the principles of molecular processes. In section VII a selected number of pure halocarbons will be discussed, with the following twofold aim: (i) this discussion should fill in the lack of information which is compound-oriented, and (ii) it might serve to illustrate the preceding sections. Lack of space within the present scope demands that the examples are limited in number; only references to newer studies will be given. Although the selection principles for the whole chapter are rather personal, the author hopes that the text is more useful this way than a complete coverage of the radiolysis results of the many individual halocarbons could be.

For the reader who is not familiar with radiation chemistry, a few important facts and definitions might be reviewed:

(1) The chemical effects of ionizing radiations almost exclusively occur through the secondary electrons, which are formed in the primary ionization act. Their energies are preferably less than about 100 eV, but a small fraction of the secondary electrons are of energies well over 1000 eV. First, the secondary electrons move and collide with their surroundings within the Coulomb field of their cation. If an electron is thermalized before it escapes from this Coulomb field it will be recaptured by its own cation. Such an ion pair is called geminate. Otherwise it will move freely within the system until it finds another cation (not its own) or an electron-accepting molecule or is trapped in the medium. Such an electron is called a free electron, belonging to a free ion pair.

(2) Electron reactions are often considered to occur with *thermalized* electrons. This need not always be so. For reactions with non-thermal electrons see section II. During the thermalization process of an electron it passes various typical energy regions. (i) If the electron energy E_e is above the ionization potential I_p of the surrounding molecules, the electron can ionize or excite to various, rather high-lying, electronic excitation levels. (ii) If E_e is below I_p but still above the lowest excitation level, it will lose energy primarily through excitation. (iii) If E_e is below the lowest excitation level but above thermal it is called a subexcited electron. It will lose further energy by scattering processes and formation of temporary negative ion states. This subexcited energy range is the main object of reactions with halocarbons discussed in this chapter.

(3) All results discussed in this chapter are derived from experiments with low Linear Energy Transfer (LET), γ- and electron-irradiations. For halocarbons no particular results are known about effects from densely ionizing radiation, as from protons, α-particles, etc. (high LET).

(4) Yields from irradiations are always expressed by the G-value, which is defined by the number of particles produced (or consumed) per 100 eV absorbed energy in the system. Dose units are 1 rad = 100 erg/g = $6{\cdot}243 \times 10^{13}$ eV/g.

II. ELECTRON ATTACHMENT

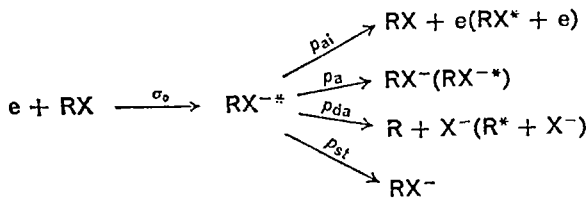
Of all the energies an electron attains during the thermalization process (see preceding section) the subexcitation energy range is one of the most interesting, concerning electron reactions with halocarbons (or any molecule with finite probability for negative ion formation). The thermalization process for subexcited electrons is governed by scattering processes and by temporary negative ion formation. If this negative ion state decays by autoionization the net result is a loss of energy for the electron involved. But if the negative ion state splits into an ionic plus neutral fragment or is itself a long-lived anion, the electron is trapped. This process is called electron attachment, being dissociative if fragments are formed immediately. Such processes have wide interest, not only in radiation chemistry, but also in upper atomosphere chemistry, chemistry of the electrical breakdowns of dielectric mediums, biochemistry and quite generally in organic chemistry for electron transfer reactions. It is believed that the toxicity of halocarbons is most likely due to electron capture processes.

In recent years electron attachment reactions were studied very actively on a molecular level, particularly with electron swarm and beam techniques. These studies are treated in a recent book by Christophorou[1] and in various reviews (e.g. references 2 and 3). The present section is an attempt to summarize the important facts for halocarbons.

A. Basic Processes

An electron of energy E_e which is captured by a halocarbon molecule will initiate one or several of the reactions (1a)–(1d). p_{ai}, p_a, p_{da} and p_{st} are the probabilities for autoionization, attachment, dissociative attachment and stabilization, respectively. Similarly the reaction cross-sections are labelled σ_{ai}, σ_a, σ_{da} or σ_{st}, and σ_0 is the cross-section for the formation of the transient negative ion state $(RX^-)^*$, normally in some excited state (electronic, vibrational and/or rotational). Its decay through autoionization (reaction 1a) corresponds to elastic scattering if RX remains in the

ground state, or inelastic scattering if RX is reformed in an excited state. In the dissociative electron attachment (reaction 1c) a chemical bond is broken. For halocarbons this is typically the carbon–halogen bond. The



(1a)

(1b)

(1c)

(1d)

collisional stabilization (reaction 1d) is characterized by its pressure dependence, in contrast to reaction (1b) where the anion is stable because of a minimum in the potential energy surface. But with halocarbons the dissociative electron attachment and the autoionization are the most favoured processes. The lifetime of the transient negative ion $(RX^-)^*$ can be as short as 10^{-14} s (one vibrational period) or more than milliseconds (see section II. C. 2). The anion is somewhat arbitrarily said to be short lived if it cannot be detected in a mass spectrometer ($\tau_{\frac{1}{2}} <$ microseconds) and long lived otherwise ($\tau_{\frac{1}{2}} >$ microseconds).

The electron-capture process is a vertical transition (Franck–Condon principles). The relaxation of the molecular structure therefore occurs after the electron is attached. For many halocarbons this relaxation process is identical to the breaking of the carbon–halogen bond. Therefore, the molecule RX suffering a dissociative electron attachment is considered diatomic-like. The process can be described by two-dimensional potential energy diagrams (see Figures 1 and 2). Before discussing these diagrams three important energy terms must be clearly defined:

(1) The *electron-affinity* (E_A of a particle) is defined as the difference in energy between the neutral molecule plus an electron at rest at infinity and the molecular negative ion, all particles being in their ground states. The actual determination of E_A-values is not straightforward. There is no experimental method known which is beyond any criticism. This difficulty is related to the necessary condition of ground state for all particles involved, including the negative ion state. Table 1A lists all E_A-values known today for halocarbon molecules and radicals.

(2) Because of the inherent difficulties in measuring the electron affinities Christophorou and Compton[16] introduced the *Vertical Attachment Energy* (VAE). This is defined as the difference in energy between the neutral molecule in its ground state plus an electron at rest at infinity and the molecular negative ion formed by addition of an electron to the neutral

TABLE 1A. Electron affinities (E_A) for halogen compounds

Compound	E_A (eV)	Method[a]	Reference
Halocarbons			
p-Chloranil	2·59	f	4
	2·5 ± 0·3	c	5
p-Bromanil	2·6	f	4
p-Iodanil	2·56	f	4
Fluorobenzoquinone	2·2 (?)	c	5
	1·5 ± 0·3	c	1, 5
CCl_4	2·12	c	6
$CHCl_3$	1·75	c	6
C_2Cl_6	1·47	c	6
Perfluorocyclobutane	0·61	b	7
Haloradicals			
Fluorobenzoquinonyl	2·4 ± 0·14	c	5
CCl_3	2·34	e	8
	⩾2·1 ± 0·35	b	9
	1·44	c	6
C_2Cl_5	1·52	c	6
Inorganic molecules[b]			
F_2	2·9 ± 0·22	b	10
Cl_2	2·52 ± 0·17	b	10
Br_2	2·87 ± 0·14	b	10
I_2	2·6 ± 0·1	b	10
SF_6	1·5 ± 0·2	c	11
	1·3	b	7
Inorganic radicals[b]			
F	3·448 ± 0·005	a	12
Cl	3·613 ± 0·003	a	12
Br	3·363 ± 0·003	a	12
I	3·063 ± 0·003	a	12
SF_5	3·66 ± 0·04	c	11
ClO_2	2·8	e	13
ClO_3	3·96	d	14
ClO_4	5·82	—	15

[a] a = photoabsorption; b = electron impact; c = equilibrium; d = lattice energies; e = estimated; f = charge-transfer spectra; g = electron scattering.

[b] Listed values for inorganic halogen compounds are for comparison only. They represent a best choice, but are not complete.

molecule without allowing a change in the internuclear separations of the nuclei involved. The vertical attachment energies for a series of aromatic halides are given in Table 1B. They are expected to be smaller than the true electron affinity of the molecule[1, 16].

(3) Another parameter often used is the *Vertical Detachment Energy* (VDE) defined as the minimum energy required to eject the electron from the negative ion in its ground state without changing the internuclear separations. The vertical detachment energy is easily obtained, but the neutral molecule is often produced in an excited state. The VDE-value is therefore not identical to the electron affinity.

TABLE 1B. Vertical attachment energies (VAE) for aromatic halogen compounds, determined by electron-scattering (these values are expected to be lower limits for the electron affinities)

Compound	VAE (eV)	Reference
1,3,5-Trifluorobenzene	−0·3	17
o-Dichlorobenzene	−0·4	18
m-Difluorobenzene	−0·6	17
Bromobenzene	−0·8	18
Chlorobenzene	−0·9	18
o-Chlorotoluene	−1·1	18
Fluorobenzene	−1·2	18

The *typical potential energy curves* for electron-attachment in Figure 1 will illustrate the definition for E_A, VAE and VDE. Because the electron-attachment process is vertical, it is clearly a resonance process: only a narrow range of electron energies as indicated by the hatching (Franck–Condon region) is effective. In Figure 1A a purely repulsive negative ion state is shown. In the region marked AI the energy of the negative ion state formed is above the neutral state. There is a finite probability for autoionization in this region. Both the reactions (1a) and (1c) may take place. The probability of interest for reaction (1c) will be given by the cross-section σ_{da} for dissociative electron-attachment. If the negative ion potential energy curve does show a shallow minimum this will not alter the dissociative process because of the excess kinetic energy of the fragments. In the case of Figure 1B a stable anion can be formed for all vertical transitions with $E(RX^{-*}) < E_1$. For energies above E_1 the attachment is dissociative and therefore reactions (1b) and (1c) can occur. The dissociative attachment cross-section σ_{da} will have a vertical onset at E_1, corresponding to the appearance potential of X^-. As a result the values for σ_{da} as well as the width of the resonance will be smaller. In Figure 1B the R—X separation for the ground state anion is much longer than for the neutral

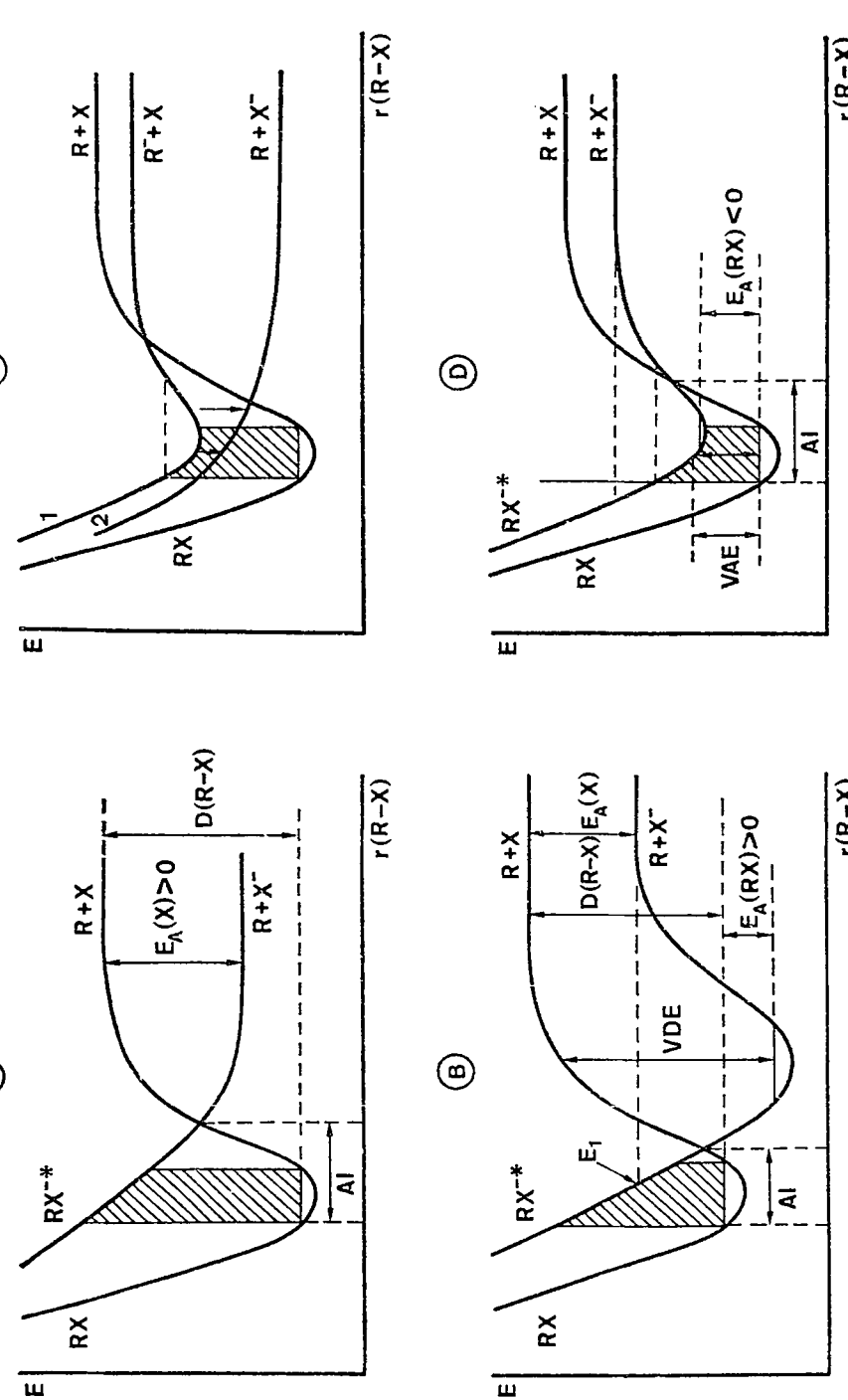


FIGURE 1. Typical potential energy curves for electron attachment processes: (A) dissociative electron attachment with purely repulsive anion state, (B) mixed dissociative and non-dissociative attachments, (C) attachment with intermediate negative anion state, (D) non-dissociative electron attachment. (The hatched area marks the Franck–Condon region; AI is the range in which autoionization is possible).

molecule. As a consequence the vertical detachment energy (VDE) is quite different from the electron affinity $E_A(RX)$. In Figure 1C the electrons are first captured into a bound state $(RX^-)_1^*$ which can undergo an internal transition into the repulsive state $(RX^-)_2^*$ due to overlap of electronic states. Figure 1D displays potential energy curves for the non-dissociative electron attachment. The negative ions formed are very short lived since the electron affinity is negative and the ground state of the anions is still within the autoionization region. From experimental results it is found that the potential energy curves in Figures 1A and 1C represent most electron capture processes with halocarbons.

The examples discussed so far are representative for experiments with variable electron energies (e.g. the methods with electron swarms and

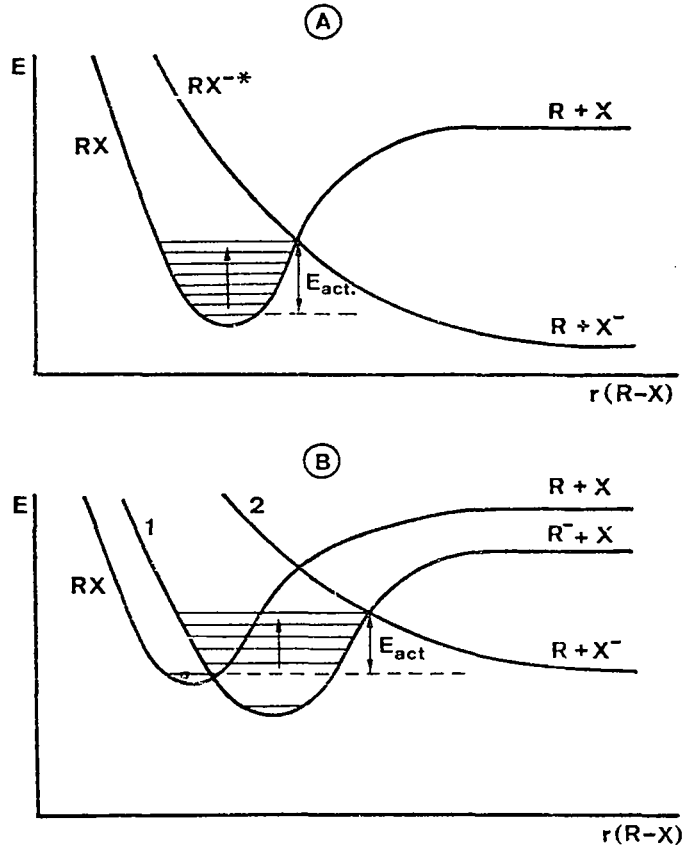


FIGURE 2. Typical potential energy curves to illustrate the thermal electron attachment processes with thermal excitation of the neutral molecule RX (A) or the intermediate anion state $(RX^-)_1^*$ (B).

electron beams). If thermal electrons only are used, electron attachment processes can still be studied, but the electron-accepting molecule must be thermally excited to populate the higher vibrational levels. Wentworth and coworkers have studied such processes[19–22] and Figure 2A illustrates the method. From the temperature dependence the activation energy E_{act} can be determined. If an intermediate anion state $(RX^-)_1$ is formed first (through *thermal* electron attachment), then this first anion state is thermally excited. The activation energy for the dissociative process is then given as shown in Figure 2B.

B. *Dissociative Attachment Cross-sections and Resonance Energies**

The experimental cross-sections σ_{da} are mostly derived from electron-swarm and electron-beam methods and from the retarding potential difference method (mass spectrometry, Lozier-tube, total ionization method)[1,3,23].† The cross-sections known today for halogenated hydrocarbons are summarized in Tables 2 and 3. (The attachment cross-section for non-halocarbons can be found in references 1 and 3.) For many of the molecules no mass analysis was done, but it is believed that the negative halogen ion is the dominant ion formed at the low energies involved[1,32]. The acceptor molecules can be classified roughly with respect to their resonance peak position. Table 2 lists all molecules with σ_{da} peaking at thermal energies, whereas in Table 3 the molecules with a dominant non-thermal resonance peak are given. In Figures 3–5 dissociative electron attachment cross-sections as a function of the mean electron energy E_e are shown for a number of typical halocarbon molecules. These will be discussed in section II. C. The values for σ_{da} which cover about six decades are obviously very sensitive to molecular details. For a given compound RX the cross-section increases strongly in changing the substituent from Cl to Br to I. Multiple halogen-substitution also enhances the cross-section. This can be clearly seen in Figure 6, where the sequences for the aliphatic chloro-, bromo- and iodo-compounds are listed separately along a logarithmic scale for the cross-section σ_{da}. Only compounds with two resonance peaks seem to be anomalous but in fact the integrated cross-section $\int_0^\infty \sigma_{da}(E_e)\,dE_e$ should be compared. In this case the anomalies disappear. It seems that the resonance energies ($E_{e,max}$) are without influence on the general sequences as shown in Figure 6. A correlation of

* Resonance energy = electron energy at which σ_{da} has its maximum.

† It must be stressed that all energies E_e given are mean values, since none of the techniques allow for measurement with a purely monoenergetic electron-beam.

TABLE 2. Cross-section σ_{da} and resonance energy $E_{e,max}$ for dissociative electron attachment. A. Molecules with σ_{da} peaking at thermal electron energies (for details see references 1 and 3)

Compound	Product ion	First peak (th)		Second peak (non-th)		Reference
		$E_{e,max}$[a] (eV)	$\sigma_{da,max}$ (cm^2)	$E_{e,max}$ (eV)	$\sigma_{da,max}$ (cm^2)	
CCl_4	Cl^- (?)	~0	$1{\cdot}6\times10^{-14}$	0·78	$5{\cdot}2\times10^{-16}$	24
		th	$2{\cdot}6\times10^{-14}$	—	—	25
CF_2Br_2	—	th	$2{\cdot}43\times10^{-14}$	—	—	25
$CFCl_3$	Cl^-	th	$1{\cdot}06\times10^{-14}$	—	—	25
		~0	$9{\cdot}5\times10^{-15}$	—	—	24
$C_2F_3Cl_3$	—	th	$3{\cdot}25\times10^{-15}$	—	—	25
CH_2Br_2	—	th	$3{\cdot}05\times10^{-15}$	—	—	25
CH_3I	—	th	$2{\cdot}35\times10^{-15}$	—	—	25
$CHBr_2—CHBr_2$	—	th	$1{\cdot}65\times10^{-15}$	0·55	$6{\cdot}5\times10^{-16}$[b]	25
CH_3CCl_3	Cl^- (?)	th	$1{\cdot}51\times10^{-15}$	0·5	$2{\cdot}7\times10^{-16}$[c]	25
CF_3Br	—	th	$1{\cdot}28\times10^{-15}$	—	—	25
C_2H_5I	—	th	$4{\cdot}50\times10^{-16}$	—	—	25
$CHCl_3$	Cl^- (?)	th	$3{\cdot}66\times10^{-16}$	0·215	$7{\cdot}32\times10^{-16}$	25
n-$C_{10}H_{21}Br$	Br^-	th	$3{\cdot}38\times10^{-16}$[d]	—	—	26
CH_3Br	—	th	$3{\cdot}08\times10^{-16}$	—	—	25
$CHFCl_2$	—	th	$1{\cdot}28\times10^{-16}$	>0·6	—[e]	25
CHF_3	—	th	$1{\cdot}08\times10^{-16}$	—	—	25
CF_3I	I^- (?)	0·05	$7{\cdot}8\times10^{-17}$	0·9	$3{\cdot}2\times10^{-17}$	1, 8
CF_3Cl	—	th	$4{\cdot}42\times10^{-17}$	—	—	25
CH_3Cl	—	th	$5{\cdot}81\times10^{-18}$	—	—	25
CHF_2Cl	—	th	$5{\cdot}81\times10^{-18}$	>0·6	—[e]	25
CH_2Cl_2	Cl^- (?)	th	$1{\cdot}48\times10^{-18}$	0·45	$3{\cdot}18\times10^{-18}$	25

[a] th = thermal energy (0·038 eV).
[b] Enhancement of the high-energy slope (presumed hidden peak).
[c] Weakly peaking within high-energy slope.
[d] Calculated from data in reference 26.
[e] Not measured beyond 0·6 eV.

TABLE 3. Cross-section σ_{da} and resonance energy $E_{e,max}$ for dissociative electron attachment. B. Molecules with σ_{da} peaking at electron energies higher than thermal (without thermal resonance) (for details see references 1 and 3)

Compound	Product ion	AP[d] (eV)	$\sigma_{da,th}$ [a, b] (cm^2)	Non-thermal resonance		Ref.
				$E_{e,max}$ (eV)	$\sigma_{da,max}$ (cm^2)	
o-$C_6H_4Cl_2$	Cl^-	—	x	0·36	$4·3 \times 10^{-16}$	27
$CHCl{=}CCl_2$	Cl^- (?)	~0	$1·8 \times 10^{-15}$	0·39	$2·84 \times 10^{-16}$	25
CF_2Cl_2	Cl^-	—	—	0·15	$1·10 \times 10^{-16}$	24
$CHCl_2{-}CH_2Cl$	Cl^- (?)	~0	$1·45 \times 10^{-17}$	0·42	$1·06 \times 10^{-16}$	25
C_6D_5Br	Br^-	—	x	0·80	$1·04 \times 10^{-16}$	27
C_6H_5Br	Br^-	—	x	0·84	$9·6 \times 10^{-17}$	27
o-$CH_3C_6H_4Br$	Br^-	—	x	0·95	$6·0 \times 10^{-17}$	27
n-$C_8H_{17}Br$	Br^-	~0	$5·2 \times 10^{-18}$	0·13	$3·22 \times 10^{-17}$	28
o-$CH_3C_6H_4Cl$	Cl^-	—	x	1·10	$2·2 \times 10^{-17}$	27
C_6H_5Cl	Cl^-	—	x	0·86	$1·4 \times 10^{-17}$	27
n-$C_6H_{13}Br$	Br^-	—	x	0·71	$7·41 \times 10^{-18}$	28
n-$C_5H_{11}Br$	Br^-	—	x	0·70	$6·13 \times 10^{-18}$	28
n-C_4H_9Br	Br^-	—	x	0·73	$5·50 \times 10^{-18}$	28
n-C_3H_7Br	Br^-	—	x	0·74	$4·14 \times 10^{-18}$	28
C_3H_5Br	Br^-	—	x	0·76	$3·95 \times 10^{-18}$	28
C_2H_5Cl	Cl^-	—	—	0·80 (?)	7×10^{-20} (?)	27
Perfluorocompounds						
CF_4	—	—	$7·27 \times 10^{-20}$	>0·6	—[c]	25
C_2F_6	F^-	2·2	—	3·75	$1·76 \times 10^{-17}$	29
	CF_3^-	2·8	—	3·75	$4·6 \times 10^{-18}$	29
	F^-/CF_3^-	2·93	—	4·51	$2·06 \times 10^{-17}$	30
C_3F_8	F^-	1·8	—	—	$3·65 \times 10^{-16}$	29
	CF_3^-	2·2	—	—	$2·3 \times 10^{-17}$	29
					$2·38 \times 10^{-16}$	30
	$C_2F_5^-$	2·1	—	—	$2·7 \times 10^{-17}$	29
	?	5·4	—	—	$1·1 \times 10^{-17}$	30
C_4F_8	F^-	3·0	—	4·3	$2·3 \times 10^{-17}$	29
		3·2	—	4·5	$7·56 \times 10^{-17}$	30
		6·2	—	6·9	$1·9 \times 10^{-17}$	30
		7·0	—	8·1	$3·6 \times 10^{-17}$	30
		9·3	—	10·4	$2·25 \times 10^{-17}$	30
	CF_3^-	5·0	—	—	—	29
	$C_4F_8^-$	~0	—	0·4	$2·14 \times 10^{-16}$	30
C_7F_{14}	$C_7F_{14}^-$, $C_7F_{13}^-$, $C_6F_{11}^-$	~0	—	0·15	$7·5 \times 10^{-15}$	31

[a] There is no resonance at thermal energies.
[b] x means that $\sigma_{da,th} \ll \sigma_{da,max}$, but absolute value is unknown.
[c] Not measured beyond 0·6 eV.
[d] Appearance potential.

TABLE 4. Resonance energies for transient negative ion formation through electron attachment[a]

Compound	Product ion	$E_{e,max}$ (eV)	Reference
$C_2H_2Cl_2$	[b]	~0·6	33
1-Chloronaphthalene	Cl^-	0·55 1·21 2·87	3
C_6H_5F	[b]	1·35	18, 34
1,3-$C_6H_4F_2$	[b]	0·6	17
1,3,5-$C_6H_3F_3$	[b]	0·3	17
1,2,3,4-$C_6H_2F_4$	[b]	~0	17
C_6HF_5	[b]	~0	17, 35
C_6F_6	[b]	<0·05	17
C_6F_5Cl	Cl^-	0·2	35
	$C_6F_5^-$	0·2	35
C_6F_5Br	Br^-	0·06	35
	$C_6F_5^-$	0·1	35
C_6F_5I	I^-	~0	35
	$C_6F_5^-$	~0	35
o-ClC_6H_4Cl	Cl^-	0·24	35
m-ClC_6H_4Cl	Cl^-	0·26	35
m-ClC_6H_4Br	Cl^-	0·31	35
	Br^-	~0	35
m-ClC_6H_4I	Cl^-	0·10	35
	I^-	~0	35
m-$ClC_6H_4NO_2$	Cl^-	0·9 3·4	35
	NO_2^-	0·9 3·3	35
m-$IC_6H_4NO_2$	I^-	0·0 0·8	35
	NO_2^-	6·1	35

[a] For some additional non-halogen-substituted pentafluorobenzenes see reference 35.

[b] The molecular anions are detected indirectly by the SF_6-scavenger technique (see e.g. reference 1).

σ_{da} with the resonance energy $E_{e,max}$, as was proposed[1,28], is generally not obvious for the halocarbons alone.

Many molecules were studied by the retarding potential method to yield relative ion efficiency curves as a function of initial electron energies[1]. These experiments do not provide absolute cross-section data. The resonance energies found by this technique for halocarbons are listed in Table 4. Some values from the SF_6-scavenger technique are also included (see section II. C. 1.c).

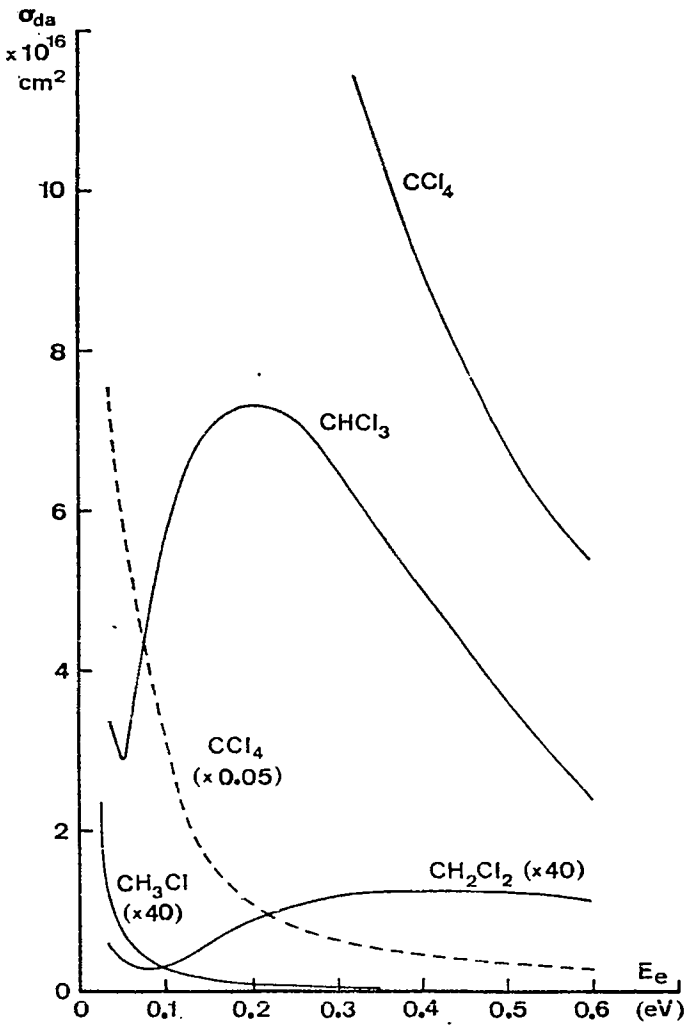


FIGURE 3. Cross-sections for dissociative electron attachments for chlorinated methane molecules[25, 26]. (Notice the different vertical scale factors.)

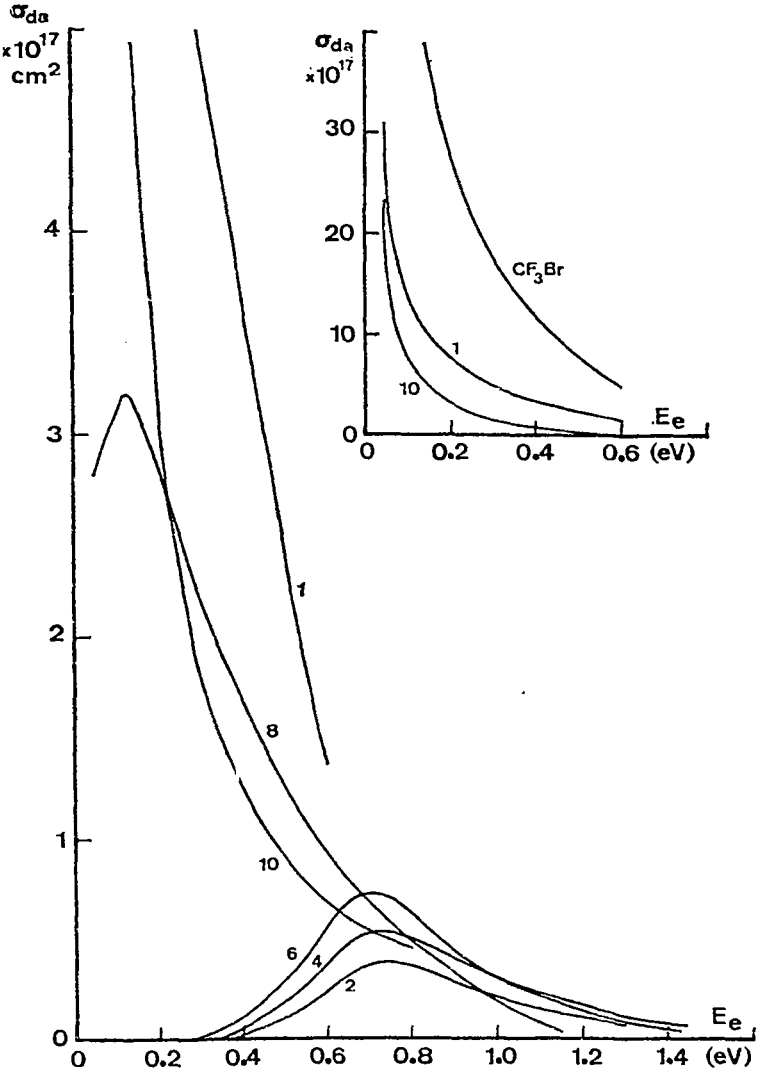


FIGURE 4. Cross-sections for dissociative electron attachments for alkyl bromides[25,26,28]. (The number of carbon atoms in the alkyl rest is used as index).

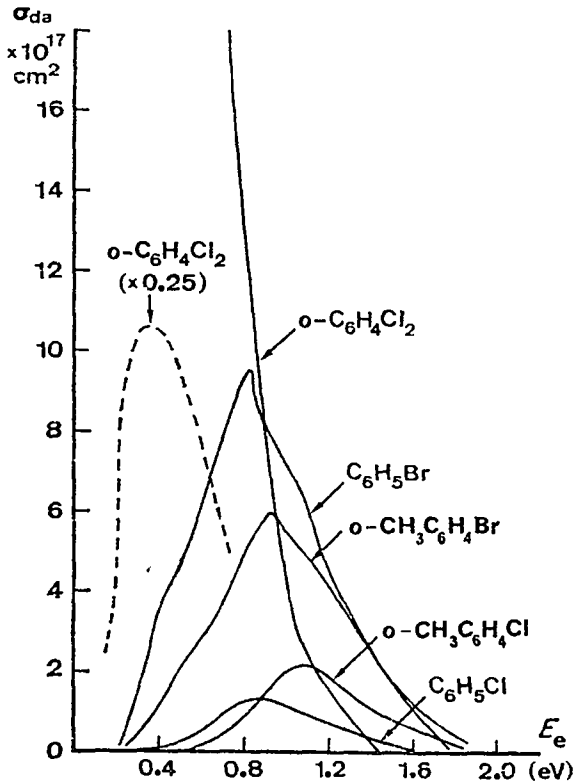


FIGURE 5. Cross-sections for dissociative electron attachment for aromatic halides[1, 27]. (Notice the different vertical scale factor for the dashed curve.) Reproduced with permission from L. G. Christophorou, *Atomic and Molecular Radiation Physics*, Wiley, London, 1971, p. 489.

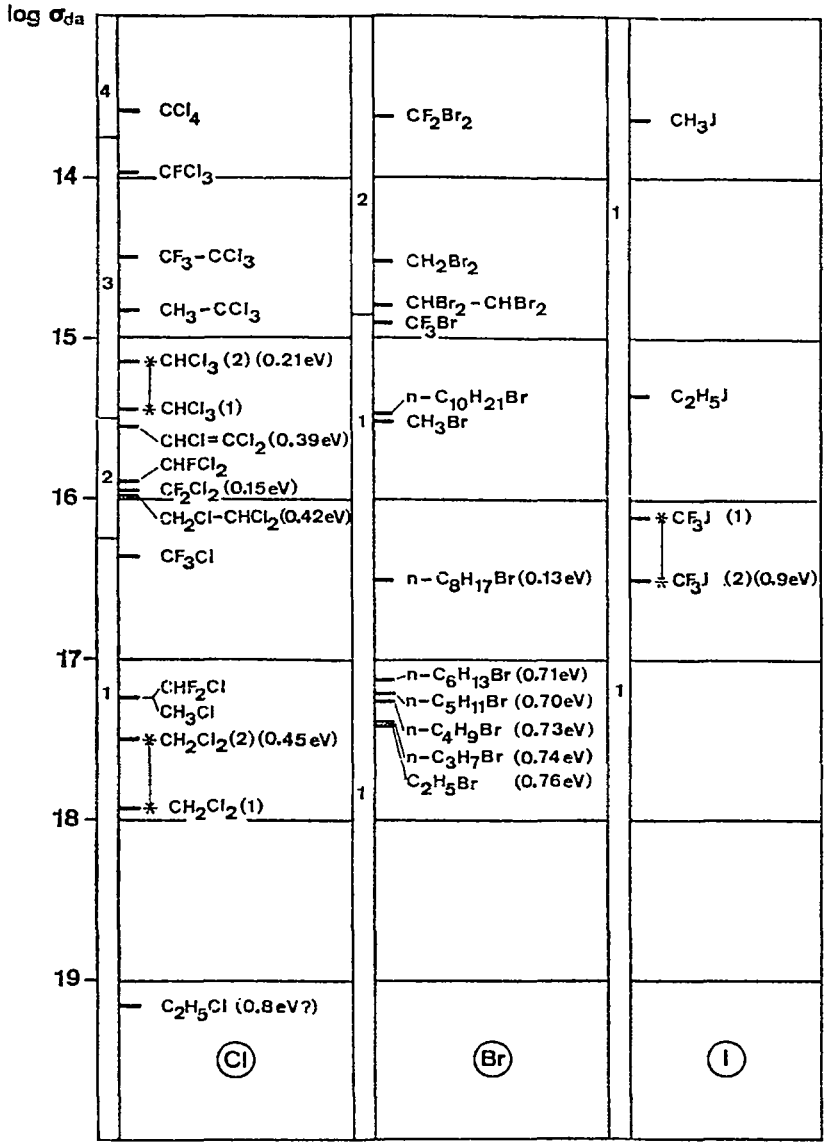


FIGURE 6. Survey of cross-sections σ_{da} for the chloro-, bromo- and iodocarbons, indicating the rules for the σ_{da}-values. (The number n in the narrow column marks the range of molecules with n halogen atoms, not counting F. The non-thermal resonance energies are given in brackets).

C. *Transient Negative Ions*

1. Short-lived anion states

All anions which have lifetimes shorter than microseconds are classified as short lived. The chlorinated methanes, a series of alkyl bromides and the aromatic halides will be discussed here as typical examples.

a. Chlorinated methanes[25,26]. Figure 3 shows the cross-section σ_{da} as a function of mean electron energies (notice the different vertical scale factors). The peak values for σ_{da} cover about four decades, supporting the rule that σ_{da} strongly increases with the number of halogen substituents in the molecule. CCl_4 is one of the most effective electron-capturing molecules known today. The second resonance peak at 0·78 eV[8,24] mentioned in Table 2 is possibly due to an experimental artifact[25]. From the strongly peaking σ_{da} at thermal energies (particularly for CCl_4 and $CHCl_3$) it must be concluded that the anion potential curve crosses the ground-state potential curve of the neutral molecule close to its minimum and that it is purely repulsive[1] (see section II. D for potential curves).

b. Alkyl bromides[25,26,28]. The resonance energies for ethyl- through *n*-hexylbromide are all about the same (0·70–0·76 eV). Their resonance cross-sections slowly increase to about double. (In Figure 4 a selection of alkyl bromides is shown.) For larger C-numbers the resonance peak is shifted towards thermal energies, for n-$C_{10}H_{21}Br$ reaching about the same thermal peak cross-section as for CH_3Br (Figure 4 inset). If all hydrogen atoms in CH_3Br are replaced by fluorine atoms the thermal peak cross-section increases by a factor of 4 (Figure 4 inset). This is a general effect as can be seen in Figure 6.

c. Aromatic halides[1,16,18,27,36]. The known cross-section spectra are reproduced in Figure 5. The resonance cross-section increases by substituting Cl with Br (or with I). At the same time the resonance energy decreases. The resonance peaks for *m*- and *p*-dichlorobenzene are close to the one for *o*-dichlorobenzene and the resonance for iodobenzene occurs at thermal energy[27]. In electron-scattering experiments (SF_6-scavenger technique, see e.g. reference 1, p. 336) for low-energy electrons with *o*-chlorotoluene, chlorobenzene, bromobenzene and *o*-dichlorobenzene scattering peaks were detected at energies corresponding exactly to the peaks of dissociative electron attachment[1,16,18]. It was concluded that the inelastic scattering process and the dissociative electron attachment are competitive processes from the same negative ion state. Similar results were found for 1-chloronaphthalene[3]. From the three peaks for σ_{da} (0·55, 1·21, 2·87 eV) the first and the third correspond in shape and position to scattering resonances. The third peak is assigned to the first π-triplet state.

A systematic study of the electronegative substitution effect on the benzene ring was carried out with a series of fluorobenzenes[17]. The peak energies for the electron attachment to C_6H_5F, 1,3-$C_6H_4F_2$, 1,3,5-$C_6H_3F_3$, 1,2,3,4-$C_6H_2F_4$ and C_6HF_5 are given in Table 4. A plot of these energies (vertical attachment energies) as a function of the number of F atoms decreases monotonously, suggesting an additive effect on the molecular electron affinity for each F atom added to the ring.

2. Long-lived anion states

The series of fluorobenzenes mentioned in the foregoing paragraph have lifetimes which lead into the class of long-lived anion states. The perfluorobenzene anion decays within about 12 μs. Long-lived anions are found preferentially for fluorinated compounds (Table 5). From theory it is

TABLE 5. Long-lived negative ion lifetimes $\tau_{\frac{1}{2}}$.

Compound	$\tau_{\frac{1}{2}}$ (μs)	$\sigma_{a,max}$[a]	Vibrational degrees of freedom	Reference
Perfluorocyclobutene	6·9	a	24	17
Perfluorocyclobutane	12·0	a	30	17
Perfluorobenzene	12·0	a	30	17
Perfluorotoluene	12·2	a	39	17
C_6F_5CN	17	b	33	35
C_6F_5Cl	17·6	b	30	35
C_6F_5Br	20·8	b	30	35
C_6F_5CHO	37	b	36	35
m-Chloronitrobenzene	47	b	36	35
Perfluorocyclopentene	50	a	33	17
$CF_3—CO—CF_3$	~60	c	24	1
Perfluorocyclohexene	113	a	42	17
Perfluoronaphthalene	123	b	48	35
Perfluorocyclohexane	450	a	48	17
Perfluoromethylcyclohexane	793	a	57	17

[a] Electron attachment resonance ($\sigma_{a,max}$) at energies (a) < 0·05 eV, (b) about 0 eV and (c) thermal.

expected that the logarithm of the half-lives should be linear with the vibrational degree of freedom for similar molecules[17]. This is roughly confirmed by Figure 7 which is based on the values of Table 5. The lifetime of perfluorotoluene deviates by about nine degrees of freedom, which may

correspond to the internal degrees of freedom of the CF_3 group. Therefore the electron might be attached to an orbital of the ring system only. The anomaly of the perfluoroacetone is not understood.

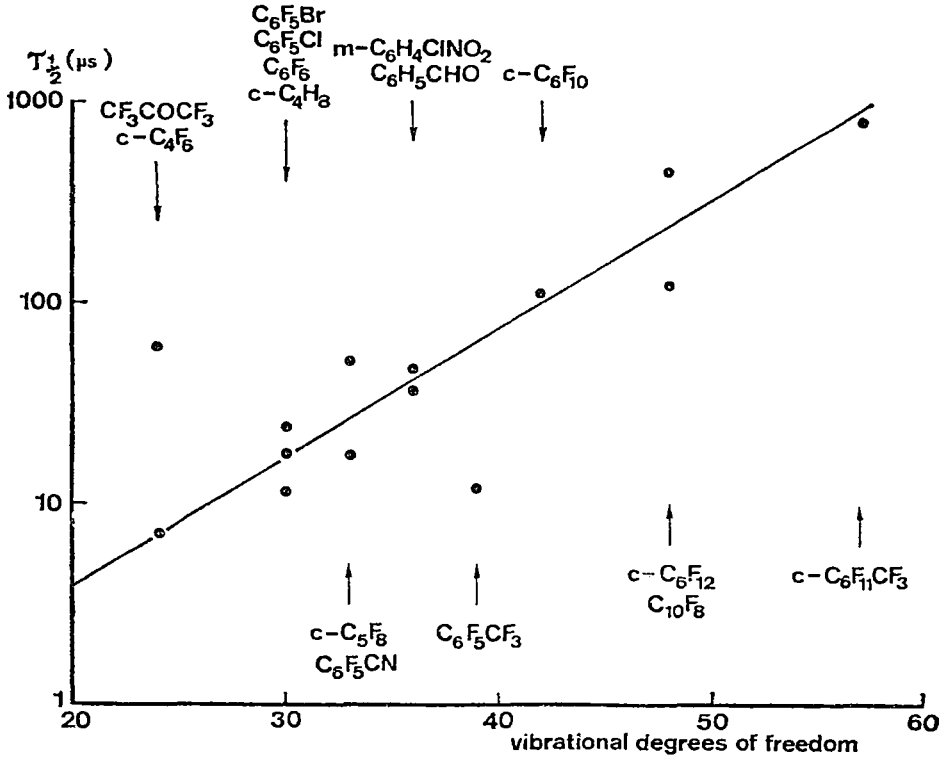


FIGURE 7. Correlation of the negative ion lifetimes with the vibrational degrees of freedom for a series of perfluorocarbons[17, 35]. (Reproduced with permission from W. T. Naff, R. N. Compton and C. D. Cooper, *J. Chem. Phys.*, 54, 212 (1971), Figure 3.)

D. Potential Energy Diagrams

From the many experimental data on the dissociative electron attachment processes potential energy curves for several halogenated hydrocarbons were derived[22, 28, 37]. For the calculation a Morse function was used for the neutral ground-state molecule (including an electron at infinity). The anion curve was an empirically modified Morse function with *one* adjustable parameter only[22, 37]. The results are basically characterized by the schematic drawings in Figure 2. The following compounds are described by the potential energy diagrams of Figure 1A or 2A: CCl_4, $CHCl_3$, CH_2Cl_2, CH_3Cl, CF_3Cl, CF_2Cl_2, $CHFCl_2$, $CFCl_3$[37], EtBr, *n*-PrBr[28]

and iodobenzene[22]. Most of them do show a very shallow minimum at large distances for the anion state. The following aromatic halides are found to fit the diagrams of Figure 2B[22]: *o*-dichlorobenzene, 3-chloroacetophenone, 1-chloronaphthalene, 1-bromonaphthalene. Similar behaviour, but with the minimum of the intermediate anion curve $(RX^-)_I^*$ higher than the minimum in the RX curve, is found for chlorobenzene, *o*-chlorotoluene, bromobenzene and *o*-bromotoluene.

TABLE 6. Experimental activation energies for thermal electron attachment (aliphatic halides from reference 37, aromatic halides from reference 22, unless indicated otherwise

Compound	E_{act} (kcal/mole)
Alkyl halides	
CH_3Cl	$12{\cdot}5 \pm 0{\cdot}4$
t-BuCl	$10{\cdot}9 \pm 0{\cdot}4$
$ClCH_2CH_2Cl$	$8{\cdot}7 \pm 0{\cdot}2$
$Cl-(CH_2)_8-Cl$	$7{\cdot}7 \pm 0{\cdot}3$
CH_2Cl_2	$7{\cdot}5 \pm 0{\cdot}4$
CF_3Cl	$7{\cdot}5 \pm 0{\cdot}2$
$CHFCl_2$	$5{\cdot}7 \pm 0{\cdot}4$
CH_3Br	$5{\cdot}7 \pm 0{\cdot}4$
$CH_2{=}CHCH_2Cl$	$5{\cdot}3 \pm 0{\cdot}3$
$C_6H_5CH_2Cl$	$3{\cdot}6 \pm 0{\cdot}2$
	2·9 [38]
CF_2Cl_2	$3{\cdot}4 \pm 0{\cdot}1$
$CHCl_3$	2·2 [38]
	$3{\cdot}1 \pm 0{\cdot}2$
$Br-(CH_2)_3-Br$	$3{\cdot}0 \pm 0{\cdot}2$
$Br-(CH_2)_2-Br$	$1{\cdot}9 \pm 0{\cdot}1$
CH_2Br_2	$1{\cdot}2 \pm 0{\cdot}2$
CH_3I	$0{\cdot}6 \pm 0{\cdot}1$
$CHBr_3$	$0{\cdot}2 \pm 0{\cdot}4$
$CFCl_3$	$0{\cdot}1 \pm 0{\cdot}1$
CCl_4	$-0{\cdot}6 \pm 0{\cdot}1$
	−0·57 [38]
Aryl halides	
o-Chlorotoluene	$10{\cdot}3 \pm 1{\cdot}2$
1-Chloronaphthalene	$9{\cdot}9 \pm 0{\cdot}3$
Chlorobenzene	$9{\cdot}2 \pm 0{\cdot}7$
o-Dichlorobenzene	$6{\cdot}9 \pm 0{\cdot}3$
o-Bromotoluene	$6{\cdot}3 \pm 0{\cdot}3$
Bromobenzene	$5{\cdot}9 \pm 0{\cdot}3$
4-Chloroacetophenone	4·8
3-Chloroacetophenone	4·6

From studies of the thermal electron attachment by the pulse-sampling technique[21] activation energies could be determined, as explained in section II. A and Figure 2. These values are given in Table 6 together with data from a pulse radiolysis study with a microwave resonance detector[38]. For CCl_4 both techniques yield the same negative activation energy*. But for chloroform and benzyl chloride the data from the rate-constant determination (pulse radiolysis) are smaller by 0·9 and 0·7 eV respectively. Also for SF_6 a similar difference of 0·9 eV appears[39,40]. This difference has large bearings on the calculation of the potential energy curves and the conclusions drawn therefrom.

All aliphatic halides in Table 6 seem to follow the schematic potential energy curves as drawn in Figure 2A. For molecules with small activation energies the anion curve must cross the ground-state neutral curve close to its minimum (e.g. CCl_4).

III. ELECTRON SCAVENGING PROCESSES

In the preceding section the electron-attachment processes were described by the energy spectrum of the attachment probability (cross-section of dissociative (σ_{da}) or non-dissociative (σ_a) attachment). But in experiments the electrons are rarely monoenergetic. For thermal electron reactions a Maxwell distribution of the electron energies has to be considered. For electron swarm experiments a Druyvesteyn distribution is assumed[1]. In radiation chemistry the electron spectrum $f(v)$ (v = velocity of the electrons) is complex and normally not known. It is defined by the slowing-down process, that means by factors such as the ionization potential, the levels of electronic excitation and the scattering cross-sections (elastic and inelastic) of the molecules involved. For many electron reactions studied a thermal electron energy distribution is assumed. But there is always a certain probability for reactions with epithermal electrons. From the electron attachment cross-sections $\sigma(v)$ (σ_{da} or σ_a) and the electron energy spectrum $f(v)$ (normalized with $\int_0^\infty f(v)\,dv = 1$) the corresponding absolute rate constant is given by

$$k = \int_0^\infty v.\sigma(v)f(v)\,dv \qquad \text{(A)}$$

If we assume that the maximum cross-section is related to the de Broglie

* The negative activation energy for the reaction $e + CCl_4$ is obviously due to the steep decrease of σ_{da} with the temperature (effect on the pre-exponential factor).

wavelength λ

$$\sigma_{max} = \frac{\lambda^2}{4\pi} = \frac{h^2}{4\pi m^2 v^2} \tag{B}$$

an upper limit for k can be estimated for reactions with thermal electrons[38]

$$k_{max} = \frac{1}{(2\pi)^{\frac{3}{2}}} \frac{h^2}{m^{\frac{3}{2}}(kT)^{\frac{1}{2}}} \tag{C}$$

If $\sigma(v)$ is strongly decreasing above thermal energies (see e.g. $\sigma_{da}(CCl_4)$ in Figure 3) then a contribution of epithermal electrons would decrease the observed rate constant. Warman and Sauer[41] used this dependence to estimate the time needed to thermalize the electrons. In 1 Torr of argon gas this is more than 50 μs: an additional 0·2 Torr of *n*-hexane reduces this time to less than 1 μs. In the following sections the electron-scavenging processes will be discussed for systems with increasing complexity and environmental influence. It must be recalled at this point that it will be necessary to consider carefully the interfering reactions such as ion and electron neutralizations and electron-transfer processes between two electron-accepting solutes[42,43], to mention but two. In general the possible interferences will not be discussed here, but the original papers should be consulted.

A. Gas Phase

There are various methods of studying thermal electron reactions in the gas phase. The data discussed here are derived (*i*) from pulse radiolysis experiments with optical detection systems or with a microwave resonance detection[44,45], (ii) from the flowing discharge method with a mass spectrometric detection[39] and (iii) from the electron cyclotron resonance method[7,46]. The rate constants for the gas-phase reactions of electrons with organic halides are summarized in Table 7. Similar to the cross-section data (Figure 6) the rate constant for CCl_4 is highest. The theoretical limit for this reaction, as calculated by equation (C), is $5{\cdot}0 \times 10^{-7}$ cm^3 s^{-1}[38], indicating that the experimental value is close to its theoretical limit. The data of Table 7 are fairly recent. This is due to recognition of the fact that such electron reactions are important in chemistry and biology and also to the development of newer techniques. Some of the differences between data from different methods are probably related to differences in the electron energy spectrum. Since the attachment cross-sections (σ_{da} or σ_a) are strongly varying with the electron energy the rate constant k, through equation (A), must also be sensitive to spectral differences (for details for

TABLE 7. Rate constants for gas-phase reactions with electrons (at room temperature unless shown otherwise)

Compound (RX)		k(e + Rx) ($cm^3\ s^{-1}$)	Reference
CCl_4		$4{\cdot}1 \times 10^{-7}$	38
		$4{\cdot}1 \times 10^{-7}$	7
$CHCl_3$		$2{\cdot}2 \times 10^{-9}$	38
CH_2Cl_2		$4{\cdot}7 \times 10^{-12}$	47
CH_3Cl		$1{\cdot}6 \times 10^{-8}$	48
CF_3Cl		$5{\cdot}2 \times 10^{-14}$	47
C_4Cl_6 (hexachlorobutadiene)		$7{\cdot}0 \times 10^{-10}$	48
CH_3Br		$1{\cdot}0 \times 10^{-11}$	48
	(393K)	$1{\cdot}3 \times 10^{-11}$ [a]	49
CF_3Br		$2{\cdot}4 \times 10^{-9}$	48
CH_3I		$5{\cdot}6 \times 10^{-8}$	48
CF_4		$5{\cdot}5 \times 10^{-13}$	48
		$< 10^{-16}$	47
CHF_3		$4{\cdot}6 \times 10^{-14}$	47
CH_2F_2		$1{\cdot}6 \times 10^{-14}$	47
CH_3F		$< 10^{-15}$	47
EtF		$< 5 \times 10^{-15}$	47
CH_3CF_3		$4{\cdot}3 \times 10^{-14}$	47
C_2F_6		$< 10^{-16}$	47
C_3F_8		$< 10^{-15}$	47
o-C_4F_8		$1{\cdot}1 \times 10^{-7}$	7
n-C_4F_{10}		$9{\cdot}6 \times 10^{-12}$	47
C_7F_{14} (perfluoro-3-methylpentane)		$9{\cdot}8 \times 10^{-8}$	50
		$8{\cdot}0 \times 10^{-8}$	51
		$5{\cdot}2 \times 10^{-8}$	7
$C_6H_5CH_2Cl$	(300K)	$1{\cdot}6 \times 10^{-10}$	38
	(393K)	$5{\cdot}1 \times 10^{-10}$	38
	(393K)	$4{\cdot}3 \times 10^{-10}$ [a]	49
C_6H_5I	(393K)	$(1 \pm 0{\cdot}5) \times 10^{-8}$ [b]	43
C_6H_5Br	(393K)	4×10^{-10} [b]	43
C_6H_5Cl	(393K)	3×10^{-10} [b]	43
C_6H_5F	(393K)	$\leqslant 2{\cdot}5 \times 10^{-12}$ [b]	43

[a] Based on $k(e + SF_6) = 2{\cdot}7 \times 10^{-7}\ cm^3\ s^{-1}$. This reference rate constant is derived from a critical survey[7] of more than a dozen published data for 300K. Since the activation energy is estimated to be close to zero, the same value is taken for 393K.

[b] Based on $k(e + C_6H_5CH_2Cl) = 5 \times 10^{-10}\ cm^3\ s^{-1}$ (393K)[38].

CCl_4 and SF_6 see reference 7). From competitive studies of halobenzenes with benzyl chloride Warman, Sauer and Johnson[43] found that the lifetime of the anion $C_6H_5Cl^-$ is long enough to enable the electron transfer reaction

$$C_6H_5Cl^- + C_6H_5CH_2Cl \longrightarrow C_6H_5Cl + C_6H_5CH_2^{\cdot} + Cl^-$$

with $k \cong 5 \times 10^{-11}$ cm^3 s^{-1}. This reaction is not found for bromobenzene and iodobenzene, in agreement with the potential energy curves calculated by Steelhammer and Wentworth[22]. Warman and Sauer[38] found that the rate constants for electron reactions with chloroform in contrast to CCl_4 and benzyl chloride did show a small pressure dependence which could be explained by a small collisional stabilization of the anion formed. This would then correspond to the expected shallow minimum in the potential energy curve of the chloroform anion state[21,37]. Johnson and Simic[52] also interpreted some of their results from product analysis in the gas-phase radiolysis of aqueous CH_3Br as being due to a relatively stable anion CH_3Br^-, again in agreement with the calculated potential energy curves for EtBr and *n*-PrBr by Christophorou and coworkers[28], if these can be taken as representative for liquids as well.

B. Non-polar Liquids

The electron-capture processes in gas phase and liquid phase are critically different and it is recommended not to apply the quantitative data from gas-phase electron attachment studies to liquid systems. CH_3Cl, for instance, in gas phase a rather inefficient electron acceptor ($\sigma_{da} = 5{\cdot}81 \times 10^{-18}$ cm^2 at thermal electron energy), is a highly efficient scavenger in liquids. This particular case is due to increased collisional stabilization of the negative ion state in liquids. In gas-phase radiolysis the distribution of electrons and positive ions immediately becomes uniform and the corresponding ion yield, easily measurable by an applied electric field, is $G_{i,gas} \cong 4$. This corresponds to the W-value of about 25 eV *. In the gas, an electron formed escapes the Coulomb field of its positive ion almost without collision. Not so in liquids where only a minor part of the electrons is able to escape and all the others recombine with their positive ions. As a result the electrons and positive ions are mostly pairs and the actual distribution is strongly non-homogeneous. The total initial yield of electrons (G_{io}) is therefore the sum of the free ion yield G_{fi} (fraction of electrons which actually leave the Coulomb field of their cations) and the yield of ion pairs which recombine G_{gi} (the so-called geminate recombination). Typical values are: $G_{fi} \cong 0{\cdot}1$, $G_{gi} \cong 3{\cdot}9$ and $G_{io} \cong 4$ (see Table 9).

* W-value = energy necessary to produce one ion pair[53].

For high LET radiation the concentration of ion pairs is locally rather high, so that electrons can combine with its neighbour cation. As a result the G_{fi} values are even lower[54].

Since about 1968 the electron scavenging with halogen compounds and other good electron acceptors is theoretically well understood, so that electron reactivities, free ion yields and geminate ion yields can be determined[55] from the analysis of products or transients which are directly related to the scavenger process, e.g. the CH_3 yield from the dissociative electron attachment to CH_3Br. It is thereby prerequisite that the product analysed ($CH_3^{\bullet}$ in the foregoing example) is not formed by other ways than by electron capture. Complications can occur (i) from radical reactions such as $H(R)+CH_3I \rightarrow CH_3+HI(RI)$, (ii) energy transfer such as $(solvent)^*+CH_3I \rightarrow CH_3+I+(solvent)$, (iii) positive ion reactions (e.g. proton transfer, electron transfer) and (iv) secondary reactions of negative ions formed, such as $e+N_2O \rightarrow N_2O^-$, the latter reacting with benzene to form $C_6H_6O^-$ which again consumes a molecule of N_2O[56]. All such complications are discussed in detail by Warman and coworkers[55].

I. Competition theory for electron scavenging

For the electron-scavenging process in non-polar solvents (e.g. RH) one must consider the competition reaction of the electron with its positive ion and with the scavenger molecule S (in the present chapter an organic halide):

$$e^- + RH^+ \xrightarrow{k_2} RH^* \longrightarrow Q + \ldots \text{(products)} \qquad (2)$$

$$e^- + S \xrightarrow{k_s} (S^-)^* \longrightarrow P + \ldots \text{(products)} \qquad (3)$$

Since the scavangeable electrons cover a wide range of kinetic energies it is not possible to assume a single k_2 (or in other words a single lifetime for the ion pairs). Based on a model by Hummel[57], Warman and coworkers[55,58] derived an expression for the correlation of the product yield (e.g. $G(P)$ for reaction 3) with the scavenger concentration (S), and α_s being the solute reactivity towards electrons:

$$G(P) = G_{fi} + G_{gi}\frac{\sqrt{[\alpha_s(S)]}}{1+\sqrt{[\alpha_s(S)]}} \qquad (D)$$

For low concentrations ($\sqrt{[\alpha_s(S)]} \ll 1$) (D) can be reduced to

$$G(P) = G_{fi} + G_{gi}\sqrt{[\alpha_s(S)]} \qquad (E)$$

This approximation is typically valid for $(S) < 10^{-3}$M and in a plot of $G(P)$ versus $(S)^{\frac{1}{2}}$ the intercept for $(S) = 0$ directly gives the free ion yield G_{fi}. With this value known, (D) can be rewritten:

$$[G(P)-G_{fi}]^{-1} = [G_{gi}]^{-1} + [G_{gi}\sqrt{\alpha_s}]^{-1}(S)^{-\frac{1}{2}} \qquad (F)$$

A plot of $[G(P)-G_{fi}]^{-1}$ versus $(S)^{-\frac{1}{2}}$ over any range of concentration (typically 10^{-5} to 1M) is linear (see Figure 8). The intercept for $(S)=\infty$ determines G_{gi} and from the slope the solute reactivity α_s can be calculated. Figure 9 demonstrates the high accuracy of equation (D) to reproduce the experimental data over a concentration range of more than five decades. Even at a concentration as high as 0·5M not all electrons are scavenged since there is not yet a limiting yield. Table 8A is a selected list of free ion

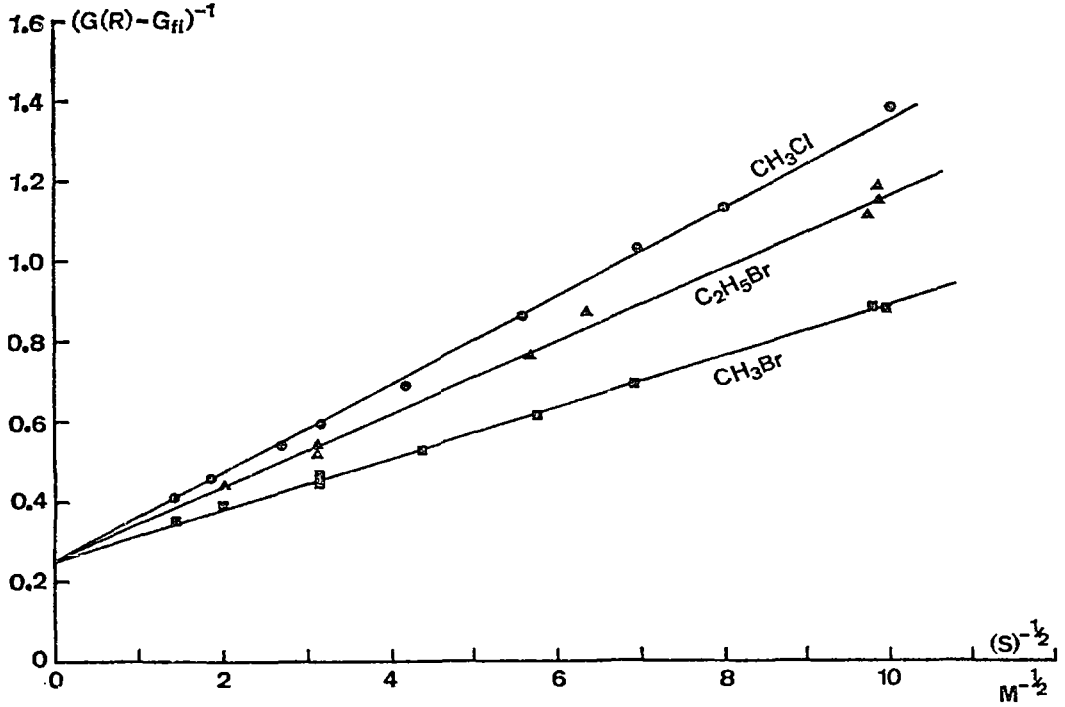


FIGURE 8. Plot of alkyl radical yields from CH_3Cl, EtBr and CH_3Br in cyclohexane solutions according to equation (F). The common intercept corresponds to $G_{gi}=3{\cdot}9$ [55]. (Reproduced from J. M. Warman, K. D. Asmus and R. H. Schuler, *ACS-Adv. Chem. Ser.*, **82** on *Radiation Chemistry*, p. 25, Figure 2, by permission of the American Chemical Society.)

yields and geminate ion yields as determined by equations (D) through (F) using halocarbons as scavengers. The data are also compared with results from other methods. Table 8B includes all known G_{fi} and G_{gi} values for halogenated solvents. All free ion yields are close to $G_{fi}=0{\cdot}1$ (except for iso-octane), and the total ion yield $G_{io}=G_{gi}+G_{fi}\cong 4$ throughout. This supports the often-made assumption that the energy necessary to form an

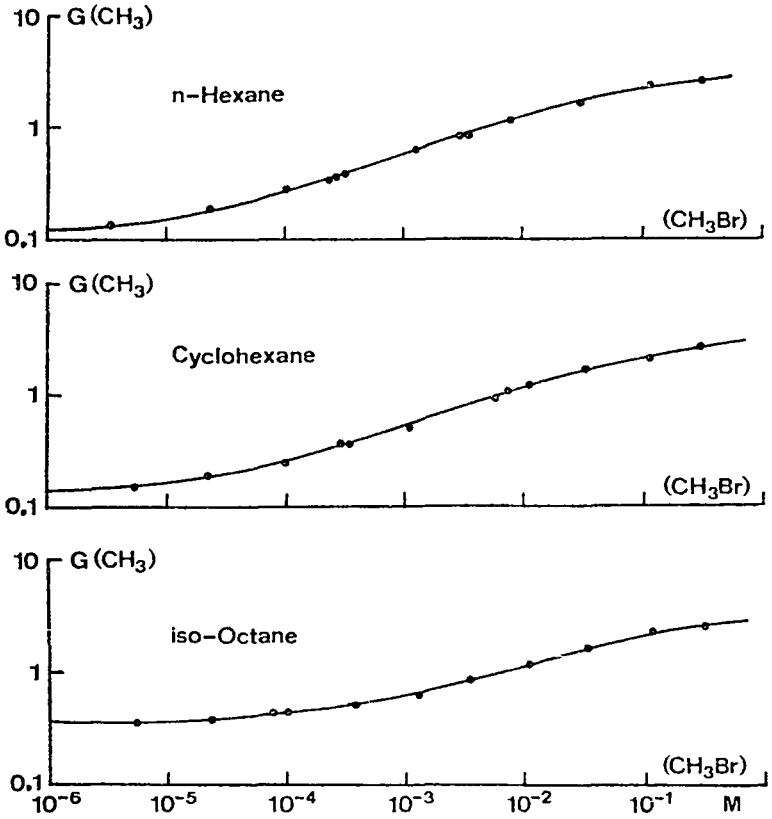


FIGURE 9. The yield of methyl radicals as a function of methylbromide concentration in *n*-hexane, cyclohexane and iso-octane[59]. (Reproduced with permission from J. M. Warman and S. J. Rzad, *J. Chem. Phys.*, **52**, 485 (1970).)

ion pair in gas phase and liquid phase is not too different. The solute reactivity α_s as determined from equation (F) is proportional to the reaction rate constant $k_s(e+S)$ [58]

$$\alpha_s = \left(\frac{K}{G_{gi}}\right)^2 k_s \qquad (G)$$

K is basically a function of the diffusion coefficient of the ionic species and of some geometrical factors of the molecule involved. The α_s-values so far known (Table 9) demonstrate a strong solvent and solute dependence.

For competitive studies with two scavengers it was often assumed that the scavengeable electron yield is constant. Many relative rate constants $k_{NO_2} = k(e+S)/k(e+N_2O)$ are given in the literature on this basis[72-74]. Since the two scavengers simultaneously compete with reaction (2) these values are not really correct and calculation of absolute values based on the

TABLE 8A. Free ion and geminate ion yields (G_{fi}, G_{gi}) determined by the scavenging methods (for additional values see references 63, 64, 66 and 67

	Method	*o*-C_6H_{12}	*n*-C_6H_{12}	3-Methyl-pentane	iso-Octane	C_6H_6
G_{fi}	Scav. C_6F_{12}	0·14 [60, 61]	0·08 [61]	0·17 [61]	0·37 [61]	—
	Scav. CH_3Br	0·13 [58, 59, 62]	0·12 [59, 62]	—	0·36 [59, 62]	—
	Scav. N_2O	0·09 [55, 56]	—	—	—	~0 [56]
	Conductivity	0·11 [63]	0·11 [63]	—	—	—
	Clearing field	0·15 [64]	0·13 [64]	0·15 [64]	0·33 [64]	0·053 [64]
	Pos. ion scav. (pulse rad.)	0·13 [65]	0·12 [65]	—	0·36 [65]	—
G_{gi}	Scav. C_6F_{12}	4·2 ± 0·2 [60]	—	—	—	—
	Scav. CH_3Br	3·8 ± 0·1 [58, 59]	3·8 [59]	—	3·9 [59]	—
	Scav. N_2O	3·9 [55, 56]	—	—	—	3·9 [56]

TABLE 8B. Free ion yields (G_{fi}) for halocarbon solvents

	Method	CCl_4	*n*-C_5F_{12}	$C_6F_{11}CF_3$	*n*-BuBr	*n*-BuCl
G_{fi}	Conductivity	0·068 [68]	—	—	0·27 [67]	0·39 [67]
	Clearing field	0·096 [66]	0·035 [66]	0·028 [66]	—	—
	Pos. ion. scav. (pulse rad.)	0·093 [65]	—	—	—	—

TABLE 9. Solute reactivity α_s for electron scavenging in various non-polar solvents

Solute (scavenger)	Solvent				
	Cyclohexane	*n*-Hexane	3-Methyl-pentane	Iso-octane	Benzene
o-C_6F_{12}	30 [60]	24 [61 a]	13 [61 a]	4 [61 a]	—
SF_6	18 [69]	—	—	—	—
CH_3Br	16·2 [58]; 15·4 [59]	17·1 [59]	—	8·2 [59]	—
N_2O	16 [55, 69]	—	—	—	~0·7 [56]
$C_6H_5CH_2Cl$	~16 [55, 58, 70]	—	—	—	—
C_4F_8	~16 [55, 71]	—	—	—	—
CH_3I	~13 [55]	—	—	—	—
CO_2	8 [69]	—	—	—	—
EtBr	7·82 [58]	—	—	—	—
CH_3Cl	5·41 [58]	—	—	—	—
EtCl	~0·5 [58]	—	—	—	—

[a] Calculation based on assumed value $G_{gi} = 4·0$.

recently published rate constant $k(e+N_2O)$[75] must be cautious. Hageman and Schwarz[70] were the first to take into account that with increased solute concentration an increased yield of electrons was available for scavenging. In analogy to the one-scavenger treatment Warman and coworkers[55] derived an expression for competition of two-electron scavengers:

$$G\,(\text{total scavenging}) = G_{fi} + G_{gi}\frac{\sqrt{[\alpha_1(S_1)+\alpha_2(S_2)]}}{1+\sqrt{[\alpha_1(S_1)+\alpha_2(S_2)]}} \qquad \text{(H)}$$

If a product from one scavenger only is analysed, e.g. P_1 from solute S_1, with (S_2) held constant, then

$$G(P_1)_{S_2} = \frac{\alpha_1(S_1)}{\alpha_1(S_1)+\alpha_2(S_2)} \times G\,(\text{total scavenging}) \qquad \text{(I)}$$

2. Scavenger studies with organic halides

The theory of the foregoing chapter was tested mostly with halocarbons as electron scavengers, although any type of scavenger is good enough (e.g. N_2O[55]). Warman and coworkers used CH_3Br as a scavenger and measured the CH_3-radical yield by its reaction with radio iodine $^{131}I_2$ to form $CH_3{}^{131}I$[58]. In another case they used the carbon-labelled $^{14}CH_3Br$ to detect the sum of all ^{14}C-products[59]. Sagert and Reid[60,61,71,76] applied perfluorocarbons as electron scavengers detecting monohydrogenfluorocarbon as a specific product (e.g. c-C_6F_{12} as scavenger yielding $C_6F_{11}H$). The underlying mechanism is a non-dissociative electron attachment to form $C_6F_{12}^-$ which, on neutralization, yields the $C_6F_{11}^*$ radical. This will then abstract a hydrogen from the hydrocarbon solvent[76]. Rajbenbach found that the small perfluorocarbons CF_4 to C_3F_8 did not scavenge electrons as expected[74,77]. This seems to be due to a larger fraction of autoionization and to less stabilization of the small molecular anions.

Quite early it was recognized that the H_2 yield from hydrocarbon solvents was reduced by electron scavengers. The following mechanism explains the effect:

$$e + C_nH_m^+ \longrightarrow C_nH_m^* \xrightarrow{f_1} C_nH_{m-2} + H_2 \qquad \text{(4a)}$$

$$C_nH_m^* \xrightarrow{1-f_1} C_nH_m \qquad \text{(4b)}$$

$$e + AB \longrightarrow A + B^- \qquad \text{(5)}$$

$$B^- + C_nH_m^+ \longrightarrow B + C_nH_m^* \xrightarrow{f_2} C_nH_{m-2} + H_2 + B \qquad \text{(6a)}$$

$$C_nH_m^* \xrightarrow{1-f_2} C_nH_m + B \qquad \text{(6b)}$$

f_1 and f_2 are the respective fractions for H_2 formation from the excited hydrocarbon, formed through neutralization. If $G(H_2)_0$ and $G(H_2)_s$ denote the H_2 yield without scavenger and with a particular concentration of the scavenger (AB), respectively, then the yield of scavenged electrons is given by

$$G(e_{scav}) = (f_1 - f_2)^{-1}[G(H_2)_0 - G(H_2)_s] \qquad (J)$$

In scavenging with CH_3Cl, the yield of $CH_3^{\bullet}$ (A in reaction 5) can be determined simultaneously to $G(H_2)_s$[55]. It is found that $(f_1 - f_2)$ is 1 for cyclohexane, which means that no H_2 is formed ($f_1 = 1, f_2 = 0$) by reaction (6). For many other hydrocarbon solvents f_1 is substantially smaller than 1: from experiments with N_2O f_1 is 0·3 for iso-octane[69].

3. Absolute rate constants

Very little is known about the absolute rate constants for electron reactions in non-polar liquids. Hummel originally estimated, based on his model for electron scavenging[57], that the reaction rate constant for benzyl chloride should be about $2{\cdot}5 \times 10^{10}$ $M^{-1}s^{-1}$. Further estimates were made by Rzad and coworkers[78] for the reaction with diphenyl 3×10^{11} $M^{-1}s^{-1}$ and with benzyl chloride $\sim 10^{11}$ $M^{-1}s^{-1}$[79]. The first direct measurement was recently accomplished with pulse radiolysis at $-80°C$ in 3-methylhexane and *n*-hexane by Richards and Thomas[75]. For both solvents the following absolute rate constants were measured by direct observation of the decay of the solvated electron:

$$k(e + CCl_4) = 2{\cdot}3 \times 10^{11}\ M^{-1}s^{-1} \quad k(e + N_2O) = 1{\cdot}1 \times 10^{11}\ M^{-1}s^{-1}$$

$$k(e + O_2) = 1{\cdot}5 \times 10^{11}\ M^{-1}s^{-1} \quad k(e + Ph_2) = 1{\cdot}9 \times 10^{11}\ M^{-1}s^{-1}$$

There were distinct indications that reactions with trapped electrons as well as with 'free' electrons must occur with possibly quite different reaction rate constants. Polak and coworkers[80] also found in scavenging experiments with alkyl and aryl halides that their results must be partly explained by reactions with epithermal electrons.

C. *Polar Liquids*

Most of the information about electron scavenging by organic halides in polar solvents is derived from aqueous solutions. A recent book on the hydrated electron by Hart and Anbar[81] thoroughly covers this subject. An additional review was written by Thomas[82]. The present discussion of aqueous systems will therefore be limited to some of the particular problems common to all polar solvents. On the other hand, the treatment

of electron reactions with halocarbons in non-aqueous polar solvents is as comprehensive as possible. The differences one expects for electron reactions changing from a non-polar to a polar solvent are characterized by the solvation energy for the electron. This energy, in principle, corresponds to the energy of maximum absorption of the solvated electron, which varies by a factor of about two: for 3-methylhexane, isopropanol, ethanol, methanol, water it is 0·8[75], 1·7, 1·8, 2·0 and 1·7 eV[83], respectively. Reactions with solvated electrons can be compared to electron-transfer reactions. But the precursor negative entity (the solvated electron) thereby disappears.

I. Competition studies

With the aim of determining relative rate constants for electron scavenging, the competition of two solutes was studied, quite similar to the method in liquid hydrocarbons, often neglecting any possibility of scavenging electrons within the spurs (with an assumed constant scavengeable primary yield of electrons). This is again not correct and rate data derived therefrom might be less reliable. On the other hand, as can be seen from Table 10, the yield of geminate electrons ($G_{gi}(e_s)$) is substantially smaller in

TABLE 10. Free ion and geminate ion yields (G_{fi}, G_{gi}) for polar solvents

Solvent	G_{fi}	G_{gi}	G_{total}
Cyclohexane[a]	0·12	4·0	4·1
Diethyl ether[84]	0·15	3·8	4·0
Ethanol[85]	1·05	3·1	4·2
Methanol[85]	1·05	3·1	4·2
Water[86]	2·6	2·2	4·8[b]

[a] Average values from Table 8 for comparison.

[b] This value was calculated from a spur model by Schwarz[87]. Since the concentration range in reference 86 was relatively small (10^{-2} to 1M) this theoretical value was applied to equation (D). The G_{fi}- and G_{gi}-values in the table were derived from curve fitting to the experimental data.

polar liquids. The error involved may therefore be smaller than in non-polar hydrocarbon solvents. Such rate constants will not be included in Table 12 (section III. C. 2), but they might still be useful (for data in alcoholic solutions see references 88–91).

The empirical scavenging formula by Warman, Asmus and Schuler[55, 58] (equation D) was also tested for polar solvents[85, 86]. Apparent deviations in

alcohols for low scavenger concentrations (typically $< 10^{-3}$M) are due to a further competitive reaction with the solvent (a reaction which is too slow in aqueous and hydrocarbon solutions):

$$e_s^- + ROH \xrightarrow{k_7} ROH^- \tag{7}$$

With the inclusion of reaction (7) the modified equation is:

$$G(e_{scav}^-) = G_{fi}(e_s^-)\frac{\delta(S)}{1+\delta(S)} + G_{gi}(e_s^-)\frac{\sqrt{[\alpha(S)]}}{1+\sqrt{[\alpha(S)]}} \tag{K}$$

δ is the ratio of the second-order rate constant for the electron-scavenging k_s (reaction 3) to the pseudo first-order rate constant k_7(ROH):

$$\delta = \frac{k_s}{k_7(ROH)} \quad \text{or} \quad \frac{k_s}{k_7(ROR')} \tag{L}$$

The results from a least square fit of equation (K) to the experimental data in methanol and ethanol[85] and in diethyl ether[84] and of equation (D) to

TABLE 11. The solute reactivity α_s (M^{-1}) and the rate constant ratio δ (M^{-1}) (see equation L) in polar solvents

Solute (scavenger)	Solvent							
	EtOEt[84]		EtOH[85]		CH_3OH[85]		H_2O[86]	
	α_s	δ	α_s	δ	α_s	δ	α_s	δ
CH_3Br	18	$5{\cdot}1 \times 10^4$	4·4	$5{\cdot}5 \times 10^4$	4·4	$5{\cdot}5 \times 10^4$	—	—
CH_3Cl	—	—	1·1	—	—	—	1·3	—
SF_6	42	—	4·3	$5{\cdot}4 \times 10^4$	9·6	12×10^4	—	—
N_2O	16	—	2·9	—	3·0	—	—	—

experimental data in water[86] are shown in Tables 10 and 11. The experimental data fit very well to the calculated curves in all cases. Nevertheless the G_{fi} value of 1·05 in methanol and ethanol is still disputed (the latest value proposed is $G_{fi}(e_s^-) = 1{\cdot}7$ for ethanol[92]).

2. Absolute rate constants

Most of the absolute rate constants for the reactions of solvated electrons with halocarbons were measured by the pulse radiolysis technique. The values known today for methanol, ethanol and ether solutions are summarized in Table 12. They are shown in comparison with selected data

TABLE 12. Absolute rate constants ($M^{-1} s^{-1}$) for electron reactions with halocarbons in polar solvents, compared with data in non-polar systems and gas phase (N_2O given for comparison)

Scavenger	Gas[a]	Hydrocarbon[b] (ϵ_d = ca. 2)	Ethanol (ϵ_d = 24·3)	Methanol (ϵ_d = 33·1)	Water[81] (ϵ_d = 80)
CCl_4	$2{\cdot}5 \times 10^{14}$	$2{\cdot}3 \times 10^{11}$ [75]	$1{\cdot}2 \times 10^{10}$ [92]	—	$3{\cdot}0 \times 10^{10}$
$CHCl_3$	$1{\cdot}3 \times 10^{12}$	—	—	—	$3{\cdot}0 \times 10^{10}$
CH_3I	$3{\cdot}4 \times 10^{13}$	—	—	—	$1{\cdot}6 \times 10^{10}$
CH_3Br	$6{\cdot}0 \times 10^{9}$	$\sim 10^{11}$ [79]	$1{\cdot}4 \times 10^{10}$ [85]	$1{\cdot}4 \times 10^{10}$ [85]	—
n-PrBr	—	—	$3{\cdot}0 \times 10^{9}$ [92]	—	—
CF_3Cl	$3{\cdot}1 \times 10^{7}$	—	—	—	$4{\cdot}4 \times 10^{9}$ [93]
CH_3Cl	$9{\cdot}6 \times 10^{12}$	—	$3{\cdot}6 \times 10^{9}$ [85]	—	$1{\cdot}1 \times 10^{9}$
$ClCH_2COOH$	—	—	$2{\cdot}0 \times 10^{10}$ [94]	—	$1{\cdot}2 \times 10^{9}$
$C_6H_5CH_2Cl$	$\sim 2{\cdot}0 \times 10^{11}$	$\sim 10^{11}$ [79]	$5{\cdot}1 \times 10^{9}$ [95]	$5{\cdot}0 \times 10^{9}$ [95]	$5{\cdot}3 \times 10^{9}$
C_6H_5I	$6{\cdot}0 \times 10^{12}$	—	—	—	$1{\cdot}2 \times 10^{10}$
C_6H_5Br	$2{\cdot}4 \times 10^{11}$	—	—	—	$4{\cdot}3 \times 10^{9}$
C_6H_5Cl	$1{\cdot}8 \times 10^{11}$	—	—	—	$5{\cdot}0 \times 10^{8}$
C_6H_5F	$\leqslant 1{\cdot}5 \times 10^{9}$	—	—	—	$6{\cdot}0 \times 10^{7}$
N_2O	$7{\cdot}2 \times 10^{7}$	$1{\cdot}1 \times 10^{11}$ [75]	$9{\cdot}4 \times 10^{9}$ [85]	$9{\cdot}4 \times 10^{9}$ [85]	$8{\cdot}7 \times 10^{9}$

[a] Extracted from Table 6. ϵ_d = dielectric constant.

[b] In reference 75 the solvent is 3-methylhexane and *n*-hexane at 193K. In reference 79 it is cyclohexane (room temperature).

Error limits: data from reference 85 ±10%; reference 94 ±35%; reference 95 ±25%; reference 92 ±13% for CCl_4 and ±7% for *n*-PrBr; the error limit in reference 75 is not given.

for water and alkane solutions as well as with gas-phase values. An extensive list of rate constants for the hydrated electrons can be found elsewhere[81]. The rate constant for the same reaction in various polar solvents does not differ very much, but it is substantially larger in non-polar alkane solutions. In the gas phase the rate constants cover a much wider range and do not follow the same sequence as in liquid systems. This latter effect can be understood in the view of reduced collisional stabilization and therefore higher probability for autoionization of the temporary negative ion state.

In liquid systems the reaction rate must be correlated with the size and mobility of the solvated electron. It is therefore not surprising that the rate constants are very similar in polar solvents with quite comparable solvation energies (1·5–2·0 eV[83]). The rate constants for electron reactions generally increase in the order of F≪Cl<Br<I. Neighbouring electron-withdrawing groups in aliphatic halocarbons enhance the reaction rate.

This was shown for the reaction of hydrated electrons by correlating the reaction rate constants k with the Taft's σ^*-function[96]. The log k is thereby approximately linear with σ^* [97]. The rate constant for benzyl chloride is substantially larger than would be expected from this correlation. It is suggested that this deviation is due to the fact that there are two centres for electron attachment, the halogen substituent and the ring π-system. Correspondingly, aromatic molecules are also electron acceptors. An electron-withdrawing substituent group on the aromatic system enhances the electron attachment to the ring and an electron-donating group makes the ring more negative, therefore reducing the reaction rate of the electron. It was shown that log k is roughly proportional to the Hammett σ-value for a large number of substituents on benzene in aqueous systems[81, 82, 98] and in isopropanol solutions[88]. But in both solvents bromobenzene and iodobenzene deviate from the linearity towards larger k-values. Obviously the electron attachment again occurs simultaneously at the ring and the halogen substituent. Recently a similar correlation of rate constants to Hammett σ-values was given for methanol, ethanol and n-propanol solutions[91] but these results are less conclusive.

The list of rate constants as given in Table 12 refers to reactions with electrons after their complete solvation. Recent experiments in picosecond pulse radiolysis[99] revealed a larger rate constant for high solute concentrations (Table 13). Also a lower initial yield of hydrated electrons was

TABLE 13. Reaction rate constants for hydrated electrons with halogen compounds from picosecond pulse radiolysis[99]

	Low concentration		High concentration		
Solute	$k \times 10^{-9}$ ($M^{-1}\,s^{-1}$)	pH	$k \times 10^{-9}$ ($M^{-1}\,s^{-1}$)	pH	Concentration range (M)
CCl_3COO^-	8·5	11	21	6·6	0·1 – 0·53
$CHCl_2COO^-$	4·2	11	10	7·5	0·1 – 1·7
CH_2ClCOO^-	1·2	11	2·5	8·5	0·25 – 1·5

found. This is interpreted as being due to incomplete solvation before reaction. The results indicate that reactions with non-hydrated ('dry') electrons do occur and that they are important at high scavenger concentration. Since biological systems constitute such highly concentrated aqueous solutions the reactions of 'dry' electrons might be quite important.

3. Products from electron scavenging

The halogen ion X^- formed through the dissociative electron attachment to the organic halide RX is quite stable and rarely takes part in the reaction mechanism in polar solvents*. However, the radical R can initiate chain reactions. Sherman[100] has shown that this occurs in alkaline, alcoholic solutions of CH_3Br and CH_3I. If R is a halogenated methyl radical in aqueous solution, then hydrolysis further breaks up the radical R. Balkas, Fendler and Schuler[101] showed that electron scavenging by $CFCl_3$ produces one fluoride ion and three chloride ions per electron captured. Similarly for low dose rates the radicals CF_2Cl (from CF_2Cl_2) and CF_3 (from CF_3Cl) hydrolyse to $2F^- + Cl^-$ or $3F^-$, respectively. For higher dose rates a second-order process (probably $CF_2 + CF_2 \rightarrow C_2F_4$) reduces the fluoride ion yield whereas the Cl^- yield did not show any dose rate effect.

D. Solids†

There are many results available about scavenging processes in organic glasses. They are mostly summarized in two well-written reviews by Willard[102] and by Hamill[103], published in 1968. It seems that the same type of dissociative electron attachment does occur in low temperature glasses as in the liquid systems. However, the yield of free ions is higher (G_{fi} in 3MP at 77K being about 0·5). Many scavenging experiments were performed with alkyl halides and with benzyl halides, the latter being ideally suitable because of the well-known benzyl radical spectrum. In recent studies by Noda and coworkers[104] in MTHF and 3MP (77K) similar spectroscopic assignments to acyl radicals $R\dot{C}O$ were possible ($R = CH_3^{\bullet}$, $Et^{\bullet}$, $C_6H_5CH_2^{\bullet}$, $C_6H_5^{\bullet}$ and $C_6H_5CH{=}C\dot{H}$), all being produced by dissociative electron attachment to the corresponding acyl chlorides. The same authors[105] measured the yield of phenyl radicals from the decay of the halobenzene anion. The relative cross-section $\sigma_{da}(C_6H_5I) : \sigma_{da}(C_6H_5Br) : \sigma_{da}(C_6H_5Cl)$ in a MTHF-glass was determined to be 1·5 : 1·0 : 1·0. In 3MP and MTHF the phenyl radical could not be measured by e.s.r. or by u.v. absorption since it reacted rapidly with the solvent to form benzene, but in an alkaline glass of water, phenyl was identified by e.s.r.

It is normally assumed that the *solvated* electron takes part in the reaction with halocarbons. In a recent pulse radiolysis experiment by Richards and

* This is not the case in non-polar solvents since X^- will form HX molecules through neutralization. These are very good electron scavengers themselves[1].

† 3MP = 3-methylpentane; MTHF = methyltetrahydrofuran.

Thomas[106] in glasses of 3-methylhexane, MTHF, cumene, ethanol or alkaline ice at 77K it was shown that the trapped electron suffers a structural change within nanoseconds, parallel to reacting with the halocarbon scavengers. This is interpreted as being due to a reorganization of the neighbouring matrix molecules of the electron. In other words, the reaction of the electron with a solute does occur simultaneously to the solvation process. Steen and coworkers[107] also found indications that their chloroacetic acid in an alcohol–water glass at 77K reacted with non-solvated electrons. The reactivities of dry and solvated electrons are generally different (see section III. C. 2).

So far all glassy systems at 77K or higher showed *dissociative* electron capture by RX. The mobility of the matrix was obviously large enough to allow the separation of the X^- from the radical R. Quite recently Sprague and Williams[108] found that the e.s.r. spectrum of the expected CH_3 radical from dissociative electron attachment to CH_3Br in a crystalline CD_3CN matrix at 77K showed a rather complex structure which appeared to be due to interaction of the radical with the bromide ion. This was a direct proof that the negative ion state was stable in such a crystalline matrix. On warming to 175K with rapid refreezing to 88K the spectrum dramatically changed to that of the radical alone. Obviously by this treatment the bromide ion was able to escape from the cage. In an earlier paper by Egland, Ogren and Willard[109] a similar behaviour of the e.s.r. spectra was found for pure crystalline alkyl iodides with an even number of carbon atoms (from C_2 up to C_8). Most likely similar arguments would explain the complex e.s.r. spectra found in these systems.

For isolated (gas-phase) molecules of alkyl halides a shallow minimum in the potential energy curve for the negative ion state was proposed (see section II. D). But because of the excess energy in the negative ion state formed through the vertical electron attachment process, this potential minimum has not so far been effective. In the crystalline states discussed above, the cage in which the negative ion is formed is hard enough to hold the $R—X^-$ together and to drain off this excess energy. The fact that the anion dissociates as soon as the matrix is softened would imply that such a potential minimum does not exist, or that it is too shallow to accommodate a proper ground-state level. In an argon matrix of 4K the electron attachment to pyridyl halogenides was also found to be dissociative[110]. On the other hand a stable anion of CCl_4 was proposed in a 3MP glass at 20K[111] *.

* Compare also the 'stable' anion in the gas phase, mentioned in section III. A and the $R + X^- \rightarrow RX^-$ combination reaction in glassy RI, as discussed in section VII. C.

IV. IONIC REACTIONS

The formation of negative ions of halocarbons is mostly an electron-attachment process as discussed in the previous sections. Other ways are by electron transfer reactions from precursor anions, e.g.[75],

$$(Ph)_2^- + PhCH_2Cl \longrightarrow (Ph)_2 + PhCH_2^{\bullet} + Cl^- \qquad (8)$$

$$k = 1{\cdot}0 \times 10^{10}\ M^{-1}\,s^{-1}$$

or from radicals in aqueous solutions, e.g.[112]

$$R\dot{C}HOH + CCl_4 \longrightarrow CCl_3 + Cl^-_{aq} + (R\overset{+}{C}HOH)_{aq} \qquad (9)$$

or by long-distance electron migration through solid silica gel to react with the adsorbed alkyl halides[113].

Positive ion–molecule reactions in the gas phase are the subject of mass spectrometric investigations and will not be discussed here. In condensed systems there are a few examples for the formation of organic halide cations:

(1) *The cation of CCl_4* represents one of the most controversial species while being one of the most studied. In irradiated alkane glasses (77K) with CCl_4 as solute, a transient absorption peaking at 480 nm appears, which was assigned to the CCl_4 cation[103,114]. It was believed to be formed through transfer of an excited positive state (simultaneous charge and energy transfer) through the matrix. Competition studies between CCl_4 and toluene in a 3MP matrix (77K) revealed that the cations of the two species are not derived from the same precursors[102,103,115]. In liquid CCl_4 the same 480 nm absorption was found by nanosecond pulse radiolysis[116]. But a sample of pure polycrystalline CCl_4 at 77K[103,117,118] does not show this absorption band, a peak at about 410 nm being assigned to the CCl_4 cation instead. In another paper the transient at 480 nm in 3MP was assigned to the radical charge-transfer complex (CT complex) $Cl{\cdot}CCl_4$[119], but this seems to be less likely[120]. At 20K, CCl_4 in methylcyclohexane (polycrystalline or glassy MCH) reveals a cationic species absorbing at 425 nm. It is postulated to be a CT complex between the cation of the matrix molecule and the CCl_4: $(MCH^+{\cdot}CCl_4)$[121]. Further discussions of the CCl_4 cation can be found in section VII. A.

(2) A low temperature matrix of pure *s- or n-butyl chloride* ('glass with many cracks') yields cations of the solvent absorbing at 360 and 540 nm[103,122]. Similar to the polycrystalline CCl_4 matrix, the secondary electrons are immobilized in this butyl chloride glass through dissociative electron attachment, whereas the positive charge can move freely by a resonance CT process. If solutes with lower ionization potentials than for

the matrix molecules are present in the matrix, the corresponding solute cations will be formed through asymmetric charge transfer[103].

(3) *Triphenylmethyl chloride* can be used as a positive charge scavenger in hydrocarbon solvents. It is followed by immediate dissociation to yield triphenylmethyl carbonium ion:

$$RH^+ + Ph_3CCl \longrightarrow Ph_3C^+ + R^\bullet + HCl \qquad (10)$$

With this reaction Capellos and Allen[65] determined the yield of free ion pairs by scavenging the positive charge quite analogously to the electron scavenging discussed previously.

Most of the halocarbons can be used as solvents to study cationic reactions. For solid-state reactions (77K) the matrices of CCl_4 and of (*n*- or *s*-)butyl chloride have already been mentioned. Such studies are reviewed by Hamill[103] and by Willard[102]. More recent results are in references 123, 124. In all these systems the radical reactions are frozen-in, the electrons are immobilized through dissociative attachment and the positive charge is transferred to the solute by a resonance process. One of the best halocarbon glasses is a 50/50 mixture of Freon-11 (CCl_3F) and Freon-114B2 (CF_2BrCF_2Br)[125]. However, for cation studies this matrix is disadvantageous because of the presence of three different halogens, thereby complicating the reaction mechanism of the solute cation. In simple halogenated liquids Dorfman and coworkers[126,127] were able to follow the formation and decay of aromatic cations by pulse radiolysis in the same manner. Their solvents were 1,1-dichloroethane, 1,2-dichloroethane, 1,1,2-trichloroethane, 1,1,2,2-tetrachloroethane and liquid *n*-butyl chloride. Contrary to the polycrystalline matrix of CCl_4 in liquid CCl_4 only few solute cations are formed[116]. Instead many chlorine atom CT complexes with the solute molecules were identified[120,128,129]. Other solvents which do not form solute cations are: 1,1,1-trichloroethane and pentachloroethane[130].

Because of the neutrality principle the ions formed by radiolysis must eventually recombine, except in very polar systems, where ionic species may be stable by solvation. Such neutralizations were observed by Mittal and Hamill[131] on warming an irradiated alkane glass. Alkyl iodide cations combined with iodide ions (from dissociative electron attachment):

$$I^- + RI^+ \longrightarrow (I{\cdot}RI)^* \longrightarrow I{\cdot}RI \qquad (11)$$

The resulting absorption was interpreted as being due to the complex of I·RI. A similar process in a 3MP glass containing bromobenzene was observed, the complex ($Br{\cdot}C_6H_5Br$) being formed by combination of Br^- and $C_6H_5Br^+$ on warming of the matrix[132]. In various similar systems such

complexes with aromatic electron donors could not be detected, the ion spectra disappearing on warming without new absorption bands[132]. Presumably this is due to the high instability of these halogen atom CT complexes towards unimolecular decays. In liquid systems where halogen atom CT complexes were observed no decision could be made as to whether the complex was formed by such ion neutralization or by simple radical mechanism[120]. But indication exists that at least part of the complexes are formed from ions[133]. Mittal[134] has used a similar neutralization process to detect possible carbonium ions R^+ in the radiolysis of liquid hydrocarbons RH. The neutralization of an X^- (from the dissociative electron attachment to AX) with R^+ yields a stable RX, which is a direct measure for the yield of carbonium ion R^+.

V. EXCITED STATES AND ENERGY TRANSFER

The excited states and correspondingly the transfer of electronic excitation are widely studied in photochemistry. It is generally recognized that these are also of high importance in radiation chemistry[135–138]. Very little direct information is available for halocarbons. Excited states detected in pulse radiolysis, e.g. for bromobenzene[139, 140], are not typical for the C—X bond, but rather for the aromatic structure. Nevertheless, many excited states of organic halogen compounds are postulated or accepted for mechanistic reasons: an excited state of an alkyl halide RX is often known to split homolytically into radicals R + X. Further, highly excited alkyl iodides RI* may undergo unimolecular elimination of HX to form an alkene (see also section VII. C). In radiation chemistry these excited RX* are often formed through energy transfer from the solvent, thereby acting as quencher for excited solvent molecules. The actual quenching process is often not obvious:

(1) In radiation chemistry a much larger variety and also higher excited states are formed than normally encountered in photochemistry.

(2) The same excited state can be formed through different channels, like direct excitation by primary radiation, by energy transfer from the solvent to the solute molecules or by ion combination reaction (neutralization).

(3) An organic halocompound can interfere with excited states through an actual quenching process or/and through charge scavenging from the precursors. The following examples illustrate these effects:

(a) In a gaseous mixture of benzene with a small amount of naphthalene Nishikawa and Sauer[141] detected the naphthalene triplet by pulse radiolysis.

Using increasing amounts of CCl_4, SF_6 or triethylamine they reduced the triplet yield by a maximum of 70%. The interpretation was that the unreduced 30% of the triplet yield was formed through energy transfer from a benzene excited state ($^3B_{1u}$) and 70% of scavengeable yield from ion neutralizations, whereby CCl_4 and SF_6 scavenge electrons and triethylamine the positive charge from the precursor cation. Similarly in a gaseous mixture of naphthalene with cyclohexane the naphthalene triplet yield could be reduced by 95% through charge scavenging with CCl_4, benzyl chloride, methyl bromide and others[142]. In all these cases the halocarbon molecules acted as electron scavengers only, but with the net effect of reducing excited states.

(b) In a high dose rate pulsed experiment Horrocks[143] studied the emission from the monomer (285 nm) and excimer (320 nm) excited states of benzene relative to the effects of O_2 and $CHCl_3$. Both monomer and excimer states behaved in a parallel manner therefore probably having the same precursor. O_2 reduced the lifetimes but left the initial yield of the excited states unaltered. In contrast, $CHCl_3$ affected the lifetime only very slightly, while reducing the initial yield substantially. This is in accord with the interpretation that oxygen quenches the excited states, whereas $CHCl_3$ scavenges electrons in competition with the formation of the anionic precursor. Here again the halocarbon is scavenging charge only. But simultaneous quenching and scavenging are possible, as seen in the next example.

(c) It is well known that excited aromatic solvent molecules can transfer their electronic excitation to solute molecules, like PBD (2-phenyl,5-(4-biphenylyl)-1,3,4-oxadiazole) leading to solute fluorescence. Oster and Kallmann[144] showed that the addition of $CHCl_3$ greatly diminished the solute fluorescence, if the mode of excitation was by radiolysis. The quenching effect of $CHCl_3$ is very small, however, if the solvent is excited to the first excited singlet state only. Levin and coworkers[145] studied solutions of PBD in *o*-xylene with various concentrations of $CHCl_3$ in detail. The relative fluorescence yield as a function of the $CHCl_3$ concentration is shown in Figure 10 for γ excitation and for u.v. excitation with wavelengths, corresponding to the three lowest singlet states, individually. It is concluded that $CHCl_3$ can actually be used as a specific quencher for excited states, particularly for the higher ones that normally would decay without emission into lower excited states, which can fluoresce or transfer their energy to fluorescent solutes. The marked increase in the 'quenching' effect of $CHCl_3$ for γ excitation is mainly due to the additional effect of electron scavenging in competition with the formation of the anionic precursor.

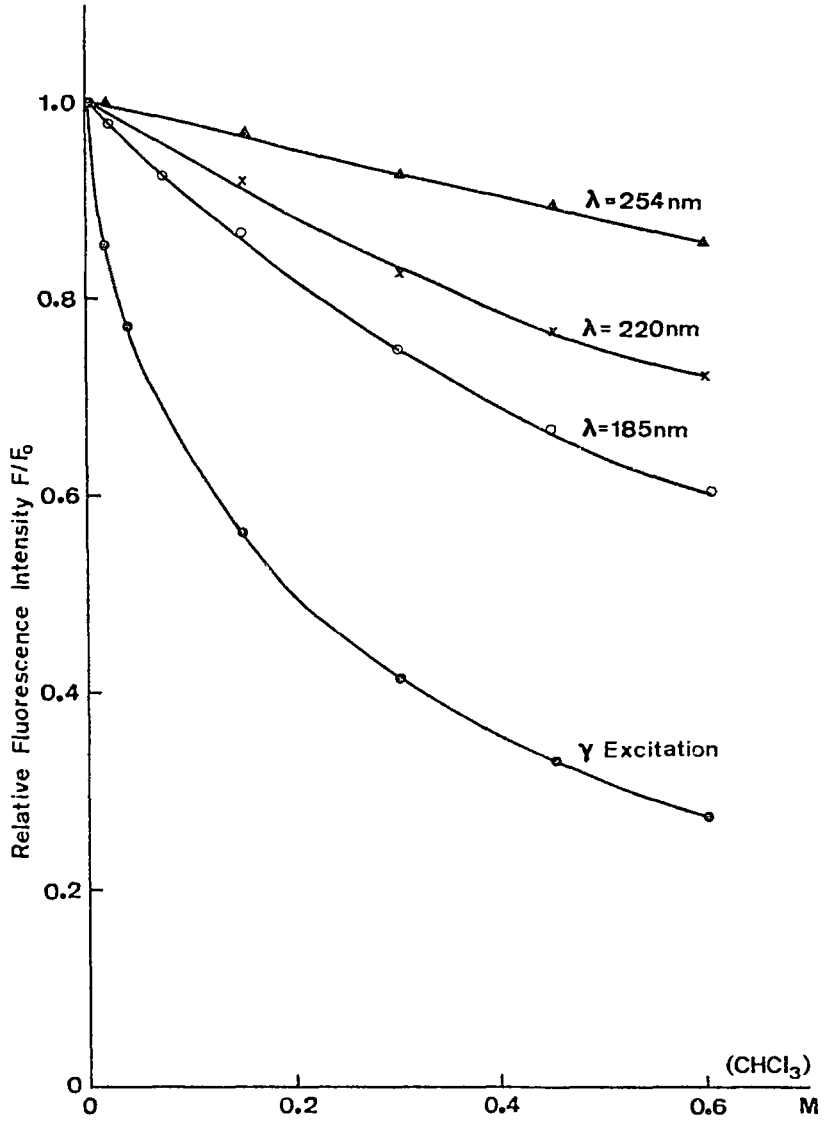


FIGURE 10. Quenching of the solute fluorescence by chloroform in a solution of $1{\cdot}5 \times 10^{-2}$M PBD (phenylbiphenyloxadiazole) in *o*-xylene, excited by u.v. and γ-radiation. (Reproduced with permission from E. Levin, M. Pope, D. Saperstein and G. K. Oster, *Chem. Phys. Letters*, 9, 210 (1971).)

VI. RADICAL REACTIONS

Radical reactions occur in almost all systems under ionizing radiation as well as in photochemistry, pyrolysis and many other methods in organic chemistry. As a consequence it is impossible to draw a line between radiation chemistry and photochemistry, to name only two fields of importance. In an attempt to characterize the radical reactions with halocarbons as they might be typical for radiation chemistry the following discussion will be limited to some of the more recent examples. They comprise (i) radical reactions as initiated through electron-attachment processes, (ii) reactions with the primary radicals in aqueous solutions, (iii) reactions of hydrogen atom and halogen atoms in organic systems and (iv) radical chain reactions.

A. Radicals Produced through Dissociative Electron Attachment

Dissociative electron attachment to halocarbons yields a neutral radical and a halide ion. This process is therefore a convenient source for radicals. If the original molecule is a polyhalocarbon, the radical will be a haloradical.

Weir, Infelta and Schuler[146,147] studied reactions of perfluoro radicals in hydrocarbon solvents. These radicals were produced by dissociative electron attachment to CF_3Br, CF_3Cl and C_2F_5Br. The rate of H abstraction from the solvent was determined by a competition technique with I_2:

$$CF_3^{\bullet} + I_2 \xrightarrow{k_{12}} CF_3I + I^{\bullet} \qquad (12)$$

$$CF_3^{\bullet} + RH \xrightarrow{k_{13}} CHF_3 + R^{\bullet} \qquad (13)$$

Similarly the addition to ethylene was measured:

$$CF_3^{\bullet} + CH_2{=}CH_2 \longrightarrow CF_3CH_2{-}CH_2^{\bullet} \qquad (13a)$$

Results of such studies are given in Table 14. The CF_3 radical abstracts hydrogen much more easily than CH_3. This can be related to the fact that CF_3 is highly non-planar and its unpaired electron has about 21% *s*-character[150], which indicates that very little rearrangement of orbitals is necessary to form CHF_3[146]. Contrary to this CH_3 is planar and the *s*-character of the unpaired electron is very small[151]. From photolysis much more data on reactions with CH_3 radicals are known. The reader might be referred to a recent comparison of CF_3, CH_3 and CCl_3 reactions by Wampler and Kuntz[152].

In *aqueous solutions* the reaction of a halocarbon with the hydrated electron is also a radical source. Results for CH_3 reactions (from CH_3I[149])

TABLE 14. Rate constants for perfluoro radical reactions

Reaction	Solvent	Mode[a]	k_{13}/k_{12}[b]	k_{13} (M^{-1} s^{-1})	Ref.
CF_3 + ethylene	Heptane	Add.	$3{\cdot}43 \times 10^{-3}$[c]	3×10^{6}[d]	147
	Water	Add.	—	$4{\cdot}0 \times 10^{7}$	93
CF_3 + propylene	Water	Add.	—	$7{\cdot}2 \times 10^{7}$	93
CF_3 + 1-butene	Water	Add.	—	$5{\cdot}3 \times 10^{7}$	93
CF_3 + 1,3-butadiene	Water	Add.	—	$5{\cdot}8 \times 10^{8}$	93
CF_3 + aniline	Water	Add.	—	$5{\cdot}2 \times 10^{6}$[e]	93
CF_3 + cyclohexane	CH	Abstr.	$3{\cdot}16 \times 10^{-5}$	3×10^{4}[d]	146
C_2F_5 + cyclohexane	CH	Abstr.	$1{\cdot}63 \times 10^{-5}$	2×10^{4}[d]	146
CF_3 + $HCOO^-$	Water	Abstr.	—	$3{\cdot}4 \times 10^{5}$	93
CF_3 + *i*-PrOH	Water	Abstr.	—	$9{\cdot}2 \times 10^{4}$	93
CF_3 + *n*-PrOH	Water	Abstr.	—	$4{\cdot}4 \times 10^{4}$	93
CF_3 + EtOH	Water	Abstr.	—	$4{\cdot}6 \times 10^{4}$	93
CF_3 + CH_3OH	Water	Abstr.	—	8×10^{3}	93
CH_3 + iso-octane[f]	iso-Octane	Abstr.	7×10^{-8}	70[d]	148
CH_3 + EtOH[f]	Water	Abstr.	—	590	149

[a] Add. = addition; abstr. = abstraction.
[b] At room temperature.
[c] $k_{13}/k_{12} = 0{\cdot}0293 \exp(-1290/RT)$.
[d] Assumed value $k_{12} \approx 10^9$ M^{-1} s^{-1} [147].
[e] Average value.
[f] For comparison.

and for CF_3 reactions (from CF_3Br [93]) are included in Table 14. Reactions with CF_3 are again much faster than with CH_3: for H abstraction about 10^2 times, for the addition to a double bond about 10^3 to 10^4 times.

In *organic solids* radical studies by the e.s.r. technique are often based on electron-attachment processes. In such experiments with ten different alkyl halides in 3MP, MTHF and MCH matrices* of 77K Shirom and Willard[153] investigated the formation and decay of the particular alkyl radicals. It was recently shown by Fenrick, Nazhat and Ogren[154] that in the case of some polycrystalline matrices the electron attachment processes are not necessarily dissociative, thereby complicating the radical e.s.r. spectrum by hyperfine splitting from the halide ion within the same matrix cage[108, 109].

B. Radical Reactions in Irradiated Aqueous Solutions

The most widely studied radical reactions in aqueous solutions are those with hydroxyl radicals and hydrogen atoms. These are easily and selectively

* MCH = methylcyclohexane.

producible through the primary radiation processes. In spite of many investigations of such reactions, only a few papers deal with halocarbons (for OH reactions see for example, references 155, 156; for H reactions see for example, references 156, 157).

OH radicals are found almost exclusively to abstract hydrogen atoms from aliphatic halocarbons[155,156] *:

$$OH + RX \xrightarrow{k_{14}} H_2O + \text{haloradical} \qquad (14)$$

For rate constants see Table 15 and reference 158. The variation of the halogen substituent has very little effect on the rate constant. With the

TABLE 15. Rate constants for the reactions with OH radicals in aqueous solution

Reactant	Mode[a]	pH	k (M^{-1} s^{-1})	Reference
$CHCl_3$	H-abstr.	9	$8{\cdot}5 \times 10^6$	155
$CHCl_3$	H-abstr.	0	$7{\cdot}4 \times 10^6$	159
CF_3COO^-	H-abstr.	9	2×10^5	160
FCH_2COO^-	H-abstr.	9	$1{\cdot}8 \times 10^7$	155
$ClCH_2COO^-$	H-abstr.	9	$3{\cdot}3 \times 10^7$	155
$BrCH_2COO^-$	H-abstr.	9	$2{\cdot}6 \times 10^7$	155
$ClCH_2COOH$	H-abstr.	1	$2{\cdot}6 \times 10^7$	161
$CH_3CHClCOO^-$	H-abstr.	9	$1{\cdot}4 \times 10^8$	156
$ClCH_2CH_2COO^-$	H-abstr.	9	$1{\cdot}9 \times 10^8$	156
$CH_3CHBrCOO^-$	H-abstr.	9	$1{\cdot}3 \times 10^8$	156
$BrCH_2CH_2COO^-$	H-abstr.	9	$1{\cdot}4 \times 10^8$	156
$ClCH_2CH_2OH$	H-abstr.	9	$5{\cdot}5 \times 10^8$	156
$BrCH_2CH_2OH$	H-abstr.	9	$4{\cdot}6 \times 10^8$	156
p-$FC_6H_4COO^-$	OH-add.	9	$2{\cdot}1 \times 10^9$	162
p-$ClC_6H_4COO^-$	OH-add.	9	$1{\cdot}9 \times 10^9$	162
p-$BrC_6H_4COO^-$	OH-add.	9	$1{\cdot}9 \times 10^9$	162
p-$IC_6H_4COO^-$	OH-add.	9	$2{\cdot}5 \times 10^9$	160
m-$IC_6H_4COO^-$	OH-add.	9	$2{\cdot}9 \times 10^9$	160
o-$IC_6H_4COO^-$	OH-add.	9	$4{\cdot}5 \times 10^9$	160
p-BrC_6H_4OH	OH-add.	5·5	7×10^9	163
C_6H_5Cl	OH-add.	10·7	$4{\cdot}2 \times 10^9$	164

[a] H-abstr. = H-abstraction; OH-add. = OH addition.

* The only proposed exception is the reaction $OH + CH_3I \rightarrow CH_3OH + I$ in aqueous solution of methyl iodide[149].

additional substituents COO^- and OH, which are known to affect the reactivity of the hydrogens on their α-carbon, the rate constant k_{14} is strongly influenced*. The resulting sequence, with increasing k_{14}, is $CHCl_3$—halogenated acetate ion—halogenated propionate ion—halogenated ethanol (Table 15). Furthermore, a plot of the rate constants (log k_{14}) for hydrogen abstraction by OH versus log k_{15} for abstraction by H atoms for the same halocarbons does show a correlation to support the conclusion that OH abstracts hydrogen only[156]. Unfortunately the choice of data is as yet too limited to make this a generally valid rule. If there is no hydrogen atom available for abstraction a very low rate constant results (e.g. CF_3COO^-, Table 15). OH reactions with aromatic compounds (as well as olefinic compounds) are always additive and close to diffusion controlled. These reactions are easily measured by the u.v. absorption of the transient adduct radical (e.g. $\lambda_{max} = 326$ nm for $HO—\dot{C}_6H_5Br$ and $\lambda_{max} = 324$ nm for $HO—\dot{C}_6H_5Cl$[165]).

Unlike the OH reactions the hydrogen atom can either abstract a hydrogen *or* a halogen from the halocarbon:

$$H^\bullet + RX \xrightarrow{k_{15}} H_2 + \text{haloradical} \qquad (15)$$

$$H^\bullet + RX \longrightarrow HX + R^\bullet \qquad (16)$$

In Figure 11 the rate constants for halogen abstraction (Figure 11A) and for hydrogen abstraction (Figure 11B) are plotted on a logarithmic scale, in separate columns for halocarbons, haloacid ions, haloacid molecules and haloalcohols and also for the number of H-carrying carbon atoms separately (C_1 and C_2). The rate constants for H abstractions are clearly within the area for abstraction reactions with *n*-alkanes, primary alcohols and acids[157] (shaded areas in Figure 11B). For halogen abstractions the rate constants are clearly blocked out according to the halogen involved: iodine abstractions do occur faster than ca. $10^9\ M^{-1}s^{-1}$, bromine abstractions range from 10^8 to $10^9\ M^{-1}s^{-1}$ and the chlorine abstraction covers the range from 10^5 to $10^8\ M^{-1}s^{-1}$ (Figure 11A). It appears that the rates for chlorine abstractions and for hydrogen abstractions are not too different, but for bromine and iodine compounds the X abstraction dominates strongly. From Figure 11A it is also seen that X abstractions from haloacid ions are mostly faster than the corresponding reaction with the acid molecule. Yet the differences are not very large. In a very recent study by Neta, Fessenden and Schuler[157] the abstraction reaction was detected by

* This would not be the case if the OH radical abstracted the halogen from the halocarbon (compare with the H atom reactions, Figure 11).

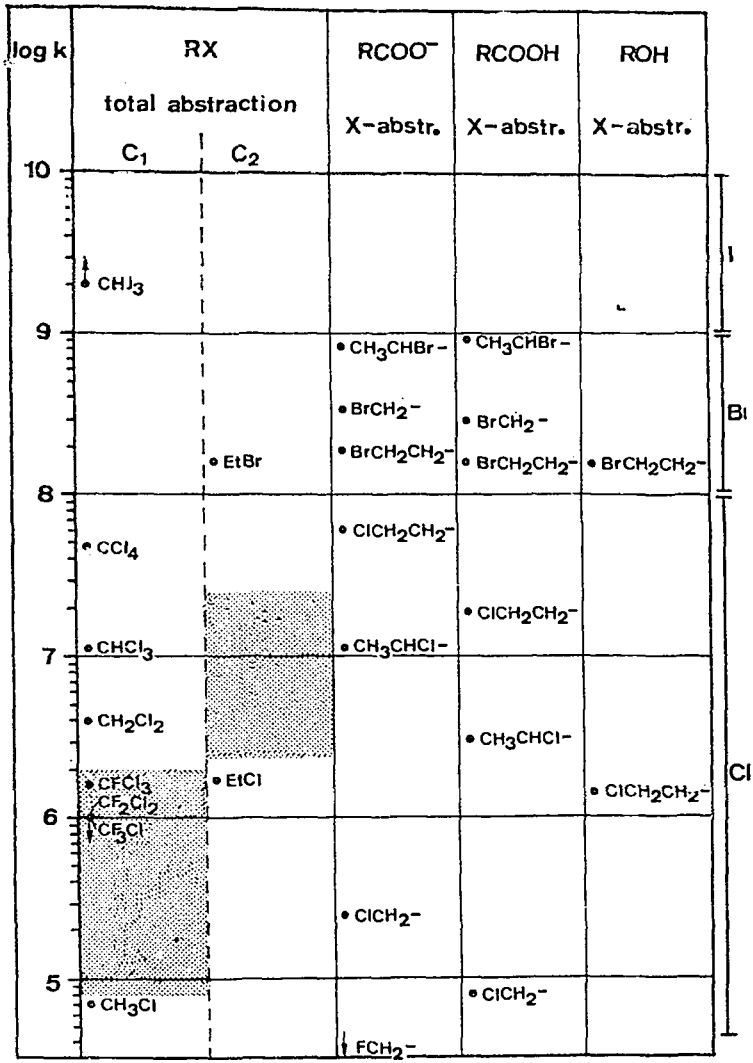


FIGURE 11. Reaction rate constants for H atoms in aqueous solutions. C_1 and C_2 indicate the number of H-carrying carbon atoms. The shaded areas in the columns C_1 and C_2 represent the region of rate constants for H abstraction, as derived from reactions with *n*-alkanes, primary alcohols and acids[157]. (Points with arrows indicate limiting values.)

A. Halogen abstraction (and total abstraction for the simple halocarbons, see text)[156, 157].

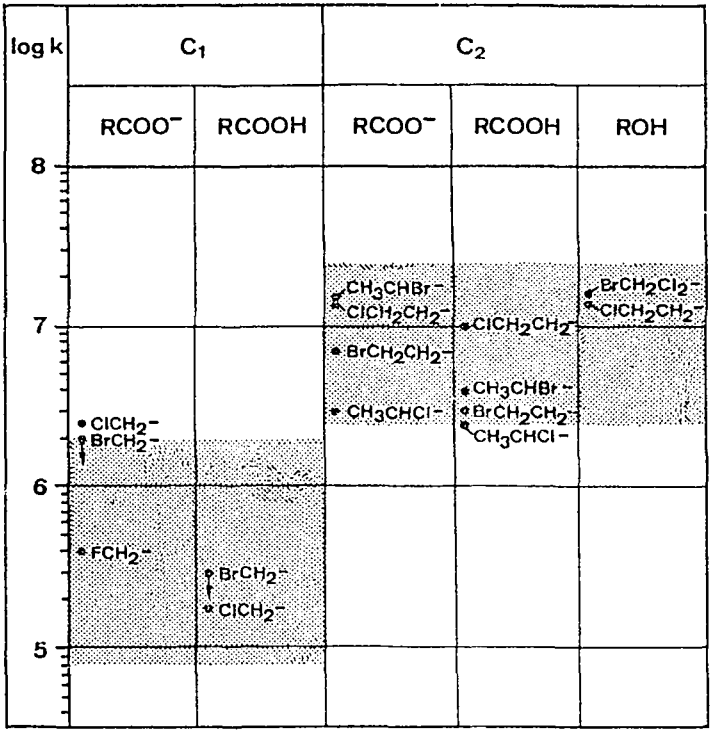


FIGURE 11. B. Hydrogen abstraction[156].

directly observing the abstracting H atoms with e.s.r. as it is formed through the reaction

$$e^- + H^+ \longrightarrow H^\cdot \qquad (17)$$

The H atoms formed this way have an initial non-equilibrium population of the four possible electron-nuclear spin levels which relaxes within 50 μs[157,166]. Neta and coworkers used a steady-state e.s.r.-method based on the competition between the chemical reaction with H atoms and the relaxation process of the H atoms. They obviously measured total abstraction, that is the sum of H abstraction and X abstraction. The results are given in the first two columns of Figure 11A. Clearly all the rate constants above the shaded area (for H abstraction from alkanes, etc.) are primarily due to X abstraction. H atom reactions with aromatic compounds are identical to the OH reactions. The H atom adds to the aromatic ring with almost diffusion controlled rate:

$$k(H + p\text{-}ClC_6H_4COOH) = (1{\cdot}13 \pm 0{\cdot}20) \times 10^9\ M^{-1}\,s^{-1}$$ [167]

The halogen substituent thereby hardly has any effect:

$$k(H + C_6H_5COOH) = (1{\cdot}00 \pm 0{\cdot}15) \times 10^9\ M^{-1}\,s^{-1}\ [167]$$

Anbar and Neta[168] studied reactions of a few haloradicals in aqueous solutions. These haloradicals, initially produced by OH reactions with H abstraction from the corresponding halocarbon, abstract the halogen from the halocarbons. The reactivity of the radicals studied followed the sequence:

$$BrCH_2\dot{C}HOH \approx ClCH_2\dot{C}HOH > (CH_2)_2\dot{C}OH > CH_3\dot{C}HOH > \dot{C}H_2OH \geqslant \dot{C}Br_2COOH$$
$$> CH_3\dot{C}BrCOOH \gg Br\dot{C}HCOOH$$

It was proposed that a charge-transfer mechanism rather than a halogen atom abstraction is important for these dehalogenation reactions. A series of inorganic radical ions was also found to induce dehalogenation of $ClCH_2COO^-$, $ClCH_2CH_2OH$ and $BrCH_2COO^-$ [169]. The metal ions thereby seem to react by an inner sphere mechanism involving halogen atom transfer.

C. Hydrogen Atom Reactions in Organic Systems

As early as 1962, Hardwick[170] very thoroughly studied the H atom reactions with halocarbons in liquid *n*-hexane by employing competitive reactions:

$$H^\bullet + n\text{-}C_6H_{14} \xrightarrow{k_{18}} H_2 + n\text{-}C_6H_{13}^\bullet \qquad (18)$$

$$H^\bullet + RX \xrightarrow{k_{19}} HX + R^\bullet \qquad (19)$$

$$\xrightarrow{k_{20}} H_2 + \text{haloradical} \qquad (20)$$

From H_2 yield measurements he was able to calculate the rate-constant ratios k_{19}/k_{18} and k_{20}/k_{18}. With a careful choice of k_{18} he then derived absolute values for k_{19} and k_{20} for a large number of alkyl halides and halogenated esters (for a list of rate constants see reference 170). In principle the reactivities for X abstraction display the same sequence as in aqueous solutions: RCl < RBr < RI. However, the rate constants are generally higher and the rates for X groups are closer to each other:

for chloro compounds $1 \times 10^8 < k_{19} < 4 \times 10^9\ M^{-1}\,s^{-1}$

for bromo compounds $1 \times 10^9 < k_{19} < 5 \times 10^9\ M^{-1}\,s^{-1}$

for iodo compounds $5 \times 10^9 < k_{19} < 2 \times 10^{10}\ M^{-1}\,s^{-1}$

For hydrogen abstraction (reaction 20) all rate constants are within the range of $0{\cdot}5 \times 10^8$ and $1{\cdot}1 \times 10^9$. There is no dependence on the molecular complexity (number of H-carrying C atoms) as has been found for aqueous solutions[157].

In a recent pulse radiolysis study the H atom reactions in the gas phase with several aromatic derivatives were studied by observing the transient absorption of the cyclohexadienyl-type radical[171]. The H addition rate constants are very little dependent on the substituents (Table 16). They are slightly smaller than corresponding rate constants in aqueous solutions[167].

TABLE 16. Gas-phase rate constants for the H-addition to aromatic hydrocarbons[171]

Reaction[a]	k at 100°C ($M^{-1}\,s^{-1}$)	E_{act} (kcal/mole)
$H + C_6H_5CF_3$	$1{\cdot}0 \times 10^8$	$5{\cdot}1 \pm 0{\cdot}8$
$H + C_6H_5F$	$1{\cdot}3 \times 10^8$	$3{\cdot}2 \pm 0{\cdot}8$
$H + C_6H_5Cl$	$2{\cdot}2 \times 10^8$	$2{\cdot}4 \pm 0{\cdot}8$
$H + C_6H_5CH_2Cl$	$2{\cdot}5 \times 10^8$	$3{\cdot}0 \pm 0{\cdot}8$

[a] For reactions with non-halogenated compounds see reference 171.

D. Reactions with Halogen Atoms

Halogen atom reactions were studied extensively in the radiolysis of chloro- and bromo-compounds. Iodine reactions were studied mostly by flash photolysis, because of its easy photolytic production. In most cases the first step of the halogen atom reaction is the formation of a transient halogen atom charge-transfer complex (CT complex)

$$X + M \longrightarrow (X{\cdot}M) \qquad (21)$$

the halogen atom being the electron acceptor, the molecule M the electron donor. These radical complexes are discussed in detail in a recent review by Bühler[120]. The Cl–CT-complexes were primarily studied by pulse radiolysis in CCl_4 solution[175], the Br complexes in $CHBr_3$ and bromobenzene[140]. The decay of the CT complexes depends critically on the halogen involved. The I atom complexes almost exclusively recombine to form I_2. With aromatic donors no ring addition could be detected. Br atom complexes with aromatic compounds yield Br_2 as well as bromocyclohexadienyl radicals and Cl atoms almost exclusively add to double

bonds or abstract H atoms from the donor. The radiolysis of pure bromobenzene[172] is chosen as an example to illustrate the decay reactions of a halogen atom CT complex. In this case $(Br{\cdot}C_6H_5Br)$=CTC is formed from free Br atoms reacting with the solvent or, to a lesser degree, by a neutralization process of $Br^- + C_6H_5Br^+$. The following decay reactions were shown to occur[172]:

$$CTC + CTC \xrightarrow{k_{22}} Br_2 \tag{22}$$

$$CTC \xrightarrow{k_{23}} Br\dot{C}_6H_5Br \tag{23}$$

$$CTC + Br\dot{C}_6H_5Br \xrightarrow{k_{24}} (C_6H_5Br_3) \longrightarrow HBr + C_6H_4Br_2 \tag{24}$$

$$CTC + C_6H_5\dot{C}_6H_5Br \xrightarrow{k_{25}} \ldots \longrightarrow HBr + C_6H_5C_6H_4Br \tag{25}$$

For single-pulse irradiation (pulse width ca. 50 ns, dose rate ca. 10^{27} eV g^{-1} s^{-1}) the G-values for the CT complex, Br_2 and HBr were determined to be $1{\cdot}8 \pm 0{\cdot}4$, $0{\cdot}11 \pm 0{\cdot}02$ and $1{\cdot}18 \pm 0{\cdot}06$ respectively. Quite clearly, from the low Br_2 yield, reaction (22) is of minor importance in the bromobenzene system. The rate constant for the unimolecular decay (reaction 23) is $k_{23} = 5{\cdot}4 \times 10^4 s^{-1}$ [172]. k_{22}, k_{24} and k_{25} were estimated to be $1{\cdot}2 \times 10^{10}$ M^{-1} s^{-1}, close to diffusion controlled.

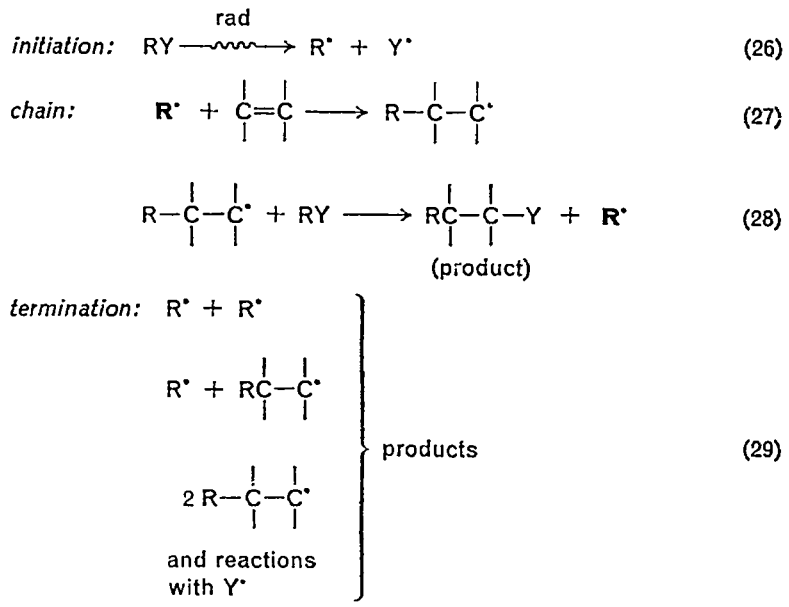
The cyclohexadienyl-type radicals, formed by X addition to an aromatic hydrocarbon (analogous to reaction 23), produce well-known absorptions in the u.v. region. Unfortunately often more than one such transient is formed simultaneously, producing close-lying, overlapping bands, difficult to analyse. Sauer and Mani[171] were able to discuss the spectra of the chlorocyclohexadienyl radicals ($ClC_6H_6^{\cdot}$), produced by $Cl + C_6H_6$ and by $H + C_6H_5Cl$. In the first case one single band at 305 nm was found, but in the second case an additional band at 320 nm must be related to the formation of three isomers, which are formed in this case only. A similar spectral difference was also found for the reactions $F + C_6H_6$ and $H + C_6H_5F$ [171].

E. Chain Reactions

Radical chain reactions are the basic processes for many industrial applications in radiation chemistry. This field has recently been reviewed by Wagner[173] and by Danno[174]. The chain reactions of interest in connexion with halocarbons are those with olefinic compounds (polymerization of haloolefins, copolymerization of olefins and haloolefins, halogenation of olefins) and with aliphatic hydrocarbons (halogenation and isomerization).

I. Olefinic compounds

The most common type of chain reaction leading to low molecular weight products is the reaction with unsaturated compounds. It is characterized by the following reaction steps (Y = hydrogen or halogen):



Because of these bimolecular termination steps high yields are found only for low dose rates (γ irradiation). If the termination is by a pseudo first-order reaction, e.g.

$$R^{\bullet} + \text{olefin} \longrightarrow RH + \text{allylic radical } (L^{\bullet}) \qquad (30)$$

(with $L^{\bullet}$ not able to abstract Y)

then high dose rates are permissible. The production of ethyl bromide (the Dow process) is by far the best known industrial process, which is based on reactions with olefins. The radiolysis of ethylene and HBr in an ethyl bromide solution is usually described by the following mechanism:

initiation: $EtBr \longrightarrow Et^{\bullet} + Br^{\bullet}$ (31)

chain: $Br^{\bullet} + CH_2{=}CH_2 \longrightarrow BrCH_2{-}CH_2^{\bullet}$ (32)

$BrCH_2{-}CH_2^{\bullet} + HBr \longrightarrow BrC_2H_5 + Br^{\bullet}$ (33)

termination: bimolecular reaction of radicals, similar to reaction (29)

The ethyl bromide yield is $G \approx 10^5$. For a detailed discussion see reference 174.

A more recent example is the condensation reaction with tetra- or trichloroethylene in alkane solutions as studied by Horowitz and Rajbenbach[175,176]. In this case the processes are as follows:

initiation: $RH \xrightarrow{\sim\sim} R^{\bullet} + H^{\bullet}$ (34)

(solvent)

(this is a simplified initiation reaction, full details in reference 177)

chain: $R^{\bullet} + C_2Cl_4 \xrightarrow{k_{35}} RC_2Cl_4^{\bullet}$ (35)

$RC_2Cl_4^{\bullet} \xrightarrow{k_{36}} RC_2Cl_3 + Cl^{\bullet}$ (36)

$Cl^{\bullet} + RH \longrightarrow HCl + R^{\bullet}$ (37)

termination: bimolecular

The same mechanism holds for trichloroethylene. In this case $k_{35} = 1{\cdot}3 \times 10^5\ M^{-1}s^{-1}$ (150°C) and $k_{36} = 2{\cdot}1 \times 10^4\ s^{-1}$ (150°C), R being the cyclohexyl radical[176]. Through this process solvent is consumed and an alkylated polychloroethylene is produced.

The dimerization of halogenated olefins represents another chain process. The chain reaction steps are:

$$X^{\bullet} + CH_2{=}CHCH_2X \longrightarrow XCH_2\dot{C}HCH_2X \quad (38)$$

$$XCH_2\dot{C}HCH_2X + CH_2{=}CHCH_2X \longrightarrow \begin{matrix} XCH_2 \\ \\ XCH_2 \end{matrix}\!\!>\!CHCH_2\dot{C}HCH_2X \quad (39)$$

$$\begin{matrix} XCH_2 \\ \\ XCH_2 \end{matrix}\!\!>\!CHCH_2\dot{C}HCH_2X \longrightarrow \begin{matrix} XCH_2 \\ \\ XCH_2 \end{matrix}\!\!>\!CHCH_2CH{=}CH_2 + X^{\bullet} \quad (40)$$

The reactions have been studied with methallyl chloride and with allyl bromide[178] using ionizing radiation to produce X initially.

2. Saturated compounds

In a solution of an aliphatic compound AX in a hydrocarbon solvent RH, the following chain reactions can be initiated by the radiation produced radical $A^{\bullet}$:

$$A^{\bullet} + RH \longrightarrow R^{\bullet} + AH \quad (41)$$

$$R^{\bullet} + AX \longrightarrow RX + A^{\bullet} \quad (42)$$

The substituent X is thereby introduced into the hydrocarbon molecule. To produce long chains, reactions (41) and (42) must be exothermic, therefore the conditions are (D = bond dissociation energy):

$$D(R{-}H) < D(A{-}H) \quad \text{and} \quad D(A{-}X) < D(R{-}X)$$

If the chain-carrying radical A can abstract a hydrogen from the product (RX) then two substituents X are introduced, and so on.

The chlorination of aliphatic hydrocarbons is one of the most typical examples for such a chain mechanism:

initiation:

$$C_mH_nCl_p \longrightarrow {}^{\bullet}C_mH_nCl_{p-1} + Cl^{\bullet} \quad (43)$$

$$\longrightarrow {}^{\bullet}C_mH_{n-1}Cl_p + H^{\bullet} \quad (44)$$

$${}^{\bullet}C_mH_{n-1}Cl_p + Cl_2 \longrightarrow C_mH_{n-1}Cl_{p+1} + Cl^{\bullet} \quad (45)$$

chain:

$$Cl^{\bullet} + C_mH_nCl_p \longrightarrow {}^{\bullet}C_mH_{n-1}Cl_p + HCl \quad (46)$$

$${}^{\bullet}C_mH_{n-1}Cl_p + Cl_2 \longrightarrow C_mH_{n-1}Cl_{p+1} + Cl^{\bullet} \quad (47)$$

For the chlorination of 1,2-dichloroethane (DCE)[174,180] the yield of chlorinated molecules is characterized by the consumption of DCE: $G(-\text{DCE}) \cong 10^6$ for the low dose rate of 10^4 rad/h. For higher dose rates lower yields result, since the termination step is again bimolecular. Other recent studies for chlorination reactions were published for methane[181], benzene[182], toluene (side-chain halogenation)[183], organosilanes[184] and chloropentane[185]. Bromination was studied for 2,3-dimethylbutane[186] and iodination for methane[187].

The isomerization of alkyl chlorides is a special type of radiation induced radical chain reaction:

initiation:

$$CH_3CH_2CH_2Cl \longrightarrow CH_3CH_2CH_2^{\bullet} + Cl^{\bullet} \quad (48)$$

$$Cl^{\bullet} + CH_3CH_2CH_2Cl \longrightarrow CH_3\dot{C}HCH_2Cl + HCl \quad (49)$$

chain:

$$CH_3\dot{C}HCH_2Cl \xrightarrow{\text{isomerization}} CH_3CHClCH_2^{\bullet} \quad (50)$$

$$CH_3CHClCH_2^{\bullet} + CH_3CH_2CH_2Cl \longrightarrow CH_3CHClCH_3 + CH_3\dot{C}HCH_2Cl \quad (51)$$

Such isomerization reactions were studied for *n*- and *s*-propylchlorides, for iso- and *t*-butyl chloride and 1-bromobutane[189]. The *G*-value for isomerization is of the order of 60.

VII. RADIOLYSIS OF SELECTED HALOCARBONS

A. Carbon Tetrachloride

Carbon tetrachloride is a unique halocarbon, since it is composed of only two elements, without hydrogen. Intermediates produced do not seem to react back with the solvent. Cl atoms and CCl_3 radicals are relatively long lived and dominant. CCl_4 therefore could be a simple radical source. Unfortunately the yields of the two final products found in γ-irradiation are rather small: $G(Cl_2) = G(C_2Cl_6) = 0{\cdot}8$ *, and this simple result does not reveal the primary processes, of which many aspects are still not understood today. The results from many investigations on *liquid* CCl_4 can be summarized as follows:

(1) With radio-chlorine as a solute it was found that chlorine atoms exchange in CCl_4 with $G(Cl_{ex}) = 7{\cdot}0 \pm 0{\cdot}7$ [190].

(2) Attempts to determine the total yield of radicals with various radical scavengers mostly failed. The lack of specificity of these scavengers causes the G-values to vary between 2·3 and 19 (for a survey see reference 179).

(3) From recent, careful scavenger studies (with Br_2, I_2, ICl, HI and others)[179] the initial yield of the primary radical was determined to be $G(Cl) = 7{\cdot}0 - 8{\cdot}3$ and $G(CCl_3) = 7{\cdot}0 \pm 0{\cdot}2$ in good agreement with the above-mentioned $G(Cl_{ex})$. It was shown that C_2Cl_4 is also an initial product with $G(C_2Cl_4) = 0{\cdot}07 - 0{\cdot}10$ [179]. In steady-state irradiations C_2Cl_4 is rapidly chlorinated to C_2Cl_6 and therefore not detectable. The yield of C_2Cl_4 was confirmed by product analysis from one-pulse irradiations, where the products are unable to react with transients.† C_2Cl_4 was also detected in gas-phase radiolysis of CCl_4–CF_4 mixtures[195].

(4) The chlorine yield from α-irradiations (high LET) is $G(Cl_2)_\alpha \cong 1{\cdot}6$ [196]. The increased yield must be due to higher initial radical concentration during the time of non-homogeneous distribution (spur reactions).

(5) An increase of temperature also increases the initial chlorine yield $G(Cl_2)_0$ from 0·8 (28°C) to 2·4 (100°C). The corresponding activation energy is about 4 ± 2 kcal/mole, a value rather close to the activation energy for self-diffusion of CCl_4 [188].

The results so far are compatible with a radical mechanism, in which the Cl atoms and CCl_3 radicals are the dominant transients. Without solutes a major part of these radicals disappears by recombination to form CCl_4.

* Published values are: $G(Cl_2) = 0{\cdot}74 \pm 0{\cdot}06$ [188], $0{\cdot}80 \pm 0{\cdot}06$ [190], $0{\cdot}8 \pm 0{\cdot}1$ [191], 0·65 [192], 0·66 [193], and $G(C_2Cl_6) = 0{\cdot}76 \pm 0{\cdot}03$ [188], $0{\cdot}80 \pm 0{\cdot}06$ [190], $0{\cdot}9 \pm 0{\cdot}1$ [191].

† With one-pulse irradiations of 50–230 krad (pulse width ca. 50 ns) the G-value for C_2Cl_4 was 0·08 from preliminary determinations[194].

The formation of C_2Cl_4 is not yet fully understood: it does not seem to be produced from CCl_2 radicals[179]. The formation of various excited states of CCl_4 must be quite important (by direct excitation or from ion neutralizations), as suggested by quencher experiments with DPPH ($G(CCl_4^*) = 10 \pm 2$) [197].

The following results from liquid systems demonstrate *ionic processes*:

(1) The free ion yield in pure liquid CCl_4 was measured by three independent methods[65, 66, 68] to be $G_{fi} \cong 0{\cdot}09$ (see Table 8B).

(2) In pulse radiolysis of pure liquid CCl_4 an absorption band centred at 475 nm was assigned to a cation of CCl_4 [116]. It decays by a fast initial reaction with a half-life of 15 ± 2 ns followed by a slow decay still visible in μs-pulse radiolysis[129, 198]. The slow part is about 4% of the fast part, therefore being quite comparable to the free ion yield.

By far the majority of studies about ionic processes in CCl_4 are *in solids* (glassy or polycrystalline), yet the results are still most controversial. This is partly due to the rather complex structures of some of the matrices, to the non-specificity of the absorption bands studied in the visible wavelength region and to the lack of knowledge of basic processes in the solid systems (charge-transfer, energy transfer, ion associations and shifts of absorption bands with temperature and structure). The results from solid systems can be summarized as follows:

(1) In irradiated *pure polycrystalline* CCl_4 at 77K or 20K two strong absorptions are detected at 345 nm and about 270 nm with a weak additional absorption band at about 410 nm [103, 118, 121]. The latter was assigned to the CCl_4^+ cation[113, 118] but the identity of the species absorbing at 345 and 270 nm is unknown. An e.s.r. spectrum with a single, asymmetric broad line centred at $g = 2{\cdot}014$ [199, 200, 201] behaves roughly similarly to the 410 nm cation band on warming. Above ca. 120K it resolved into a four-line and ten-line spectrum before disappearing at about 200K [199]. It was postulated that the single-line spectrum may be due again to the cation CCl_4^+, although it could not be properly distinguished from CCl_3 or CCl_4^- [200].

(2) CCl_4 solutions in *hydrocarbon glasses* irradiated at 77K reveal a typical absorption band at 470 nm and a much weaker one at ca. 360 nm [102, 103, 202]. With matrices of higher viscosity (either a harder matrix at 77K [202] or the same matrix at 20K [111, 121]) the 360 nm band strongly increases, whereas the 470 nm absorption is shifted at the same time to shorter wavelengths[121].

(3) In a *polycrystalline alkane matrix* (e.g. methylcyclohexane at 20K) a very broad absorption at 425 nm is interpreted as being due to an ionic charge transfer complex: $(MCH^+ \cdot CCl_4)$[121].

The interpretation of the 470 nm band, which appears in glassy hydrocarbons only, has passed through many stages: assignment to an anion of CCl_4 [203] (revoked later on), to a cation of CCl_4 [102,114], to a CT-complex $Cl \cdot CCl_4$ [202] and from photochemical studies (where the same band appears) to a colour centre[204,205,206]. It seems to be true that this band responds to positive *and* negative scavenging. The 360 nm band in glasses was assigned to CCl_4^+ [202], but also tentatively to a caged-in CCl_4^- [111].

From all these facts and postulates about ionic processes it is very difficult at the present stage to get a clear view of the processes and transients involved. Nevertheless it might be worth while to stress a few essential points:

(1) CCl_4 is its own electron scavenger. An electron will add dissociatively onto the next CCl_4 molecule immediately it is thermalized (see Figure 3 for σ_{da} in gas phase). This occurs regardless of any Coulomb field present. The geminate recombination therefore does not occur with the thermalized electron, but rather with the Cl^- from the dissociative attachment, yielding a chlorine atom on neutralization with the cation. This recombination process most likely is slower, since a much larger anion must be moved instead of an electron. The free or geminate ions are CCl_4^+/Cl^- or CCl_3^+/Cl^- pairs instead of the usual ion–electron pairs.

(2) The major differences in the radiolysis of liquid and solid-state CCl_4 are the following: (i) The anion formed at the end of the electron thermalization path will be caged-in, either as CCl_4^- or Cl^-, depending on the hardness of the matrix, (ii) the initial cation will not dissociate but remains CCl_4^+ (similar cage effect) but a resonance charge-transfer process might occur in the matrix.

(3) In an alkane glass matrix with CCl_4 as solute a positive charge transfer from alkane cation to CCl_4 is most unlikely because of their ionization potentials: $I_p(CCl_4) = 11{\cdot}47$ eV and $I_p(\text{alkane}) \approx 10$ eV. A simultaneous transfer of charge and excitation does not seem to be very probable. It has been postulated in the case of the methylcyclohexane matrix that the ionic CT complex ($MCH^+ \cdot CCl_4$) might be formed[121]. Another possible path could be a positive charge-transfer from the alkane cation to the preformed CCl_3 radical ($I_p(CCl_3) = 8{\cdot}7$ eV).

B. Chloroform

The radiolysis of chloroform is discussed here as an example for an alkyl chloride and differs from CCl_4 by the fact that an additional carbon–hydrogen bond is reactive. As a consequence, primary radicals produced in the radiolysis of $CHCl_3$ react back with the solvent resulting in a much

larger variety of products. Cl_2 is not formed any more[193,207]. Every chlorine atom produced immediately abstracts a hydrogen from $CHCl_3$ yielding HCl. Extensive studies with radical scavengers, dose rate and temperature variation reveal an almost complete radical mechanism, except for the CCl_4 formation[207-210] (compare the selected G-values in Table 17). The major radicals produced are $CHCl_2^{\cdot}$, $Cl^{\cdot}$ and $CCl_3^{\cdot}$. A small additional amount of CCl_2 is formed. The following reaction mechanism was proposed and is compatible with all results:

primary radical formation

$$CHCl_3 \xrightarrow{\sim\sim} CHCl_2^{\cdot} + Cl^{\cdot} \tag{52}$$

secondary radical formation

$$Cl^{\cdot} + CHCl_3 \longrightarrow HCl + CCl_3^{\cdot} \tag{53}$$

$$CHCl_2^{\cdot} + CHCl_3 \longrightarrow CH_2Cl_2 + CCl_3^{\cdot} \tag{54}$$

product formations

$$2\ CHCl_2^{\cdot} \longrightarrow sym\text{-}C_2H_2Cl_4 \tag{55}$$

$$CHCl_2^{\cdot} + CCl_3^{\cdot} \longrightarrow C_2HCl_5 \tag{56}$$

$$2\ CCl_3^{\cdot} \longrightarrow C_2Cl_6 \tag{57}$$

additional minor radical reactions

$$CHCl_3 \xrightarrow{\sim\sim} CHCl_3^{*} \longrightarrow CCl_2{:} + HCl \tag{58}$$

$$CCl_2{:} + CHCl_3 \longrightarrow C_2HCl_5^{*} \tag{59}$$

$$C_2HCl_5^{*} \xrightarrow{+M} C_2HCl_5 \tag{60}$$

$$C_2HCl_5^{*} \longrightarrow C_2Cl_4 + HCl \tag{61}$$

It was shown that the radical–solvent reaction (54) is much slower than the H abstraction by Cl (reaction 53). The reaction rate constant k_{54} was determined to be $9{\cdot}6 \times 10^4 \exp(-6700/RT)\ M^{-1}s^{-1}$ [209]. At room temperature (25°C) $k_{54} = 1{\cdot}3 \pm 0{\cdot}2\ M^{-1}s^{-1}$ [210]. The radical combination reactions (55)–(57) are close to diffusion controlled. From a computer optimization the following ratio yields: $k_{55}:k_{56}:k_{57} = 1{\cdot}0:1{\cdot}5:1{\cdot}0$ [209]. The C_2Cl_4 yield is unaffected by radical scavengers[208], by positive-ion scavengers[207] and by dose rate variation from about 10^{15} to 10^{24} eV $g^{-1}s^{-1}$ [210]. Only a small positive temperature coefficient could be detected (Table 17). The comparison with pyrolysis of $CHCl_3$ (500°C), where HCl and C_2Cl_4 are the principal products[212] then suggests the reactions (58)–(61)[207].

TABLE 17. Typical product yields in the radiolysis of $CHCl_3$

Dose rate ($eV\ g^{-1}\ s^{-1}$)	ca. 5×10^{24}	$1{\cdot}6 \times 10^{16}$	$1{\cdot}6 \times 10^{16}$	$1{\cdot}6 \times 10^{16}$	$4{\cdot}8 \times 10^{15}$	$1{\cdot}2 \times 10^{16}$	$1{\cdot}2 \times 10^{16}$	$1{\cdot}2 \times 10^{16}$
Temperature (°C)	25	25	25	25	−67	−57	26	63
Scavenger	—	—	0·48M NH_3	$\frac{d(product)}{d(NH_3)}$	Solid	Liquid	Liquid	Liquid
Reference	210	210	207	—	208	209	209	209
Molecular yields (*G*)								
CCl_4	0·94	0·89	0·23	−	0·88	0·6	0·7	0·9
C_2Cl_4	0·078	0·085	0·091	~0	0·06	0·032	0·076	0·094
CH_2Cl_2	0·2	1·9	2·4	+	0·79	0·27	2·2	3·4
$C_2H_2Cl_4$	1·5	0·73	0·77	~0	0·12	1·14	0·67	0·66
C_2HCl_5	1·8	1·6	1·9	+	2·4	1·98	1·48	0·98
C_2Cl_6	0·85	2·0	2·6	+	0·33	0·74	2·40	3·3
HCl	[a]	[a]	[a]	[a]	3·4	4·1[b]	5·3[c]	[a]
$-CHCl_3$	[a]	[a]	[a]	[a]	8·1	8·7	12·2	14·5
Radical yields (*G*)								
Cl	[a]	[a]	[a]	[a]	[a]	4·1[b]	5·4	5·5
$CHCl_2$	5·0	5·0	5·8	+	[a]	4·3[b]	4·7	5·6
CCl_3	3·5	5·6	7·1	+	[a]	3·8[b]	6·8	8·0

[a] Not determined.
[b] Interpolated values from references 208, 209.
[c] From reference 208; dose rate ca. 10^{15} $eV\ g^{-1}\ s^{-1}$; an earlier value was $G(HCl) = 5{\cdot}4$ (dose rate ca. 6×10^{14} $eV\ g^{-1}\ s^{-1}$) [211].

For experiments with very high dose rates[210] (ca. 5×10^{24} eV g^{-1} s^{-1}) yield calculations from the reaction mechanism made it necessary to include radical combinations with the Cl atoms:

$$Cl + CHCl_2 \longrightarrow CHCl_3 \quad (62)$$

$$Cl + CCl_3 \longrightarrow CCl_4 \quad (63)$$

$$Cl + Cl \longrightarrow Cl_2 \quad (64)$$

For this large dose rate the interference from these reactions (62)–(64) is about 10%.

From the calculated reaction model[209] spur yields for several temperatures were calculated. Typical values at 26°C are:

product yields: $G(C_2H_2Cl_4)_{spur} = 0{\cdot}34$

$G(C_2HCl_5)_{spur} = 0{\cdot}18$

radical yields: $G(CHCl_2^{\bullet})_{spur} = 0{\cdot}86$

$G(CCl_3^{\bullet})_{spur} = 0{\cdot}22$

The behaviour of the CCl_4 product yield is not compatible with a radical mechanism, nor is an excited state the precursor[207]. In the gas phase CCl_4 is not formed[213]. Only positive-ion scavengers (NH_3, *n*-BuOH) are able to reduce the CCl_4 yield[207] (see Table 17). A test with equation (D) (section III. B. 1) for ion scavenging confirms the positive-ion precursor*. The most likely scavenging reactions are:

$$CHCl_3^+ + NH_3 \longrightarrow NH_4^+ + CCl_3^{\bullet} \quad (65)$$

$$CHCl_3^- + NH_4^+ \longrightarrow NH_4Cl + CHCl_2^{\bullet} \quad (66)$$

The additionally formed radicals are responsible for the increased yield of C_2HCl_5, C_2HCl_6 and CH_2Cl_2 (Table 17). In solid-state radiolysis of $CHCl_3$ (see Table 17) the yield of CCl_4 and CH_2Cl_2 is about equal. In this case the most likely process would be the neutralization of $CHCl_3^-$ (stable within a cage of the matrix) and $CHCl_3^+$ (mobile by the resonance charge transfer process):

$$CHCl_3^- + CHCl_3^+ \longrightarrow CCl_4 + CH_2Cl_2 \quad (67)$$

In gas phase this cannot occur since $CHCl_3^-$ immediately decays to form Cl^-. To explain the CCl_4 yield in *liquid* $CHCl_3$ it is therefore assumed that

* G(P) in formula (D) corresponds in this case to the decrease in CCl_4 yield.

the lifetime of the $CHCl_3$ anion is long compared to the neutralization process, therefore reaction (67) is also valid for liquid $CHCl_3$. From the analysis of equation (D) it is found that the total yield of ion-precursor is about 1. The free ion yield is undetectable, that is $G_{fi} \leqslant 0{\cdot}04$. The reactivities α_s are given in Table 18, compared with the scavenger reactivities in

TABLE 18. Reactivity α_s of the positive ion scavengers NH_3 and *n*-BuOH

Solvent	Scavenger	
	NH_3	*n*-BuOH
$CHCl_3$ [207]	6 ± 2	16 ± 4
Cyclohexane[a]	0·97[b]	1·1[b]
Cyclohexane[a]	ca. 0·3[b]	ca. 1

[a] Earlier published data were analysed by equation (D); details are in reference 207.
[b] Deuterated scavenger: ND_3 or n-C_4H_9OD.

cyclohexane solution. The reactivity α_s in $CHCl_3$ is much larger: the geminate neutralization in $CHCl_3$ is between two molecular ions ($CHCl_3^-$, $CHCl_3^+$), therefore is substantially slower than the positive ion–electron neutralization in cyclohexane. With such larger lifetimes of the positive ion in $CHCl_3$ the scavenger efficiency obviously must also be larger.

C. Alkyl Iodides

In the radiolysis of gaseous and liquid alkyl iodides a large fraction seems to be related to radical reaction and excited states. Information about ionic processes is derived primarily from the solid systems and from gas-phase mass spectrometric studies. Quite generally the product yields are not very high because back reactions are important.

The reactions involved are best known in the gas phase. They are summarized hereafter for CH_3I, recently discussed very extensively by Donovan and Hanrahan[214]:

primary processes

$$CH_3I \longrightarrow CH_3 + I \text{ (partly excited)} \qquad (68)$$

$$\longrightarrow CH_3I^+ + e \qquad (69)$$

secondary radical reactions

$$I + I + M \longrightarrow I_2 + M \qquad \text{third-order reaction (M is mainly } CH_3I \text{ or the wall)} \qquad (70)$$

$$CH_3^* + CH_3I \longrightarrow CH_4 + CH_2I^\bullet \qquad \text{H abstraction} \qquad (71)$$

$$- \longrightarrow CH_3^\bullet + CH_3I \qquad \text{thermalization} \qquad (72)$$

$$\longrightarrow C_2H_6 + I^\bullet \qquad \text{minor reaction} \qquad (73)$$

$$CH_3 + CH_3(+ M) \longrightarrow C_2H_6(+ M) \qquad \text{dimerization} \qquad (74)$$

radical reaction with products

$$CH_3^\bullet + I_2 \longrightarrow CH_3I + I^\bullet \qquad (75)$$

$$CH_2I^\bullet + I_2 \longrightarrow CH_2I_2 + I^\bullet \qquad (76)$$

ionic reactions[227,228]

$$e + CH_3I \longrightarrow CH_3 + I^- \qquad (77)$$

$$\begin{aligned} (CH_3I^+)^* &\longrightarrow CH_3I^+ \quad 100 \\ &\longrightarrow CH_3 + I^+ \quad 53 \\ &\longrightarrow CH_3^+ + I \quad 28 \\ &\longrightarrow CH_2I^+ + H \quad 14 \end{aligned} \qquad \left.\right\} \text{ratio from mass spectrum (50–70 eV)} \qquad (78)$$

$$CH_3I^+ + CH_3I \longrightarrow (CH_3ICH_3)^+ + I \qquad (79)$$

$$CH_3^+ + CH_3I \longrightarrow (CH_3ICH_3)^+ \qquad (80)$$

$$CH_2I^+ + CH_3I \longrightarrow I_2^+ + C_2H_5^\bullet \qquad (81)$$

Neutralizations finally yield: $CH_3^\bullet$, $I^\bullet$, $H^\bullet$, $Et^\bullet$, HI.

H reactions

$$\text{with solvent} \quad H^\bullet + CH_3I \longrightarrow HI + CH_3^\bullet \qquad (82)$$

$$\text{with product} \quad H^\bullet + I_2 \longrightarrow HI + I^\bullet \qquad (83)$$

$$H^\bullet + HI \longrightarrow H_2 + I^\bullet \qquad (84)$$

Reaction (82) is probably the major source for HI in CH_3I.

products from molecular eliminations

It is proposed that

$$CH_3^* + CH_3I \longrightarrow C_2H_6^* + I^\bullet \qquad (85)$$

$$C_2H_6^* \longrightarrow C_2H_4 + H_2 \qquad (86)$$

but the formation of C_2H_4 is not yet quite clear.

From product analysis the importance of the various steps can be estimated (see Table 19). About one-third of the initial product yield is

TABLE 19. Initial product yields from the radiolysis of pure gaseous CH_3I at 300 Torr (25°C)[214]

Product	G	Product	G
CH_4	$2{\cdot}9 \pm 0{\cdot}1$	C_2H_4	$0{\cdot}065 \pm 0{\cdot}003$
CH_2I_2	$1{\cdot}4 \pm 0{\cdot}3$	I_2	$0{\cdot}16 \pm 0{\cdot}02$
H_2	$0{\cdot}55 \pm 0{\cdot}05$	HI	$0{\cdot}13 \pm 0{\cdot}02$
C_2H_6	$0{\cdot}07 \pm 0{\cdot}01$	C_2H_2	$0{\cdot}12 \pm 0{\cdot}01$

formed by radical reactions, ethane by about 90%. The remaining fraction is due to reactions with hot radicals or ionic processes. CH_2I_2, H_2 and C_2H_4 are not scavengeable. If HI is used as a radical scavenger, the initial methane yield is $G(CH_4) \approx 25$. This might stress the large fraction of back reaction occurring in these systems[214]. Scavenging with phosphine gave an initial yield of $G(CH_3) = 12{\cdot}6$[215] *.

In the radiolysis of EtI about two-thirds of the products are explained by radical reactions[217]. For EtI, as well as for all higher RI, a unimolecular dissociation also occurs[218, 221].

$$RI^* \longrightarrow HI + \text{alkene} \qquad (87)$$

From mass spectrometry it was shown that EtI and PrI (but not CH_3I) form dimer cations[222]:

$$RI^+ + RI \longrightarrow (RI)_2^+ \qquad (88)$$

This was supported by spectral data in solid systems (see below).

In pulse radiolysis of liquid cyclohexyl iodide[223], methyl, ethyl and isopropyliodide[224] a transient spectrum, peaking at 400 nm and being very asymmetric towards the red, was assigned to a possible charge-transfer complex I·RI, but this assignment is not yet certain[120]. A weak and faster decaying absorption at about 650–750 nm is probably due to a cationic species, in analogy to results in solid RI (see below).

The alkyl iodides at 77K are able to form a glass or polycrystalline matrix, dependent on the cooling method. The e.s.r. spectra of the transients formed in the two matrices are drastically different. In the glassy matrix and in the polycrystalline matrix of alkyl iodides RI with an odd number of

* CF_3I has a much simpler reaction mechanism, since there is no F abstraction, the only products being CF_4, C_2F_4, C_2F_6 and I_2 though back reactions are also dominant. With Br_2 as scavenger, $G(CF_3Br)$ is $20{\cdot}1$[216].

C atoms, the e.s.r. spectrum is the one of the corresponding radical R. The polycrystalline RI with even C-numbers displays a very complex (1000 Gauss wide) spectrum, which changes to the spectrum of R on warming to about 145K, followed by rapid refreezing to 77K. A detailed discussion of the spectra, as well as of differences in product yield, is given by Willard[102] and coworkers[109]. The complex spectrum shows hyperfine splitting from the iodine, which indicates that negative ions RI^- are caged-in in the polycrystalline matrices of even-numbered alkyl iodides and I^- can be freed only by warming[109].

Fenrick and coworkers[154] have recently investigated the further decay of the radical R produced in a glassy matrix. Their results were interpreted as being due to the recombination of R with I^- to form a stable RI^-, corresponding to the potential energy diagram discussed in section II. D, but the latter anion did not yield an e.s.r. spectrum. From these results one must conclude that the primary caged-in ion–radical pair $(R\cdots I^-)$ in a polycrystalline matrix is in a different state from the anion RX^- proposed to be formed from the decay of R in the glassy matrix.

From optical spectroscopy of the transients formed in glassy alkyl iodides (EtI, *n*-BuI, *i*-BuI and *n*-pentyl iodide) an absorption band at about 750 nm was assigned to a dimeric cation $(RI)_2^-$[235]. The corresponding monomeric cations RI^- have absorptions at about 440–480 nm and could be detected in dilute RI-solutions in hydrocarbon matrices[151, 235].

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The Chemistry of The Carbon–Halogen Bond
Edited by Saul Patai

CHAPTER 13

The biochemistry of carbon–halogen compounds

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ABBREVIATIONS

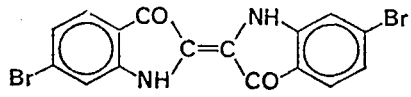
ADP:	Adenosine diphosphate
AMP:	Adenosine monophosphate
ATP:	Adenosine triphosphate
CoA:	Coenzyme A
2,4-D:	2,4-Dichlorophenoxyacetic acid
DDA:	Bis-(*p*-chlorophenyl)acetic acid
DDD:	1,1-Dichloro-2,2-bis-(*p*-chlorophenyl)ethane
DDE:	1,1-Dichloro-2,2-bis-(*p*-chlorophenyl)ethylene
DDT:	1,1,1-Trichloro-2,2-bis-(*p*-chlorophenyl)ethane
DIHPP:	3,5-Diiodo-4-hydroxyphenylpyruvate
DIT:	3,5-Diiodotyrosine
DNA:	Deoxyribonucleic acid
E.FAD E.$FADH_2$	Oxidized and reduced forms of a flavine adenine dinucleotide–enzyme complex
FAD $FADH_2$	Oxidized and reduced forms of flavine adenine dinucleotide
FH_2:	Dihydrofolic acid
FH_4:	Tetrahydrofolic acid
FMN:	Flavine mononucleotide
GSH:	Glutathione (γ-glutamylcysteinylglycine)
GSR:	*S*-Alkylglutathione
MIT:	3-Iodotyrosine
NAD^+ NADH	Oxidized and reduced forms of nicotinamide adenine dinucleotide
$NADP^+$ NADPH	Oxidized and reduced forms of nicotinamide adenine dinucleotide phosphate
P_i:	H_3PO_4 and charged forms
PP_i:	$H_4P_2O_7$ and charged forms
RCOCoA:	Acyl coenzyme A derivative
T_3:	3,5,3′-Triiodothyronine
T_4:	3,5,3′,5′-Tetraiodothyronine (thyroxine)
TRF:	Thyrotropin releasing factor
TSH:	Thyrotropin (thyroid stimulating hormone)
UDP:	Uridine diphosphate
UDP-Glu:	Uridine diphosphate glucuronic acid

I. INTRODUCTION

The number of compounds containing covalently bound halogens which are produced by living organisms is very small; in all, a few dozen of such compounds are known. The majority of these are secondary metabolites of fungi. Although these metabolites appear to have no essential function in the metabolism of the organisms which produce them, some of them have achieved considerable importance due to their antibiotic activities. Some of the more important halo metabolites are discussed below.

In the case of the higher animals only one class of carbon–halogen compound is known, namely the iodo derivatives of tyrosine and thyronine. These compounds are, however, of enormous importance in the regulation of growth and control of the metabolic activities of the organism and aspects of their chemistry and biological functions will be discussed in detail.

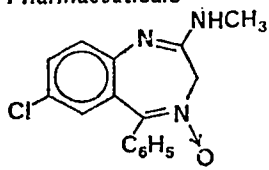
Of limited importance but of some historic interest is the occurrence in certain Mediterranean molluscs (e.g. *Murex brandaris*) of a leuco compound which on exposure to air gives a purple dye; this dye, Tyrian Purple, was much prized in ancient times. The structure of the dye was investigated by Friedlander in 1909 and the compound was shown to be 6,6′-dibromoindigotin (**1**).



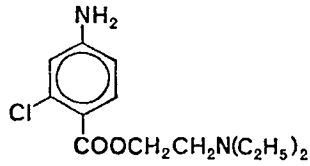
(1)

One other aspect of the biological importance of carbon–halogen compounds which must be considered is the introduction of organochlorine compounds into the biosphere by man. Organochlorine compounds have found uses as chemotherapeutic agents and pesticides and in industry as solvents, flame retardant agents and electrical insulators. A representative selection of such compounds is shown in Figure 1. Much has now been written about the deleterious effects on the environment which have occurred due to widespread use of these compounds, particularly the organochlorine insecticides. The pharmaceutical compounds are used in relatively small amounts and are hence less important from the point of view of environmental pollution; similarly, the industrial organochlorine compounds are generally used in closed systems and, provided the necessary precautions are taken, it should be possible to prevent their entry into the biosphere. The harmful effect of the indiscriminate use of insecticides was first brought to the attention of the public by the publication in 1962 of Rachel Carson's book *Silent Spring*[1]. The thesis of this

Pharmaceuticals

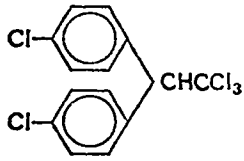


Chlordiazepoxide
(tranquillizer)

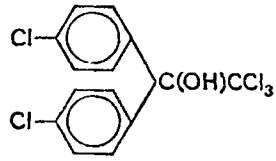


Chloroprocaine
(local anaesthetic)

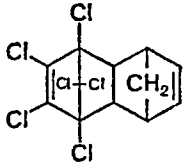
Agricultural chemicals



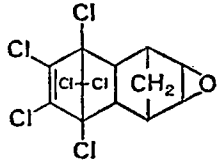
DDT (pesticide)



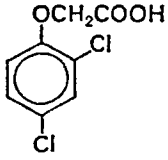
Dicofol (pesticide)



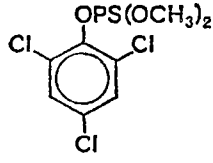
Aldrin (pesticide)



Dieldrin (pesticide)

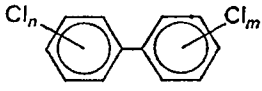


2,4-D (herbicide)



Fenchlorphos (herbicide)

Industrial chemicals



Polychlorinated biphenyls

Chlorinated naphthalenes

FIGURE 1. Some important synthetic organochlorine compounds.

book was not that insecticides should not be used but rather that they were being used with little or no advance investigation of their effects on soil, water, wildlife and man. The publication of this book led to considerable debate, some of it extremely acrimonious (see, for example, the account given in reference 2). Since this time a very large amount of work has been expended on analysis of pesticide residues in the environment[3,4] and on the assessment of harmful effects on living organisms[5–8]. The major problems encountered with compounds of this type are firstly that their rate of degradation by biological systems is slow and secondly that they are concentrated by living systems. A single example should help to illustrate this point[2]. In the Lake Michigan ecosystem it has been shown that the level of DDT in the mud of the lake bed averages 0·014 ppm. In the food chain shrimps : fish : herring gulls the levels were found to be 0·44, 5·0 and 100 ppm respectively. The high level in the gulls at the top of this food chain was sufficient to prevent 30% of their eggs from hatching. Many similar cases have been cited in the references given above and it is beyond the scope of this article to consider the problem of pollution in detail. It is obviously a problem of considerable importance and one in which the author feels himself insufficiently expert to add to the extensive arguments already in the literature. The discussion of organochlorine compounds which follows will, therefore, be limited to what is known about the processes of metabolism of these compounds and, in particular, metabolic processes involving dehalogenation. The more general questions of whether the use of organochlorine pesticides should be continued, and, if so, the controls which should be introduced to limit the way in which they are used, will not be discussed further.

II. FUNGAL METABOLITES CONTAINING CHLORINE

Many of the lower forms of life carry out what is known as secondary metabolism, that is, the biosynthesis from intermediates of normal metabolic processes of compounds which play no obvious part in the economy of the organism. The production of terpenes by the higher plants is an obvious example. The secondary metabolites of fungi are of interest in the present context in that some of them contain covalently bound chlorine. Fungal species which produce chloro metabolites frequently biosynthesize the corresponding bromo metabolites if grown in media containing bromide ions rather than chloride ions, but under these conditions the deshalo analogues are usually major products[9,10]. Attempts to produce the corresponding fluoro and iodo metabolites have not been

successful[11,12]. A review of halo metabolites has been published[13] and a recent monograph has given a survey of fungal metabolites in general[14].

A. Structural Types

With few exceptions, the fungal chloro metabolites have the chlorine atom bonded to carbon in a five- or six-membered ring. Exceptions to this are the important antibiotic chloramphenicol[15] (4) and mollisin[16] (5). In these two cases, both chlorine atoms are bound to a single carbon atom, a situation which is also found for the cyclopentane derivative caldariomycin[17,18] (2). The compound with the highest chlorine to carbon ratio so far isolated is drosophilin A[19] (3).

In addition to the naphthoquinones (e.g. 5) other bicyclic metabolites have been isolated with fused rings; these include chromones (e.g. sordidone[20,21] (6)) and isocoumarins (e.g. 5,7-dichloro-8-hydroxy-6-methoxy-3-methyl-3,4-dihydroisocoumarin[22] (7)). Non-fused bicyclic systems are

FIGURE 2. Structural types of chloro metabolites.

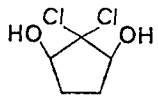
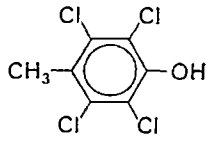
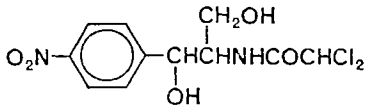
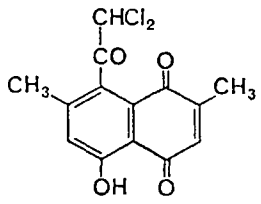
Type	Typical structure	Producer organism
Cyclopentanes	 (2)	*Caldariomyces fumago*
Phenols	 (3)	*Drosophila subatrata*
Phenylserinols	 (4)	*Streptomyces venezuelae*
Naphthoquinones	 (5)	*Mollisia caesia*

FIGURE 2 (*cont.*).

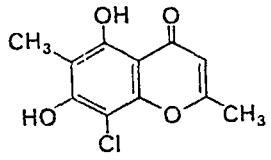
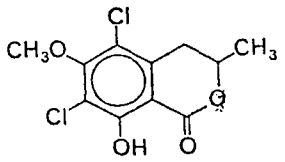
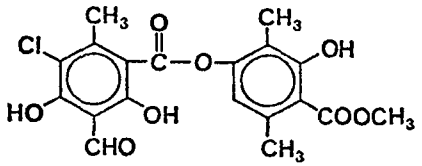
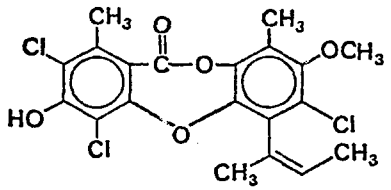
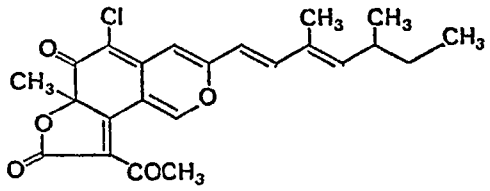
Type	Typical structure	Producer organism
Chromones	 (6)	*Lecanora sordida*
Isocoumarins	 (7)	*Sporormia affinis*
Depsides	 (8)	*Parmelia* species
Depsidones	 (9)	*Aspergillus nidulans*
Azaphilones	 (10)	*Penicillium hirayamae*

FIGURE 2 (*cont.*).

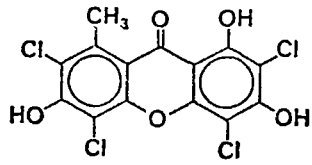
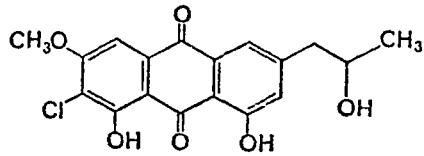
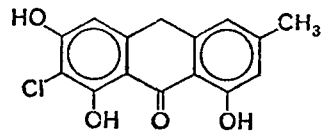
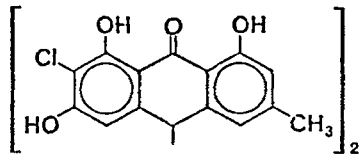
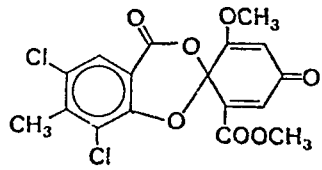
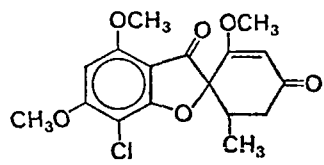
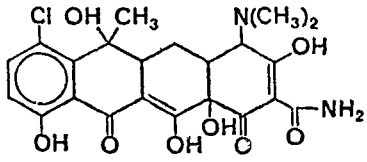
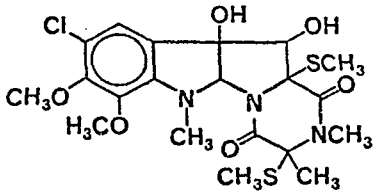
Type	Typical structure	Producer organism
Xanthones	 (11)	Various lichens
Anthraquinones	 (12)	*Penicillium nalgiovensis*
Anthrones	 (13)	*Aspergillus fumigatus*
Dimeric anthrones	 (14)	*Anaptychia obscurata*
Spirans	 (15)	*Aspergillus terreus*
Tetracyclines	 (16)	*Penicillium* species

FIGURE 2 (*cont.*).

Type	Typical structure	Producer organism
Tetracyclines	 (17)	*Streptomyces* species
Sporidesmins	 (18)	*Sporidesmium bakeri*

represented by the depsides (e.g. chloroatranorin[23] (**8**)); various *aspergillus* species produce analogues of the depsides in which ring closure results in a fused tricyclic system (e.g. nidulin[24] (**9**)). Other tricyclic fused ring systems are the azaphilones (e.g. 7-*epi*-5-chloroisorotiorin[25] (**10**)), xanthones (e.g. thiophanic acid[26] (**11**)), anthraquinones (e.g. nalgiolaxin[27,28] (**12**)) and anthrones (e.g. 2-chloro-1,3,8,-trihydroxy-6-methylanthrone[29] (**13**)); dimeric anthrones have also recently been isolated (e.g. flavoobscurin B[30] (**14**)). Two major types of spirans have been identified. In compounds related to geodoxin[31] (**15**) the central ring is six-membered whereas in the griseofulvins[32–34] (**16**) the central ring is five-membered; precursors of griseofulvin have been isolated from *Penicillium patulum* in which the spiran system is not formed (e.g. griseophenone A[35] (**21**)). The most complex of the chloro metabolites are the tetracyclines (e.g. chlorotetracycline[36] (**17**)) which are of great importance due to their antibiotic properties, and the sporidesmins (e.g. sporidesmin D[37,38] (**18**)).

B. Chloro Metabolites of Special Interest

Although a considerable amount of work has been done on the chloro metabolites in general[13], particular effort has been devoted to those species

which have antibiotic activities. Of these, the most important are chloramphenicol, griseofulvin and the tetracyclines.

1. Chloramphenicol

The organism from which chloramphenicol **4** is obtained was isolated independently from Venezuelan soil[39] and from soil in Illinois[40]. The antibiotic was isolated and crystallized in 1948[41] and its structure was established as D-*threo*-2-dichloroacetamido-1-*p*-nitrophenylpropan-1,3-diol[15]. Chloramphenicol was found to be active against a wide range of organisms (for a review, see reference 42); in particular it was effective against the rickettsiae of typhus[43]. The drug has been used in the treatment of typhoid fever, brucellosis, pertussis, gonorrhoea and various tropical diseases. Prolonged therapy with chloramphenicol may, however, lead to undesirable side-effects[42].

The biosynthesis of chloramphenicol has been reviewed by Gottlieb[44]. Two aspects of the molecule are of particular interest from the point of view of biosynthesis, namely the origin of the nitro group and the mechanism of introduction of the two chlorine atoms. Unfortunately, neither of these problems has been completely solved. Recent work[45] suggests that the nitro group is introduced by direct oxidation of an amino group as the last step in the biosynthesis, but the enzyme system catalysing the reaction has not been isolated. Chlorination occurs in an earlier step but the details of this have not been elucidated. The solution of these problems would be assisted by the development of a high producing strain of *Streptomyces venezuelae*, but owing to the fact that chloramphenicol for therapeutic use is produced synthetically, such a strain has not been developed.

2. Griseofulvin

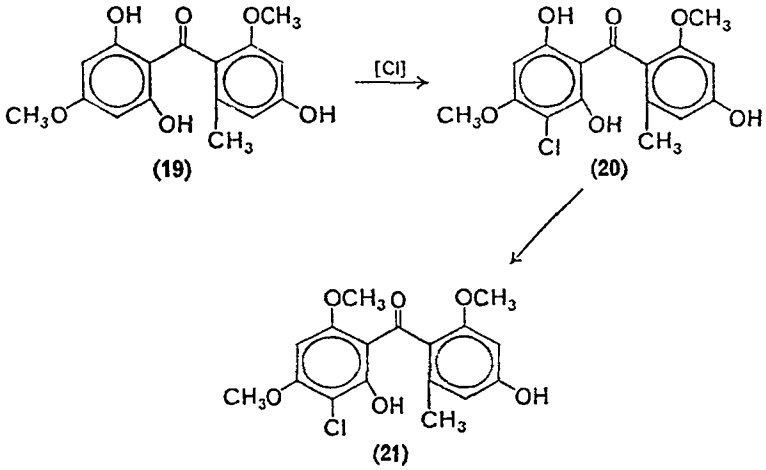
Griseofulvin, **16**, was first isolated in 1939[32] from the mycelium of *Penicillium griseofulvum*. The compound is, in fact, produced by many strains of *Penicillium* and *P. patulum* is now used for commercial production. In chloride-deficient media *P. griseofulvum* produces the dechloro analogue[46] and when bromide ions are added to such a medium the bromo analogue is produced[47].

Griseofulvin is a powerful fungistatic agent exerting its effect by interfering with the synthesis of cell wall material; it is effective, however, only against those fungi whose cell walls contain mainly chitin[48]. Griseofulvin has been used successfully in the treatment of fungal infections in man and of ringworm infections of cattle (see reference 49).

Fungal pathogens of plants[48] are also susceptible to treatment with griseofulvin, but cheaper methods are generally available for control of fungal diseases in plants.

The chemistry of griseofulvin has been extensively examined[49]. The absolute configurations of both asymmetric centres are known[33]; the systematic name of the compound is (2S,6′R)-7-chloro-4,6,2′-trimethoxy-6′-methylgris-2′-en-3,4′-dione. Total syntheses of the optically active chloro and bromo compounds have been reported and racemic fluoro and iodo analogues have been synthesized[49].

The biosynthesis of griseofulvin in *P. patulum* has been investigated[49,50] and the timing of introduction of the chlorine atom tentatively assigned[51]. It is suggested that griseophenone *c* (**19**) is the chloride acceptor producing griseophenone *b* (**20**) which on methylation yields griseophenone *a* (**21**) (equation 1); spiran formation and reduction then complete the bio-



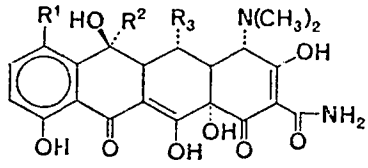
(1)

synthetic sequence. Inhibition of the chlorination reaction in *P. patulum* by chloride deficiency or inhibition with bromide led to an accumulation of **19** and synthesis of only a small amount of griseofulvin; there appears to be no route from **19** to dechlorogriseofulvin in this organism[51].

3. Tetracyclines

The tetracyclines are a family of related compounds with the general formula shown overleaf (**22**). The parent compound (**22c**) has $R^1 = R^3 = H$ and $R^2 = CH_3$. Chlorotetracycline (**22e**) was the first of the group to be isolated[52]. The compound was found to be a broad-spectrum antibiotic effective in the inhibition not only of micro-organisms susceptible to penicillin but also of many Gram-negative bacteria, rickettsiae and

penicillin-resistant staphylococci (the clinical applications of tetracyclines have been reviewed by Florey[42]). The use of excessive doses of chlorotetracycline leads to undesirable side-effects[42], including liver damage and



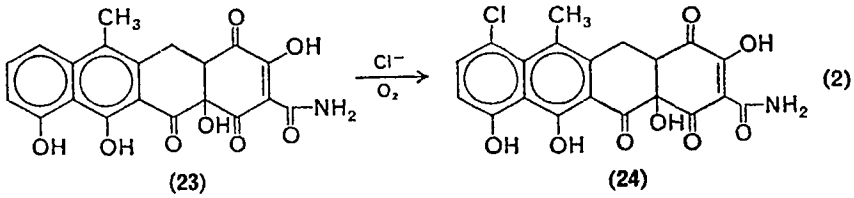
(22)

(22)	R^1	R^2	R^3	Name
a	H	H	H	6-demethyltetracycline
b	Cl	H	H	7-chloro-6-demethyltetracycline
c	H	CH_3	H	tetracycline
d	H	CH_3	OH	5-hydroxytetracycline
e	Cl	CH_3	H	7-chlorotetracycline

effects in the alimentary canal. It is widely held that the latter effects are attributable to vitamin deficiency induced by destruction of *Escherichia coli* in the gut; vitamin therapy greatly diminishes these side-effects[53]. The other members of the family which are important therapeutically are oxytetracycline (**22d**) and tetracycline (**22c**)[42]. Oxytetracycline was isolated by Finlay and collaborators[54] and the structure determined by Hochstein and coworkers[55]. Little difference was found between the antibacterial effects of oxytetracycline and chlorotetracycline. On the other hand, side-effects seem to be more severe in the case of oxytetracycline[42] and on this account chlorotetracycline is to be preferred. Tetracycline was originally prepared by dechlorination of chlorotetracycline[56,57], but was subsequently isolated from a streptomycete by Minieri and coworkers[58]. Again, the pattern of antibiotic activity is similar to those of the other two members of the family[42]; in this case, however, gastro-intestinal irritation appears to be less severe.

The biosynthesis of tetracyclines has been extensively studied (for a review, see McCormick[59]), but mainly from the point of view of the origin of the carbon skeleton. The main interest in the present case is the origin of the chlorine atom of chlorotetracycline and 7-chloro-6-demethyltetracycline. It has been suggested that chlorination occurs in the reaction

shown below (equation 2). Compound **23** was found to be a precursor for both tetracycline and 7-chlorotetracycline biosynthesis whereas the 4-amino analogue of **24** was a precursor only for chlorotetracycline and



(2)

(23)

4-ketodedimethylaminoanhydrotetracycline

(24)

4-ketodedimethylaminoanhydro-7-chlorotetracycline

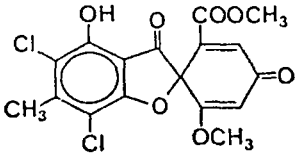
the 4-aminodechloro analogue of **24** was a precursor only for tetracycline. Hence it was argued that the sequence of events is chlorination of **23** to yield **24** followed by transamination of the keto group at position 4 to produce the corresponding 4-amino derivative of **24**[59]. No evidence has yet been obtained, however, about the mechanism of chlorination.

C. Biosynthesis of Chloro Metabolites

The modes of biosynthesis of the carbon skeletons of many of the compounds listed in Figure 2 have been investigated; these have been extensively reviewed by Turner[14]. In the present context, interest in biosynthesis of chloro metabolites centres around the timing and the mechanism of introduction of the chlorine atom. Unfortunately, information on these points is rather sparse.

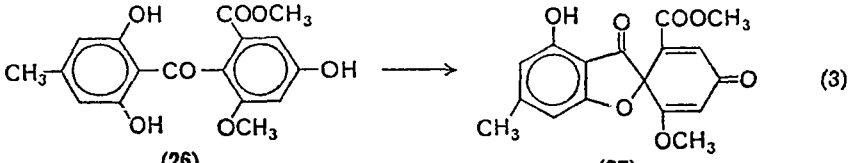
In general, it seems that chlorination occurs at an intermediate stage in biosynthesis and not as a terminal step[13]. This has been demonstrated in several cases by the inability of the producer organism to chlorinate the corresponding dechloro metabolite. For example, *N*-acetyl-*p*-nitrophenylserinol (the dechloro analogue of chloramphenicol) was not chlorinated by *Streptomyces venezuelae*[60]. Similarly, tetracycline was not a substrate for the system which produces 7-chlorotetracycline[61]; in this case, the timing of chlorination has been established with a fair degree of certainty, as described above. It should be pointed out in this context that the timing of introduction of chlorine into chloro metabolites with apparently similar structures may differ considerably. A clear example of this is in the biosynthesis of griseofulvin (**16**) and the related compound geodin (**25**). As discussed in section II. B. 2. the substrate for chlorination in the biosynthesis of griseofulvin is griseophenone *c* (**19**), i.e. chlorination occurs before formation of the spiran ring system. The biosynthesis of

geodin in *Aspergillus terreus* has been studied by Rhodes and coworkers[62]. Evidence was presented for a biosynthetic pathway in which sulochrin (**26**)



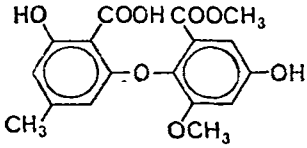
(25)

is converted to dechlorogeodin (**27**) (equation 3). Dechlorogeodin is then chlorinated in two stages to give first the monochloro derivative and then geodin; hence in this case the substrate for chlorination is the preformed



(26) (27) (3)

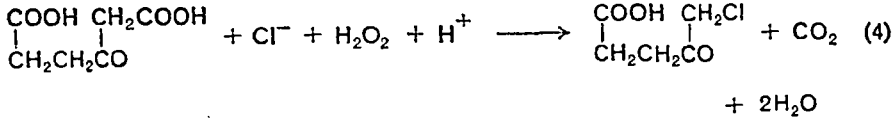
spiro compound and chlorination is the terminal step in biosynthesis. It is of interest that under conditions of chloride deficiency in cultures of *A. terreus*, the final products of biosynthesis are dechlorogeodin and asteric acid (**28**), the latter being produced by opening of the spiran ring. Addition



(28)

of chloride ions to such a culture results in conversion of the accumulated dechlorogeodin and asteric acid to geodin.

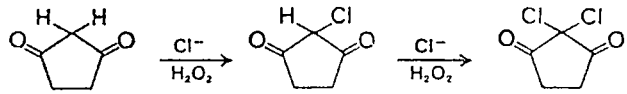
The enzymological aspects of chlorination have been examined by Hager and coworkers[63–65]. They first showed that an extract of dried mycelial powders of *Caldariomyces fumago* catalysed the conversion of β-ketoadipic



(4)

acid into chlorolaevulinic acid (equation 4). The reaction involved hydrogen peroxide and it was suggested that the process involves oxidation of chloride ions to an unspecified positively charged species.

Subsequently[65], the enzyme catalysing this process was isolated in a pure form from *C. fumago*. The chloroperoxidase was found to be a protein of molecular weight 40,000 and containing 25–30% carbohydrate; the enzyme also contains as a prosthetic group ferriprotoporphyrin IX. The specificity of the purified enzyme was studied in detail, and it was found to promote synthesis of halogen compounds from substituted phenols, β-diketones and β-ketoacids. For example, with cyclopentane-1,3-dione, a two-stage process was observed in which first 2-chlorocyclopentane-1,3-dione and then the corresponding dichloro compound were formed (equation 5)[66]. The 2,2-dichlorocyclopentane-1,3-dione (**29**) was converted to caldariomycin (**2**) by growing cultures of *C. fumago* but this does not necessarily mean that this is the natural biosynthetic sequence.



(5)

(29)

Studies were also carried out on the halide specificity of chloroperoxidase[65]. For example, in the halogenation of tyrosine, the relative rates with chloride, bromide and iodide were 1 : 4·8 : 5·1; fluorotyrosine was not produced. Similarly, with 1,1-dimethyl-4-chlorocyclohexane-3,5-dione the relative rates of production of the 4,4-dichloro and 4-bromo-4-chloro analogues were 1 : 2; again fluoride was not a substrate and it acted as an inhibitor for halogenation with chloride and bromide. The results are consistent with the hypothesis that halogenation by chloroperoxidase involves oxidation of the halogen ion, since the rates of reaction mirror the ease of oxidation of the ions. Lack of production of fluoro metabolites by organisms grown in a fluoride-containing medium is consistent with the specificity of chloroperoxidase. In the case of iodide ions, the non-production of iodo metabolites is probably due to the toxicity of iodine to fungi.

The fact that a variety of substituted phenols, β-diketones and β-ketoacids are chlorinated by the chloroperoxidase of *C. fumago* has led to the suggestion that similar enzyme systems are involved in the biosynthesis of other chloro metabolites[50, 59]. By reference to the discussion above, it can be seen that the substrates for chlorination in the biosynthesis of geodin, griseofulvin and tetracycline are of this type. Chlorination with concomitant decarboxylation (cf. the production of chlorolaevulinic acid) has also been proposed in some cases, for example mollisin (**5**)[67] and nidulin (**9**)[68]. It is evident, however, that even if there is a basic similarity between the enzyme systems responsible for chlorination in different fungi

there must also be substantial differences; for example it is necessary to explain why chlorination takes place at the griseophenone stage in griseofulvin biosynthesis but at the grisan stage in geodin biosynthesis. The elucidation of these factors will require extensive investigation of the individual systems.

III. THYROID HORMONES

A. *Introduction*

All vertebrates possess an endocrine gland called the thyroid which elaborates a series of compounds (Figure 3) containing covalently bound iodine. In man, the gland is a follicular structure weighing about 25 g lying adjacent to the trachea, whereas some lower forms (e.g. the cyclostomes) do not have the follicles organized into a regular structure. The thyroid hormones are essential for the maintenance of normal body functions in the adult animal and for the growth and development of the neonatal animal; the hormones are also involved in the processes of metamorphosis from larval to adult forms, e.g. from tadpole to adult frog. All aspects of the chemistry, physiology and biochemistry of the thyroid have been the subject of a recent monograph[69].

The most easily quantitated effect of injection of thyroid hormones into an adult animal is increased rate of metabolism and consequent increased rate of oxygen consumption; the tissues mainly affected are diaphragm, epidermis, gastric mucosa, heart, kidney, liver, pancreas, salivary gland and skeletal muscle[70]. The basic underlying mechanism of these changes is not known, but recent work suggests that the increased metabolic rate is a result of increased protein synthesis[71].

The clinical results of either under-production (hypothyroidism) or over-production (hyperthyroidism) of hormones by the thyroid are severe (reference 69, sections 3 and 4). Thyroid hormones are essential for development of the central nervous system. Hence an inadequate supply of hormones during intra-uterine development or during early postnatal life produces cretinism; early treatment with thyroid hormones partially alleviates the symptoms of this condition. Hypothyroidism at a later stage results in growth retardation and lack of sexual development. In adults, the most common symptoms of hypothyroidism are fatigue, weakness, intolerance to cold and mental impairment; ultimately the condition may lead to coma and death. In pre-coma stages, administration of thyroid hormones is an effective treatment. Hyperthyroidism is manifested by symptoms such as nervousness, palpitations, fatigue, weight loss with good appetite, diarrhoea, heat intolerance and excessive perspiration and

physical changes such as prominence of eyes and neck. The condition varies greatly in severity from that in which the patient is unaware of the condition to an acute form in which heart failure, extreme loss of weight or fever with uncontrollable temperature rise results in death. Treatment of hyperthyroidism may be effected by antithyroid drugs (see section III. C. 4) which prevent hormone synthesis, by subtotal thyroidectomy or by partial destruction of the thyroid with radioiodine; of these methods, the last mentioned appears to be preferred.

B. Chemistry of the Thyroid Hormones

The structures of the most important iodo compounds produced in the thyroid are shown in Figure 3. Thyroxine (**33**) (3,5,3′,5′-tetraiodo-L-thyronine) was first isolated from thyroid tissue in 1915[72] and its structure was determined in 1927[73]. Subsequently Gross and Pitt–Rivers[74] showed that the 3,5,3′-triiodothyronine (**32**) was also present in the thyroid and in the plasma, and that this compound was physiologically more active than thyroxine itself; the plasma level of this compound is, however, much lower than that of thyroxine. Mono- and diiodotyrosines (**30** and **31**) are not physiologically active; these compounds are intermediates in the biosynthesis and metabolism of thyroid hormones.

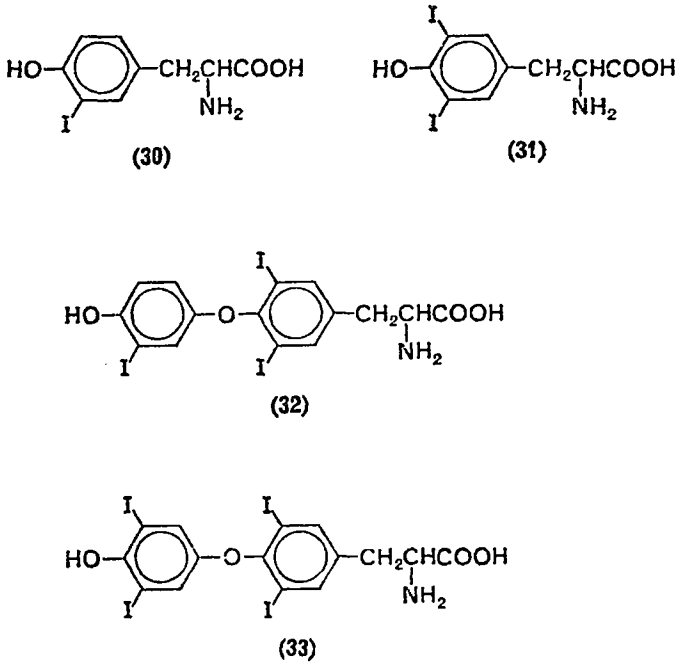
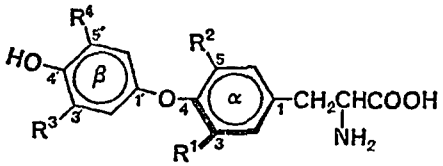


FIGURE 3. Structures of some iodo compounds produced by the thyroid.

Considerable effort has been expended on investigations of which features of the thyroxine molecule are essential for biological activity. These studies have involved synthesis of analogues of thyroxine and assessment of their activity[75]. Features of the molecule which have been modified are the alanine side-chain, substituents in the α- and β-ring systems and of the ether oxygen. It is important to consider these modifications in the light of the conformation of thyroxine (Figure 4). The ether oxygen atom imposes a non-linear relationship on rings α and β. In addition the iodine atoms at positions 3 and 5 of ring α restrict rotation about the $C_{(1')}$—O bond such that the preferred conformation of the plane of ring β is at right angles to that of ring α. This has the effect of making the 3′ and 5′ positions of ring β non-equivalent spatially. This conformation



Thyroxine: $R^1 = R^2 = R^3 = R^4 = I$

Ring α is perpendicular to the plane of the paper and ring β is in the plane of the paper

FIGURE 4. Conformation of thyroxine analogues.

of thyroxine appears to be important for biological activity since, whereas the replacement of the ether oxygen by sulphur leads to retention of activity, the diphenyl analogue in which the benzene rings are directly linked and linearly related is without activity. Replacement of the alanine side-chain by short-chain fatty acid residues does not abolish activity; the acetate analogue was most active, having 35% of the activity of thyroxine. The 4′-hydroxyl group appears to be important. Replacement of this group by methyl produced an inactive analogue of thyroxine; the 4′-deoxy analogue was active *in vivo* but this was due to an oxidation process resulting in the regeneration of thyroxine.

Replacement and substitution of the iodine atoms have been studied. The level of activity falls rapidly in the series tetrabromo-, tetrachloro- and tetrafluorothyroxine. A list of other thyroxine analogues whose activities have been tested is given in Table 1[75]. When the 3,5 substituents in ring α are iodine, then the compound with iodine at position 3′ but unsubstituted at position 5′ is more active than thyroxine. Replacement of the 3′-iodo substituent with alkyl groups results in increasing activity from methyl to isopropyl and then a decrease with *t*-butyl, *s*-butyl, phenyl and cyclohexyl.

The importance of the 3′-substituent is emphasized by the fact that 2′,3′-dimethyl-3,5-diiodothyronine is physiologically active whereas 2′-5′-dimethyl-3,5-diiodothyronine is not. In the case of the 3,5-positions of the α-ring, bromine is the only substituent which will effectively replace

TABLE 1. Biological activities of thyroxine analogues (cf. Figure 4)

R^1	R^2	R^3	R^4	Relative activity
I	I	I	I	100
I	I	I	H	464
I	I	Me	H	65
I	I	Et	H	56
I	I	*i*-Pr	H	617
I	I	*t*-Bu	H	239
I	I	*s*-Bu	H	59
I	I	Ph	H	10
I	I	C_6H_{11}	H	1
I	I	Br	Br	75
i-Pr	*i*-Pr	I	H	0
s-Bu	*s*-Bu	I	H	0
Br	Br	*i*-Pr	H	265
Br	Br	I	I	75
I	H	I	H	Inhibitory
I	H	I	I	Inhibitory

iodine of those that have been tested; indeed 3′-isopropyl-3,5-dibromothyronine is comparable in activity with 3,5,3′-triiodothyronine[76]. In summary, the requirements for thyroxine-like activity seem to be iodo or bromo substituents at the 3- and 5-positions of ring α, and a bulky substituent in the 3′-position of ring β; the latter need not be a halogen. Of considerable interest are 3,3′-diiodothyronine and 3,3′,5′-triiodothyronine; neither of these compounds has thyroxine-like activity and they are in fact inhibitors of the activity of the natural hormones. This clearly shows the importance of the 5-iodo substituent for physiological activity.

On the basis of these considerations, Jorgensen[77] has presented a hypothetical model of the hormone receptor site. Ring α and the alanine side-chain are thought to be responsible for binding the hormone to the receptor site, whereas the 4′-hydroxyl group and the 3′-substituent of ring β are supposed to interact with a functional site thus affecting its behaviour. The molecular events consequent on binding to the receptor site are unknown.

C. Biosynthesis of Thyroid Hormones

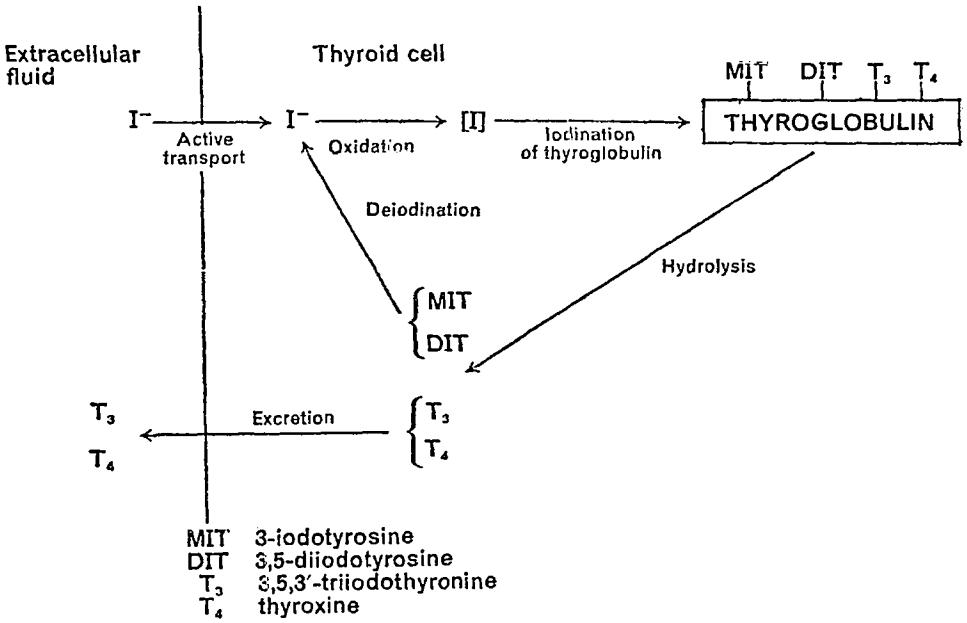


FIGURE 5. Schematic representation of the biosynthesis of thyroid hormones.

The main processes involved in the biosynthesis of thyroid hormones are shown schematically in Figure 5. These processes will be discussed individually.

1. Transport of iodide ions[78, 79]

The thyroid gland has the ability to concentrate iodide ions from the plasma. Iodide ions are actively transported into the thyroid cells and it has been shown that, in the case of the rat for example, under conditions where thyroid hormone synthesis is blocked, the concentration of iodide ions inside the thyroid is 25 to 100 times greater than that in the serum. The transport process is inhibited by many monovalent anions (e.g. ClO_4^-, SCN^-); under these conditions the intracellular iodide ions diffuse out into the plasma.

2. Iodination of thyroglobulin

The substrate for iodination reactions in the thyroid is not free tyrosine or thyronine, but rather some of the tyrosine residues of a specific protein substrate called thyroglobulin[80]. The protein is a tetramer of molecular weight 660,000[81] containing about 10% carbohydrate[82]; the four subunits

of the protein are thought to be identical but this has yet to be firmly established. The tetramer contains approximately 125 tyrosine residues. Typically, when the thyroglobulin contains 1% by weight of bound iodine, the numbers of these residues converted to iodotyrosine, diiodotyrosine and thyroxine are about ten, six and five respectively[83]. Hence by no means all of the tyrosine residues are susceptible to iodination.

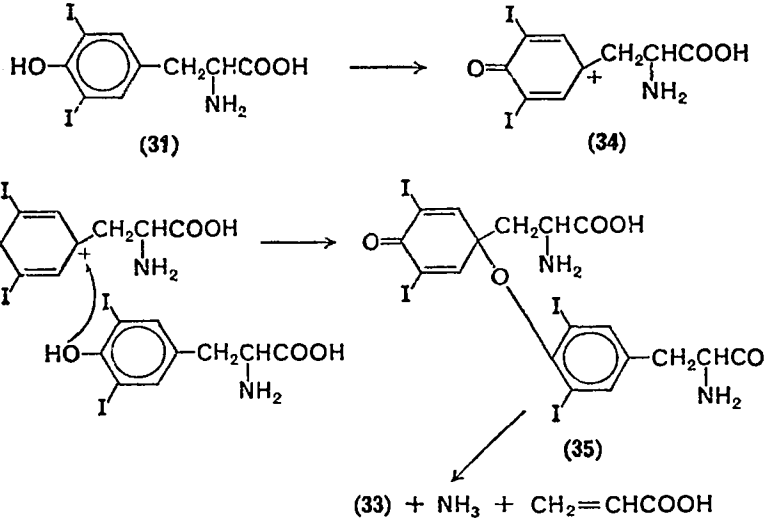
Iodide ions taken up by the thyroid are very rapidly incorporated into thyroglobulin; less than 1% of iodine in the thyroid is in the form of free iodide ions[84]. The mechanism of iodination remains obscure, however. It is generally considered that the process of iodination must be preceded by oxidation of I^- to either I^+ or IOH_2^+ [85] (cf. chlorination reactions in fungi, section II. C); in view of the efficiency of molecular iodine in aromatic iodination, however, it is possible that this species is active in biological iodination reactions. There is no direct evidence for this except that iodination reactions in the thyroid are blocked by reducing agents. In the absence of evidence of any other candidate, the assumption is usually made that the oxidizing agent is hydrogen peroxide. The thyroid gland does indeed contain peroxidases which, in the presence of iodide ions, hydrogen peroxide and a substrate such as thyroglobulin, catalyse iodination reactions *in vitro*[86]. The significance of these enzymes in thyroid hormone biosynthesis remains to be established.

Another hypothetical protein which has been implicated in thyroid hormone biosynthesis is 'tyrosine iodinase'[87]. There seems to be no need to invoke the existence of such an enzyme from the point of view that, once an oxidized form of iodine is produced, it will rapidly iodinate proteins without the intervention of an enzyme. Conversely, however, since iodine in the thyroid is specifically incorporated into thyroglobulin and not into other cellular proteins, it might be argued that an enzyme is required to direct the iodination specifically towards thyroglobulin.

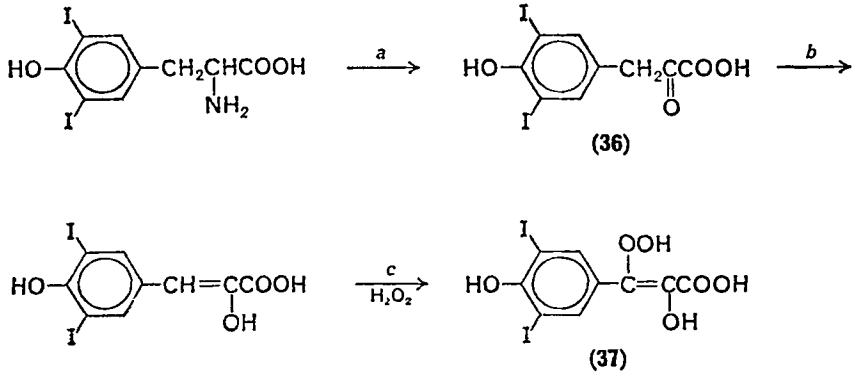
Although it is clear that iodotyrosines are formed by iodination of tyrosine residues in thyroglobulin, the subsequent coupling of pairs of iodotyrosines to produce iodothyronine is not well understood. That this is indeed the sequence of events is indicated by the observation that injection of ^{131}I into animals results in a rapid rise of radioactivity in iodotyrosines whereas the rise of radioactivity in thyroxine is much slower[88].

The coupling of diiodotyrosine residues to form thyroxine under the influence of oxidizing agents has been studied[89]. A mechanism proposed for this process is shown in equations (6) and (7). Oxidation of one molecule of diiodotyrosine **31** yields a quinonoid intermediate **34**; this then couples with a second molecule of diiodotyrosine to produce a *p*-quinol ether **35**. Loss of an alanine side-chain from **35** produces thyroxine. An

alternative mechanism has been proposed[90] in which the β-ring system is provided by 3,5-diiodo-4-hydroxyphenylpyruvate (DIHPP, **36**) which is derived by oxidative deamination of 3,5-diiodotyrosine. The coupling reaction would then be similar to that given in reactions (6) and (7).



These suggestions relate to the synthesis of thyroxine in non-enzymic model systems. In the thyroid, at least one ring of thyroxine is provided by thyroglobulin-bound 3,5-diiodotyrosine. Whether the second ring system similarly originates from within the thyroglobulin or from an external source (e.g. as diiodotyrosine or DIHPP) is not known. Recently, trace amounts of free DIHPP have been found in rat thyroid tissue[91] and this observation has promoted a more detailed study of the possible involvement of this compound in thyroxine biosynthesis. Blasi, Fragomele and Covelli[110] have found enzymes in thyroid tissue which catalyse the conversions in reaction sequence (8). Reaction *a*, catalysed by a trans-



aminase, produces DIHPP (**36**). A tautomerase (reaction *b*) converts **36** to the corresponding enol form and a peroxidase (reaction *c*) catalyses the formation of the hydroperoxide (**37**). Compound **37** is then thought to react with thyroglobulin-bound diiodotyrosine, but this essential step in the process has yet to be demonstrated.

3. Release of thyroid hormones

Release of thyroid hormones from thyroglobulin for secretion into the system requires hydrolysis of the thyroglobulin molecule by proteolytic enzymes. Extensive studies of the proteolytic enzymes in thyroid tissue have been carried out[92] but it is not clear whether or not these enzymes are responsible for liberation of thyroid hormones *in vivo*. Hydrolysis of iodinated thyroglobulin yields not only thyroxine and small quantities of 3,5,3′-triiodothyronine, but also monoiodo- and diiodotyrosines. The tyrosine derivatives are not secreted by the thyroid, but are rapidly deiodinated by the action of iodotyrosine deiodinase; this enzyme is specific for free iodotyrosines and does not attack the thyroglobulin-bound derivatives[93]. The iodide ions released in this process are then reincorporated into thyroglobulin (Figure 5).

4. Antithyroid compounds

Compounds are known which inhibit the various processes of thyroid hormone biosynthesis; several of these are useful in the treatment of hyperthyroidism (section III. A). The inhibitory effect of certain monovalent anions on the uptake of iodide ions by the thyroid[79] has already been mentioned (section III. C. 1). Ions such as perchlorate, pertechnecate, perrhenate and tetrafluoroborate are concentrated by the thyroid but are not metabolized. Thiocyanate inhibits both the accumulation of iodide ions by the thyroid and the iodination reactions.

Of the compounds which inhibit thyroxine biosynthesis by blocking the iodination and coupling reactions, the most useful therapeutically are the thionamides[94] (Figure 6). The mechanism of action of these compounds has not been clearly defined, but it is known that thionamides inhibit the oxidation of iodide by peroxidases isolated from thyroid glands[95]. An alternative, or perhaps supplementary, role of thionamides in the prevention of iodination reactions has been proposed[96], based on the hypothesis that the iodinating agent may be a sulphenyl iodide derivative of a sulphydryl group in tyrosine iodinase. The formation of a compound of this type is shown in equation (9), where E—SH represents a sulphydryl

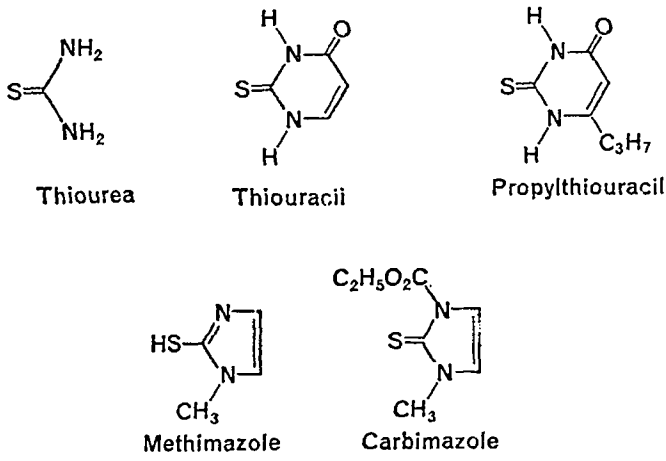


FIGURE 6. Structures of thionamide antithyroid compounds.

group (the side-chain of cysteine) in the enzyme. Thionamides could then react with E—SI to yield a disulphide compound (equation 10) and thus prevent iodination from taking place.

$$E\text{—}SH \xrightarrow[(H_2O_2)]{I^-} E\text{—}SI \tag{9}$$

$$E\text{—}SI + S{=}C\begin{matrix}NH\text{—}\\NH\text{—}\end{matrix} \longrightarrow E\text{—}S\text{—}S\text{—}C\begin{matrix}N\text{—}\\NH\text{—}\end{matrix} + HI \tag{10}$$

5. Control of thyroxine production

In general the production of hormones by endocrine glands is subject to delicate and complex controls. This is true in the case of thyroxine and a considerable amount of knowledge has been accumulated concerning this system[97]; the essential features of the control system are shown in Figure 7. The production of thyroxine is, at least in part, under the control of the nervous system. Stimulation of the hypothalamus causes the release of TRF (thyrotropin releasing factor). This substance is passed into a portal vein which carries the TRF directly to the anterior part of the pituitary gland. TRF then stimulates the release by the pituitary of TSH (thyroid stimulating hormone or thyrotropin). TSH is carried in the blood stream to the thyroid gland and stimulates the output of thyroxine by the gland.

The system is subject to negative feedback controls in that high levels of hormone in the circulation inhibit the production of TSH by the pituitary gland and may inhibit secretion of TRF by the hypothalamus; the evidence for the inhibition of TRF release by thyroxine is, however, conflicting[97].

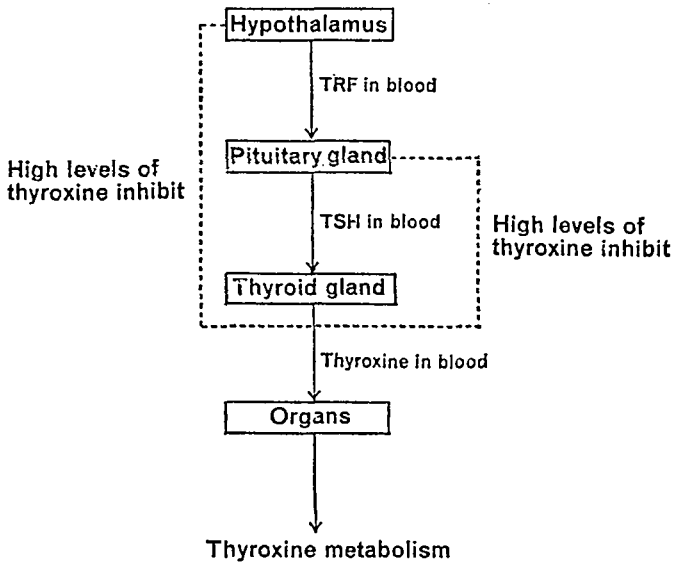
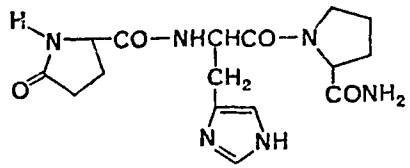


FIGURE 7. The control of production of thyroxine by the thyroid gland.

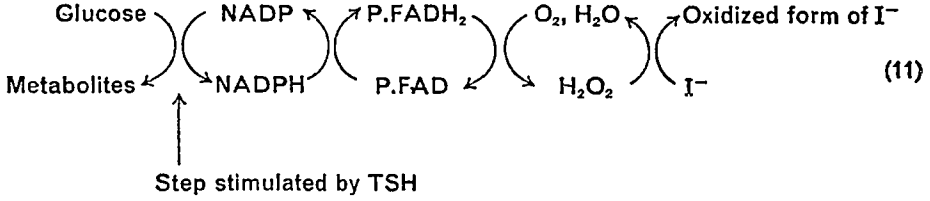
The first mentioned of these factors, namely, neural control of thyroxine production, is the most recently established. The main influence of the hypothalamus under normal conditions appears to be to regulate the set-point of thyroxine production. If the hypothalmic–pituitary link is interrupted, then thyroxine production continues at a steady but reduced level; inhibitory effects of administration of thyroid hormone are more pronounced under these circumstances[98]. The detailed mode of action of TRF is not understood but it appears that the compound stimulates the release of preformed TSH by the pituitary gland[99]. Administration of sufficiently large quantities of thyroxine blocks the effect of TRF; similarly the inhibitory effect of thyroxine on TSH secretion can be overcome by large amounts of TRF[100]. TRF is active *in vivo* at the nanogram level and the amount contained in the hypothalamus is correspondingly small. This fact made the isolation and characterization of TRF a matter of extreme difficulty. This has now been achieved independently by Schally[101] and Guillemin[102] and their collaborators; some hundreds of thousands of hypothalami were required to provide sufficient material for structural

studies. The compound has been shown to be a tripeptide, pyroglutamyl-histidinylprolineamide (38). Compound **38** has been synthesized and found to be identical with natural TRF in its action.



(38)

TSH is a much more complex molecule than is TRF. The compound has been isolated from human pituitary glands[103] and shown to be a basic glycoprotein with a molecular weight of 28,000. TSH is stored in the basophilic cells of the pituitary and its secretion is stimulated by TRF; conversely, thyroxine decreases the release of TSH by the pituitary. The effects of TSH on the thyroid are complex. TSH administration leads to a general increase in the rate of intermediary metabolism in the thyroid[104] and in particular to increased glucose and protein metabolism. Associated with this effect are increases in the rate of formation and release of thyroxine; the connexion between these effects is not well understood. TSH has a stimulatory effect on the transport of iodide ions into the thyroid[105]; this effect seems to be associated with an increase in protein synthesis in the gland. Iodination of thyroglobulin is also increased by TSH[106]. This effect may be correlated with increased glucose metabolism and a related increase in NADPH production; NADPH stimulates iodination reactions in the thyroid by a mechanism which may involve reduction of flavoproteins which then react with oxygen to produce hydrogen peroxide. The involvement of hydrogen peroxide in iodination reactions has been discussed in section III. C. 2. A possible scheme for the role of TSH in iodination can be represented[85] by sequence (11). TSH



(11)

also appears to have a stimulatory effect on the coupling reaction. This again would be explicable in terms of an increased availability of hydrogen peroxide if the reactions shown in sequence (8) are indeed involved in the coupling reaction.

Proceeding further along the pathway to thyroxine secretion, it has been shown that TSH stimulates the proteolysis of iodinated thyroglobulin (section III. C. 3)[107]. The basis of the stimulation of hormone release probably results either from an activation of thyroidal proteases or from a modification of the thyroglobulin structure which renders the molecule more susceptible to proteolysis. Proteolysis liberates mono- and diiodotyrosines as well as the active hormones (section III. C. 3). The iodotyrosines are deiodinated by an enzyme which is dependent on NADPH[93]. TSH administration stimulates the activity of iodotyrosine deiodinase initially by raising the level of NADPH; there is evidence, however, that prolonged stimulation with TSH results in increased enzyme synthesis[108]. It can be seen from the discussion given above that TSH exerts several stimulatory effects on thyroxine production and release. It seems, however, that the origins of these effects may reside in a single basic phenomenon, namely, the stimulation of intermediary metabolism.

Control of thyroxine biosynthesis by TSH is itself regulated by the level of thyroxine in the blood (see Figure 7). The thyroid responds to yet another controlling factor, namely the level of thyroxine stored within the gland. This autoregulatory mechanism operates to increase iodide accumulation when the hormonal store decreases and conversely to inhibit accumulation when the gland contains high levels of the hormone[109]. The mechanism of autoregulation is not known.

D. Metabolism of Thyroid Hormones

Thyroxine is metabolized in the peripheral tissues with a half-life of about 7 days. The principal route of metabolism seems to be deiodination, since in humans after administration of radio-labelled thyroxine, 80–90% of the radioactivity is recovered in the urine as iodide ions[111]. Most studies of deiodination *in vivo* and *in vitro* have used thyroxine labelled in the β-ring and it is generally agreed that these iodine atoms are removed with little or no change of the thyronine moiety[112]. More recent studies using 3,5-[^{125}I]-thyroxine[113] have shown that the iodine atoms in the α-ring are also removed; the diphenyl ether moiety of the thyroxine structure is left intact but the alanine side-chain undergoes partial degradation to the acetate analogue. The analogue of thyroxine in which the alanine side-chain is replaced by acetate undergoes deiodination after injection *in vivo*[114], but it is not clear whether the natural sequence is side-chain oxidation followed by deiodination or vice versa.

Iodothyronine-deiodinating enzyme systems have been detected in homogenates from a wide variety of tissues including liver, kidney, muscle,

brain and heart, but in spite of intensive studies very little progress has been made in the purification and characterization of the enzyme systems. Part of the difficulty may be due to the practice of adding flavine mononucleotide to assay systems; it is now known that this can lead to photocatalysed non-enzymic deiodination of thyroxine[115]. In addition, it has recently been shown that homogenates of rat liver contain an inhibitor of deiodination which can be removed by dialysis[116]. Problems of this sort have impeded progress in the study of deiodinases.

One of the most successful studies to date is that of Tata[117] who carried out a partial purification of a thyroxine deiodinase from the soluble fraction of rabbit skeletal muscle homogenates. The enzyme preparation was active against thyroxine and triiodothyronine but much less so against the iodotyrosines; it is thus clearly different from the iodotyrosine deiodinase (section III. C. 3). Debromination of bromo analogues of the natural substrates was catalysed, but less efficiently. The activity of the preparation was enhanced both by FMN and by Fe^{2+} ions but there was a difference in the products in the two cases. With Fe^{2+} in the assay system, all the iodine was liberated as iodide ions; with FMN, on the other hand, 40% of the iodine was transferred to contaminating proteins.

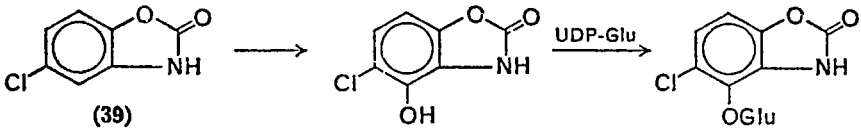
It is evident that insufficient information is presently available to allow speculation about the mode of action of iodotyrosine and iodothyronine deiodinases. An understanding of these enzymes will require their isolation in a state of purity and a detailed study of their catalytic properties.

IV. METABOLISM AND TOXICITY OF SYNTHETIC HALOGEN-CONTAINING COMPOUNDS

A. Introduction

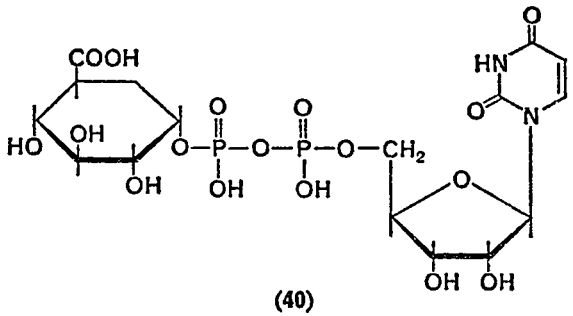
Carbon–halogen compounds are of limited occurrence in animals. Hence it is, perhaps, not surprising that the metabolic interconversions of compounds of this type are often such as to leave the carbon–halogen bonds intact. A general pattern for the metabolism of compounds such as chlorine-containing drugs is introduction into the molecule of reactive groups, for example, amino, carboxyl, hydroxyl, followed by conjugation of the modified drug and then excretion. The introduction of the reactive group necessary for conjugation is usually achieved by oxidation, reduction or hydrolysis. These reactions are catalysed by enzymes present in the liver; the enzymes appear to be of low specificity and have not been well characterized. A few examples of these processes will be given[118].

An example of an oxidative metabolic route is provided by the muscle relaxant, chlorobenzoxazolinone (**39**). This compound rapidly undergoes hydroxylation at the 6-position followed by conjugation to the glucuronide (reaction 12)[119]. Formation of glucuronides is the most common route of

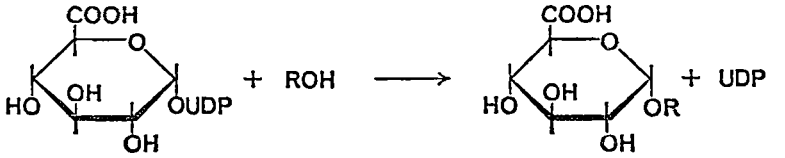


(12)

conjugation of foreign compounds. The glucuronide moiety is provided by uridine diphosphate glucuronic acid (**40**) (UDP-Glu); with alcohols, the



product is the corresponding ether (reaction 13). These compounds are highly water-soluble and are rapidly excreted in the urine. Other frequently encountered conjugates are sulphates and glycinates.



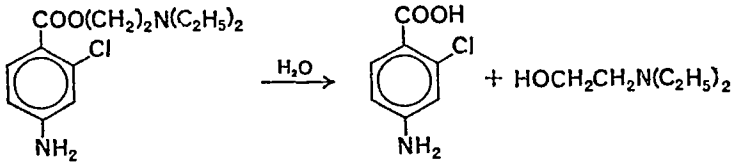
(13)

The hypnotic, chloral hydrate (**41**), provides an example of reductive metabolism. This compound is reduced to trichloroethanol (which may be the substance responsible for the action of the drug) and excreted as the glucuronide conjugate (reaction 14). A substantial fraction of the drug is

$$\underset{(41)}{Cl_3CCH(OH)_2} \longrightarrow Cl_3CCH_2OH \xrightarrow{\text{UDP-Glu}} Cl_3CCH_2O\text{—Glu} \qquad (14)$$

also excreted as trichloroacetic acid which is derived from oxidation of trichloroethanol and directly from chloral hydrate. The fatal dose of the drug is about 10 g but its effects are potentiated by simultaneous ingestion of ethanol.

Chloroprocaine (**42**), a potent local anaesthetic, is metabolized by hydrolysis to 2-chloro-4-aminobenzoic acid and *N*,*N*-diethylaminoethanol (equation 15). The benzoic acid derivative is excreted partly unchanged and partly as the glucuronide[118].

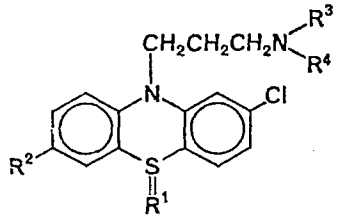


(15)

(**42**)

The examples so far given are of drugs with relatively simple metabolic pathways. In some cases, however, the metabolic processes are much more complex. For example, the important tranquillizer, chlorpromazine, yields over twenty urinary metabolites[120]. The structure of chlorpromazine (**43**, R^1 —, R^2 = H, R^3 = R^4 = CH_3) and its principal metabolites is shown in Table 2. The hydroxylated metabolites are excreted both free and

TABLE 2. Urinary metabolites of chlorpromazine



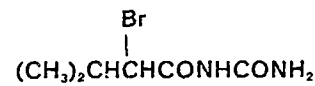
(**43**)

Metabolite	R^1	R^2	R^3	R^4
S-Oxide	O	H	CH_3	CH_3
Monodemethyl	—	H	H	CH_3
Didemethyl	—	H	H	H
Monodemethyl-*S*-oxide	O	H	H	CH_3
Didemethyl-*S*-oxide	O	H	H	H
7-Hydroxy	—	OH	CH_3	CH_3
Monodemethyl-7-hydroxy	—	OH	H	CH_3
Didemethyl-7-hydroxy	—	OH	H	H
7-Hydroxy-*S*-oxide	O	OH	CH_3	CH_3

conjugated with glucuronic acid. Again it can be seen that the chlorine atom is retained in the metabolites. Hence it seems that, given a route to easily excretable metabolites, there appears to be little tendency for

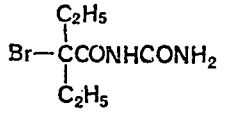
dechlorination of chlorine-containing compounds to occur. This point will be returned to in section IV. B below.

The same argument does not seem to hold for bromine-containing compounds. For example, the hypnotic agent bromvaletone (**44**) appears



(44)

to be completely metabolized in man to yield bromide ions; no metabolites of the carbon skeleton have been found[118]. Similarly, carbromal (**45**) undergoes debromination to yield diethylacetylurea (**46**)[121] and is also metabolized to 2-ethyl-2-hydroxybutyric acid (**47**). Carbromal has a relatively low acute toxicity (10–25 g), but prolonged treatment with the



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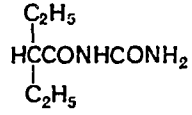

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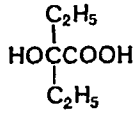


(47)

drug may lead to high levels of bromide ions in the blood (100 μg/ml) with associated psychiatric disturbances. Hence it appears that carbon–bromine bonds are more reactive *in vivo* than are carbon–chlorine bonds. Relatively few drugs contain fluorine and iodine, and the metabolism of these has not been studied. Iodinated hydrocarbons are metabolized, however (see section IV. B), whereas fluorinated hydrocarbons are probably not. Some fluorine-containing compounds are highly toxic; the biochemistry of these is particularly interesting and will be dealt with in section IV. C.

B. Halogenated Hydrocarbons

The metabolism and toxicity of these compounds are of some interest due to their use as anaesthetics and their widespread application as industrial solvents[122]. Many of these compounds are highly volatile and are largely excreted by exhalation. There is evidence, however, that even when exhalation is the major route of excretion, some metabolism does occur.

Carbon tetrachloride is of moderate toxicity, the minimum lethal dose being 3–5 ml. The compound is rapidly absorbed from the lungs and gastro-intestinal tract and to some extent from the skin. Ingestion of carbon tetrachloride causes damage to many tissues, particularly the liver

and kidneys; these effects are greatly increased when alcohol is taken at the same time. The majority of ingested carbon tetrachloride is exhaled (80–90%) but the remainder is metabolized. McCollister and coworkers[123] found that 20% of the non-exhaled material was metabolized to carbon dioxide and the rest to an unidentified water-soluble metabolite.

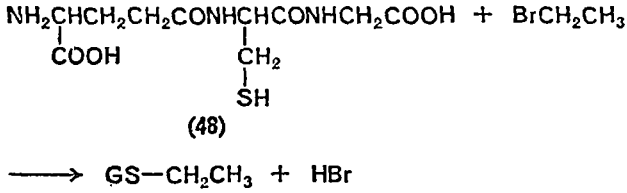
Chloroform is used as a general anaesthetic. A concentration of 2% in air is sufficient to induce anaesthesia and the lethal dose is about 10 ml. After ingestion of chloroform, 90% of the material is exhaled but small amounts can be detected in the blood for up to 8 hours[118]; there is no evidence for the occurrence of dehalogenation of chloroform in man.

Of the halogenated ethanes, the pentachloro- and 1,1,2,2,-tetrachloro-derivatives are not of great industrial importance. Tetrachloroethane is of interest, however, in that it is thought to be metabolized to some extent to oxalic acid by a process of hydrolysis and oxidation[124]. This could account in part for the toxicity of the compound; the minimum fatal dose is about 3 ml. Of the trichloroethanes, the 1,1,2-isomer is the more toxic but is of little industrial importance; there seems to be no evidence for its metabolism[122]. The 1,1,1-isomer is widely used and has to some extent displaced carbon tetrachloride as an industrial cleaning agent since it is of lower toxicity. The majority of ingested 1,1,1-trichloroethane is exhaled, but a small amount is converted to trichloroethanol and excreted as the glucuronide. Little is known about the metabolism of 1,1-dichloro- and 1,2-dichloroethanes except that slow dehalogenation occurs in the rabbit[125]. It has been postulated[126] that metabolism of these compounds would lead to acetic acid and oxalic acid respectively, but this has not been verified. Tetrachloroethylene is used industrially as a solvent and therapeutically as an antihelmintic agent and in the latter application is to be preferred to carbon tetrachloride since it produces less damage to the liver. The lethal dose is about 10 g; the compound is slowly metabolized to an unknown water-soluble metabolite[118].

Trichloroethylene is very widely used as a solvent and as an anaesthetic. Exposure to trichloroethylene vapour over long periods can lead to chronic poisoning which may result in permanent blindness; cases of addiction have also occurred[118]. In contrast to the other chlorinated hydrocarbons, excretion of ingested trichloroethylene is not mainly by exhalation. The compound is metabolized to chloral hydrate[127], which is then further metabolized as described in section IV. A. No details are available concerning the conversion of trichloroethylene to chloral hydrate.

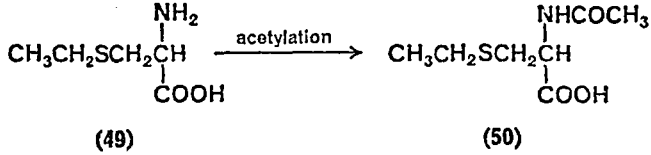
Of some interest is the metabolism of the monohalogen derivatives of the lower hydrocarbons. These compounds are very volatile and are largely excreted by exhalation; the residual compounds, however, undergo

metabolism to produce the corresponding mercapturic acids. For example, Thompson and coworkers[128] found that about 1% of ethyl bromide administered to animals was excreted as ethylmercapturic acid (**50**). A route to this compound was postulated which involved displacement of bromine by the —SH group of glutathione (GSH, γ-glutamylcysteinylglycine, **48**) to yield *S*-ethylglutathione (equation 16). *S*-Ethylglutathione



(16)

was supposed to undergo hydrolysis mediated by the enzyme glutathionase to yield *S*-ethylcysteine (**49**) which on acetylation produced ethylmercapturic acid (**50**) (reaction 17). The nature of the acetylating agent was not



(17)

specified. Ethyl iodide also gave rise to ethylmercapturic acid. Similar results were obtained with *n*-propyl chloride, bromide and iodide, *n*-propylmercapturic acid being produced in all three cases[129]. It seems that this is a common metabolic route for the monohalogenated hydrocarbons in animals and may in fact have a wider significance as discussed in the next section.

C. Fluorine-containing Compounds

1. Fluoroacetic acid

The toxic properties of fluoroacetic acid may legitimately be described in a section devoted to synthetic halogen-containing compounds since the substance was first obtained synthetically in 1896[130]. No report was made of its toxicity at that time, but subsequently the compound was found to be more toxic than, for example, hydrogen cyanide or phosgene[131]. In 1944 the remarkable discovery was made that fluoroacetic acid is the toxic principle of the poisonous South African plant Gifblaar (*Dichapetalum cymosum*)[132]. This observation led to intensive study of the biochemistry and toxicology of this and related compounds[133]. A fascinating monograph

has been devoted to this subject[134] and is recommended for a more detailed coverage than is possible here.

The toxicity of fluoroacetic acid is very high, but there are substantial differences in the doses required to kill different animals (Table 3)[135]. The

TABLE 3. The toxicity of fluoroacetic acid in different species[135]

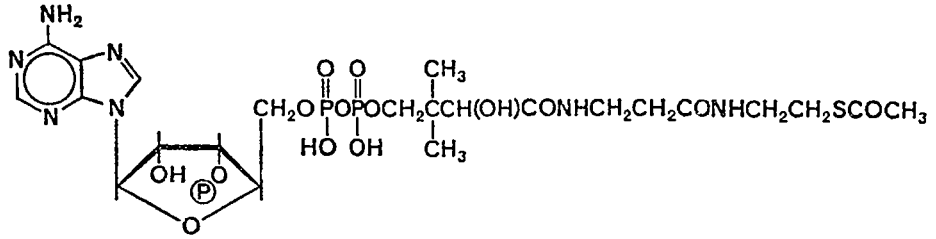
Species	LD_{50} [a] (mg/kg)
Dog	0·06
Cat	0·20
Rabbit	0·50
Horse	1·0
Man	2–10
Rat	5
Frog	150
South African clawed toad	> 500

[a] LD_{50}—dose in mg/kg body weight required to kill 50% of a batch of animals.

dog is particularly sensitive whereas the frog and toad can tolerate relatively large amounts of the compound. Man appears to be moderately sensitive but the figure given in Table 3 must be taken with reserve since the data are limited. Fluoroacetic acid does not seem to be toxic to plants (see later). The immediate cause of death also varies from species to species. In the rabbit injection of fluoroacetic acid results in convulsions followed by cardiac arrest, in the dog the effect is mainly on the central nervous system whereas in the rat the cause of death is respiratory depression; the response in the rhesus monkey and probably in man is a mixture of these[135]. The high toxicity of fluoroacetic acid has led to its use as a rodenticide[136]. The compound must, however, be used with considerable care due to its toxicity to man and domestic animals. The carcasses of animals killed by fluoroacetic acid remain toxic for long periods; for example dogs have been killed by eating rats up to 10 weeks after the rats had been poisoned by fluoroacetic acid[134]. Nevertheless, the substance can be used with safety if sufficient care is taken[137].

In spite of the differences in degree of toxicity and in type of response to fluoroacetate poisoning encountered with different animals, it appears that the biochemical mechanism of toxicity is common in all susceptible species. The important observations which led to an understanding of the mode of action of fluoroacetic acid were that the compound causes accumulation of citric acid in tissues *in vivo*[138] and that the accumulation

of citric acid in a suspension of mitochondria was due to blockage of the citric acid cycle[139]. The citric acid cycle is of central importance in the metabolic activity of cells (for a discussion see, for example, reference 140); consequently a disturbance to this cycle would result in gross malfunction of the organism. At the simplest level, the citric acid cycle may be considered as a device for the oxidation of acetate to carbon dioxide. Its importance transcends this, however, since the cycle represents the meeting point of nearly all the metabolic processes occurring in the cell[140]. Acetate enters the cycle in the form of acetyl coenzyme A (CH_3CO—CoA, **51**); a condensation reaction with oxaloacetic acid (**52**) occurs catalysed by the enzyme citrate synthase to produce citric acid (**53**, reaction 18). Citric acid



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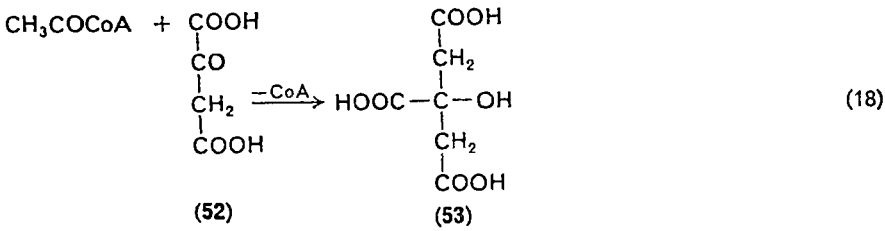

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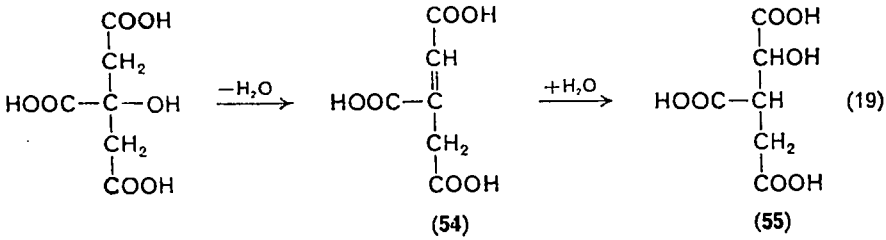


(54) (55) (19)

then undergoes dehydration to *cis*-aconitic acid (**54**) and the latter is rehydrated to yield isocitric acid (**55**) (reaction 19); both steps are catalysed by the enzyme aconitase. A series of reactions then occurs involving two decarboxylations and ultimate regeneration of oxaloacetic acid thus completing the cyclic process and effecting the oxidation of acetate to carbon dioxide[140].

The build-up of citric acid in cells poisoned by fluoroacetic acid would suggest that fluoroacetic acid acts by inhibiting the enzyme aconitase. This, however, is not the case. Liébecq and Peters[139] proposed that fluoroacetic acid is converted by the normal processes of the cell into fluorocitric acid and it is this species which is the toxic agent; they termed this metabolic conversion of a non-toxic into a toxic species 'lethal synthesis'. In the initial stages of the process, fluoroacetic acid substitutes for acetic acid in the acetate thiokinase reaction to yield fluoroacetyl-CoA (**56**, reaction 20); ATP, AMP and PP_i are adenosine triphosphate, adenosine monophosphate

$$FCH_2COOH + ATP + CoA \longrightarrow \underset{(56)}{FCH_2COCoA} + AMP + PP_i \qquad (20)$$

and pyrophosphate respectively. Fluoroacetyl-CoA and oxaloacetate then react in a process analogous to reaction (18) to yield fluorocitric acid. This process is catalysed by citrate synthase, but at a slower rate than the reaction of the normal substrates. It has now been fully demonstrated that fluorocitric acid is indeed a powerful competitive inhibitor of aconitase[141,142]. Moreover, Peters and colleagues[143] have isolated fluorocitric acid from kidney homogenates poisoned with fluoroacetic acid. Hence lethal synthesis as the basis of the toxicity of fluoroacetic acid is well established.

The non-toxicity of fluoroacetic acid to plants is of interest. In this context it has been recently shown that lettuce plants can defluorinate the compound[144]. After feeding lettuce plants with fluoro-[^{14}C]-acetic acid, the radioactive products were examined. About 2% of the radioactivity was associated with fluorocitric acid, but 50% was accounted for as *S*-carboxymethylglutathione and *S*-carboxymethylcysteine. Hence it seems that the lettuce is able to defluorinate fluoroacetic acid by a mechanism similar to that by which animals metabolize halogenoalkanes (section IV. B).

2. Compounds metabolized to fluoroacetic acid

Difluoro- and trifluoroacetic acids are not toxic to animals since they cannot substitute for the natural substrates in reactions leading to citric acid analogues. It is not surprising, on the other hand, that derivatives of fluoroacetic acid which can be converted to free fluoroacetic acid by common metabolic operations such as oxidation or hydrolysis are comparable in toxicity to fluoroacetic acid itself; some examples are shown in Table 4[134]. It is also of interest to compare the toxicities of fluorine compounds forming an homologous series, such as the ω-fluorocarboxylic acids. Kharasch and colleagues[145] initiated the examination of such series

by showing that whereas 4-fluorobutyric acid is more toxic than fluoroacetic acid, 3-fluoropropionic acid is non-toxic. A more extensive series of such compounds is shown in Table 5[146]. It can readily be seen that in a

TABLE 4. Toxicity of compounds related to fluoroacetic acid

Compound	LD_{50} (mice) (mg/kg)
FCH_2COOH	6–10
FCH_2CHO	6
FCH_2COOCH_3	6–10
FCH_2CONH_2	6–10
FCH_2COCl	6–10
$(FCH_2CO)_2O$	6–10
FCH_2CN	25
FCH_2CH_2OH	10

TABLE 5. Alternating toxicity of ω-fluoro carboxylic acids: $F(CH_2)_nCOOH$

Value of n	LD_{50} (mice) (mg/kg)
1	6
2	60
3	0·65
4	>100
5	1·35
6	40
7	0·64
8	>100
9	1·5
10	57·5
17	5·7

compound $F(CH_2)_nCOOH$, if n is odd then the compound is toxic whereas if n is even the compound is non-toxic. The same generalization applies to compounds $F(CH_2)_nCOX$ where X is a substituent which can be removed metabolically to yield $F(CH_2)_nCOOH$.

The alternating toxicity of the ω-fluorocarboxylic acids can readily be understood in terms of the known mechanism of breakdown of fatty acids

in vivo. The reactions involved in the process are shown in Figure 8[147]. The sequence is initiated by formation of the acyl-CoA derivative catalysed by a thiokinase (*a*). The flavoprotein, acyl dehydrogenase (EFAD, reaction *b*), catalyses α,β-dehydrogenation of the CoA-derivative and the

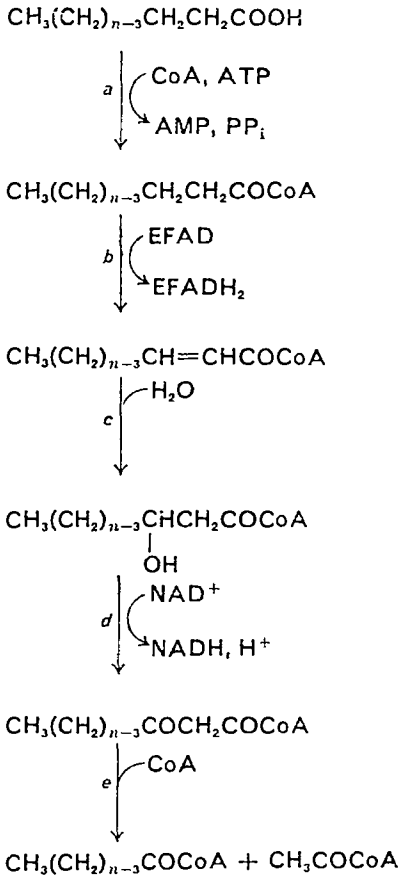


FIGURE 8. The β-oxidation pathway for the metabolism of fatty acids.

unsaturated species is hydrated by enoylhydratase (reaction *c*). A second reductive reaction (*d*) catalysed by the NAD^+-dependent enzyme β-hydroxyacyl dehydrogenase produces the β-ketoacyl-CoA derivative which finally undergoes thiolytic cleavage (reaction *e*) catalysed by β-ketoacyl thiolase to yield acetyl-CoA and the CoA ester of the fatty acid two carbon atoms shorter than the original molecule. Obviously if *n* is odd then repeated operation of the cycle results in complete degradation

of the fatty acid to $(n+1)/2$ molecules of acetyl-CoA. If n is even, on the other hand, $(n/2)-1$ molecules of acetyl-CoA and one molecule of propionyl-CoA are produced; the latter arises from the methyl terminal end of the fatty acid. The corresponding ω-fluoro fatty acids are able to substitute for the normal substrates in these reactions and it is evident that the nature of the final fluorine-containing compound will depend on whether n in $F(CH_2)_nCOOH$ is odd or even. If n is odd (e.g. 4-fluorobutyric acid) then the products are $(n-1)/2$ molecules of acetyl-CoA and one molecule of fluoroacetyl-CoA; hence the molecule gives rise to a toxic product. If n is even (e.g. 5-fluorovaleric acid), then the products are $(n/2)-1$ molecules of acetyl-CoA and one molecule of fluoropropionyl-CoA; the latter is not toxic since it cannot give rise to fluoroacetic acid. These conclusions are fully supported by the data in Table 5. One point which is worthy of comment is that compounds such as 4-fluorobutyric and 6-fluorohexanoic acid are more toxic than fluoroacetic acid itself. This may be due either to higher permeability of cells to the long-chain derivatives or to the long-chain derivatives being better substrates for the enzymes of the β-oxidation pathway.

The alternation of toxicity in homologous series such as the ethyl and methyl esters, aldehydes, amides and acylhalides follows the same pattern as that of the fluorocarboxylic acids[134]. Other series seem superficially to behave differently. For example with the fluoroalcohols $F(CH_2)_nOH$, those members for which n is even are toxic whereas those where n is odd are non-toxic. This is due to the fact that the metabolic transformation is such as to oxidize the terminal alcoholic group (equation 21). Thus

$$F(CH_2)_nOH \longrightarrow F(CH_2)_{n-1}COOH \qquad (21)$$

fluoroethanol yields fluoroacetic acid. Similar considerations apply in the series of halides, methyl ketones, ethers, thiols and amines[134]. Hence, in general, for a compound $F(CH_2)_nCH_2CH_2X$ if the metabolism of group X involves a process such as that shown in equation (22) then compounds

$$F(CH_2)_nCH_2CH_2X \longrightarrow F(CH_2)_nCH_2COOH \qquad (22)$$

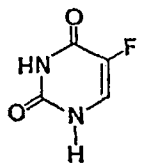
with n even are toxic whereas if the metabolic conversion is as shown in equation (23), then members with n odd are toxic. Hence in order to

$$F(CH_2)_nCH_2CH_2X \longrightarrow F(CH_2)_nCOOH \qquad (23)$$

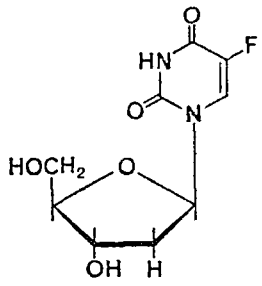
predict the toxicity of ω-fluoro compounds it is necessary to know the mode of metabolism of that class of compound.

3. 5-Fluorouracil

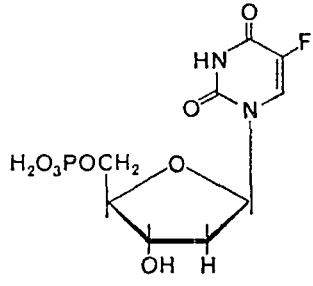
This compound is of interest since it is useful in the treatment of colorectal tumours[148]. In animals 5-fluorouracil (**57**) is converted to the corresponding deoxyribonucleoside (**58**) by a process which is not fully understood and then to the deoxyribonucleotide (**59**) by transphosphoryla-



(**57**)

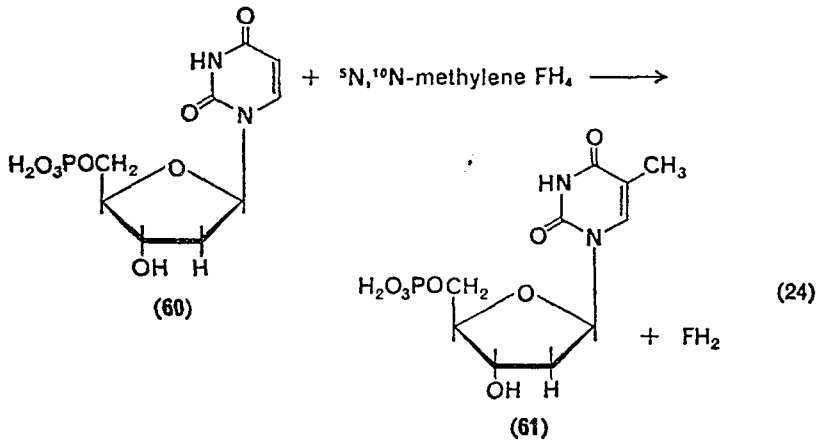


(**58**)



(**59**)

tion from ATP. In the normal processes of DNA biosynthesis, deoxyuridylic acid (**60**) is converted to thymidylic acid (**61**) by a reaction in which a one-carbon fragment is transferred to **60** from $^{5}N,^{10}N$-methylene-tetrahydrofolic acid (reaction 24); this is catalysed by the enzyme thymidylate synthetase[149]. Compound **59** cannot substitute for **60** in this reaction,



(**60**)

(**61**)

(24)

but it is a powerful inhibitor of thymidylate synthetase and thus prevents the synthesis of one of the essential components of DNA. Although 5-fluorodeoxyuridylic acid prevents the normal processes of DNA replication and cell division, it is effective in controlling the rapid cell division characteristic of tumours in amounts which are not lethal to the patient. It should be noted that there is a clear analogy between the mechanisms of

toxicity of 5-fluorouracil and fluoroacetic acid. In both cases the compounds themselves are non-toxic but are transformed into toxic substances by the normal processes of the organism; that is, the compounds are able to substitute for the normal substrates of some of the enzymes within the organism, but the products of these transformations then act as inhibitors of the next enzyme in the metabolic sequence.

It is interesting that the chloro-, bromo- and iodo-analogues of **59** behave differently. In these cases the halogenated deoxyuridine is incorporated into DNA in place of thymine, yielding a functionally defective nucleic acid. This probably reflects the fact that the higher halogens have van der Waals radii sufficiently similar to that of the methyl group to ensure that the enzyme system responsible for the synthesis of DNA mistakes the halogen analogues for the natural substrate. In the case of fluorodeoxyuridylic acid, the discrepancy in size of the substituent is presumably too great to allow this to happen.

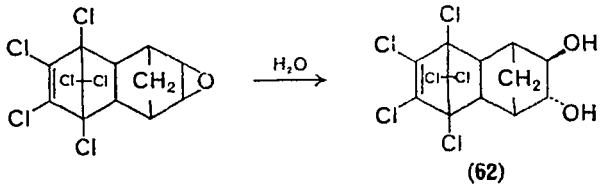
D. Pesticides

The metabolic fate of organochlorine insecticides is attracting increasing attention[8]. Although these compounds are considered to be persistent it is now apparent that they do undergo slow metabolism both in insects and in higher animals. In view of the discussion given in section IV. A concerning the metabolic stability of the carbon–chlorine bond, it might be expected that the organochlorine insecticides would undergo transformation to polar metabolites with chlorine contents identical with those of the parent compounds; this is indeed the case with aldrin, for example. In other cases, however, dechlorination does, in fact, constitute a major metabolic route; this presumably reflects the fact that the chlorinated structure is not susceptible to modification *in vivo* without previous dechlorination. An important example here is DDT. Examples of both of these types of process will be discussed below.

1. Metabolism without dechlorination

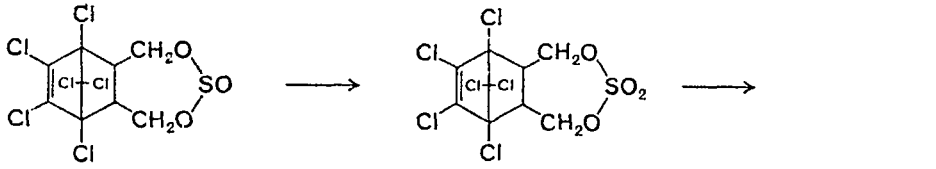
Aldrin (Figure 1) is representative of pesticides of this type. In most insects, aldrin is converted into dieldrin by epoxidation and it has been suggested that the latter is the principal toxic agent[150]. Epoxidation is also the first step in the metabolism of aldrin in animals[151]; subsequent reactions then occur to yield more polar products. In the rabbit, for example, 86% of ingested aldrin is excreted in the urine as 6,7-*trans*-dihydroxydihydroaldrin (**62**), probably formed by hydrolysis of dieldrin (equation 25)[152]. A major metabolite found in the bile of rats was thought to be the glucuronate of **62**[153].

The metabolism of endosulfan **63** by mammals does not appear to have been studied, but in the locust a series of metabolites have been identified, suggesting that the interconversions shown in scheme (26) take

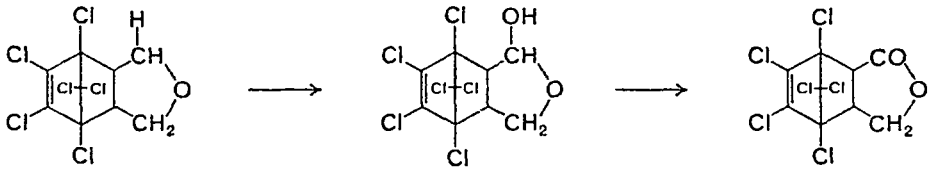


(25)

(62)



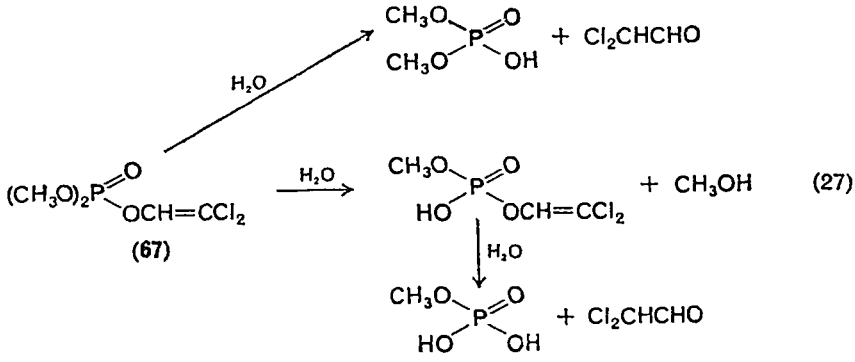
(63) (64) (26)



(65) (66)

place[154]. Oxidation to endosulfan sulphate **64** is followed by elimination of the elements of sulphur trioxide to produce the ether **65**; this is then hydroxylated and oxidized to the lactone **66**.

The metabolism of the important insecticide dichlorvos **67** has been studied by Casida and coworkers[155]. The compound is rapidly hydrolysed in mammals by the routes shown in scheme (27). The dichloroacetaldehyde formed is reduced to dichloroethanol and excreted.



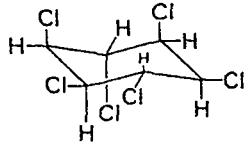
(67)

(27)

This small selection of examples illustrates the principle that metabolism of molecules susceptible to oxidative or hydrolytic reactions occurs without carbon–chlorine bond cleavage.

2. Metabolism involving dechlorination

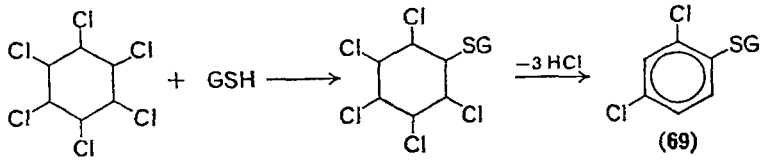
The most exhaustively examined insecticides in this group are the 1,2,3,4,5,6-hexachlorocyclohexanes and DDT (1,1,1-trichloro-2,2-bis-(*p*-chlorophenyl)ethane, Figure 1). Of the former only the γ-isomer (**68**)



(**68**)

is active as an insecticide; it is also known as lindane gammexane, 666 and by several other names. In rats, the compound has an oral LD_{50} of 100 mg/kg. DDT is less toxic to animals; the oral LD_{50} in rats is 200 mg/kg. Both lindane and DDT have the disadvantage that they are insoluble in water but soluble in non-polar solvents and hence tend to accumulate in animal fats; they are metabolized only slowly.

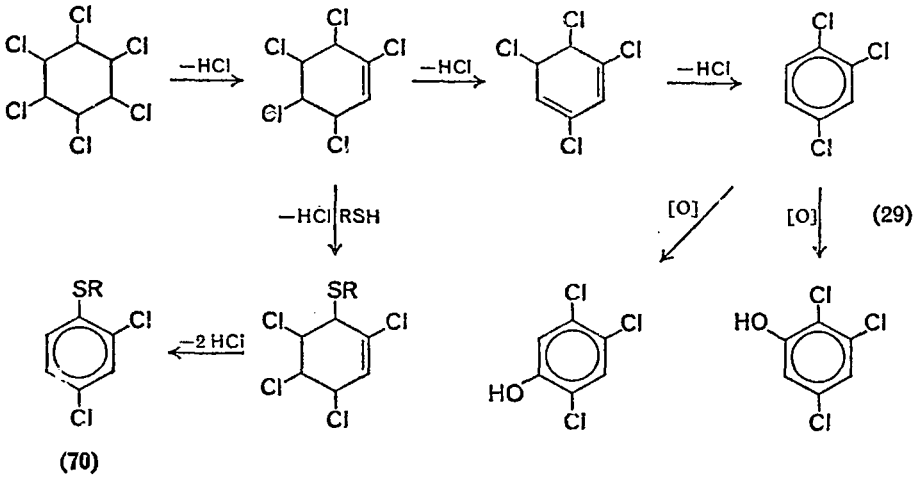
The metabolism of lindane by insects has been examined extensively[8], particularly with reference to development of resistance to the insecticide. It has been claimed[156] that the major product of metabolism in lindane-resistant house flies is pentachlorocyclohexene, but subsequently[157] this compound was shown to be only a minor metabolite. Experiments using radio-labelled lindane have shown that the majority of the compound when administered to house flies is converted into water-soluble metabolites[158]. Alkaline hydrolysis of these metabolites gave mainly a mixture of dichlorothiophenols. In the case of cattle ticks and locusts the major product of metabolism of lindane is *S*-(2,4-dichlorophenyl)glutathione (**69**)[159]. Thus the metabolic process may be represented as shown in equation (28). Recently, an enzyme system capable of metabolizing lindane has been isolated from house flies. In addition to lindane, the enzyme system rapidly metabolized γ-1,3,4,5,6-pentachlorocyclohex-1-ene;



(**69**) (28)

hence this compound may be the intermediate metabolite of lindane *in vivo*.

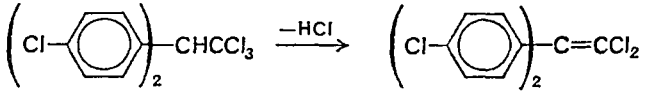
Enzyme preparations from animal tissues were found to be inactive in the metabolism of lindane, but effective in metabolizing γ-pentachlorocyclohexene[160]. Experiments with rats have shown that the main urinary metabolites of lindane are 2,4-dichlorophenylmercapturic acid (**70**), 2,3,5- and 2,4,5-trichlorophenols and sulphate and glucuronide conjugates of the phenols[161]. Available evidence suggests that the main routes of metabolism of lindane in rats are as shown in scheme (29) where R is $-CH_2CHCOOH$ (NHCOCH$_3$).



(29)

(70)

The major route of detoxication of DDT in house flies is by dehydrochlorination to yield DDE (**71**, equation 30); DDE is at least 500 times less toxic than DDT. The enzyme catalysing this reaction has been

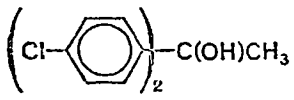


(30)

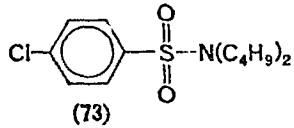
(71)

isolated and shown to be dependent on glutathione for activity[162]. DDT-resistant flies effect this conversion much more rapidly than do DDT-sensitive flies[163]. Recently[162] a study has been made of specific inhibitors of DDT-dehydrochlorinase; this is of interest in the search for effective synergists for DDT in resistant species. Two compounds

which have been found useful in this respect are 1,1-bis(*p*-chlorophenyl)-ethanol (**72**) and *N*,*N*-dibutyl-*p*-chlorobenzenesulphonamide (**73**). Metabolites other than DDE are produced by some species. For example, *Drosophila melanogaster* metabolizes DDT by hydroxylation to 2,2-bis-(*p*-chlorophenyl)-2-hydroxy-1,1,1-trichloroethane[164].

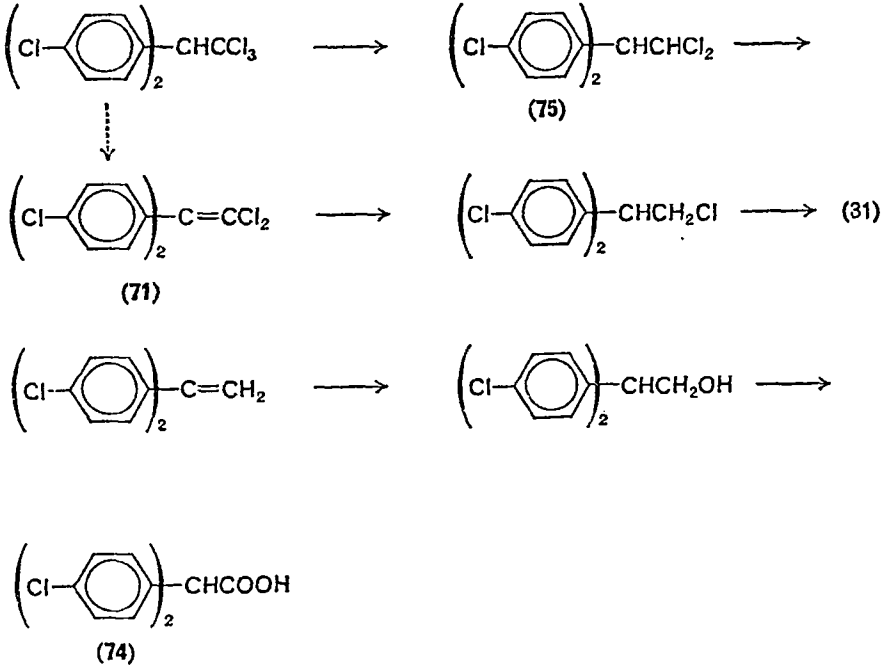


(72)



(73)

The metabolism of DDT by rabbits[165], rats[166] and in man[167] has been shown to produce bis(*p*-chlorophenyl)acetic acid (DDA, **74**) as the principal excretion product. A pathway for the metabolism of DDT in rat has recently been proposed based on analysis of liver and kidney tissue after massive DDT administration[168]; this pathway is shown as sequence (31). The first step in this process, that is conversion of DDT



to DDD (**75**) has been demonstrated with homogenates of rat liver[169]. It is possible, however, that there is a route directly from DDT to DDE (**71**) analogous to that occurring in insects.

Finally, the involvement of glutathione in the detoxication of lindane and DDT, at least in insects, should be emphasized and compared with

the route for metabolism of halogenated alkanes in animals (section IV. B) and of fluoroacetic acid in plants (section IV. C. 1). This might be taken to argue for a common evolutionary origin for the enzyme systems catalysing these diverse processes. The extent of the similarity and the mode of action of these enzymes will not, however, be understood until much more work has been done on their isolation and characterization.

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The Chemistry of The Carbon–Halogen Bond
Edited by Saul Patai

CHAPTER 14

Perchloro-, perbromo- and periodo-compounds

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I. INTRODUCTION

In this chapter recent developments in perhalocarbon* chemistry are discussed with emphasis on the novel aspects of the topic and comprehensive coverage of the literature is not claimed. Where appropriate, comparisons with fluorocarbon analogues are made and the effects of perhalogen substitution on the chemical and physical properties of the molecule and, in particular, on functional groups within the molecule are stressed. Halocarbon chemistry, especially chlorocarbon chemistry, has undergone a renaissance in recent years and mention should be made of several recent reviews[1–8] and one text[9] covering certain aspects of the subject. The majority of industrial organochlorine compounds are aliphatic or aromatic chlorinated hydrocarbons which find use as solvents, e.g. carbon tetrachloride, flame retardants, dielectric fluids and insulators, and as pesticides, e.g. polychlorobiphenyls. Indeed, the contamination of our environment by the widespread use of organochlorine insecticides has caused considerable concern[10].

Perhalogenated compounds are good candidates for mass spectroscopic studies since chlorine is composed of two isotopes, ^{35}Cl and ^{37}Cl, whose relative abundance is ca. 3 : 1 and bromine is composed of two isotopes, ^{79}Br and ^{81}Br, of almost equal abundance. Thus the mass spectra of perchloro- and perbromo-carbon derivatives show envelopes of peaks whose relative intensities are characteristic of the number of halogens present in the fragment ion[11]. Furthermore, the isotopes ^{35}Cl, ^{37}Cl, ^{79}Br and ^{81}Br all have spin values $I = \frac{3}{2}$ while ^{127}I (100%) has a spin of $\frac{5}{2}$. Thus all these isotopes have a quadrupole moment so the rapidly developing

* The prefix halo- refers only to chlorine, bromine or iodine in this chapter.

technique of nuclear quadrupole resonance (n.q.r.) spectroscopy can give valuable structural information for perhalogenated compounds[12].

Properties of halogen atoms which influence the chemical behaviour of organic molecules include size, electronegativity and carbon–halogen bond energies (Table 1). An outstanding illustration of the steric effect of the

TABLE 1. Some properties of halogen substituents

Halogen	Covalent radius[a]	Van der Waal's radius[b]	Electro-negativity[c]	Average of carbon–halogen bond energy[d]
F	0·64	1·35	3·98 (4·10)	116
Cl	0·99	1·80	3·16 (2·83)	79
Br	1·14	1·95	2·96 (2·74)	66
I	1·33	2·15	2·66 (2·21)	57

[a] In Å. L. Pauling, *The Nature of the Chemical Bond*, Cornell University Press, New York, 3rd ed., 1960, p. 224.

[b] In Å. See above, p. 260.

[c] Estimated using Pauling's method by A. L. Allred, *J. Inorg. Nucl. Chem.*, **17**, 215 (1961). Values in parentheses are those of A. L. Allred and E. G. Rochow, *J. Inorg. Nucl. Chem.*, **5**, 264 (1958).

[d] In kcal/mole. F. A. Cotton and G. Wilkinson, *Advanced Inorganic Chemistry*, Wiley, New York, 2nd ed., 1966, p. 100.

larger chlorine substituents compared to fluorine is the remarkable inertness of the perchlorinated carbon radical $(C_6Cl_5)_3C\cdot$ [4] and the related carbanion $(C_6Cl_5)_3C^-$ [13] and carbonium ion $(C_6Cl_5)_3C^+$ [14]. The carbonium ion can be isolated as stable dark green crystals of $(C_6Cl_5)_3C^+SbCl_6^-$. In contrast $(C_6F_5)_3C^+$ is unstable relative to the triphenylmethyl cation and has only a transient existence in 96% sulphuric acid[15]. Thus it appears that steric shielding rather than electronic effects is responsible for the stability of $(C_6Cl_5)_3C^+$, although ^{19}F n.m.r. data indicate substantial deshielding of the *p*-fluorine atoms in $(C_6F_5)_3C^+$ in fluorosulphonic acid[16].

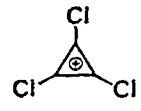
The effective electronegativities of trihalomethyl groups, estimated by different methods[17–20], follow the expected order $CI_3 < CBr_3 < CCl_3 < CF_3$. The σ_I and σ_{R^0} substituent parameters for CX_3 (X = F, Cl, Br)[20a] and C_6X_5 (X = F, Cl)[21] groups have been evaluated from ^{19}F n.m.r. data of substituted fluorobenzenes. The order of inductive electron withdrawal is $CF_3 > CCl_3 > CBr_3 \simeq C_6F_5 \simeq C_6Cl_5$. The CCl_3, CBr_3, C_6F_5, C_6Cl_5 substituents show an insignificant resonance effect, but for CF_3 there is net charge-transfer from the phenyl π system to the substituent. An electronic effect of considerable importance in perhaloaromatic chemistry is the

interaction of the *p* electrons of the halogen substituents and the aromatic π system. For example, pentafluorophenol ($pK_a = 5{\cdot}5$) is a weaker acid than pentachlorophenol ($pK_a = 5{\cdot}2$) at 25°[22]. It has also been suggested that the stability of conjugated chlorocarbons, e.g. the trichlorocyclopropenium ion, is due in part to π interaction between non-bonding pairs on chlorine with carbon.

This chapter begins with a discussion of conjugated cyclic halocarbons, followed by a section on perhalo-aromatic and -hetero-aromatic compounds and then a section on perhalo-carbonium ions, -carbanions and perhalocarbon radicals. The next section, which precedes the section on dihalocarbenes and perhalo-arynes and -hetarynes, is concerned with perhalocarbon derivatives of metals and metalloids since organometallic derivatives are often the most convenient precursors of these short-lived intermediates. A final section is devoted to structural and spectroscopic studies of perhalocarbon compounds.

II. CONJUGATED CYCLIC HALOCARBONS

Within the last eight years important advances have been made in the chemistry of cyclic conjugated polyenes $(CCl)_x^{y\pm}$ and their bromocarbon analogues, particularly by West and coworkers[2]. Before 1964 only hexachlorobenzene (5) was known, but recently the species $C_3Cl_3^+$, $C_3Br_3^+$, $C_7Cl_7^+$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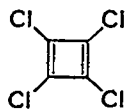
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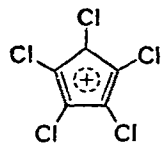
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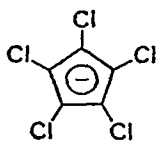
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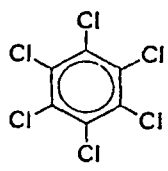
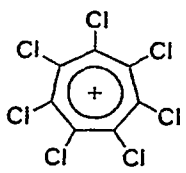
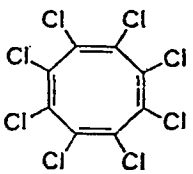

(5)(6π)


(6)(6π)

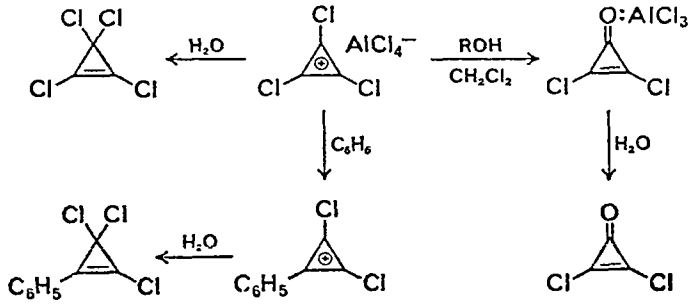

(7)(8π)

and C_8Cl_8 have been isolated and good evidence for the existence of C_4Cl_4, $C_5Cl_5^+$ and $C_5Cl_5^-$ has been presented. The species **1**, **4**, **5**, **6** with $4n+2$ π-electrons are expected to be aromatic and hence stabilized while **2**, **3** and **7** contain $4n$ π-electrons and are therefore antiaromatic[23].

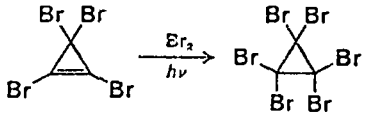
A. Trichloro- and Tribromo-cyclopropenium Ions

The trichlorocyclopropenium ion (**1**) is conveniently prepared from tetrachlorocyclopropene[24] and a powerful chloride acceptor Lewis acid, e.g. $AlCl_3$, $SbCl_5$[25]. The simple infrared spectrum of **1** is consistent with a symmetrical structure and the C—C stretching force constant is much larger than for other aromatic species, including hexachlorobenzene[25]. Therefore the C—C bond in **1**, and probably in other cyclopropenium ions[26], must be shorter and stronger than in any other known aromatic compounds. The C—Cl stretching force constant is also abnormally large with a partial double-bond character of 0·16 estimated from n.q.r. measurements of the asymmetry parameter ($\eta = 0{\cdot}35$) of the ^{35}Cl nuclei in **1**[27]. Thus about half of the positive charge on **1** is delocalized through the π system onto the chlorine atoms.

Rapid hydrolysis of the tetrachloroaluminate salt of **1** regenerates the chlorocarbon tetrachlorocyclopropene, a reaction which is typical of chlorocarbon cations (cf. $C_3Cl_5^+AlCl_4^- \xrightarrow{H_2O} C_3Cl_6$)[28]. Controlled hydrolysis of **1** leads, via an intermediate aluminium complex, to the dangerously explosive dichlorocyclopropenone[29]. Replacement of chlorines in **1** by aryl groups can be achieved by Friedel–Crafts-type condensation with aromatic hydrocarbons[30].

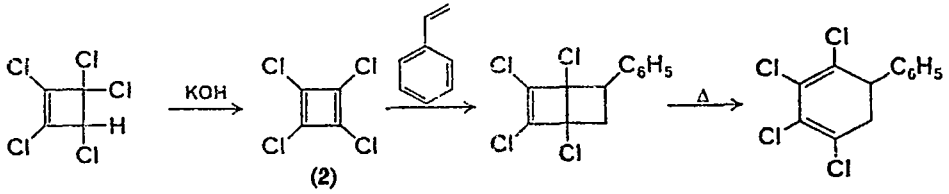


Tetrabromocyclopropene is easily prepared by the halogen exchange reaction which occurs when tetrachlorocyclopropene and boron tribromide are mixed[31]. It can be converted to a salt of the tribromocyclopropenium ion $C_3Br_3^+$ with aluminium bromide[2] and with bromine under ultraviolet light it is rapidly converted to hexabromocyclopropane[31].



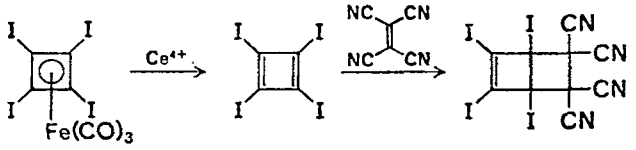
B. Tetrachloro- and Tetraiodo-cyclobutadiene

Scherer and Meyers have reported evidence for tetrachlorocyclobutadiene as a reaction intermediate in the dehydrohalogenation of 3-H-pentachlorocyclobutene[32]. The diene can be trapped stereospecifically by styrene or cyclohexadiene and, in the absence of a trapping agent, a C_8Cl_8 isomer is formed (see section II. F). The easy generation of **2** suggests stabilization of the butadiene structure by π bonding involving chlorine p orbitals. Although the bromine and fluorine analogues of **2** are



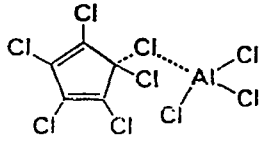
(2)

unknown, tetraiodobutadiene has recently been trapped as an adduct with tetracyanoethylene, following oxidative decomposition of the iron tricarbonyl complex[33].

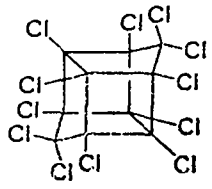


C. Pentachlorocyclopentadienide Cation

Interaction of hexachlorocyclopentadiene with aluminium chloride gives a red adduct, $C_5Cl_6AlCl_3$, which is apparently a partially ionic, chlorine-bridged complex[34]. This complex is probably an intermediate in the



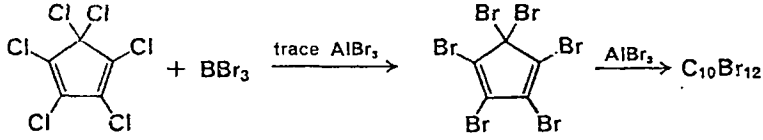
well-known dimerization of hexachlorocyclopentadiene to the 'Prins dimer' (**8**) $C_{10}Cl_{12}$[35]. Evidence for the existence of $C_5Cl_5^+$ (**3**) comes from



(6)

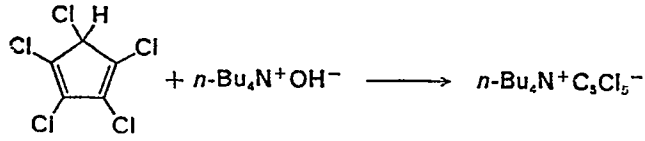
electron spin resonance spectra of solutions of hexachlorocyclopentadiene in antimony pentafluoride, which indicate that $C_5Cl_5^+$ exists at least in part in a triplet state below 77K [36]. Temperature variation experiments suggest that the triplet state is the ground state for 3[36] and as expected for an antiaromatic system it is highly reactive.

$C_5Cl_5^+$ and partially brominated cyclopentadiene cations are undoubtedly involved as intermediates in the chlorine–bromine exchange reaction that occurs between boron tribromide and hexachlorocyclopentadiene in the presence of a trace of aluminium bromide[37]. Hexabromocyclopentadiene is the final product and it reacts with aluminium bromide to give the perbrominated Prins dimer[37] or with chloro- or fluoro-sulphonic acid to give the chloro- or fluoro-sulphonate of the Prins dimer[38].



D. Pentachlorocyclopentadienide Anion

True salts of $C_5Cl_5^-$ (4) with large cations, e.g. n-Bu_4N^+ have recently been isolated and characterized spectroscopically[39,40]. Although



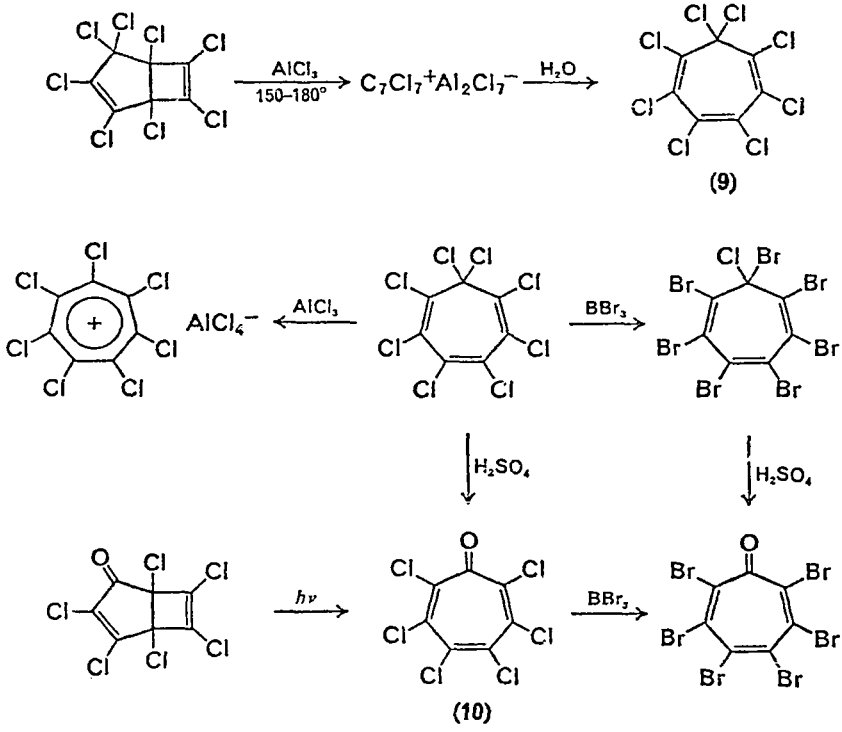
the ion 4 has six π-electrons and so should be aromatic, these salts are thermally unstable. Above $-15°$ decomposition occurs to give decachloro-bis(cyclopentadienyl) and other products[40] apparently via the pentachlorocyclopentadienyl radical[41] rather than via the carbene, tetrachlorocyclopentadienylide.

The salts $R_4N^+C_5Cl_5^-$ (R = n-Pr, n-Bu, n-heptyl), n-$Bu_4P^+C_5Cl_5^-$ and $C_5H_5NCH_3^+C_5Cl_5^-$ show the simple infrared spectra expected for an ion

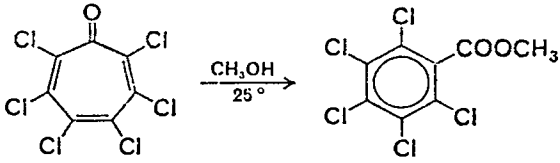
of D_{5h} symmetry (i.e. one ring absorption and one C—Cl stretching absorption). The thallium salt C_5Cl_5Tl (prepared from thallium ethoxide and pentachlorocyclopentadiene), however, shows enough interaction of the cation with the anion to lower the symmetry to C_{5v}. Although all five chlorines in 4 are chemically equivalent, in a crystal lattice they could not be crystallographically equivalent. Consistent with this prediction, the n.q.r. spectra of $C_5Cl_5^-$ salts show for n-$Bu_4P^+C_5Cl_5^-$ a 1 : 1 : 1 : 1 : 1 quintet and for n-$Pr_4N^+C_5Cl_5^-$ a 2 : 2 : 1 triplet[40]. The C—Cl stretching frequencies for the series $C_3Cl_3^+$, 735; C_6Cl_6, 694; $C_5Cl_5^-$, 657–681 cm^{-1} are in agreement with the predicted C—Cl σ bond strengths $C_3Cl_3^+ > C_6Cl_6 > C_5Cl_5^-$ since the positive charge on the ring in $C_3Cl_3^+$ would be expected to strengthen and shorten the C—Cl σ bond, polarizing its electron pair towards carbon.

E. Heptachlorotropylium Ion

The $C_7Cl_7^+$ ion (6) has been prepared from octachlorobicycloheptadiene[42,43] and aluminium trichloride in the critical temperature range 150–180°[44]. Although $C_7Cl_7^+$ is unlikely to be planar (because of

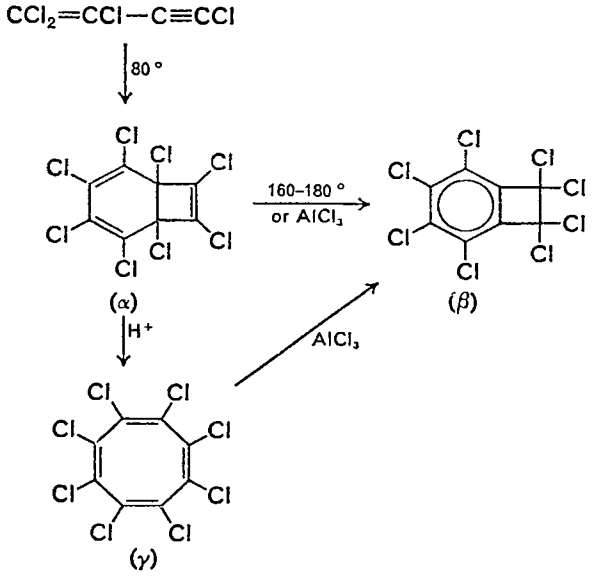


Cl—Cl interactions) it seems to be at least as stable as $C_3Cl_3^+$, and, like $C_3Cl_3^+$, it undergoes arylation with aromatic hydrocarbons. Hydrolysis converts **6** to octachlorocycloheptatriene (**9**) which undergoes a number of interesting transformations[44]. Perchlorotropone (**10**), the first known perhalogenated tropone, has also been prepared photochemically by Scherer[45]. It very readily undergoes the well-known tropone to benzoate rearrangement.



F. Octachlorocyclooctatetraene

Perchlorobutenyne[46] spontaneously dimerizes above 80° to crystalline 'α'-C_8Cl_8, which at higher temperatures or in the presence of Lewis acids is rapidly transformed to 'β'-C_8Cl_8, octachlorobenzocyclobutene[47]. Treatment with protonic acids converts 'α'-C_8Cl_8 to a third isomer, 'γ'-C_8Cl_8 [48].

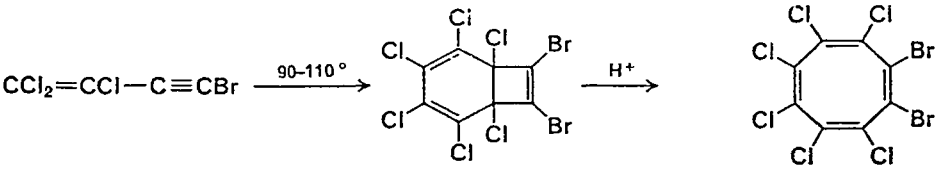


The structure of 'α'-C_8Cl_8 is assigned as octachlorobicyclo-[4.2.0]-octatriene-[2.4.7] on the basis of ozonolysis which gives tetrachlorophthalic acid anhydride and its n.q.r. spectrum[49]. The structure shown for 'β'-C_8Cl_8 was originally suggested on the basis of chemical and spectroscopic

evidence[46] and is consistent with the observed n.q.r. spectrum[49]. 'γ'-C_8Cl_8 shows n.q.r. lines which fall close together with frequencies normal for vinyl chlorines suggesting that all eight chlorines have nearly identical chemical environments. Furthermore, 'γ'-C_8Cl_8 has zero dipole moment and an extremely simple infrared spectrum with bands at 1570, 1160, 900 and 730 cm^{-1} and is therefore identified as octachlorocyclooctatetraene[49]. The C_8Cl_8 isomer obtained from the dimerization of tetrachlorocyclobutadiene (see section II. B) has an infrared spectrum quite different from that of 'γ'-C_8Cl_8 and it has been suggested that the former isomer may be octachlorocubane or octachlorotricyclooctadiene[32]. Indeed, it can be converted to 'γ'-C_8Cl_8 on heating[50].

Octachlorocyclooctatetraene, like octakis(trifluoromethyl)-cyclooctatetraene[51], is remarkably inert to electrophilic reagents and oxidizing agents. For example, it is inert to bromine, aqueous potassium permanganate and ozone, and even survives boiling with fuming nitric acid. This lack of reactivity is attributed to steric shielding of the double bonds by the bulky chlorine atoms.

Hexachlorodibromocyclooctatetraene has recently been synthesized by a route analogous to that described for octachlorocyclooctatetraene[52].

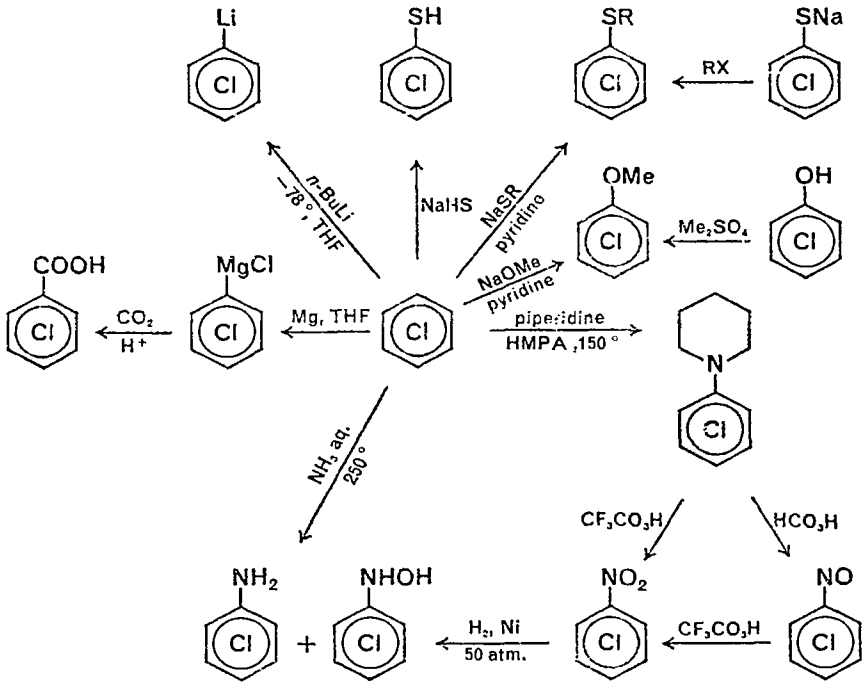


III. PERHALO-AROMATIC AND -HETEROAROMATIC COMPOUNDS

A. Hexahalobenzenes

Hexachloro- and hexabromo-benzene have been known for a long time but their substitution reactions have not been the subject of detailed study, unlike those of hexafluorobenzene[22]. In general, hexahalobenzenes are readily susceptible to attack by nucleophilic reagents and some typical reactions of hexachlorobenzene are shown in Scheme 1.

In the formation of $C_6X_4(OMe)_2$ isomers (X = F, Cl, Br) from hexahalobenzenes and sodium methoxide significant differences in orientation patterns are observed (Table 2)[53]. These results can be rationalized in terms of Burdon's orientation rules for polyhaloaromatic compounds[56] in which halogens are considered to be electron-repelling in π-systems (I_π effect)[57, 58].



SCHEME 1. The preparation of pentachlorophenyl derivatives via nucleophilic reactions of hexachlorobenzene.

The order of reactivity of aryl halides as leaving groups in aromatic S_N reactions is usually $F^- \gg Cl^- > Br^-$ and in both polychloro-[55,59] and polybromo-fluorobenzenes[53] only the fluorine atoms are replaced by nucleophiles.

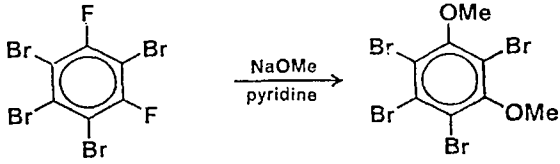
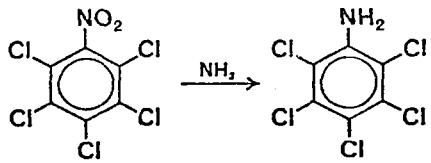


TABLE 2. Formation of $C_6X_4(OMe)_2$ isomers from C_6X_6 and NaOMe

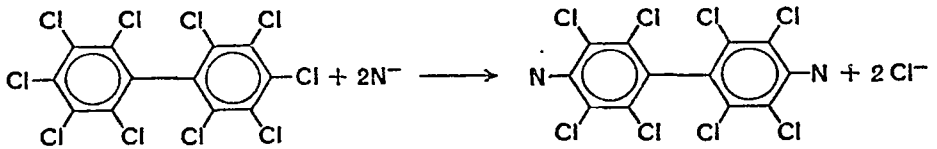
X	*o*	*m*	*p*	Reference
F	16	32	52	54
Cl	25	64	6	55
Br	—	100	—	53

Hexabromobenzene, unlike its chloro- or fluoro- analogues, undergoes protodebromination when treated with sodium methoxide in methanol and ethyl methyl ketone to give a mixture of tetrabromobenzenes[53]. A mechanism involving nucleophilic attack on halogen has been suggested by Bunnett and coworkers[60-62] to explain the dehalogenation and isomerization in some oligohalobenzenes and this mechanism is likely to apply also to reactions of hexabromobenzene.

In nucleophilic substitution reactions of C_6Cl_5X where X is an electron-donor group, e.g. NH_2, NHMe, NMe_2, OMe, attack is expected to occur at the carbon atom with the greatest fractional positive charge. ^{35}Cl n.q.r. frequencies, which are determined by the degree of deviation from spherical symmetry of the electron density around the chlorine atom and hence are related to the positive charge on carbon, have been used to correlate the observed orientation patterns in nucleophilic substitution reactions of C_6Cl_5X [63]. If X is an electron-acceptor group, e.g. NO_2 replacement of Cl is not observed[63]. In decachlorobiphenyl, however, nucleophilic substitution



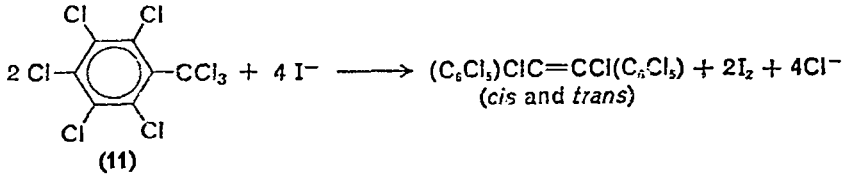
occurs readily in the *p*-position[64]. The 4,4'-dilithio and -diGrignard reagents can be prepared in the conventional way from decachlorobiphenyl[64].



B. Perchloro-toluene and -p-xylene

Ballester and coworkers have used the powerful nuclear chlorinating agent $S_2Cl_2/SO_2Cl_2/AlCl_3$ to prepare perchlorotoluene (**11**) from 2,3,5,6-tetrachloro-1-trichloromethylbenzene and perchloro-*p*-xylene (**12**) from *p*-bis(trichloromethyl)benzene[65]. Perchlorotoluene is also formed by heating octachloroheptatriene to 190°[44]. The high steric strain in **11** greatly assists both homolytic and heterolytic fission of the α-C—Cl bonds

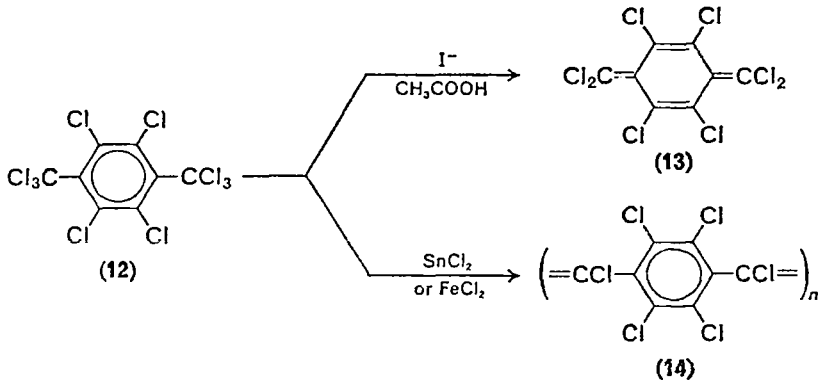
so that thermal decomposition occurs below 200° and hydrolysis to give pentachlorobenzoic acid is easily achieved[66]. The 'positive halogen' reaction of **11** with potassium iodide in aqueous acetic acid produces *cis*- and *trans*-perchlorostilbenes in almost equal amounts via the intermediates, perchlorobenzyl radical and the dimer perchlorobibenzyl[66].



(11)

In contrast to perchlorotoluene, *trans*-perchlorostilbene is stable to 400° and withstands such reagents as sulphuric acid and fuming nitric acid, possibly due to the high carbon(trigonal)–chlorine bond energy. Heating either *cis*- or *trans*-perchlorostilbene to 400° fails to produce isomerization, a fact which is attributed to steric inhibition of resonance in the transition state of the isomerization by the *o*-chlorine atoms, since heating *cis*-α,2,3,4,5,α′,2′,3′,4′,5′-decachlorostilbene at 260° causes some isomerization[69].

An extension of the dechlorination reaction of **11** to perchlorinated aromatics with more than one alkyl side-chain provides a versatile route to macromolecular chlorocarbon polymers, if dechlorinating agents other than iodide ion are used[67,68]. The chlorocarbon polymer **14** and related macromolecular chlorocarbons exhibit exceptionally high thermal stability (up to 500°) and chemical inertness[68].



(12) (13) (14)

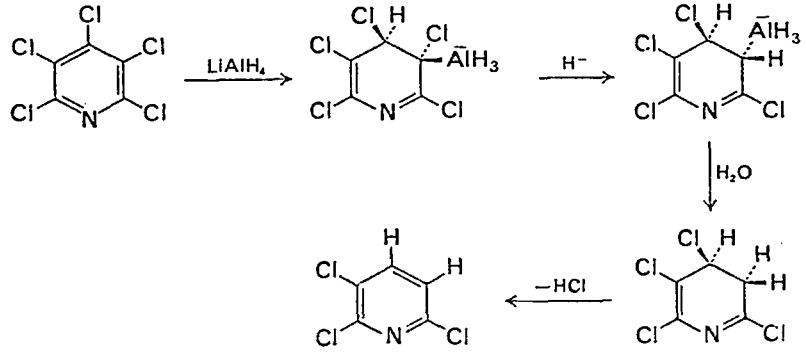
C. Pentahalopyridines

Pentahalopyridines, like hexahalobenzenes, are readily susceptible to nucleophilic attack which can occur at the 2(6)- or 4-positions. Whereas pentafluoropyridine is substituted by all nucleophiles exclusively in the 4-position[70–73], pentabromo- and pentachloro-pyridine both give some 2-substituted product, in addition to 4-substituted product, with larger nucleophiles. The effect is greater for pentabromopyridine due to steric 'deflection' from the 4-position by the larger bromine atoms to the less hindered 2-position[74]. Indeed in non-polar solvents nucleophilic substitution of pentabromo- and pentachloro-pyridine takes place exclusively in the 2(6)-position, although in ethanol some 4-substituted product is also obtained (Table 3)[74].

TABLE 3. Percentage yields of mono-substituted isomers in the reactions of pentabromo- and pentachloro-pyridine with various nucleophiles

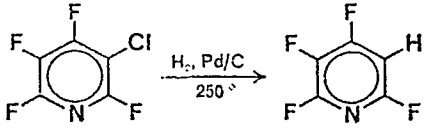
Nucleophile	Solvent	C_5Br_5N		C_5Cl_5N		Reference
		4-	2-	4-	2-	
HO^-	Ethanol	100	—	100	—	75
MeO^-	Methanol	66	34	85	15	76
Me_2NH	Benzene	—	100	—	100	77
	Ethanol	15	85	34	66	77
$C_5H_{10}NH$	Benzene	—	100	4	96	77
	Ethanol	15	85	37	63	77
$MeNH_2$	Dioxan	48	52	68	32	78

The reduction of pentachloropyridine by lithium aluminium hydride to give 2,3,6-trichloropyridine as the main product has been rationalized on the basis of the following mechanism[79]:



With 3,5-dichloro-2,4,6-trifluoropyridine only the fluorine atoms are replaced by an excess of lithium aluminium hydride to give 3,5-dichloropyridine[79].

In contrast the reaction of 3-chloro-2,4,5,6-tetrafluoropyridine with hydrogen over palladized charcoal results in preferential reduction of the C—Cl bond[80]. Pentahalopyridines and related perhalogenated *N*-heteroaromatic compounds are very weak bases because of the electron-withdrawing halogen substituents, and they are therefore resistant to

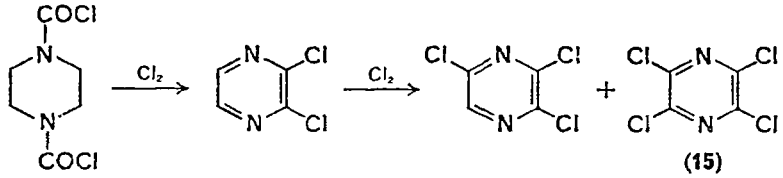


N-oxidation by the usual reagents, e.g. peracetic acid[81]. A mixture of an organic peracid and sulphuric acid, however, gives excellent conversions of perhalogen-substituted *N*-heterocycles to the corresponding *N*-oxides[82]. When pentabromopyridine is oxidized with boiling peroxytrifluoroacetic acid, protodebromination, described earlier for polybromobenzenes[53], occurs to give the three isomeric tetrabromopyridine 1-oxides in addition to pentabromopyridine 1-oxide[74]. The competition between nucleophilic substitution on carbon and on halogen is apparently characteristic of polybromoaromatic compounds. It is not found in polyfluoro- and polychloro-aromatic compounds, but is observed in polyiodo-aromatic systems[62].

D. Miscellaneous Perhalogenated Heterocyclic Compounds

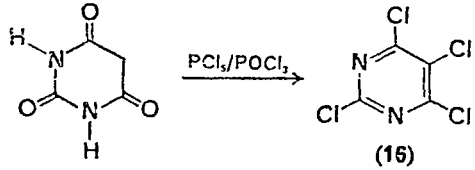
The review by Holtschmidt and coworkers[8] includes polychloroheterocyclic compounds which can be prepared either by high temperature chlorination[83] or by ring-closure reactions. Phosphorus pentachloride is often used as the chlorinating agent especially for pentachloropyridine which is prepared in 97% yield using a $PCl_5 : C_5H_5N$ molar ratio 12 : 1 at 350° in a rocking autoclave for 14 hours[84]. At lower temperatures considerable amounts of the tetrachloropyridine isomers are obtained in addition to pentachloropyridine[85].

Tetrachloropyrazine (**15**) is conveniently prepared by treatment of 2-chloro- or 2-hydroxy-pyrazine with phosphorus pentachloride under autogeneous pressure at 320° for 15 hours, or from 2,5-diketopiperazine with the same reagent at 250°[86]. In addition to **15**, trichloropyrazine is also obtained by chlorination of *N*,*N*′-bis(chlorocarbonyl)piperazine[87,88].



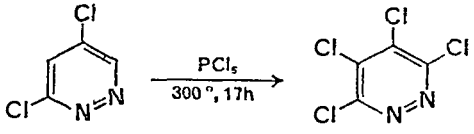
(**15**)

Tetrachloropyrimidine (**16**) has been prepared in moderate yield from barbituric acid using a $PCl_5/POCl_3$ mixture[89]. The chlorination of the



(**16**)

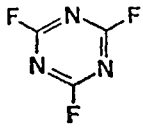
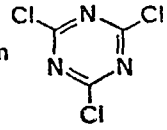
readily available 3,6-dichloropyridazine with phosphorus pentachloride is now the preferred route to tetrachloropyridazine (**17**)[90] rather than the earlier synthesis from maleic hydrazide and phosphorous oxychloride[91].



(**17**)

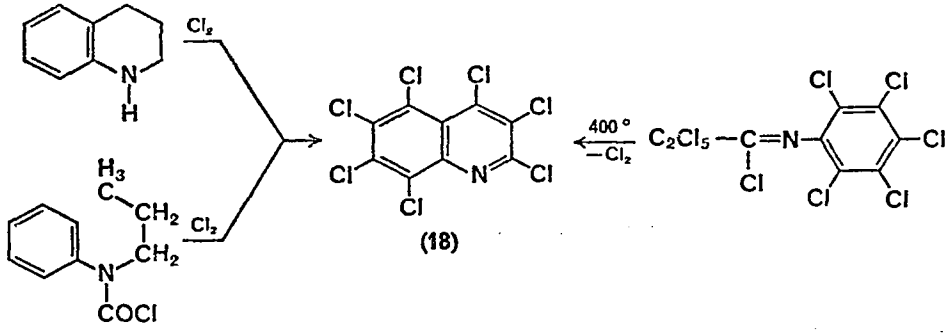
The preparation of the perchloro-isomers (**15**–**17**) has been reinvestigated recently, since they were desirable precursors for the perfluoro-analogues via fluorination with potassium fluoride[22]. Indeed, fluorination appears to be the only reaction of the perchloro-compounds which has been investigated in detail. In contrast many nucleophilic reactions of the perfluoro-derivatives have been studied, and extensive use has been made of ^{19}F n.m.r. spectra for the determination of substitution patterns. A comparison has been made of the reactions of nucleophiles with cyanuric chloride and cyanuric fluoride (Table 4)[92]. Generally, the chloride is less reactive towards nucleophilic reagents and stepwise replacement of chlorines can be achieved.

TABLE 4. A comparison of the reactions of nucleophilic reagents with cyanuric fluoride and cyanuric chloride

Nucleophile	No. of equivalents	Product from 	Product from 
NH_3	Excess	2,4-Diamino-6-fluoro-*s*-triazine (90%)	Mixture of mono- and di-substituted products
Et_2NH	7·0	2,4-Bis(diethylamino)-6-fluoro-*s*-triazine (74%)	2,4-Bis(diethylamino)-6-chloro-*s*-triazine (100%)[a]
$C_6H_5NH_2$	6·0	Triphenylmelamine (100%)[a]	2,4-Bis(phenylamino)-6-chloro-*s*-triazine (100%)[a]
H_2O	5·5	Cyanuric acid (94%)	Mixture of cyanuric acid and cyanuric chloride
CH_3OH	3·0	2,4,6-Tris(methoxy)-*s*-triazine (77%)	Mixture of di- and tri-substituted product

[a] Crude product.

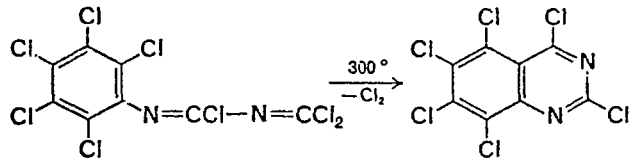
Heptachloroquinoline (**18**) is formed in moderate yield on high temperature chlorination of 1,2,3,4-tetrahydroquinoline[93] or *N*-chlorocarbonyl-*N*-propylaniline[94]. The latter reaction involves ring closure with the formation of a C—C bond as does the cyclization of *N*-pentachlorophenylpentachloropropionimidoyl chloride at 400° to give **18** in 81%



yield[95]. Chlorination of quinoline with phosphorus pentachloride is not a practical proposition but direct chlorination of quinoline in the presence of aluminium chloride at 140° gives mainly tetrachloroquinoline and then

further chlorination with phosphorus pentachloride in an autoclave at 315–330° gives 78% of **18**[96]. Similarly, chlorination of isoquinoline at 150°, in the presence of aluminium trichloride, gives hexachloroisoquinoline (87%) which on further chlorination with phosphorus pentachloride at 270° yields heptachloroisoquinoline (68%)[96]. Like other perhalogenated nitrogen heterocyclics, perchloro-quinoline and -isoquinoline show no basic properties, although they dissolve in concentrated sulphuric acid. They are readily converted to the corresponding perfluorocompounds by reaction with potassium fluoride at elevated temperatures[96].

Hexachloroquinazoline[95] (**19**) and hexachloroquinoxaline[97] (**20**) have been prepared by ring-closure reactions. At higher temperatures (600°)



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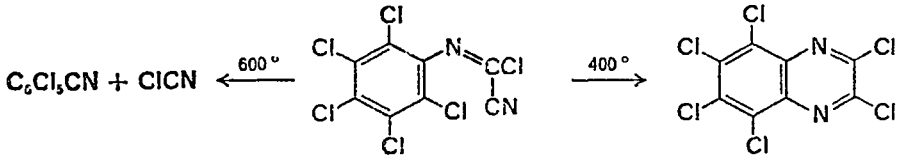
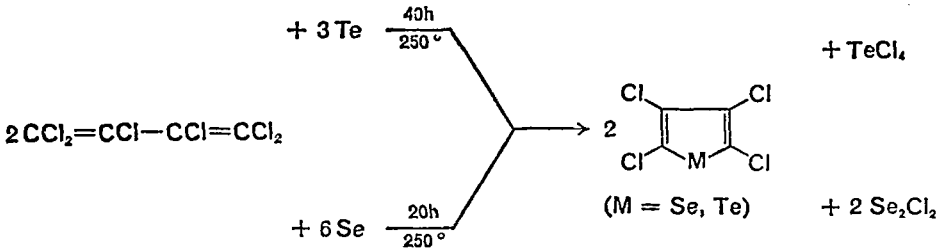


(20)

the decomposition of *N*-pentachlorophenylcyanoformimidoyl chloride gives pentachlorobenzonitrile and cyanogen chloride in high yield[98].

Another successful application of PCl_5 as a chlorinating agent involves the preparation of perchloroimidazo[1,2-a] pyridine[99].

Tetrachlorothiophene is readily accessible from the reaction between hexachlorobutadiene and sulphur at elevated temperatures[100] and the selenium and tellurium analogues have been prepared similarly[101].

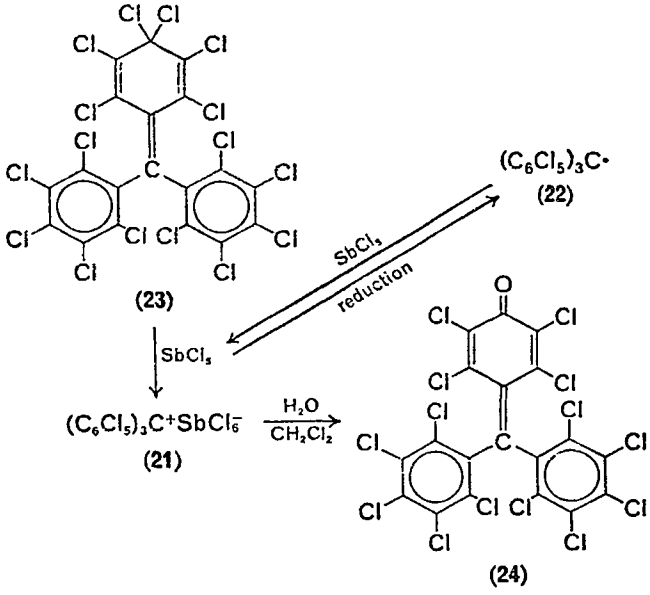


IV. PERHALOCARBON RADICALS, CARBONIUM IONS AND CARBANIONS

One of the most remarkable features of perhalocarbon chemistry is the inertness of the species $(C_6Cl_5)_3C^+$, $(C_6Cl_5)_3C^-$ and $(C_6Cl_5)_3C^{\cdot}$. Compared to their hydrocarbon or fluorocarbon analogues they are thermally very stable and chemically inert, a fact which is attributed to complete steric shielding of the central carbon atom by the *o*-chlorine atoms.

A. *Perchlorotriphenylcarbonium Ion, $(C_6Cl_5)_3C^+$*

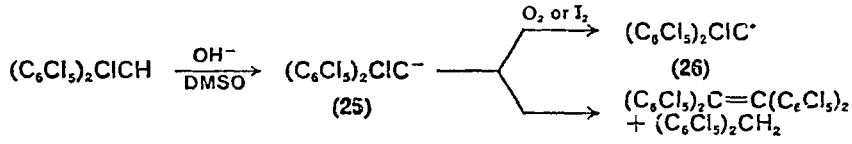
Perchlorotriphenylcarbonium hexachloroantimonate (**21**) has been isolated as dark-green crystals after oxidation of the perchlorotriphenylmethyl radical (**22**) with antimony pentachloride, or from perchloro-3-diphenylmethylene cyclohexa-1,4-diene (**23**) and antimony pentachloride in sulphuryl chloride[14]. The unusual hydrolysis product of **21**, perchloro-α-α-diphenylquinomethane (**24**), is indicative of the steric shielding of the central carbon atom as is the stability of the ion to water.



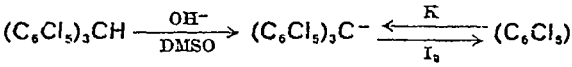
B. *Perhalocarbanions*

A large number of perchloro- and perbromo-alkyl derivatives of alkali metals have been synthesized[1,6,7,102], e.g. $LiCCl_3$, $LiCCl{=}CCl_2$, LiC_5Cl_5, $Na^+CBr_3^-$, $K^+CBr_3^-$ (see also sections II. D and V. A). Characteristically these reagents decompose vigorously at low temperatures with elimination

of metal halide and they are therefore difficult to handle. In distinct contrast, deep-blue solutions of the perchlorodiphenylcarbanion (25) can be kept at 25° for long periods without appreciable decomposition[4b]. Under certain conditions, however, perchlorotetraphenylethylene and/or α,α-decachlorodiphenylmethane are formed via a carbene mechanism[4b].



The wine-red perchlorotriphenylcarbanion (27) can also be obtained by C—H heterolysis in the presence of base or by reduction of the corresponding radical with potassium[104]. The ease of C—H heterolysis in the

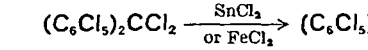


above reactions has been attributed to (i) accumulated electron-withdrawing effects of the chlorines, (ii) release of B strain when the α-carbon goes from sp^3 to sp^2 hybridization and (iii) resonance stabilization in the carbanions[103].

Although the potassium salt of $(C_6Cl_5)_3C^-$ cannot be isolated, the tetraethylammonium salt $(C_6Cl_5)_3C^-NEt_4^+$ is obtained as a garnet-coloured, crystalline powder on addition of tetraethylammonium bromide to a tetrahydrofuran solution of the potassium salt[104]. The stability of **27** towards water or ethanol indicates that $(C_6Cl_5)_3CH$ is a very strong acid. Moreover, the comparable stabilities of $(C_6Cl_5)_3C^-$ and $(C_6Cl_5)_3C^+$ suggest that steric shielding of the α-carbon atom rather than electronic effects accounts for the stability of these species.

C. Perchloroarylalkyl Radicals

As indicated in the previous section the perchlorinated carbon radicals, perchlorodiphenylmethyl (**26**) and perchlorotriphenylmethyl (**22**), are formed by oxidation of the corresponding carbanions, and **22** is also obtained by reduction of $(C_6Cl_5)_3C^+$ [14]. The synthesis of **26** has also been achieved by reduction of perchlorodiphenylmethane with tin(II) chloride[67], or iron(II) chloride[103], or by mercury and ultrasonics[103].



22 is the perchlorinated analogue of Gomberg's radical $(C_6H_5)_3C^\cdot$, the classic example of a 'stable' free radical. Solutions of triphenylmethyl,

however, are readily oxidized and concentration of these solutions leads to the separation of crystals of the dimer, 1-diphenylmethylene-4-tritylcyclohexa-2,5-diene[104a, b, c]. In contrast, the perchlorinated radicals exhibit exceptional stability both in solution and in the solid state, for which magnetic measurements indicate complete dissociation. Dilute solutions of **22** show no detectable change over several months and it has been concluded that the half-life of this radical is of the order of decades[103]. **22** is, however, light sensitive in solution, but this fact can be used to advantage in the synthesis of perchlorotriphenylmethane. The less stable

$$(C_6Cl_5)_2C^{\bullet} + Cl_2 \xrightarrow{h\nu} (C_6Cl_5)_3CCl$$

26 has a half-life of 2–3 days in solution in air at 25°, but can be kept as a solid for years with but little decomposition. The inertness of these radicals towards chemical reagents is remarkable in that it is greater than most tetravalent carbon compounds. For example **22** is inert towards bromine, chlorine or concentrated nitric acid and it has therefore been suggested that they should be called *inert free radicals*.

The chemical inertness of **22** and the simplicity of the infrared spectrum can be attributed to the high symmetry (D_3) of its helicoidal configuration. The molecule is propeller-shaped with the α-(tricovalent) carbon protected from attacking species by the six *o*-chlorine atoms. **26** is not so inert because of the lesser shielding at the α-carbon and it undergoes hydrogen

$$(C_6Cl_5)_2ClC^{\bullet} + C_6H_5CH_3 \longrightarrow (C_6Cl_5)_2CHCl + C_6H_5CH_2^{\bullet}$$

$$(C_6Cl_5)_2ClC^{\bullet} + C_6H_5CH_2^{\bullet} \longrightarrow (C_6Cl_5)_2ClCCH_2C_6H_5 \xrightarrow{-HCl} (C_6Cl_5)_2C{=}CHC_6H_5$$

abstraction with toluene[104]. The formation from the perchloro-radicals of perchloro-carbanions and -carbonium ions is an electron-transfer process which does not require formation of a new bond with the α-carbon. Therefore, steric shielding does not prevent these reactions.

V. CHLOROCARBON AND BROMOCARBON DERIVATIVES OF METALS AND METALLOIDS

Halogen substitution of organic groups attached to a metal is expected to alter (i) the nature of the metal–carbon bond and (ii) the donor or acceptor properties of the metal in such derivatives. The possibility of intra- or inter-molecular metal–halogen interactions is also of great interest. In particular the limiting case, in which such interactions result in metal halide eliminations to give synthetically useful transient organic species (e.g. dihalocarbenes, tetrahalobenzynes) is of considerable importance. While the chemistry of fluorocarbons and their derivatives with metals

and metalloids has been a fashionable area of research for some time[105–110], the corresponding chlorocarbon and bromocarbon compounds have only recently received attention[1]. Now that suitable synthetic routes to perchloro- and perbromo-lithium and perchloro- and perbromo-magnesium reagents are available, rapid progress in this area of organometallic chemistry can be expected.

A. Lithium Derivatives

1. Preparation

Organolithium compounds are important reagents for both organic and organometallic syntheses and suitable conditions for the preparation of a large number of perchloro- and perbromo-carbon lithium reagents by either metallation or metal–halogen exchange have recently been discovered (Table 5).

TABLE 5. Reaction conditions for the preparation of chlorocarbon and bromocarbon lithium reagents

Lithium reagent	Method of preparation	Reaction conditions	Reference
CCl_3Li	$CCl_3H + n$-BuLi	−110°, THF	111–113
CCl_3Li	CCl_3Br + MeLi	−115°, Ether	111, 112, 114
CBr_3Li	$CBr_3H + n$-BuLi	−110°, Trapp mixture[a]	115
CBr_3Li	CBr_4 + RLi (R = Ph, *n*-Bu)	−110°, Trapp mixture	116
$CCl_2{=}CClLi$	$CCl_2{=}CClH + n$-BuLi	−110°, Trapp mixture	117
$CCl_2{=}CClLi$	$CCl_2{=}CClBr + n$-BuLi	−110°, Ether	117
$CCl_2{=}C{=}CClLi$	$CCl_2H{-}CCl{=}CHCl + n$-BuLi	−110°, Trapp mixture	118
$ClC{\equiv}CLi$	*trans*-$CHCl{=}CHCl$ + MeLi	0°, Ether	119
C_6Cl_5Li	$C_6Cl_5H + n$-BuLi	−80°, THF	120
C_6Cl_5Li	$C_6Cl_6 + n$-BuLi	−78°, THF	121
C_6Cl_5Li	$C_6Cl_6 + n$-BuLi	−10°, Ether	121
C_6Br_5Li	$C_6Br_6 + n$-BuLi	−75°, Ether	122
C_5Cl_5Li	C_5Cl_5H + RLi (R = alkyl)	[b]	123
C_5Cl_5Li	C_5Cl_6 + Li	[b]	124
C_5Cl_4NLi	$C_5Cl_5N + n$-BuLi	[c]	125, 126
C_5Cl_4NLi	$C_5Cl_5N + n$-BuLi	−70°, THF	127, 128
C_5Br_4NLi	$C_5Br_5N + n$-BuLi	−75°, Ether	122
C_4Cl_3SLi	$C_4Cl_4S + n$-BuLi	−25°, Ether	129

[a] Trapp mixture is THF : diethylether : pentane in 4 : 1 : 1 ratio.
[b] Not specified.
[c] Solvent dependent.

2. Reactions of perhalocarbons with lithium metal

Although organolithium compounds are often prepared by direct reaction between an organic halide and lithium metal[130], only one successful preparation of a halocarbon lithium reagent by this route has been reported[124]. In general, the reaction of perhalocarbons with lithium metal may lead to the formation of a perhalocarbon lithium reagent initially, but secondary reactions are usually observed. For example, the reaction between lithium metal and tetrachloroethylene in tetrahydrofuran at $-80°$ in the presence of triorganosilanes gives compounds of the type $R_3SiC{\equiv}CCl$, presumably via lithium chloroacetylide[131].

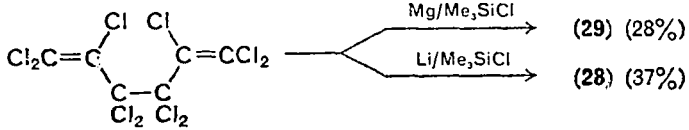
Gilman and coworkers discovered that a variety of halocarbons including hexachlorobenzene[132], hexachloropropene[133] and octachloropropane[133], on treatment with lithium in tetrahydrofuran in the presence of an excess of chlorotrimethylsilane yields tetrakis(trimethylsilyl)allene (**28**). Significantly they have shown that the tetraene (**29**) is also produced in low yield from both aromatic[134] and aliphatic[135] halocarbons. Since the tetraene is easily converted to the allene by lithium and chlorotrimethylsilane, it is reasonable to conclude that **29** is an intermediate in the formation of **28** from halocarbons and lithium or magnesium metal

$$(Me_3Si)_2C{=}C{=}C(SiMe_3){-}C(SiMe_3){=}C{=}C(SiMe_3)_2$$
(29)

$$\downarrow \; Li/Me_3SiCl$$

$$2(Me_3Si)_2C{=}C{=}C(SiMe_3)_2$$
(28)

in the presence of excess of chlorotrimethylsilane. Indeed the reaction of decachlorohexa-1,5-diene (synthesized from hexachloropropene and copper bronze)[136] with magnesium and chlorotrimethylsilane produces the tetraene, **29**, whereas in the presence of lithium the allene is formed[133].



Unexpected products are also formed in the reaction of hexachlorobutadiene with metals and chlorotrimethylsilane in tetrahydrofuran[133]. Again the course of the reaction is metal-dependent and, using lithium or sodium, hexakis(trimethylsilyl)but-2-yne (**30**) is formed, whereas

magnesium gives bis(trimethylsilyl)buta-1,3-diyne (**31**). Surprisingly, the reaction of tetrachlorothiophene with lithium and chlorotrimethylsilane

$(Me_3Si)_3C-C\equiv C-C(SiMe_3)_3$ (**30**)

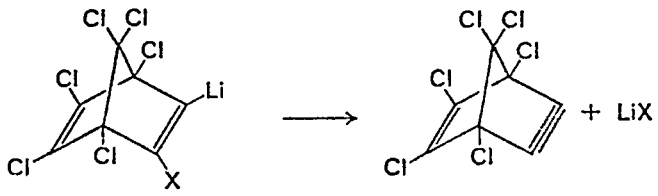
$Me_3Si-C\equiv C-C\equiv C-SiMe_3$ (**31**)

in tetrahydrofuran also gives low yields of **30**[5]. Possible reaction schemes for the remarkable dehalogenations of perhalocarbons by metals, particularly lithium, have been discussed in detail[5].

3. Thermal stability

The thermal stability of perhaloalkyl-lithium reagents is low and decomposition, often vigorous, occurs at low temperatures (ca. −80°) by elimination of lithium halide. As a general rule, tetrahydrofuran solvent[113] has a stabilizing influence compared to diethyl ether on perhaloalkyl-lithium reagents[114] but, in contrast, trichlorovinyl-lithium[117], pentachlorophenyl-lithium[121], tetrachloro-4-pyridyl-lithium[128], and 2-lithiotrichlorothiophene[129] are appreciably less stable in tetrahydrofuran than in diethyl ether solution. The pentahalophenyl-lithium reagents C_6X_5Li (X = F, Cl, Br) show greater stability with respect to lithium halide elimination than the corresponding *o*-halophenyl-lithium derivatives[137], probably due to stabilization of the carbanion by electron withdrawal by the five halogen atoms. The stability sequence $C_6Cl_5Li > C_6F_5Li > C_6Br_5Li$ found for the pentahalophenyl-lithium reagents in diethyl ether solution is not expected on the basis of the lattice energies of the lithium halides and may be due to the insolubility of lithium fluoride. The thermolysis of pentahalophenyl-lithium reagents, e.g. C_6Cl_5Li[138], provides a good source of the extremely reactive dienophile, tetrachlorobenzyne (see section VI. B).

The perhalonorbornadienyl-lithium reagents (**32**) and (**33**) exhibit much greater thermal stability than perhaloalkyl-lithium reagents, since the elimination of lithium halide should be energetically unfavourable due to the high strain energy of the intermediate **34**[139].



[X = Cl (**32**); X = Br (**33**)] (**34**)

B. Magnesium Derivatives

The synthesis and reactions of α-haloalkyl-magnesium reagents have been reviewed[140]. In general, perhalocarbon magnesium reagents are more difficult to prepare but thermally more stable than the corresponding lithium reagents. Metalation or metal–halogen exchange reactions can be used to prepare trichloromethylmagnesium chloride, CCl_3MgCl [141]. Perhalo-aryl and -hetaryl Grignard reagents can be prepared from magnesium and the appropriate perhaloaromatic compound, if the reaction conditions are carefully controlled. The use of solvents such as tetrahydrofuran and/or 'entrainers' such as 1,2-dibromoethane are often necessary to enable reasonable yields of the reagents to be prepared (Table 6).

TABLE 6. Preparation of Grignard reagents from perhalocarbon compounds

Method of preparation	Solvent	Product[a]	Reference
$CCl_3Br + iso\text{-}PrMgCl$	THF, −80°	CCl_3MgCl	141
$CCl_3H + iso\text{-}PrMgCl$	THF/HMPA(20%), −80°	CCl_3MgCl	141
$C_6Cl_6 + Mg$	Et_2O[b], reflux	C_6Cl_5MgCl (65)	142
$C_6Cl_6 + Mg$	THF, reflux	C_6Cl_5MgCl (high)[c]	143, 144
$C_6Br_6 + Mg$	THF[b], reflux	C_6Br_5MgBr (25)	145
$C_5Cl_5N + Mg$	Et_2O[b], reflux	4-C_5Cl_4NMgCl (47)	146
$C_5Cl_5N + Mg$	Et_2O, reflux	4-C_5Cl_4NMgCl (88)	147
$C_5Cl_5N + Mg$	THF, −10°	4-C_5Cl_4NMgCl (80)	148
$C_5Br_5N + Mg$	Et_2O[b], reflux	4-C_5Br_4NMgBr (43)	145
$C_4Cl_4S + Mg$	Et_2O[b], reflux	2-C_4Cl_3SMgCl (17)	129, 149 150
$C_4Cl_4S + Mg$	THF, reflux	2-C_4Cl_3SMgCl (60)	151
$C_4Cl_4S + Mg$	THF[b], ambient temperature	2-C_4Cl_3SMgCl (98)	152
$C_4Br_4S + Mg$	—	2-C_4Br_3SMgBr	150

[a] % yields in parentheses.
[b] Using the entrainment technique.
[c] Accompanied by a little 1,4-$C_6Cl_4(MgCl)_2$.

C. Group IV A Derivatives

1. Synthesis

The synthesis of perhalocarbon derivatives of Group IV A elements by direct halogenation is useful only for silicon and germanium because of facile metal–carbon bond scission by halogens. Perchlorinated alkyls

of silicon and germanium can, however, be prepared by chlorination of alkylsilicon halides in the presence of ultraviolet light and/or free radical initiators[153-158]. The availability of a wide range of perhalocarbon-lithium

$$Me_2SiCl_2 \xrightarrow[AZIB]{Cl_2,\ u.v.} (CCl_3)_2SiCl_2$$

$$(CH_2SiCl_2)_3 \xrightarrow[CCl_4]{Cl_2,\ u.v.} (CCl_2SiCl_2)_3$$

AZIB = α,α'-Azobis(isobutyronitrile)

and -magnesium reagents (see sections V. A and V. B) has opened the way for the preparation of perhalocarbon derivatives of Group IV A elements by conventional organometallic synthesis[1]. In fact the preparation of a trimethylsilyl derivative has often been used to characterize a new perhalocarbon-lithium reagent.

A number of novel routes to the formation of perhalocarbon–metal bonds have been applied to germanium, tin and lead. The reaction of carbon vapour, generated from a carbon arc, with germanium tetrachloride gives $(Cl_3Ge)_2CCl_2$ as the major product together with small amounts of CCl_3GeCl_3 [159]. The insertion of germanium dibromide into the C—Br bond of carbon tetrabromide yields tribromomethyltribromogermane[160].

$$GeBr_2 + CBr_4 \longrightarrow Br_3CGeBr_3$$

Both Sn—N [161,162] and Pb—O [163] bonds react with weakly acidic haloforms under mild conditions to give trihalomethyl–metal compounds.

$$R_3SnNR'_2 + HCX_3 \longrightarrow R_3SnCX_3 + R'_2NH$$

(R = Me, Et, *n*-Bu; R′ = Et; X = Cl, Br) [152]

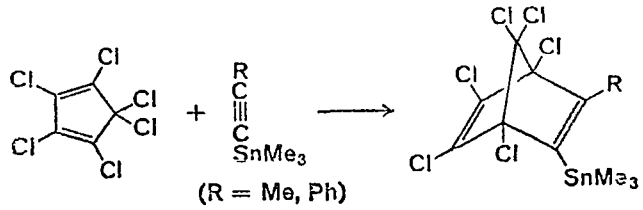
(R = R′ = Me; X = Cl) [161]

$$Ph_3PbOMe + HCX_3 \longrightarrow Ph_3PbCX_3 + MeOH$$

(X = Cl, Br)

(Trichloromethyl)triphenyllead has also been prepared by the reaction of triphenyllead methoxide with hexachloroacetone[163], or by the addition of triphenylplumbyl-lithium to an excess of carbon tetrachloride at $-60°$ [164]; at room temperature the disubstituted product, $(Ph_3Pb)_2CCl_2$, is formed[164].

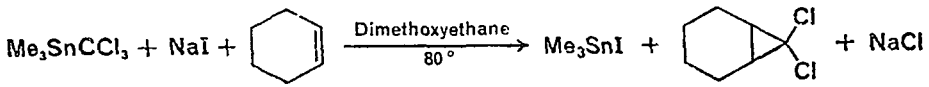
Diels–Alder reactions between hexachlorocyclopentadiene and trimethyltinacetylenes yield polychloronorbornadienyl derivatives of tin[165].



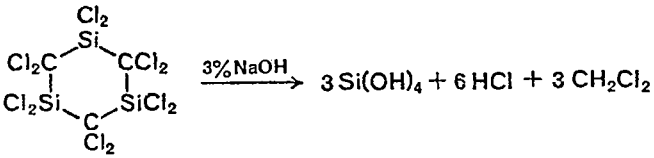
When 5,5-dimethoxytetrachlorocyclopentadiene is used, however, aromatization of the adduct occurs to give 1,2-bis(trimethyltin)tetrachlorobenzene as the main product[165].

2. Reactions

A characteristic reaction of perhaloalkyl Group IV A metal compounds is the migration of chlorine from the organic side-chain to the metal under the influence of heat. Thus both CCl_3SiCl_3[166] and trimethyl(trihalomethyl)-tin compounds[167] have been investigated as sources of dihalocarbenes, but they are inferior to trihalomethylmercury compounds for this purpose (see section VI. A). A second method for generating dihalocarbenes, which requires milder conditions than the thermolytic process, is the sodium iodide procedure[168–170]. This reaction occurs via nucleophilic displacement at tin of CCl_3^- ion by iodide ion.



The silicon–perhalocarbon bond is quite polar due to the relatively high electronegativity of perhalocarbon groups and it is thus susceptible to hydrolysis by dilute aqueous alkali. This reaction has been used to provide structural evidence for both silicon–perchloroalkyl and –perchloroaryl compounds, for example the formation of methylene chloride on hydrolysis of perchloro-1,3,5-trisilacyclohexane[157]. Similarly, alkaline hydrolysis of



the Si—C_6Cl_5 bond gives pentachlorobenzene and this reactivity detracts from the otherwise promising properties of silicone polymers containing chlorinated phenyl groups, namely improved lubricating properties,

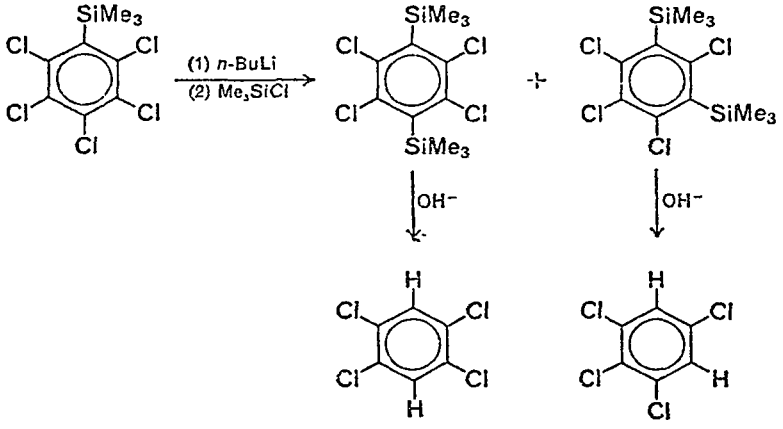
greater resistance to acid cleavage and higher thermal stability than hydrocarbon analogues. Pentahalophenyltin compounds are even more susceptible to nucleophilic-assisted hydrolysis and both $Me_3SnC_6Cl_5$ and $Me_3SnC_6F_5$, although stable in aqueous ethanol, are converted to the corresponding pentahalobenzene on addition of a trace of fluoride

$$Me_3SnC_6X_5 \xrightarrow[H_2O]{F^-/EtOH/} C_6X_5H + Me_3SnOH$$
$$(X = Cl, F)$$

ion[161,171]. The $Sn—C_6Cl_5$[161] or $Sn—C_6F_5$[171] bond is readily cleaved by electrophilic reagents, e.g. boron trichloride, but, in contrast, a methyl group is cleaved from tin in Me_3SnCCl_3 by boron trichloride[161].

$$Me_3SnCCl_3 + BCl_3 \longrightarrow Me_2Sn(CCl_3)Cl + MeBCl_2$$

Pentachlorophenylsilicon compounds undergo metal–halogen exchange in preference to $Si—C_6Cl_5$ cleavage with *n*-butyl-lithium at low temperatures. With $Me_3SiC_6Cl_5$, exchange takes place mainly in the *p*-position although some *m*-substitution also occurs as determined by alkaline hydrolysis[172]. In contrast, the lability of the $C_6Cl_5—Si$ bond is demon-



strated by the observation that cleavage of the silicon–carbon bond occurs in preference to Si—H metalation in the reaction of organolithium reagents with pentachlorophenylsilanes of the type $(C_6Cl_5)R_2SiH$ (R = Me, Ph)[172,173]. Addition of $Me_3SiC_6Cl_5$ to the carbonyl group of

$$(C_6Cl_5)R_2SiH \xrightarrow[(2)Me_3SiCl]{(1)R'Li} C_6Cl_5SiMe_3 + R_2R'SiH$$
$$(R' = Me, Ph)$$

benzaldehyde is reminiscent of the reaction of Grignard or lithium reagents with carbonyl compounds[174].

$$C_6X_5SiMe_3 + PhCHO \longrightarrow (C_6X_5)PhCHOSiMe_3 \xrightarrow{hydrol} (C_6X_5)PhCHOH$$

(X = Cl, F)

D. Derivatives of Transition Metals

i. σ-Bonded derivatives

The product obtained from the reaction of tetrakis(triphenylphosphine)-platinum with carbon tetrachloride is thought to be a mixture of *cis*- and *trans*-$(Ph_3P)_2Pt(CCl_3)Cl$ [175], but the only examples of well-characterized perhaloalkyl–transition metal compounds are the $XCCo_3(CO)_9$ types (X = Cl, Br) prepared from carbon tetrahalides and $Co_2(CO)_8$ [176,177], or by treatment of the anion $[Co(CO)_4]^-$ with carbon tetrachloride[178]. Many metal carbonyls are oxidized by carbon tetrahalides and spectroscopic measurements obtained in such solutions are often irreproducible[179]. For example, solutions of tungsten hexacarbonyl in carbon tetrachloride yield phosgene by a process which apparently involves reversible reaction between $W(CO)_6$ and O_2, rather than the primary intermediacy of $W(CO)_5$ [180]. In contrast, under suitable conditions molybdenum hexacarbonyl is oxidized by certain halogen compounds, e.g. CCl_4 with production of free radicals such as $\dot{C}Cl_3$ which are capable of initiating the polymerization of vinyl monomers[181]. The initial step in the thermal reaction between $Mo(CO)_6$ and CCl_4 in a donor solvent such as ethyl acetate is ligand exchange leading to $Mo(CO)_5EtOAc$; the latter is then oxidized by the halide to a derivative of Mo^I with formation of $\dot{C}Cl_3$ radicals. Secondary, relatively slow oxidation of the Mo^I species produces a derivative of Mo^V [182]. With carbon tetrabromide the oxidation of

$$Mo(CO)_6 + EtOAc \longrightarrow Mo(CO)_5EtOAc + CO$$

$$Mo(CO)_5EtOAc + CCl_4 \longrightarrow Mo^I + \dot{C}Cl_3$$

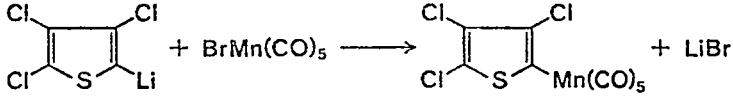
$Mo(CO)_6$ in ethyl acetate at 80° proceeds rapidly by a chain process which is inhibited by olefinic species[183].

The first pentachlorophenyl transition metal compounds to be prepared were derivatives of iron, cobalt and nickel[184,185]. More recently a wide

$$(PhEt_2P)_2CoCl_2 + 2\,C_6Cl_5MgCl \longrightarrow (PhEt_2P)_2Co(C_6Cl_5)_2 + 2\,MgCl_2$$

range of nickel derivatives and some palladium compounds have been reported[186–188]. Compared to phenyl–metal compounds, the pentachlorophenyl derivatives exhibit enhanced thermal and oxidative stabilities attributed to the steric and electronic properties of the C_6Cl_5 group. Chatt and Shaw suggested that the electronegative chlorine atoms make an important contribution to stability by withdrawing electrons from the metal atom into the aromatic system, so increasing metal–carbon π-bonding[184]. At the same time the energy gap between the highest occupied bonding orbital and the lowest unoccupied orbital of the metal–carbon bond will increase with the result that the M—C bond will have greater stability with respect to homolytic dissociation. It has been found, however, that the Ni—Aryl bond lengths in $(\pi\text{-}C_5H_5)Ph_3PNiAryl$ [1·919 ± 0·013 Å (Aryl = C_6H_5); 1·914 ± 0·014 Å (Aryl = C_6H_5)] are indistinguishable within experimental error, indicating that although the Ni—C bond order is greater than unity, π-bonding is not more important for the C_6F_5 derivative[189–191]. It is noteworthy, therefore, that a single crystal X-ray diffraction study of *trans*-$(PPh_2Me)_2Ni(C_6F_5)(C_6Cl_5)$ shows the Ni—C_6Cl_5 distance (1·905 ± 0·010 Å) to be significantly shorter than the Ni—C_6F_5 distance (1·978 ± 0·009 Å)[192]. It is unlikely that the differences in Ni—C_6Cl_5 and Ni—C_6F_5 bond lengths are steric in origin, but possible reasons for the shorter and therefore stronger Ni—C_6Cl_5 bond include (i) the *trans*-effect of a C_6Cl_5 ligand being greater than that of a C_6F_5 ligand, (ii) the Ni—C_6Cl_5 σ bond being stronger than the Ni—C_6F_5 σ bond, or (iii) increased $d\pi$–$p\pi$ metal → ligand back-donation for the Ni—C_6Cl_5 bond relative to the Ni—C_6F_5 bond.

Some trichloro-2-thienyl derivatives of nickel, iron and manganese have been prepared from 2-lithiotrichlorothiophene[129]. Like the pentachlorophenyl compounds, the trichloro-2-thienyl–metal complexes show greater stability towards heat and aerial oxidation than their hydrocarbon analogues.



There has been considerable interest recently in the use of organocopper compounds in organic synthesis. Gilman and coworkers have prepared pentachlorophenylcopper (35) from C_6Cl_5Li or C_6Cl_5MgCl and copper(I) iodide, or from lithium dimethylcopper and hexachlorobenzene[193–196]. (2,3,5,6-Tetrachloro-4-pyridyl)copper, trichloro-2-thienylcopper and 3,4-dichloro-2,5-dicopper thiophene have also been reported[197]. Like pentafluorophenylcopper[197–200], 35 is thermally more stable than phenylcopper[201],

which is highly reactive and difficult to handle. The low reactivity of **35** is indicated by the lack of reaction with chlorosilanes, but with acid chlorides pentachlorophenyl ketones are formed exothermically.

$$C_6Cl_5Cu + CH_3COBr \longrightarrow C_6Cl_5COCH_3 + CuBr$$

(35)

$$2\ C_6Cl_5Cu + (COCl)_2 \longrightarrow C_6Cl_5COCOC_6Cl_5 + 2\ CuCl$$

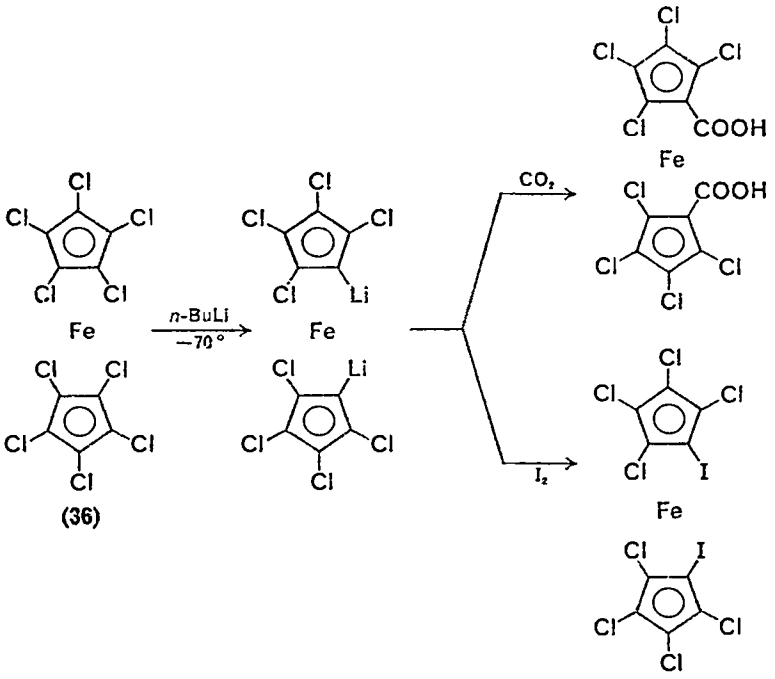
(35)

2. π-Bonded derivatives

The reactions of perhaloolefins with zero-valent complexes of nickel[202,203], palladium[204] and platinum[175,205] have been studied, but π-perhaloolefin complexes have been isolated only for platinum. Both nickel and palladium form trihalovinyl–metal halides, possibly via isomerization of an intermediate tetrahaloolefin π-complex.

π-Complexes of platinum with tetrachloroethylene can be prepared by treating the olefin with $(Ph_3P)_4Pt$ in benzene at 105°[175] or with *cis*-$PtCl_2(PPh_3)_2$ and hydrazine hydrate under mild conditions[205]. In polar solvents the olefin complex $Pt(CCl_2{=}CCl_2)(PPh_3)_2$ isomerizes to give $PtCl(CCl{=}CCl_2)(PPh_3)_2$[206]. Kinetic studies of this rearrangement in hydroxylic solvents indicate that the rate-determining step is close to the S_N1 (lim.) solvolysis of the tetrachloroethylene ligand which involves an ionic intermediate $[Pt(CCl{=}CCl_2)(PPh_3)_2]^+$[207]. $Pt(CF_2{=}CFCl)(PPh_3)_2$ has been observed to undergo a similar rearrangement to give *trans*-$PtCl(CF{=}CF_2)(PPh_3)_2$ on heating[208]. Apart from the ease of isomerization, $Pt(CCl_2{=}CCl_2)(PPh_3)_2$ was found to be more stable than other $Pt(olefin)(PPh_3)_2$ complexes and, for example, tetrachloroethylene readily displaces either stilbene or diphenylacetylene from their complexes with platinum[175].

Perhalometallocenes are expected to have considerable theoretical as well as practical importance. Perchloroferrocene (**36**), the first example of such compounds, has been prepared from 1,1′-dichloroferrocene by a sequence of reactions involving metalation with *n*-butyl-lithium followed by exchange chlorination with hexachloroethane[209]. Unlike any other metallocene, **36** is unaffected by heating with concentrated nitric acid. It undergoes metal–halogen exchange with *n*-butyl-lithium at low temperatures to give a dilithio derivative which can be carbonated or iodinated. The ^{35}Cl n.q.r. spectrum of perchlororuthenocene $Ru(C_5Cl_5)_2$ shows the expected three-line pattern of intensity 2 : 2 : 1, but the frequencies are shifted >3 MHz upfield from those of $C_5Cl_5^-$, close to those of C_6Cl_6[40].



The raising of the frequency of $Ru(C_5Cl_5)_2$ is probably caused by repulsion of the p_z lone pairs on chlorine by the adjacent chlorine on the other ring or by filled metal orbitals. The X-ray crystal structure shows that the chlorine atoms are bent away from the metal, as expected for this repulsion, and the molecule is eclipsed with nearly perfect D_{5h} symmetry[210].

E. Mercury Derivatives

The preparation of compounds of the type $PhHgCCl_nBr_{3-n}$ ($n = 0$–3) is easily accomplished by the reaction of phenylmercuric chloride with the appropriate haloform in the presence of the *t*-butanol monosolvate of commercial, unsolvated potassium *t*-butoxide[211]. Best results are obtained if the reactants are mixed in a molar ratio 1 : 1·5 : 1·4 in tetrahydrofuran at −25°. The available evidence indicates that this reaction proceeds by

$$PhHgCl + CHX_3 + t\text{-BuOK} \xrightarrow{-25°} PhHgCX_3 + KCl + t\text{-BuOH}$$

(X = Cl, Br)

nucleophilic displacement of halide ion from mercury by the trihalomethyl anion, and not by dihalocarbene insertion into the mercury–halogen bond[212], since only $PhHgCCl_3$ was obtained from phenylmercuric

bromide and chloroform in the presence of potassium *t*-butoxide[213]. Other preparations of trihalomethylmercury compounds include photochemical reactions[214,215], the use of trichloromethyl-lithium[216], and

$$CCl_3Br + Hg \xrightarrow{u.v.} CCl_3HgBr$$

$$2\,CCl_3Li + HgCl_2 \longrightarrow (CCl_3)_2Hg + 2\,LiCl$$

$$2\,CX_3COONa + HgY_2 \longrightarrow (CX_3)_2Hg + 2\,CO_2 + 2\,NaY$$

$$(X = Cl, Br;\ Y = Cl, OAc)$$

decarboxylations[217-219]. Phenyl(trihalomethyl)mercury compounds are excellent diahalocarbene transfer agents (see section VI. A).

A number of different procedures have been used in the synthesis of pentachlorophenylmercury compounds. These include the use of C_6Cl_5MgCl [220] or C_6Cl_5Li [121] reagents, mercuration of pentachlorobenzene[221], and decarboxylation of mercury salts of pentachlorobenzoic acid[222]. The latter route is particularly useful for the synthesis of mixed aryl pentachlorophenylmercury compounds. Bis(pentachlorophenyl)-cadmium has been prepared by decarboxylation of $Cd(OOCC_6Cl_5)_2$ [223].

$$C_6Cl_5CO_2HgPh \longrightarrow C_6Cl_5HgPh + CO_2$$

Pentachlorophenylmercury compounds are characterized by their high melting points, thermal stability and low solubility. An electronegative group attached to mercury increases the acceptor properties of the metal and complexes between $(C_6F_5)_2Hg$ [224] or $(C_5F_4N)_2Hg$ [225] and, for example, 2,2′-bipyridyl can be isolated. Acceptor complexes of this type are not formed by $(C_6Cl_5)_2Hg$ [226] or $(C_5Cl_4N)_2Hg$ [126]. The lack of complex formation is probably not due to differences in electronegativity, since C_6Cl_5 and C_6F_5 exert a similar inductive electron-withdrawing effect[21].

A few comparisons have been made between the reactivity of pentachlorophenylmercury derivatives and other organomercury compounds. The ease of cleavage of groups from mercury by hydrogen

$$C_6Cl_5HgC_6F_5 + HCl \longrightarrow C_6Cl_5HgCl + C_6F_5H$$

chloride follows the order $C_6H_5 > C_6F_5 > C_6Cl_5 > CH_3$ [220,225,227]. In contrast to its pentafluorophenyl analogue, bis(pentachlorophenyl)mercury is not rapidly cleaved by iodide in ethanol[228], although this reagent, and other halides, cause pentachlorophenylmercuric chloride to disproportionate[229].

$$2\,C_6Cl_5HgCl + 4\,X^- \longrightarrow (C_6Cl_5)_2Hg + HgX_2^{2-} + 2\,Cl^-$$

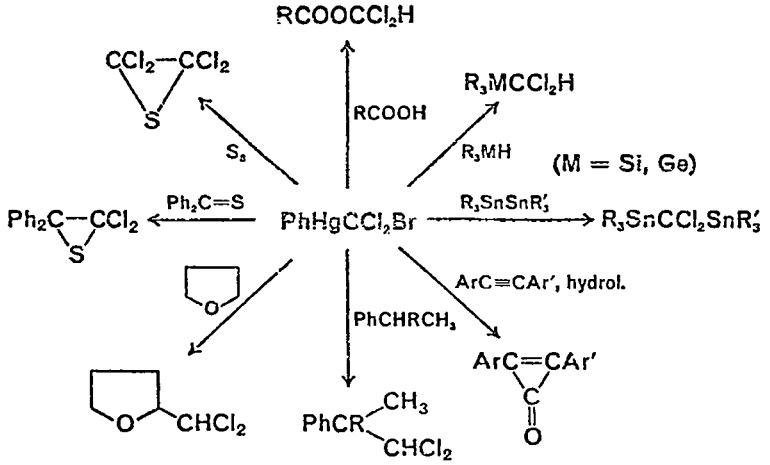
$$(X = Cl, Br, I)$$

On the other hand, pentachlorophenylmercuric bromide is cleaved to pentachloroiodobenzene by iodine in dimethylformamide or by tri-iodide ion in various solvents[230]. The reaction with iodine follows first-order kinetics and that with tri-iodide follows second-order kinetics. The suggested mechanisms involve nucleophilic catalysis by the solvent and by tri-iodide, respectively.

VI. DIHALOCARBENES, TETRAHALOBENZYNES AND PERHALOHETARYNES

A. Trihalomethylmercury Compounds as Dihalocarbene Precursors

The early development of dihalocarbene chemistry has been documented in two books[231,232]. Much of the recent work has been focused on investigations of the extremely versatile dihalocarbene transfer reagents, $PhHgCX_3$ (X = F, Cl or Br), by Seyferth and coworkers. One aspect of this work which has been reviewed by Seyferth is the preparation of *gem*-dihalocyclopropanes[3]. Some indication of the wide scope of dichlorocarbene transfer reactions of $PhHgCCl_2Br$ is given in Scheme 2. They

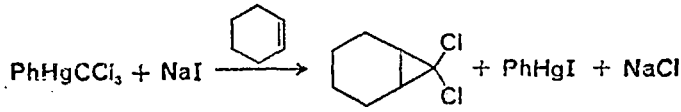


SCHEME 2. Dichlorocarbene transfer reactions of $PhHgCCl_2Br$.

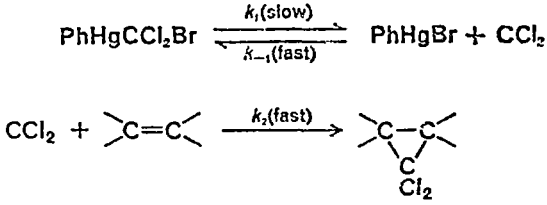
include addition to diarylacetylenes[233,234], to the C=N[235], C=S[236], and C=O[237,238] bonds; insertions into the C—H bond[239–242], the Si—H bond[243–245], the Ge—H bond[244], and Sn—Sn[246], Si—Hg and Ge—Hg bonds[247], the Sn—X bond[248], and B—C bond[249], and into HCl[250]. Dichlorocarbene insertions (via $PhHgCCl_2Br$) into Si—C and Ge—C

bonds of silacyclobutane[251], 1,3-disilacyclobutane[252] and germacyclobutane[252] ring systems with consequent ring enlargement have also been observed. Miscellaneous reactions include those with diazoalkanes ($R_2CN_2 \rightarrow R_2C{=}CX_2$)[253], the one-pot Wittig reaction with triphenylphosphine and carbonyl compounds[254], and deoxygenation of pyridine *N*-oxide[255].

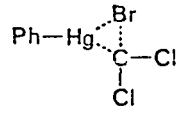
Dihalocarbenes are generated from phenyl(trihalomethyl)mercury compounds either by thermolysis (e.g. at 80° in benzene for $PhHgCCl_2Br$) or, particularly for the more stable compounds such as $PhHgCCl_3$ and $PhHgCCl_2F$, by the sodium iodide procedure[170, 256]. It is generally agreed



that the Doering–Hoffman procedure[257] for transfer of CX_2 to olefins involves free dihalocarbene as an intermediate[231, 232, 258, 259]. However, not all thermal reactions of $PhHgCCl_2Br$ proceed by a free carbene mechanism. For $PhHgCCl_2Br$–olefin reactions, kinetic studies support a mechanism involving free CCl_2[260–262]. Since the reaction rates are insensitive to electronic factors for $ArHgCCl_2Br$ compounds (Ar = *p*-XC_6H_4;



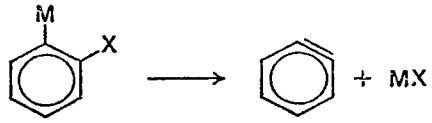
X = H, Cl, F, Me, MeO) a concerted CCl_2 extrusion process via a cyclic transition state is envisaged and explains the preference for PhHgBr elimination over PhHgCl[263]. A free CCl_2 intermediate is also involved in



the reaction of $PhHgCCl_2Br$ with organosilicon hydrides[243], but reactions of $PhHgCX_3$ compounds with substrates containing atoms with lone pair electrons, e.g. N, P, probably occur via initial attack by nitrogen or phosphorus at mercury[254, 264].

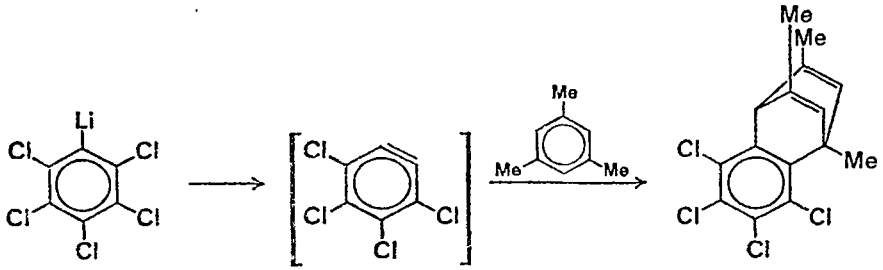
B. Tetrahalobenzynes

A classical route to arynes involves the elimination of metal halide from *o*-haloaryl derivatives of metals[265]. Pentahalophenyl-lithium and

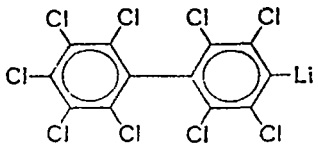


(X = halogen)

-magnesium reagents are thus potential precursors of tetrahalobenzynes. Heaney and coworkers demonstrated that tetrachlorobenzyne can be conveniently generated by heating pentachlorophenyl-lithium[266]; like tetrafluorobenzyne[267], tetrachlorobenzyne is an extremely reactive dienophile and can be trapped by aromatic hydrocarbons, e.g. mesitylene[266], or with furan[268]. Tetrachlorobenzyne can also be generated from the Grignard



reagent, C_6Cl_5MgCl, or by the aprotic diazotization of tetrachloroanthranilic acid[266]. In contrast to pentachlorophenyl-lithium, C_6Cl_5MgCl is stable in refluxing benzene but gives tetrachlorobenzyne adducts when heated with mesitylene or *p*-xylene at reflux. Tetrabromobenzyne, generated from pentabromophenyl-lithium, gave low yields of the expected adducts with aromatic hydrocarbons and with furan[122]. The lithium reagents **37** and **38** derived from decachlorobiphenyl yield mono- and di-arynes which have been trapped with 1,2,4,5-tetramethylbenzene[64].



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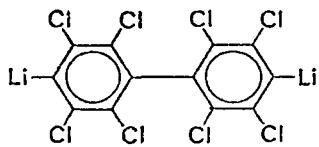

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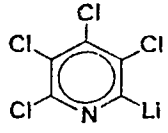
C. Perhalohetarynes

The position of metal–halogen exchange between *n*-butyl-lithium and pentachloropyridine is solvent-dependent and either of the lithium reagents (**39**) or (**40**) may result[125,126]. Thus, in principle, either trichloro-



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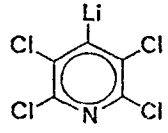

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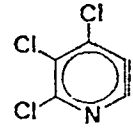

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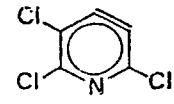
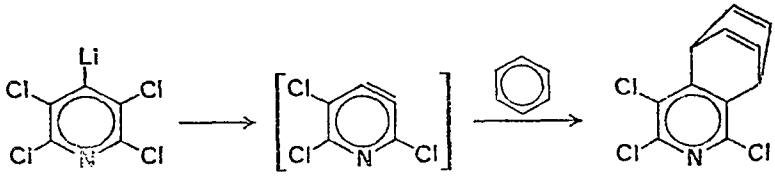


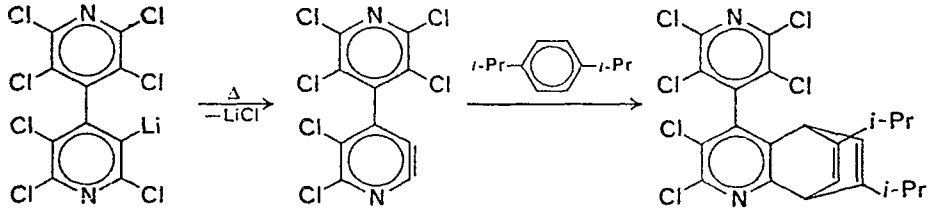
(42)

2-pyridyne (**41**) or trichloro-3-pyridyne (**42**) could be generated by elimination of lithium chloride from the lithium reagents **39** and **40**, respectively. It has been possible to trap **42**, generated in this way, with aromatic hydrocarbons[269], but attempts to generate **41** were unsuccessful.



Tribromo-3-pyridyne, generated from tetrabromo-4-pyridyl-magnesium bromide, gave the expected adducts with aromatic hydrocarbons in better yields than when the corresponding lithium reagent was used, probably due to the higher reaction temperatures necessary for decomposition of the Grignard reagent[122].

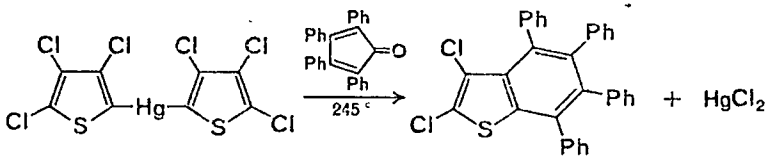
Pyrolysis of 3-lithioheptachloro-4,4′-bipyridyl[270] (**43**) and other 4-substituted trichloro-3-pyridyl–lithium compounds[271], provides a source of the elusive 2-pyridynes.



(43)

Attempts to generate dichloro-2-thiophyne from trichloro-2-thienyl-lithium have been unsuccessful, but heating bis(trichloro-2-thienyl)-mercury with tetraphenylcyclopentadienone gave the expected adduct of

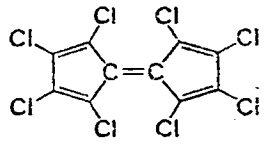
dichloro-2-thiophyne[129]. The formation of the adduct does not, however, necessarily imply the intermediacy of the hetaryne, since it could be formed by addition–elimination sequences[265].



VII. STRUCTURAL AND SPECTROSCOPIC STUDIES

A. X-ray Studies

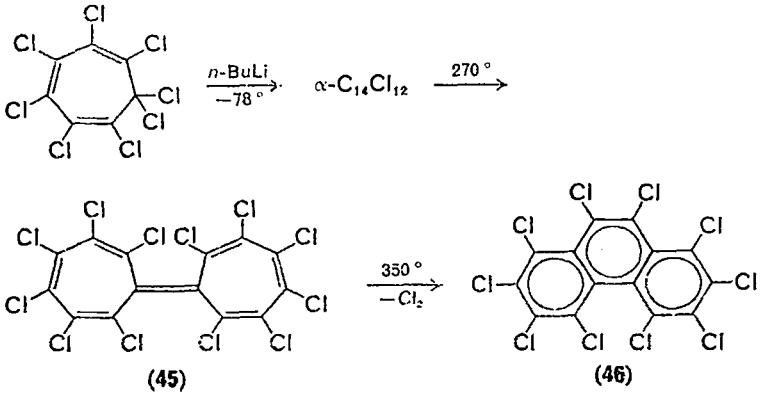
A number of X-ray diffraction studies have been reported which establish unambiguously the structure of certain perchlorocarbons. The large size of chlorine, relative to hydrogen, often results in molecular distortion due to Cl—Cl repulsions, although in a number of examples the intramolecular Cl—Cl distances are considerably shorter than the sum of two chlorine van der Waal's radii (3·60 Å)[272–275]. An X-ray study of the deep-violet octachloropentafulvalene (44)[276] shows that the central C=C bond adopts a length of 1·49 Å which is considerably longer than



(44)

a double bond. The two halves of the molecule are twisted through an angle of 41°, thus limiting conjugation. In contrast to hexachlorobenzene, which possesses a centre of symmetry implying that the chlorine atoms lie alternately above and below the plane of carbon atoms[277], the two chlorine atoms on one side of the ring in **44** both lie below the plane of carbon atoms and the two chlorine atoms on the other side lie above this plane.

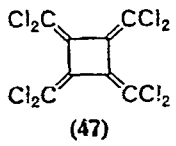
Perchloroheptafulvalene (**45**), prepared from octachlorocycloheptatriene[278], has a 14π-electron system and has therefore sometimes been classed as aromatic, although theoretical studies suggest that it should contain localized single and double bonds[279]. The structure of **45** is decidedly non-planar with strongly alternating bond lengths which correspond well with those expected for *localized* double bonds and



(45) (46)

sp^2–sp^2 single bonds[278]. The bond alternation is more marked than in the parent hydrocarbon[280]. On heating to 350°, **45** loses chlorine to give the known decachlorophenanthrene (**46**) in high yield[281].

The structure of perchloro[4]radialene (**47**), prepared by thermal dimerization of perchlorobutatriene[282], is expected to be non-planar because of steric repulsions between the chlorine atoms (Cl··· Cl contacts would be 2·69 Å in a planar molecule). The molecule is indeed found to



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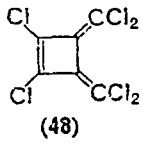

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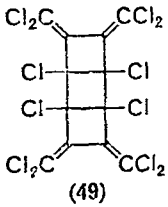

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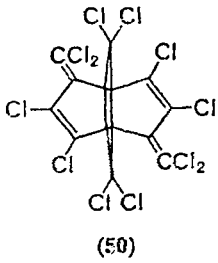


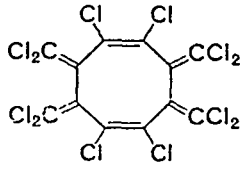
(50)

be highly non-planar and conforms very closely to molecular D_{2d} symmetry[272]. Deformation of the molecule from a planar geometry is achieved largely by bending of the four-membered ring to a dihedral angle of 153·5°. As a result the intramolecular Cl ··· Cl contacts are increased to values > 3·30 Å. The C—C distances in the ring are normal for single bonds between sp^2 carbons, and the exocyclic C=C distances compare closely to the values found for tetrachloroethylene[283]. The bond distances, therefore, give no evidence for conjugation in **47**, although a simple Hückel calculation predicts an appreciable amount of conjugation in *planar* tetramethylenecyclobutane[284].

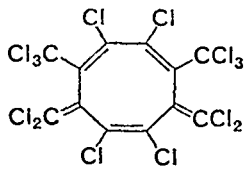
The pyrolytic reaction of perchloro-(3,4-dimethylenecyclobutene) (**48**) gives at least four isomeric compounds of formula $C_{12}Cl_{12}$[285]. The

structures of two of these isomers have been established as perchloro-(3,4,7,8-tetramethylenetricyclo[4.2.0.0]octane) (**49**)[273] and perchloro-(4,8-dimethylenetricyclo[3.3.2.0]deca-2,6-diene (**50**)[274]. The three four-membered rings in **49** adopt an unexpectedly simple chair-like configuration and, in spite of the relatively small intramolecular Cl ··· Cl contacts, the two dichloromethylene groups in the same conjugated system are nearly coplanar. As a result the molecule has approximate C_{2h} symmetry. Two of the C—C distances of the central four-membered ring are somewhat longer than the normal single-bond distance, but this is also found in octachlorocyclobutane[286].

The third of the $C_{12}Cl_{12}$ isomers derived from the thermal decomposition of **48** is thought to be perchloro-(3,4,7,8-tetramethylenecycloocta-1,5-diene) (**51**) since an X-ray analysis of the dichloride of **51** reveals it to have the structure **52**[275]. The cyclooctatriene (**52**) has a symmetry of C_2 with the ring



(51)



(52)

in a somewhat distorted tub form compared to that of cyclooctatetraene. The fourth isomer (**53**) is thought to have the same two-dimensional structure as **51** but a different conformation. The X-ray analysis of the two $C_{12}Cl_{12}$ isomers **49** and **50** and of the dichloride **52** has made possible an explanation of the isomerization reactions of the pyrolysis products of **48**.

$$(48) \xrightarrow{160^\circ} (49) \xrightarrow{200^\circ} (51) + (53) \xrightarrow{250^\circ} (50)$$

Several complexes of tetrahalomethanes with aromatic and heterocyclic molecules have been reported[287–291], and a crystalline complex of carbon tetrabromide with 1,4-diazabicyclo-[2.2.2]octane has been isolated[292]. The crystal structure of the *p*-xylene carbon tetrabromide compound has been determined[293], and the most interesting feature of the structure is the packing arrangement of the molecules. Half of the bromine atoms are each directed toward the centre of a benzene ring at a distance of 3·34 Å from that centre (0·2 Å less than the sum of the van der Waal's radii). Each benzene ring has such a bromine atom on each side, giving rise to a zigzag chain of molecules. There is no evidence of bonding from one chain to another. This arrangement suggests interaction of the bromine atoms with

the π-electrons of the ring and it is reasonable to classify this as a charge-transfer complex.

A complete single crystal X-ray analysis shows that perchlorotropone[294], in contrast to tropone[295], is non-planar with a boat-shaped ring. The available data indicate that the C—Cl distances in compounds containing *ortho*-chlorine atoms, e.g. pentachlorophenol[296], tetrachlorophthalic anhydride[297], are close to 1·709 Å, while isolated C—Cl distances (even when *para* to each other) are close to 1·737 Å [298].

B. Nuclear Quadrupole Resonance (n.q.r.) Spectra

All the halogens, except fluorine, have commonly occurring isotopes with a quadrupole moment, so that perhalo-organic compounds are well suited to n.q.r. studies (see section I)[12]. For the ^{35}Cl, ^{37}Cl, ^{79}Br and ^{81}Br nuclei with spin $\frac{3}{2}$, only one transition is observed in the n.q.r. spectrum with frequency $\nu = (e^2Qq/2h)(1+\frac{1}{3}\eta^2)^{\frac{1}{2}}$ where eQ = quadrupole moment of the nucleus, q = field gradient, η = asymmetry parameter.

For even quite large values of η, however, this is almost indistinguishable from e^2Qq and so, for a given nucleus, the n.q.r. frequency is determined by the field gradient at the nucleus produced by the electron distribution in the molecule. In such cases, the asymmetry parameter η can only be determined by observation of the n.q.r. Zeeman effect. If chlorine is attached to an unsaturated carbon atom then the lone pair electrons participate in bonding and give rise to resonance forms of the type:

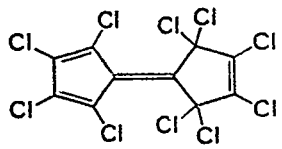
$$C{=}C{-}Cl \longleftrightarrow C^{-}{-}C{=}Cl^{+}$$

which contribute to the ground state of the molecule. The loss of cylindrical symmetry about the C—Cl bond, arising from the partial double-bond character, gives rise to an asymmetry parameter. The extent of carbon–halogen π-bonding can be estimated quantitatively from values of η[299]. N.q.r. spectra must be obtained in the solid state and so multiple lines in the spectrum can arise from chemically equivalent atoms in a molecule occupying non-equivalent positions in the crystal lattice of the solid as well as from chemically non-equivalent atoms in the molecule. For example, the n.q.r. spectrum of carbon tetrachloride shows sixteen separate resonances[300]. In general, however, the frequency difference for lines resulting from non-equivalent lattice positions is small compared to the differences encountered for chemically non-equivalent nuclei in a molecule. ^{35}Cl n.q.r. frequencies are largely determined by electron distribution around the chlorine atom, which is spherically symmetrical for Cl^-. The n.q.r. frequency thus gives a measure of the degree of deviation from spherical symmetry of the electron density around the chlorine atom.

West and coworkers have used n.q.r. spectra extensively to obtain structural information in their studies of perchlorocarbon compounds, e.g. tetrachlorocyclopropene[27], octachlorocycloheptatriene[44], octachlorocyclooctatetraene and other C_8Cl_8 isomers[48], trichlorocyclopropenium ion[301], pentachlorocyclopentadienide ion[40] and perchlororuthenocene[40]. In perchlorinated four-, five-, six- and seven-membered rings the vinyl halogens resonate at lower frequencies than the geminal chlorines, e.g. in hexachlorocyclopentadiene the vinyl halogens are observed at 36·9–37·5 MHz while the geminal chlorines are found at 38·1–39·1 MHz[302]. However, in cyclopropenes the order is in fact reversed and the vinyl halogens resonate at higher frequencies[27], consequently an earlier assignment of the n.q.r. spectrum of tetrachlorocyclopropene was incorrect[301].

A more recent study of hexachlorocyclopentadiene revealed two distinguishable n.q.r. spectra[303], one of which was in agreement with the previously reported spectrum[302]. The spectra clearly arise from two distinct solid phases of C_5Cl_6 and explain its complicated freezing behaviour[304]. In the n.q.r. spectrum of octachloropentafulvalene (**44**) the four chlorine atoms *'ortho'* to the central C=C bond resonate at higher frequencies than the other four chlorine atoms due to strong non-covalent, repulsive interactions which decrease the ionic character of the C—Cl bonds[304a]. This interpretation is in agreement with the X-ray structure of **44** described in section VII. A[276].

N.q.r. spectra played a major role in the elucidation of the structures of the $C_{10}Cl_{10}$ isomers **54** and **55** obtained from the chlorination of **44**[305].



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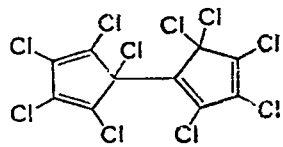
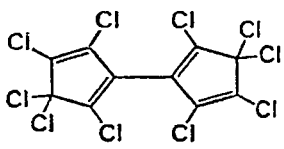


(55)

Three other $C_{10}Cl_{10}$ isomers (**56–58**) are formed from **54** and **55** either under the influence of heat or in the presence of Lewis acid catalysts. Structures were assigned on the basis of n.q.r., ultraviolet and mass spectra[305].



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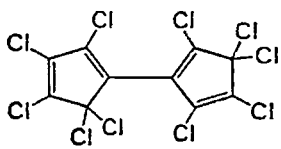

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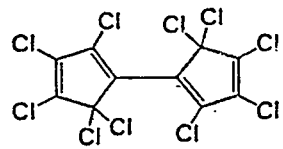
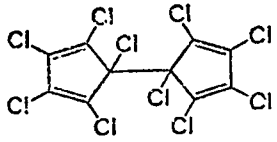


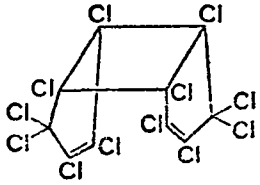
(58)

The thermal isomerization of decachlorobi-2,4-cyclopentadien-1-yl (**59**) also gives a mixture of chlorocarbons of which **56–58** are the major constituents[306]. The chlorination of **59** gives a $C_{10}Cl_{12}$ isomer for which

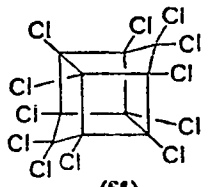


(59)

structure **60** has been proposed, in disagreement with an earlier suggestion[307,308], on the basis of infrared, ^{13}C n.m.r. and ^{35}Cl n.q.r. spectra.

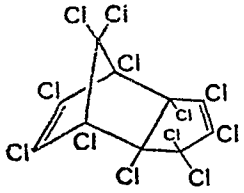


(60)

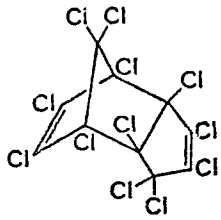


(61)

Under mild conditions **60** is transformed by aluminium chloride to the isomeric cage chlorocarbon (**61**). Two other $C_{10}Cl_{12}$ isomers formed as minor products in the light-catalysed chlorination of **59** are shown to be the *endo* and *exo* isomers of a methanoindene chlorocarbon, **62** and **63**.



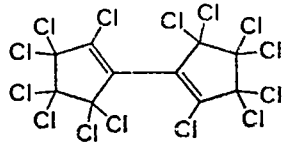
(62) *exo*



(63) *endo*

The light-catalysed chlorination of **56**, **57** and **58** yields a $C_{10}Cl_{14}$ chlorocarbon as the major product, which is assigned structure **64**, on the basis of its ^{13}C n.m.r. spectrum, which shows five peaks of equal intensity, ultraviolet spectrum and chemical behaviour[306] *.

* References 305 and 306 illustrate well the application of ^{35}Cl n.q.r., ^{13}C n.m.r., mass and other spectroscopic techniques to the determination of structures of isomeric perchlorocarbons.



(64)

The ^{81}Br n.q.r. spectrum of the *p*-xylene–CBr_4 complex[309] shows two lines as expected from its known structure (see section VII. A) which reveals only two crystallographically inequivalent bromine atoms in the unit cell[293], and the benzene–CBr_4 spectrum is similar. However, the spectra of the *o*-xylene, mesitylene and 2,4,6-collidine complexes all show three lines[309]. The structural features responsible for the additional line are not known.

C. Mass Spectra

Mass spectrometry is a very useful technique for studying perchloro- or perbromo-carbon compounds since chlorine is composed of two isotopes, ^{35}Cl and ^{37}Cl, whose relative abundance is approximately 3 : 1 and bromine is composed of two isotopes, ^{79}Br and ^{81}Br, which are almost equally abundant. Thus positively charged ions which contain several chlorine and/or bromine atoms give rise to envelopes of peaks with relative intensities characteristic of the number of chlorine and/or bromine atoms in the fragment ion (Table 7).

The fragmentation patterns of a number of perchloroaryl organometallic compounds $(C_6Cl_5)_3P$[310], $Me_3SiC_6Cl_5$[310], *o*- and *p*-$(Me_3Sn)_2C_6Cl_4$[311], C_6Cl_5HgCl[312] and $(C_6Cl_5)_2Hg$[312] have been studied. No metastable ions were observed in the mass spectrum of $(C_6Cl_5)_3P$ but the presence of peaks corresponding to $(C_6Cl_4)_2P^+$, $(C_6Cl_4)_2^+$ and PCl_2^+ indicate elimination of PCl_2 or Cl_2 followed by P. The removal of successive chlorine atoms from the molecular ion is more prevalent than is the corresponding removal of fluorine or hydrogen from $(C_6F_5)_3P$ or $(C_6H_5)_3P$. When only one pentachlorophenyl group is attached to a metalloid atom, as in $Me_3SiC_6Cl_5$, no ions corresponding to $(C_6Cl_4)_2^+$ are found although fragments which indicate halogen abstraction by silicon are observed. Pentachlorophenylmercury chloride yields $C_6Cl_4^+$ as the most intense ion, formed by preferential elimination of $HgCl_2$. Fragmentation by elimination of $HgCl_2$ is

$$C_6Cl_5HgCl^+ \xrightarrow{-HgCl_2} C_6Cl_4^+$$

less important for bis(pentachlorophenyl)mercury[312]. The observation that ions which result from migration of chlorine to tin, e.g. $(CH_3)_2SnCl^+$,

TABLE 7. Relative probabilities of occurrence of peaks at masses M, (M + 2), (M + 4), etc., in the spectra of molecules containing various numbers of atoms of chlorine and bromine where M is the mass corresponding to molecules containing only ^{35}Cl and ^{79}Br atoms

Atoms present	Relative probability of occurrence of peaks at masses								
	M	M+2	M+4	M+6	M+8	M+10	M+11	M+14	M+16
Br	0·5057	0·4943							
Br_2	0·2557	0·4999	0·2443						
Br_3	0·1293	0·3792	0·3707	0·1208					
Br_4	0·0654	0·2557	0·3749	0·2443	0·0597				
Br_5	0·0331	0·1616	0·3160	0·3089	0·1510	0·0295			
Br_6	0·0167	0·0981	0·2397	0·3124	0·2290	0·0895	0·0146		
Br_7	0·0085	0·0579	0·1697	0·2765	0·2702	0·1585	0·0516	0·0072	
Br_8	0·0043	0·0335	0·1144	0·2237	0·2733	0·2137	0·1044	0·0292	0·0036
Cl	0·7540	0·2460							
ClBr	0·3813	0·4971	0·1216						
$ClBr_2$	0·1928	0·4399	0·3072	0·0601					
$ClBr_3$	0·0975	0·3177	0·3728	0·1823	0·0297				
$ClBr_4$	0·0493	0·2089	0·3458	0·2764	0·1051	0·0147			
$ClBr_5$	0·0249	0·1300	0·2780	0·3106	0·1898	0·0594	0·0073		
$ClBr_6$	0·0126	0·0781	0·2049	0·2945	0·2495	0·1239	0·0330	0·0036	
$ClBr_7$	0·0064	0·0457	0·1422	0·2502	0·2718	0·1860	0·0779	0·0181	0·0018
Cl_2	0·5685	0·3710	0·0605						
Cl_2Br	0·2875	0·4686	0·2140	0·0299					
Cl_2Br_2	0·1454	0·3791	0·3398	0·1209	0·0148				
Cl_2Br_3	0·0736	0·2636	0·3592	0·2291	0·0672	0·0073			
Cl_2Br_4	0·0372	0·1696	0·3120	0·2934	0·1473	0·0369	0·0036		
Cl_2Br_5	0·0188	0·1042	0·2416	0·3026	0·2195	0·0915	0·0201	0·0018	
Cl_2Br_6	0·0095	0·0620	0·1737	0·2724	0·2606	0·1548	0·0554	0·0108	0·0009
Cl_3	0·4287	0·4196	0·1369	0·0149					
Cl_3Br	0·2168	0·4241	0·2766	0·0752	0·0074				
Cl_3Br_2	0·1096	0·3216	0·3495	0·1748	0·0409	0·0036			
Cl_3Br_3	0·0554	0·2168	0·3357	0·2611	0·1071	0·0221	0·0018		
Cl_3Br_4	0·0280	0·1370	0·2769	0·2980	0·1832	0·0641	0·0118	0·0009	
Cl_3Br_5	0·0142	0·0832	0·2078	0·2876	0·2400	0·1230	0·0376	0·0063	0·0004
Cl_4	0·3232	0·4218	0·2064	0·0449	0·0037				
Cl_4Br	0·1634	0·3731	0·3129	0·1247	0·0240	0·0018			
Cl_4Br_2	0·0827	0·2694	0·3426	0·2177	0·0738	0·0128	0·0009		
Cl_4Br_3	0·0418	0·1771	0·3065	0·2795	0·1450	0·0430	0·0068	0·0004	
Cl_4Br_4	0·0211	0·1102	0·2425	0·2928	0·2115	0·0934	0·0247	0·0036	0·0002
Cl_5	0·2437	0·3976	0·2594	0·0846	0·0138	0·0009			
Cl_5Br	0·1232	0·3215	0·3277	0·1710	0·0488	0·0073	0·0004		
Cl_5Br_2	0·0623	0·2235	0·3246	0·2485	0·1092	0·0278	0·0038	0·0002	
Cl_5Br_3	0·0315	0·1438	0·2746	0·2861	0·1780	0·0681	0·0157	0·0020	0·0001
Cl_6	0·1838	0·3597	0·2934	0·1276	0·0312	0·0041	0·0002		
Cl_6Br	0·0929	0·2727	0·3262	0·2096	0·0789	0·0175	0·0021	0·0001	
Cl_6Br_2	0·0470	0·1839	0·2998	0·2672	0·1435	0·0478	0·0097	0·0011	0·0001
Cl_7	0·1386	0·3164	0·3097	0·1684	0·0549	0·0108	0·0012	0·0001	
Cl_7Br	0·0701	0·2285	0·3130	0·2383	0·1110	0·0326	0·0059	0·0006	
Cl_8	0·1045	0·2727	0·3114	0·2032	0·0829	0·0216	0·0035	0·0003	

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$CH_3SnCl_2^+$ and $SnCl^+$, are more abundant in the mass spectra of perchloroaryl–tin compounds than the corresponding fluorine-containing ions in the mass spectra of perfluoroaryl–tin compounds is indicative of the weakness of C—Cl bonds relative to C—F bonds[311].

Mass spectra have been particularly useful in identifying the chlorocarbon products formed in the reactions of carbon vapour with covalent chlorides. The following compounds, formed in very low yields, were identified solely on the basis of their mass spectra, $CCl_2{=}CClGeCl_3$, $CCl_2(PCl_2)_2$ and $CCl_2{=}CClPCl_2$[159].

D. Electron Spin Resonance (e.s.r.) Spectra

The e.s.r. spectra of a number of perchlorinated radicals including perchlorodiphenylmethyl (**26**) and perchlorotriphenylmethyl (**22**)[313], trichloromethyl[314], pentachlorocyclopentadienyl[315], bis(trichloromethyl)-nitroxide[316], and α,α-dichloro-*N*-dichloromethylnitrone[317] have been reported.

In solution, **22** showed only one peak with g = 2·0030, a normal value for trivalent carbon radicals. The linewidth of ~4 MHz was attributed to unresolved ring chlorine splittings. **26** shows a quadruplet due to coupling with the α-chlorine nucleus with hyperfine splitting ~6 MHz. The g value for **26** and related perchlorinated radicals is ~2·0050[103], higher than that for the free electron. Except for band broadening (~5 MHz), there is no evidence of interaction with the aromatic chlorines. Apparently stabilization by resonance plays a minor role in **26** and **22** and related radicals and their inertness to chemical attack at *ring* carbon atoms is probably due to low spin delocalization on them[103].

A ten-line e.s.r. spectrum with intensities appropriate for interaction with three nuclei of spin $\frac{3}{2}$ has been observed in the photolysis of carbon tetrachloride in the presence of di-*t*-butyl peroxide and trialkylsilanes and is attributed to the trichloromethyl radical[314]. The g factor is 2·0091.

The e.s.r. spectrum of the pentachlorocyclopentadienyl radical, prepared by photolysis of hexachlorocyclopentadiene, has been reported[315]. The isotropic g value (g = 2·008 ± 0·001) and the chlorine splittings are consistent with D_{5h} symmetry. Trapping of the radical by matrix techniques indicates that it has a good thermodynamic stability.

The reaction of nitrosyl chloride with sodium trichloromethylsulphinate below 0° provides an improved synthesis of trichloronitrosomethane[318].

$$CCl_3SO_2Na + NOCl \longrightarrow CCl_3NO + SO_2 + NaCl$$

Trichloronitrosomethane prepared in this way exhibits an e.s.r. spectrum consistent with the presence of small amounts of bis(trichloromethyl)

nitroxide[316]. Interaction of the unpaired electron with the ^{14}N nucleus gives rise to a triplet with a splitting larger than that observed for bis(trifluoromethyl) nitroxide[319,320] but smaller than in dialkyl nitroxides[321]. Bis(trichloromethyl) nitroxide is less stable than the fluorinated analogue[319,322], and the e.s.r. signal decays to one-half of its original intensity in 7 h.

α,α-Dichloro-(*N*-trichloromethyl)nitrone (**65**), prepared by the thermal decomposition of liquid trichloronitrosomethane[323], is attacked by chlorine atoms or phenyl radicals and the α,α-dichloro-(*N*-dichloromethyl)-nitrone radical (**66**) is formed[317]. Extensive delocalization of the unpaired

$$Cl^{\bullet} + \underset{(65)}{CCl_3\overset{+}{N}(\bar{O})CCl_2} \longrightarrow \underset{(66)}{{}^{\bullet}CCl_2\overset{+}{N}(\bar{O})=CCl_2} + Cl_2$$

electron in **66** is indicated by the low value of the nitrogen hyperfine coupling compared to the value for bis(trichloromethyl)nitroxide[317].

E. Infrared Spectra

Carbon–halogen stretching frequencies appear as strong characteristic absorptions in the range 900–650 cm^{-1} (C—Cl) and 650–500 cm^{-1} (C—Br). For example, at 810–700 cm^{-1} and at 621–605 cm^{-1} for CCl_3 and CBr_3 derivatives (Sn, Pb, Hg), respectively[1]. In C_6Cl_5–metal compounds ν(C—Cl) is observed at 698–670 cm^{-1} [121,186,222,324]. C—Cl and C—Br bending modes are expected to fall below 250 cm^{-1}, e.g. at 200 cm^{-1} in $C_3Cl_3^+$ [25]. Perhalogen substitution is expected to cause shifts in the characteristic vibrational frequencies of other functional groups in the molecule. For example, in perchlorinated benzene derivatives the C=C skeletal in-plane vibration, normally located around 1500 cm^{-1}, is found at 1350 cm^{-1} [68].

F. Ultraviolet Spectra

Ballester and coworkers have used ultraviolet spectroscopy extensively in their studies of perchlorinated aromatic compounds[66,68,103,325], which show the essential features found in other benzene derivatives except that the B band is shifted bathochromically and its usual fine structure is diminished. In particular compounds having trichloromethyl groups flanked by two *ortho*-chlorine atoms show an abnormally large shift of the B band to higher wavelengths and the fine structure is lost. The effect is especially pronounced for perchloro-*p*-xylene ($\lambda = 365$ nm) and is due to molecular distortion caused by the interaction of the bulky trichloro-methyl group with two *ortho*-chlorine atoms (Table 8)[325]. The large bathochromic shift in the B band observed for $(p\text{-}C_6Cl_4\text{-}SiMe_2OSiMe_2—)_2$ also suggests either deformation of the aromatic nuclei and/or some trans-annular interaction between the two aromatic rings, as has been found for

TABLE 8. Ultraviolet spectra of perchlorinated aromatic compounds[a, b]

Compound	λ_{max} (nm)	$\epsilon \times 10^{-3}$	Reference
C_6Cl_5H	298	0·39	325
	289	0·37	
C_6Cl_6	298	0·23	325
	291	0·25	
$C_6Cl_5SnMe_3$	301	0·39	161
	292	0·37	
$C_6Cl_5SiMe_3$	305	0·66	161
	296	0·55	
$(p\text{-}C_6Cl_4SiMe_2OSiMe_2—)_2$	318	3·07	326
	311	2·60	
$C_6Cl_5PPh_2$	308	4·51	327
$(C_6Cl_5)_2PPh$	312	9·5	327
$(C_6Cl_5)_3P$	317	14·05	327
$C_6Cl_5CH_3$	293	0·17	325
	286	0·21	
$C_6Cl_5CCl_2H$	308	1·12	325
	297	0·98	
$C_6Cl_5CCl_3$	319	1·42	325
$p\text{-}CCl_3C_6Cl_4CCl_3$	365	3·00	325

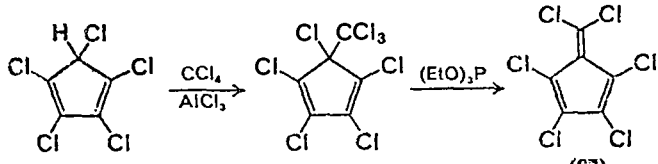
[a] In cyclohexane.
[b] The higher intensity *E* band at 220–240 nm is present in all compounds.

paracyclophanes[328]. The molar absorptivities of the B band for the series $(C_6Cl_5)_nPPh_{3-n}$ ($n = 1, 2, 3$) increase additively, indicating that there is no interaction between pentachlorophenyl groups[327].

G. Dipole Moments

It has recently been emphasized that the possibility of complex formation must be considered when determining dipole moments of chlorocarbon compounds in solution[329]. Octachloropentafulvalene (**44**) in solution has a significant dipole moment 0·40 D (cyclohexane), 0·95 D (benzene), 1·58 D (mesitylene). These values are clearly consistent with the formation of a molecular complex with the solvent. Hexachloropentafulvene (**67**) has a dipole moment of 1·00 D (cyclohexane) significantly higher than that found for the parent hydrocarbon 0·49 D (gas phase)[330] indicating a certain contribution from a dipolar structure to the ground state of **67**. It is noteworthy that the lower reactivity of **67**, for which an improved preparation was reported, compared to hexachlorocyclopentadiene has been attributed to stabilization from the dipolar resonance

form[331]. Atomic polarizations were neglected in the dipole moment determinations, although it has not been established that this is justifiable for chlorocarbons[329].



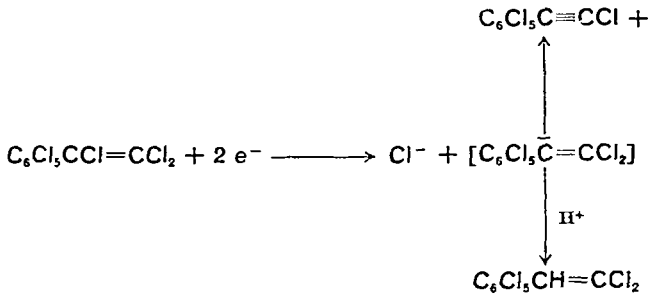
(67)

H. Electrochemical Studies

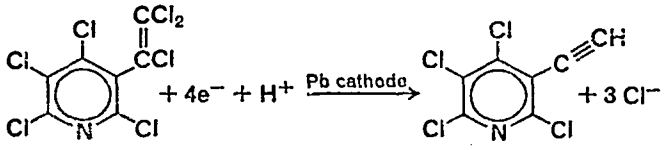
Polarographic studies of carbon tetrahalides in acetonitrile or dimethyl formamide point to the formation of dihalocarbenes as intermediates in the electrochemical reduction[332]. In aqueous ethanol the reduction of hexachlorobutadiene at a dropping mercury electrode takes place in several steps which can be represented by the overall reaction[333]:

$$CCl_2{=}CCl{-}CCl{=}CCl_2 + 8\,e^- + 4\,H^+ \longrightarrow CHCl{=}CH{-}CH{=}CHCl + 4\,Cl^-$$

The polarographic reduction of octachlorocyclopentene and hexachlorocyclopentadiene in neutral or weakly basic solutions proceeds via the pentachlorocyclopentadienide ion (section II. D), which is adsorbed on the mercury surface, thus hindering further reduction[334]. The polarographic method can be used for the quantitative determination of these two perchlorocarbons[334]. Octachlorostyrene is reduced electrochemically at a lead cathode in 1 : 1 methanol : dimethoxyethane containing 5% water to give pentachloroethynylbenzene as the major product together with β,β,2,3,4,5,6-heptachlorostyrene and 2,3,5,6-tetrachloroethynylbenzene[335]. The initial step is probably cleavage of the α-C—Cl bond leading to an anion which, after β-elimination of chloride, gives a chloroacetylene analogous to the primary product proposed in the electrolytic reduction



of hexachlorobutadiene[333]. The reduction of heptachloro-2- and -3-vinylpyridine follows a similar course giving ethynyltetrachloropyridines as the major products[335].



I. Miscellaneous Studies

The first ionization potentials of chloroethylenes, measured by photoelectron spectroscopy[336], decrease with increase in chlorine substitution showing that conjugating effects outweigh the inductive effect. As a consequence of the greater inductive effect of fluorine, the first ionization potential of tetrafluoroethylene is lower than that of tetrachloroethylene. Other recent detailed structural studies of perhaloethylenes include electron diffraction ($CBr_2{=}CBr_2$)[337], ultraviolet spectrum ($CCl_2{=}CCl_2$)[338], and vibrational spectra ($CX_2{=}CX_2$; X = F, Cl, Br, I)[339].

Two groups of workers[340,341] have concluded from X-ray studies that hexachlorobenzene is planar and has normal bond lengths and this was confirmed by an electron diffraction study[342]. On the other hand, Strand[337,343] assigned S_6 symmetry to hexabromobenzene, with alternate bromine atoms lying above and below the plane of the ring, as judged from the Br ··· Br separation of *ortho* substituents. This distance, determined by X-ray studies, is 3·28 Å in hexabromobenzene[344] and 3·26 Å in pentabromotoluene[345], significantly shorter than twice the van der Waal's radius of bromine, 3·9 Å.

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The Chemistry of The Carbon–Halogen Bond
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CHAPTER 15

Electrochemistry of the carbon–halogen bond

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I. INTRODUCTION

The field of organic electrochemistry has experienced a most dramatic growth during the past decade[1–18]. One of the strongest driving forces in this development has been the hope that judicious selection of reaction conditions (e.g. electrode material, electrode potential, solvent, supporting electrolyte) would permit selective oxidation or reduction of functional groupings in organic molecules. These expectations have been met by success in so many cases that by now electrochemical methods of synthesis should be standard tools for the organic chemist. This review will treat the electrochemistry of the carbon–halogen bond, a subject of considerable importance due to the central position occupied by halogen compounds in organic chemistry.

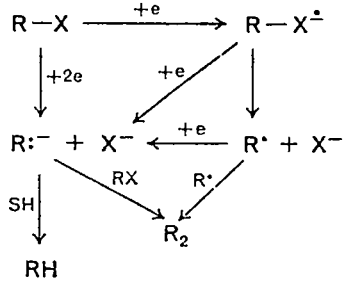
While numerous sources[3, 6, 15–20] have reviewed the literature of polarography of organic halides, the preparative aspects have been neglected to a large extent. Thus a survey of the current literature dealing with the electrochemical reactions of the carbon–halogen bond and their synthetic applications is appropriate at this time. It will be the objective to provide a reasonably complete, critical treatise of reductive and oxidative reactions of the carbon–halogen bond. It will not, however, be our purpose to chronicle the vast literature of organic polarography, a task which has been to a large measure accomplished in the articles referred to above. Polarographic data (of which an excellent compilation[3] is available) will be introduced to the extent necessary to clarify the problem under consideration. Nor shall we deal with the important areas of electrochemical halogenation[1b, 5] and electroreductive coupling[21] involving halogen-containing compounds, except as such coupling may result directly from carbon–halogen bond reduction[22]. Finally, since there are so many textbooks and reviews which treat electrochemical techniques and their application in organic chemistry[2, 3, 9–12], there is no need to include such background material here. A knowledge of the most elementary principles of electrochemistry will be sufficient to follow the treatment in this chapter.

II. GENERAL REACTION TYPES

For the purposes of the present discussion, electrochemical reactions of the carbon–halogen bond will be divided according to whether the electrochemical step is reductive or oxidative in nature. Oxidative reactions of organic halides are limited in example and are as yet largely unexplored. The vast majority of work so far deals with electroreduction of halides and this latter topic will be considered first.

A. Cathodic Reactions

A general formulation of the several possible steps in the electroreduction of a carbon–halogen σ bond is shown in Scheme 1. The many questions that



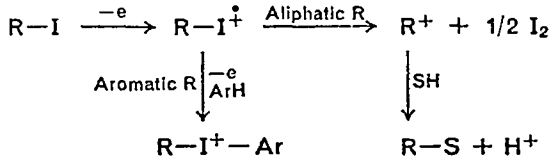
SCHEME 1

can arise regarding the mechanism of this reduction are apparent from an inspection of Scheme 1. The orientation of the carbon–halogen bond relative to the electrode surface, the possibly concerted nature of the first electron transfer and carbon–halogen bond rupture steps, the stereochemical fate of the carbanionic intermediate, and the origin of the coupling product (radical–radical coupling versus S_N2 displacement) are a few such questions. Moreover, the role of the electrode material and its possible participation in the reaction (via adsorption and/or formation of organometallic species), which is not explicitly stated in Scheme 1, is obviously also a very important and complicated problem. Since electrolytic fission of the carbon–halogen bond is an irreversible process and usually requires a strongly negative cathodic potential, systematic examination of many of these questions has been hampered by the difficulty in applying conventional electroanalytical approaches. As a consequence the answer to most of the above questions is obscured by a body of conflicting results. A detailed examination of studies which bear on each of these questions is presented in section III.

B. Anodic Reactions

Oxidation reactions of organic halides in which the halogen atom is involved are almost completely confined to iodo compounds, since the more electronegative halogens either make the appropriate compounds so difficulty oxidizable that they fall outside the accessible range of anodic potentials or cause the reactions of interest to take place in other parts of the molecule (e.g. oxidation of iodobenzene in acetic acid/0·5M sodium acetate largely gives compounds formed by a change of the valence state of

the iodine atom, whereas under identical conditions the other halobenzenes give nuclear acetoxylation products[23]). Oxidation of iodo compounds occurs so as to produce products which appear to arise from carbonium ion intermediates if the substrate is derived from an aliphatic system. In contrast, aromatic iodides couple to produce iodonium salts (Scheme 2). The meagre literature on this topic is considered in detail in section IV.



SCHEME 2

III. CATHODIC REACTIONS

A. Ease of Reduction by Halogen Types

With the exception of a few special cases of mixed halogen compounds in which the halogens are conjugated with each other (section III. B. 1. d), the ease of reduction of carbon–halogen bonds follows the expected order, I > Br > Cl > F. The isolated C—F bond cannot be electrochemically reduced below the solvent cut-off limit. However, when the C—F functionality is adjacent to an aromatic or carbonyl moiety, reduction has been reported to occur (section III. B. 2). Table 1 shows a typical array of reduction potentials for simple halomethanes which illustrates the trend in ease of reduction. Table 2 shows further examples of similar trends in other

TABLE 1. Half-wave potentials ($E_{\frac{1}{2}}$ in volts) for reduction of halomethanes[a, b] versus the saturated calomel electrode (sce)[21]

Compound	$-E_{\frac{1}{2}}$ for X =		
	Cl	Br	I
CH_3X	2·23	1·63	1·63
CH_2X_2	2·33	1·48	1·12
CHX_3	1·67	0·64	0·49
CX_4	0·78	0·3	—

[a] The parent compound, methane, is not reducible under the conditions employed.
[b] In 75% dioxan–water with 0·05M tetraethylammonium bromide as supporting electrolyte.

series of halides. It should be noticed that only the reduction of the C—F bond seems to be dependent on the pH of the solution. Thus, the half-wave potential for reduction of phenacyl fluoride[25] moves to less cathodic values

TABLE 2. Half-wave potentials for reduction of RX (due to the differing reaction conditions, these values are only strictly comparable within each series)

R	$-E_{\frac{1}{2}}$ for X =			
	F	Cl	Br	I
$HOCOCH_2^-$	—	1·64[a]	0·55[b]	0·16[b]
$CH_3COCH_2^-$	—	1·13[c]	0·35[c]	0·14[c]
$PhCOCH_2^-$	1·02[d,e]	0·55[f]	0·20[g]	—
$CH_2{=}CH{-}CH_2^-$	—	2·13[h]	1·29[h]	0·23[h]
$CNCH_2CH_2^-$	—	—	1·7[i]	1·2[i]

[a] Reference 26.
[b] Reference 27.
[c] Reference 28.
[d] Reference 25.
[e] pH-independent value (above pH = 6).
[f] Reference 29.
[g] Reference 30.
[h] Reference 24.
[i] Reference 31.

as the pH decreases, which has been ascribed to assistance by a proton in the rate-determining step (formation of the rather weak acid, hydrogen fluoride).

It is instructive to compare the cathodic reduction of carbon–halogen bonds with the reduction of other types of single bonds. Table 3 shows

TABLE 3. Half-wave potentials for reduction of phenacyl derivatives, $PhCOCH_2X$, to acetophenone (values taken in the pH-independent region, if required)

X	$-E_{\frac{1}{2}}$ versus sce	pK of HX
HO^-[a]	1·41	14
PhO^-[a]	1·22	10
PhS^-[c]	1·22	6·5
CH_3COO^-[a]	1·30	4·8
$PhCOO^-$[a]	1·27	4·4
F^-[b]	1·02	3·2
ONO_2^-[a]	0·46	−1·4
Cl^-[a]	0·55	−7
Br^-[c]	0·20	−8

[a] Reference 29. [b] Reference 25. [c] Reference 30.

E_i data on the reduction of phenacyl derivatives, all of which have been shown to give acetophenone on controlled potential electrolysis (cpe). Figure 1 demonstrates that these half-wave potentials correlate reasonably

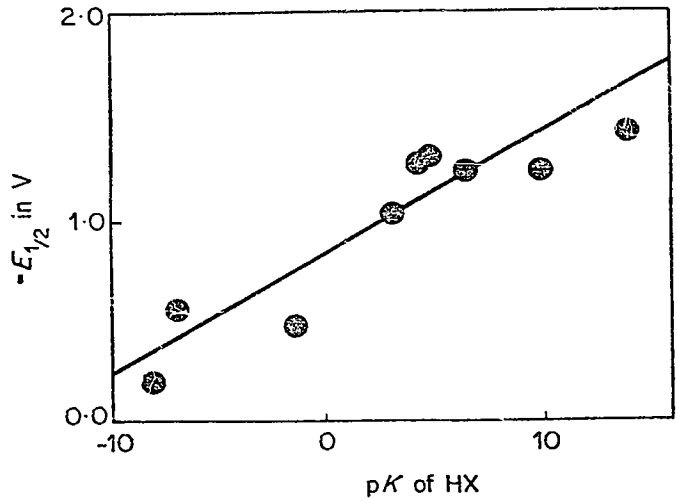


FIGURE 1. Plot $-E_i$ for phenacyl derivatives, $PhCOCH_2X$, versus pK of the corresponding acid, HX (see Table 3).

well with the leaving group tendencies of the X groups, as expressed by the pKs of the corresponding acids HX.

B. Ease of Reduction by Organic Moiety

It is helpful further to subdivide consideration of organic halides according to the nature of the organic fragment, inasmuch as this factor appears to have a large effect on both the ease of reduction and the nature of the products.

1. Monohalides

Most monohalides (except fluorides and often simple alkyl chlorides) can be reduced at a mercury electrode in readily available aprotic solvents such as *N*,*N*-dimethylformamide (DMF)[32] or acetonitrile[33]. Bromides are most often employed as substrates since they are usually chemically stable, easily prepared and reduced at potentials which are less cathodic than for chloro compounds. The products are those of reduction, either a 2e/molecule reduction in which the halogen atom is replaced by a hydrogen atom, or a 1e/molecule reduction in which a coupling product (R—R from

R—X) is formed. The latter product tends to predominate in systems for which the stability of the corresponding radical/carbanion is relatively high due to conjugative stabilization. Occasionally, intermediate radicals can react with the electrode material and form organometallic compounds (section III. 9). In general, the current efficiency of the reduction is moderate to low, particularly with isolated monohalides for which so negative a potential is required that reduction of the solvent and/or supporting electrolyte becomes a significant competing reaction.

a. Compounds with isolated C-Hal bonds. Saturated aliphatic and alicyclic monobromides are reduced in the range of −(2·1–2·5) V versus sce in DMF/0·01 M tetraethylammonium bromide[34–36, 137], as can be seen from the half-wave potentials listed in Table 4. This is a seemingly narrow potential

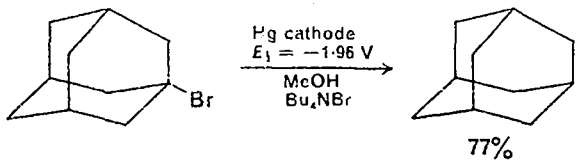
TABLE 4. Half-wave potentials for aliphatic, mono- and bicyclic bromides in DMF/0·01M tetraethylammonium bromide

R in R—Br	$-E_{\frac{1}{2}}$, V versus sce	Reference
Et	2·17	137
Pr	2·22	137
i-Pr	2·27	137
Bu	2·24	137
i-Bu	2·34	137
t-Bu	2·19	137
Pentyl	2·27	137
Neopentyl	2·46	137
Hexyl	2·29	137
Decyl	2·29	137
Cyclopropyl	2·36	35
Cyclobutyl	2·36	35
Cyclopentyl	2·19	35
Cyclohexyl	2·29	35
1-Bicyclo[2.2.2]octyl	2·48	36
1-Adamantyl	2·38	36
endo-Norbornyl	2·43	36
exo-Norbornyl	2·34	36
trans-4-*t*-Butylcyclohexyl	2·45	36
cis-4-*t*-Butylcyclohexyl	2·32	36

range, but it should then be kept in mind that the maximum difference, 0·31 V, between two compounds in the table (ethyl bromide and 1-bromobicyclo[2.2.2]-octane) corresponds to a maximum ratio between two rate constants of roughly 10^{10} (for a 2e-process). It is, of course, not necessary

that this difference entirely reflects ratios between rate constants, but we think it is important to emphasize this point in view of the mechanistic conclusions that have been drawn on the basis of these and similar results (for a further discussion, see section III. B. 6. c).

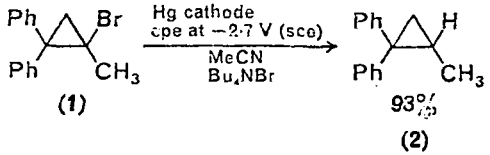
For the few reported cases in which the product(s) of saturated aliphatic or alicyclic halides have been isolated and identified, they appear to be simple reduction products[24,30,37-39]. Horner and Röder[37] report a 77% yield of adamantane from the reduction of 1-bromoadamantane (equation 1) and similarly high yields for the reduction of 1-bromonorcamphor and



(1)

1-bromotriptycene were obtained. Ethane is the principal product of the reduction of ethyl bromide (equation 2)[38]. The substituted cyclopropyl bromide (**1**) cleanly gives the corresponding hydrocarbon (**2**) (equation 3)

$$EtBr \xrightarrow{\text{Pb cathode}} \underset{90\%}{C_2H_6} + \underbrace{C_2H_4 + n\text{-}C_4H_{10}}_{10\%} \qquad (2)$$



(3)

in excellent yield[39]. 1,5-Dibromopentane, in which the two reducible groups are remote from each other, reduces in high yield to pentane (equation 4)[30].

$$Br(CH_2)_5Br \xrightarrow[\substack{\text{DMF}\\ Bu_4NClO_4}]{\substack{\text{Hg cathode}\\ \text{cce at } 0{\cdot}3\text{–}0{\cdot}5 \text{ amp}^*}} CH_3(CH_2)_3CH_3 \qquad (4)$$

b. Conjugated halides. The denotation 'conjugated' is here used in its *formal* sense, i.e. the carbon–halogen bond is said to be conjugated with a double bond; using it in its *theoretical* sense, as is commonly done nowadays, it should be taken to denote halides in which the corresponding radical and carbanion are stabilized by conjugation with an appropriate functional group, e.g. the carbonyl or nitro group.

* Cce is the abbreviation for constant current electrolysis.

The effect of conjugation of the carbon–halogen bond with any other functional group is to render the reduction potential more positive (see Table 2). The same result is encountered when a good leaving group (i.e. another halogen atom) is placed on a β-carbon atom (see section III. B. 3). A most dramatic example of the conjugative effect can be seen in the reduction of ω-bromoacetophenone[30], which undergoes 2e-reduction at $-0{\cdot}05$ V versus the normal calomel electrode (nce) to form acetophenone. Similarly, Elving and Van Atta[28] have observed relatively positive potentials for the series of haloacetones (cf. Table 2). The effect of conjugation with the nitro group is very large, Armand[40,41] reporting that bromonitromethane reduces very easily at $-0{\cdot}05$ V versus sce (equation 5).

$$O_2NCH_2Br \xrightarrow[E_{\frac{1}{2}} = -0{\cdot}05 \text{ V (sce)}]{\text{Hg cathode}} O_2NCH_3 \qquad (5)$$

Chloronitromethane is also reduced very easily at $-0{\cdot}45$ V versus sce. Although these studies were principally polarographic in nature, cpe experiments in several cases showed that halide reduction occurs at a less cathodic potential than nitro group reduction, in spite of the fact that the nitro group is considered to be the most easily reduced among all functional groupings. This is presumably due to the combination of halogen being a much better leaving group than the nitro group and the nitro group a much better conjugative group than halogen, thus rendering splitting of the C—Hal bond the favoured reaction mode (equation 5).

Elving and coworkers have examined extensively the effect of a geminal carboxyl group on the polarographic behaviour of halides[27,42–44], and although their efforts were largely directed towards studying the influence of pH on reduction potential and elucidation of mechanism, it is apparent from their data that for the carboxyl group, even at high pH when the carboxyl group is present completely in the carboxylate anion form, the effect on the first transition state for reduction is a stabilizing one (equation 6)[27]. The stabilizing effect is even more pronounced at lower pH[42], and

$$BrCH_2CO_2^- \xrightarrow[\substack{E_{\frac{1}{2}} = -1{\cdot}31 \text{ V (sce)} \\ \text{pH 10, } H_2O}]{\text{Hg cathode}} CH_3CO_2^- \qquad (6)$$

Czochralska[45] reported the reduction of **3** to occur in good yield at a very positive potential for a carbon–chlorine bond (equation 7). An interesting

$$\underset{\textbf{(3)}}{\overset{\displaystyle CO_2H}{\overset{|}{\underset{|}{PhCCH_3}}\overset{|}{\underset{Cl}{}}}} \xrightarrow[\substack{E_{\frac{1}{2}} = -1{\cdot}05 \text{ V (Ag/AgCl)} \\ 96\% \text{ EtOH} \\ Et_4NCl}]{\text{Hg cathode}} \underset{\textbf{(4)}}{\overset{\displaystyle CO_2H}{\overset{|}{PhCHCH_3}}} \qquad (7)$$

effect was noticed by Smirnov and Markova[46] in the reduction of alkyl chloroacetates, in that the half-wave potential changed to less cathodic values with increasing chain length of the alkyl group, e.g. from $-1{\cdot}55$ to $-1{\cdot}24$ V (versus sce in 50% ethanol–water/KCl) for methyl and nonyl chloroacetate, respectively. This phenomenon is possibly due to an increase in adsorbability of the ester with increasing chain length. Since no such change is observed for *n*-bromoalkanes (Table 4) this interpretation should be treated with reserve until further data have accumulated.

Conjugation of the carbon–halogen bond with carbon–carbon double bonds (Table 2) or arene rings exerts a similar stabilizing effect. Benzyl bromide is reduced at $-1{\cdot}22$ V versus sce[47], about 1·0 V more positive than an isolated carbon–bromine bond (Table 1) (equation 8). The presence of

$$PhCH_2Br \xrightarrow[DMF]{\substack{\text{Hg cathode}\\ E_{\frac{1}{2}} = -1{\cdot}22\text{ V (sce)}}} PhCH_3 \qquad (8)$$

ring substituents in benzylic halides, regardless of their nature and orientation, appears to render reduction more facile[48,49], although significant disagreement on this question is to be found[50,51]. The details of this problem are examined in section II. B. 6. c.

c. Vinyl halides. Vinyl halides are reduced at potentials which are more positive than the reduction potential of the corresponding olefinic hydrocarbon. As a consequence, two polarographic waves are usually observed for the reduction of vinyl halides, and it is often possible to isolate the intermediate olefinic hydrocarbon[52] by cpe around E_1 (equation 9). For

$$\text{>C=C<}\!\!\begin{matrix}\\ X\end{matrix} \xrightarrow[+2e\ -X^-,\ +H^+]{E_1} \text{>C=C<}\!\!\begin{matrix}\\ H\end{matrix} \xrightarrow[+2e\ +2H^+]{E_2} \text{>CH—CH}_2\text{—} \qquad (9)$$

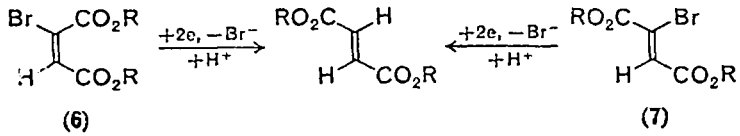
$$|E_2| > |E_1|$$

example, bromotriphenylethylene (**5**) can be reduced at a controlled potential to produce an excellent yield of the corresponding olefinic hydrocarbon[53] (equation 10). There is agreement that reduction of vinyl

$$\underset{\textbf{(5)}}{Ph_2C{=}CPhBr} \xleftarrow[\text{cpe at } -1{\cdot}8\text{V (sce)}]{\text{Hg cathode}} \underset{93\%}{Ph_2C{=}CHPh} \qquad (10)$$

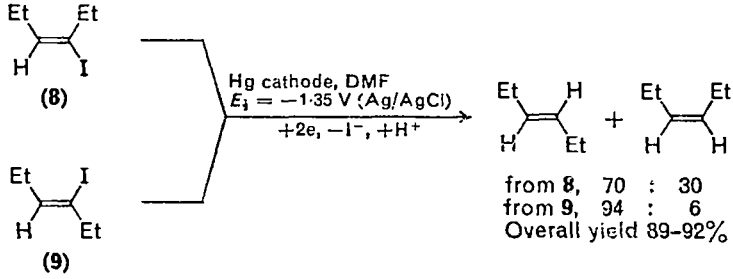
bromides proceeds by initial addition of an electron to the lowest vacant π molecular orbital[53] to produce a radical anion of significant lifetime and that the radical anion is then protonated to form a neutral radical of likewise significant lifetime. The neutral radical is then reduced in a second

1e-transfer to a carbanion which gives the final product in a second protonation step. If the vinyl halide is suitably substituted, equilibration of stereoisomers can in principle take place at any of these intermediate stages. Thus Elving and coworkers[54] found that fumarate ester was produced from the reduction of both isomeric bromo diesters (**6**) and (**7**) (equation 11).



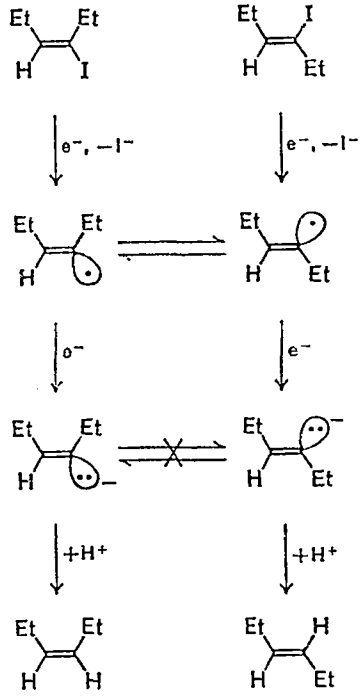
(6) (7) (11)

Fry and Mitnick[55] observed that the major product of the reduction of both *trans*- (**8**) and *cis*-3-iodo-3-hexene (**9**) was *trans*-3-hexene, formed in distinctly higher yields from the *trans*-isomer (**8**) (Scheme 3). They found

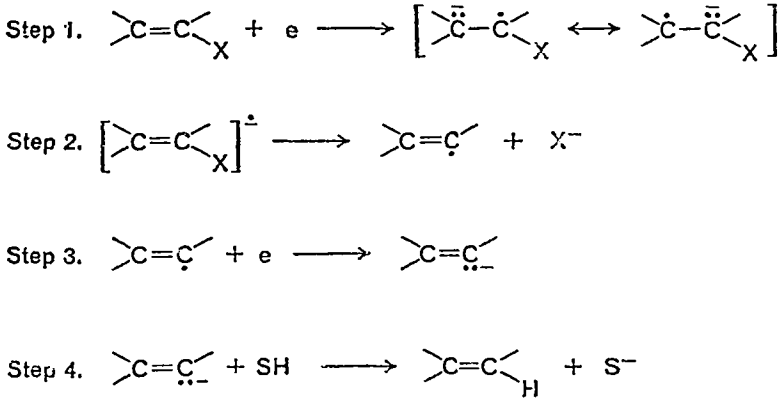


SCHEME 3

that the addition of phenol did not alter the product ratio in either case, as could be expected if phenol served as a good carbanion trapping agent in DMF. As a consequence, these authors proposed that partial equilibration of isomers at the radical stage and none at the carbanion stage was occurring (Scheme 4). This was considered evidence for 1e reduction by the authors. However, subsequent investigation by the same research group[56] has clearly shown that phenol is not always a good proton source for electrochemically generated carbanions, probably because it is not incorporated in the electrode double layer. Consequently the validity of the earlier claim is doubtful. In view of the demonstrated configurational stability of vinyl radicals[57,58] it is doubtful whether a concerted 2e addition, with elimination of halide ion, occurs in these cases. The more plausible sequence is that indicated below: consecutive 1e reductions, with an interspersed chemical step (Scheme 5). Elving and coworkers[54]



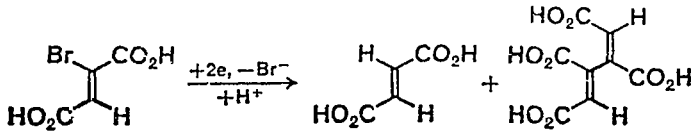
SCHEME 4



SCHEME 5

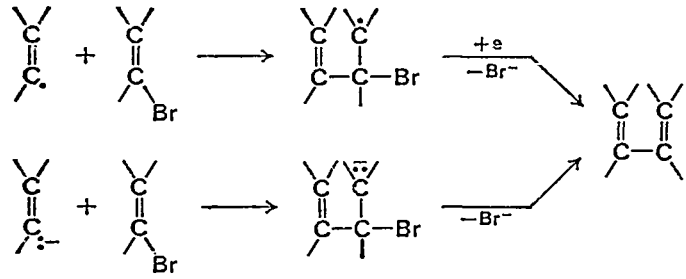
reported the formation of some coupling products, in addition to carbon–halogen reduction product, during the cathodic reaction of bromomaleic acid, but not during the similar reaction of bromofumaric acid. Miller and

Riekena[53] reported dimer formation in that reduction as well (equation 12). Such a dimer could arise by bimolecular reaction of either the radical or the



(12)

anion with unreacted bromoolefin (Scheme 6). A polarographic study[53] of the reduction of a series of substituted bromoethylenes established the



SCHEME 6

stepwise nature of the reduction sequence (i.e. that the bromoolefin is more easily reduced than the corresponding olefin; see Table 5) and the influence

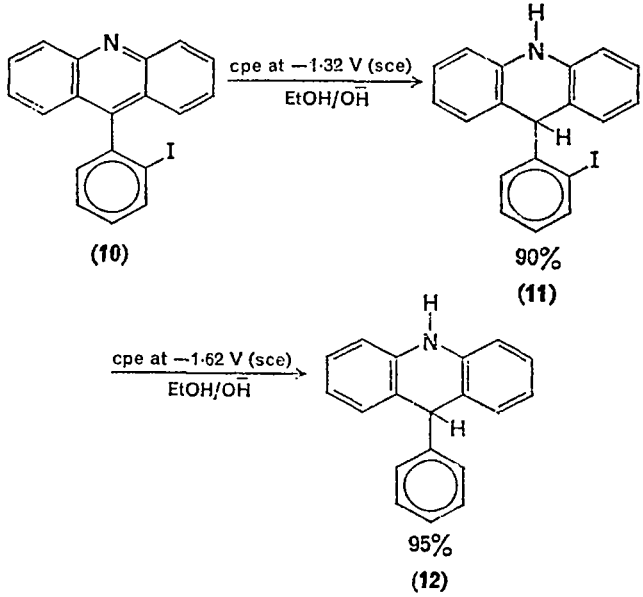
TABLE 5. Half-wave potentials for bromoolefins, $R^1R^2C{=}CR^3Br$ in 75% dioxan–water/Bu_4NI (sce) [53]

R^1	R^2	R^3	$-E_{\frac{1}{2}}$ [a] (1)	$-E_{\frac{1}{2}}$ [b] (2)
Ph	Ph	Ph	1·60	1·99
An[c]	Ph	Ph	1·63	2·04
Ph	Ph	An[c]	1·66	2·09
Ph	Ph	H	1·80	2·08
H	H	Ph	1·86	2·31
Ph	H	H	1·98	2·33
H	H	H	2·46	—
Me	H	H	>2·6	—
$Ph_2C{=}CHPh$			1·97	—
$Ph_2C{=}CHAn$			2·05	—

[a] First two-electron wave.
[b] Second two-electron wave.
[c] *p*-Anisyl.

of the substituents on the ease of reduction. Although an aryl group in any position exerts a stabilizing effect on the intermediate, the effect of an α-aryl group is much more pronounced. Replacement of a phenyl by an anisyl group at either ethylenic carbon exhibits a small but perceptible destabilizing effect. Perhaps this observation speaks for the anionic nature of the transition state for the rate-controlling step. The pronounced stabilizing influence of α- compared to β-phenyl substitution may be taken as evidence for an intermediate radical (cf. Scheme 5, steps 2 and 3).

d. Aryl halides. Aryl halides have been reduced by a number of investigators, aryl iodides being the most studied of this class of halides. Here Lingane and coworkers[59] have reported a now classical example of the utility of the electrochemical method in organic synthesis. Controlled potential reduction of the iodophenylcarbazole **10** gave two two-electron reduction steps, producing first the dihydroaryl iodide **11** and then the halogen-free product **12** (equation 13)[60]. Since the reduction potential of



the two steps differed by several tenths of a volt, it was possible to select a controlled potential such that the first step proceeded completely to the exclusion of the second. It is noteworthy that both products could be isolated in excellent yield—a result that was not possible in this system by purely chemical reduction. Several other successful selective reductions of polyfunctional molecules were recently described by Fry and coworkers[60],

the most notable one being the cathodic reduction of *p*-bromo-γ-chlorobutyrophenone to form γ-chlorobutyrophenone.

An extensive study on the polarographic behaviour of aromatic halides has been published recently[50]. Table 6 shows some of these results, as well

TABLE 6. Half-wave potentials of substituted phenyl halides

Substituent	$-E_{\frac{1}{2}}$ for		
	Ar—I[a, b]	Ar—Br	Ar—Cl
m-NMe_3^+			
p-NMe_3^+	0·91	1·34	
p-CN		1·26	1·36
m-CN		1·29	
p-CF_3	1·01	1·53	
p-COMe	1·04	1·15	
p-COC_6H_5	0·96	1·06	
m-CF_3	1·00	1·52	
m-Br	0·96	1·45	
m-COMe		1·19	
m-Cl	0·98 (1·56)	1·53	
m-I	0·92		
m-F			
p-I	1·91		
p-Br	1·08 (1·61)	1·54	
p-Cl	1·06 (1·61)	1·61	1·85
p-CHO	0·96		1·20
m-OMe	1·19 (1·64)	1·76	
p-F	(0·72, 1·66)[c]		
m-C_6H_5	1·15	1·58	
β-naphthyl	1·16	1·47	
p-NHCOMe	(1·66)	1·88	2·09
H	1·21 (1·68)	1·81	2·13
p-C_6H_5	1·16 (1·68)	1·56	
m-Me	1·22 (1·71)	1·85	2·16
p-Me	1·23 (1·74)	1·84	2·16
m-NMe_2			2·23
p-OEt	(1·75)	1·82	
p-OMe	1·25 (1·75)	1·84	2·15
p-OC_6H_5		1·72	
p-NMe_2	1·35	1·97	
p-NH_2	(1·76)	1·96	

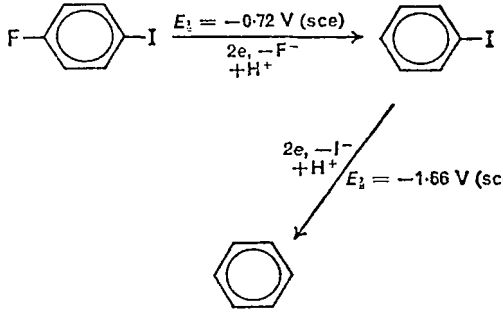
[a] The first set of values[50] refers to the system DMF/0·02M Et_4NBr (versus Ag/AgBr reference electrode).

[b] Values in parantheses[61] were measured in 90% ethanol–H_2O at pH 7 (versus sce).

[c] Two 2e-waves were observed.

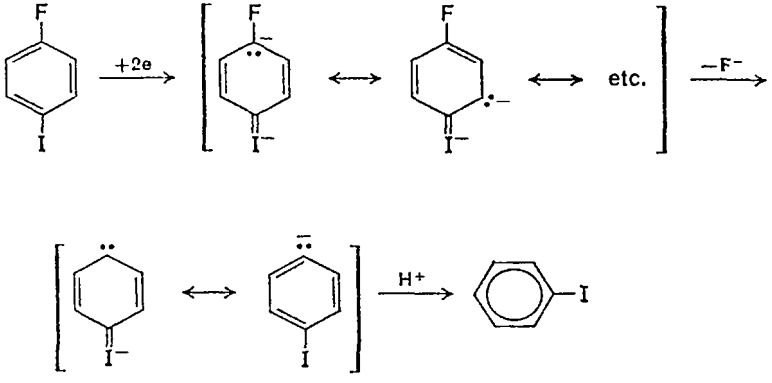
as some earlier results on aryl iodides obtained by Colichman and Liu[61]. Reasonably good correlations between $E_{\frac{1}{2}}$ and σ (or σ^-) values were obtained. As can be seen from Table 6, the variation of $E_{\frac{1}{2}}$ is rather small for a wide range of substituents (σ-values for chloro, bromo and iodo derivatives being $-1{\cdot}15$, $-1{\cdot}66$ and $-2{\cdot}0$, respectively). Nevertheless, the results clearly indicate that the carbon of the carbon–halogen bond is becoming negative as the system moves into the transition state of the potential-determining step. Values for the half-wave potentials for the reduction of iodobenzoic acids[61,63] corroborate this conclusion.

The work of Colichman and Liu[61] provides another interesting insight into the effect of conjugation on reduction potential. Whereas aryl monofluorides fail to be reduced at all in the available potential region, *p*-fluoroiodobenzene reduces at a remarkably anodic potential ($E_{\frac{1}{2}} = -0{\cdot}72$ V) yielding iodo- rather than fluorobenzene as the product (equation 14). At a potential normal for reduction of an aryl–I bond



(14)

(cf. Table 6) a second 2e-reduction occurs. The effect of the *p*-iodo substituent in facilitating the reduction of the C—F bond may be viewed as conjugative (Scheme 7).



SCHEME 7

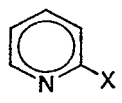
A similar effect has been noted[62,64] during the reduction of highly fluorinated benzoic acids. Thus the *p*-fluorine atom of pentafluorobenzoic acid was reduced to form 2,3,5,6-tetrafluorobenzoic acid at a cathode potential (Hg versus sce) of −1·20 V in 20% sulphuric acid, whereas at more negative potentials 2,3,5,6-tetrafluorobenzyl alcohol and pentafluorobenzyl alcohol were the principal products. Generally, cathodic reduction appears to be very useful for highly fluorinated compounds, as for example in the formation of polyfluorobenzenes from polyfluoro-1,3- and -1,4-cyclohexadienes[65], e.g. hexafluorobenzene from octafluoro-1,3-cyclohexadiene. Other easily reducible fluorides include trifluoromethyl-substituted aromatic compounds[66,67], which in certain cases are reduced in one single 6e-step (see section III. B. 2).

This same conjugative effect can be observed during the reduction of a series of polyiodophthalic acids* and their salts[63]. The first iodine atom is readily removed from the tetraiodo derivative and from the values of $E_{\frac{1}{2}}$ it appears to be removed most easily from position 4 or 5. The second iodine atom may be removed from position 4 in the 3,4,6-triiodo compound. Electroreduction of iodoaromatics in the presence of deuterium oxide has recently been described as an excellent method for the preparation of labelled materials of very high isotopic purity in small quantities[203].

The reduction of a number of nitroaryl halides has been reported[69–71], but in view of the ease of reducibility of the nitro group itself[15], it is difficult to evaluate the results in these cases. Dependence of $E_{\frac{1}{2}}$ on pH has been reported for iodophenols[72] and iodoanilines[73].

Diphenyliodonium salts have been investigated in detail with regard to their polarographic behaviour[74]. Cpe at −1·6 V versus sce of diphenyliodonium hydroxide and its *p,p'*-dimethyl and *p,p'*-dimethoxy derivatives at a mercury cathode gave fair yields of the corresponding diarylmercury[75].

Among other unsaturated halogen compounds, monohalopyridines have been the most extensively studied. Earlier polarographic studies by Holubek and Volke[76] demonstrated that the isomeric iodo- and bromopyridines (**13**, **14**, **15**; X = I, Br) could be reduced at a mercury electrode in



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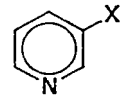

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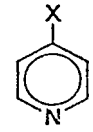
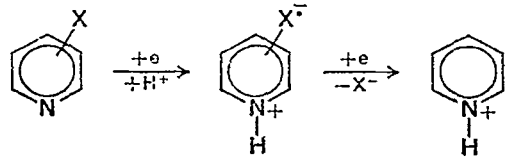


(15)

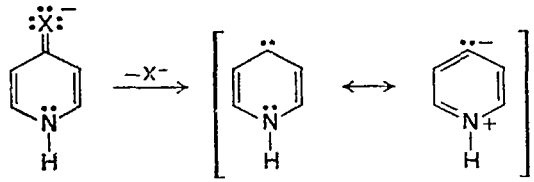
* Values reported for iodinated phthalic 'anhydrides' in this paper must actually refer to either those of the acids or the sodium or ammonium salts (in some cases, even the corresponding phthalamic acids), since this type of anhydride hydrolyses very quickly in aqueous solution[68].

acid solution to give each a single two-electron wave, the 'height of which decreased' with increasing pH. 4-Chloropyridine could not be reduced below the solvent limit. Subsequently, Evilia and Diefenderfer[77] re-examined the polarographic characteristics of monohalopyridines and determined that $E_{\frac{1}{2}}$ increased linearly with increasing pH. They concluded that the mechanism is composed of two one-electron steps at low pH (equation 15), but is different at high pH. It is possible that the intermediate



(15)

draws some stabilization from structures such as **17** and **18** in equation (16). However, the observation by Evilia and Diefenderfer that the three isomeric iodopyridines (**13**, **14**, **15**; X = I) are all reduced at the same



(16)

(16) (17) (18)

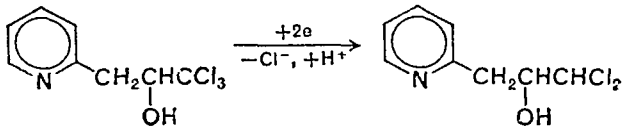
potential suggests that in these cases at least stabilization occurs before the loss of halogen from the ring. Tirorofled[70] had earlier reported the reduction of halopyridines as well.

Fuginaka and coworkers[78] showed that 6-chloroquinoline could be reduced to quinoline and a few halopyrimidines have been reported to reduce to the corresponding pyrimidines. Sugino and Shirai[79,80] reported the high yield reduction of 2-amino-4-chloropyrimidine and of the 6-methyl homologue. Czochralska[81] has also reported the electrochemical reduction of some halopyrimidines and a recent review[82] gives additional examples of the reduction of heterocyclic halogen compounds.

2. Geminal polyhalides

A number of investigations concerning the ease of reduction of geminal di- and trihalides has established that the presence of more than one halogen atom lowers the potential at which reduction of the first carbon–halogen bonds occurs. As early as 1939 it was reported[83] that electro-reduction of the trichloromethyl derivative **19** led to a 50% yield of the

dichloromethyl compound (**20**) (equation 17). Subsequently Elving and Bennett[84] reported that a related compound, 2,2,2-trichloroethanol, was reduced readily in a two-electron process, but then could not be reduced



(17)

further. Significantly, they could not reduce the corresponding di- or monochloroethanol and hence proposed that the reduction of 2,2,2-trichloroethanol was a single C—Cl bond reduction (equation 18).

$$Cl_3CCH_2OH \xrightarrow[\substack{E_{\frac{1}{2}} = -1{\cdot}67\ V\ (sce)\\ 07\%\ MeOH\\ Bu_4NI\\ +2e,\ -Cl^-,\ +H^+}]{Hg\ cathode} Cl_2CHCH_2OH \qquad (18)$$

In another study Elving and coworkers[27] examined the polarographic characteristics of a series of haloacetic acids at different values of pH. Bromoacetic acid gave one two-electron wave in the pH range 1–12, whereas di- and tribromoacetic acid gave two and three distinct reduction waves, respectively (see Table 7). Although all three acids gave pH-dependent half-wave potentials which rose sharply (in the negative

TABLE 7. Half-wave potentials for reduction of bromoacetic acids[27]

Compound	$-E_{\frac{1}{2}}$ (1)[a]	$-E_{\frac{1}{2}}$ (2)[b]	$-E_{\frac{1}{2}}$ (3)[c]
Br_3CCO_2H	0·32	0·41	1·31
Br_2CHCO_2H	0·41	1·31	—
$BrCH_2CO_2H$	1·30	—	—

[a] First two-electron wave.
[b] Second two-electron wave.
[c] Third two-electron wave.

direction) at the pK_a of the acid, they all gave distinctly different reduction potentials at pH values high enough for the acids to be fully ionized (cf. Table 7), suggesting they could be selectively reduced under properly controlled preparative conditions. Elving and Tang[42] observed a similar result studying the chloroacetic acids (Table 8). Again, the identity of the potential for the single two-electron reduction of dichloroacetic acid with

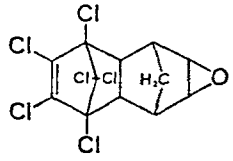
that of the second wave for the reduction of trichloroacetic acid strongly implicates the former as an intermediate in the reduction of the latter. Indeed Meites and Meites[85] have developed a method for the precise

TABLE 8. Half-wave potentials for reduction of chloroacetic acids at pH values between 6·8 and 8·2

Compound	$-E_{\frac{1}{2}}$ (1)[a]	$-E_{\frac{1}{2}}$ (2)[b]	pH
Cl_3CCO_2H	0·84	1·57	8·19
Cl_2CHCO_2H	1·57	—	8·19
$ClCH_2CO_2H$	>2·0	—	6·8–8·8
CH_3CO_2H	>2·0	—	6·8–8·8

[a] First two-electron wave.
[b] Second two-electron wave.

quantitative determination of trichloroacetate in the presence of a large excess of dichloroacetate, based on controlled potential coulometry at a mercury cathode at −0·8 V (sce). Another analytical application has been found in the determination of the active components in dieldrin and aldrin (**21** and **22**). Here it has been shown by cpe that reduction can take place



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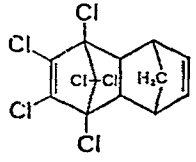


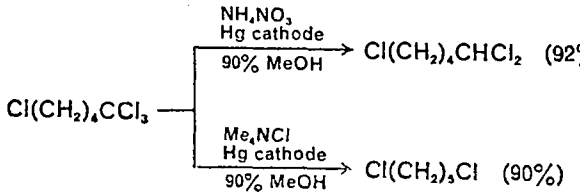
(22)

almost exclusively with replacement of one of the chlorine atoms on the 1,4-methane bridge by hydrogen[86]. However, stepwise replacement by hydrogen of 4–5 chlorine atoms of these molecules has also been achieved[87].

Preparative applications include the very interesting possibility of reducing aliphatic trichloromethyl compounds, readily available by telomerization reaction of olefins with carbon tetrachloride or chloroform, selectively to dichloromethyl and chloromethyl compounds[88]. An example is given in equation (19). Waste liquors from the chlorination of acetic acid, containing predominantly di- and trichloroacetic acid, can be reduced to chloroacetic acid on a magnetite electrode[89].

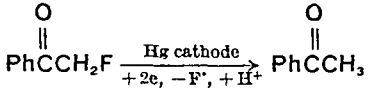
The reduction of several dihalides, including 1,1-dibromo- and 1-bromo-1-chlorocyclopropyl derivatives has been studied in some detail[90, 91], as has

the reduction of several geminal 2,2-dihalonorbornyl derivatives[56]. The nature of these studies is such as to call for their inclusion in other sections of this chapter (section III. B. 7. a and c, respectively).



(19)

A very interesting situation prevails with respect to the reduction of several *gem*-trifluoromethyl compounds. Elving and Leone[25] first reported in 1957 the reduction of phenacyl fluoride to acetophenone (equation 20),

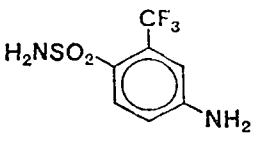


(20)

a reduction facilitated by the α-carbonyl group (cf. section III. B. 1. b). Lund[92] later reported the surprising observation that several appropriately substituted trifluoromethylaryl halides were polarographically reduced in a six-electron process, as illustrated in equation (21), to give the corresponding

(21)

toluene derivative. Whereas he reported that trifluoromethylbenzene, 3-trifluoromethylaniline and 3-trifluoromethyl-4-sulphamidoaniline (**23**) were not reduced below −2·0 V (sce) at a mercury electrode in aqueous methanol, he noted that benzothiadiazine (**24**) and 5-trifluoromethyl-2,4-disulphamidoaniline (**25**) were both reduced at ~ −1·7 V (sce), consuming six electrons. Cohen and coworkers[67] extended the work of Lund to include



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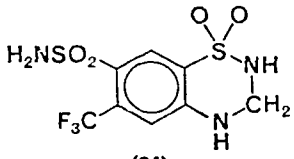

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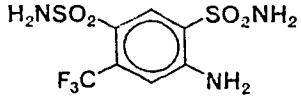


(25)

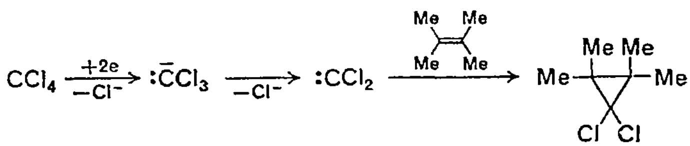
the polarographic behaviour of a large number of other trifluoromethylbenzene derivatives. They established that in aqueous solutions all three fluorine atoms were removed simultaneously, while in DMF the reduction occurred in one, two or three two-electron steps, depending on the nature of the substituents present on the aryl ring. Substituents which were

electron-withdrawing by inductive and resonance effects, located *para* to the trifluoromethyl group, facilitated direct six-electron reduction of the —CF_3 group. This unusual reduction behaviour has been confirmed in recent preparative work by Coleman and coworkers[66]. Stocker and Jenevein[93] have reported a similarly facile six-electron reduction of α,α,α-trifluoroacetophenone on attempts to form the corresponding pinacol (equation 22). Some α-fluoroacetophenone could, however, be isolated

$$PhC(=O)CF_3 \xrightarrow[+BH^+]{+6e,\ -3F^-} PhC(=O)CH_3 \qquad (22)$$

during conditions of short electrolysis time. Stocker and coworkers[94] later encountered the same problem in the attempted electropinacolization of *p*-trifluoromethylacetophenone by cpe in acetonitrile/Et_4NBr. Under these conditions predominant dehalogenation took place, whereas the desired pinacol was obtained in 87% yield in 80% ethanol–water.

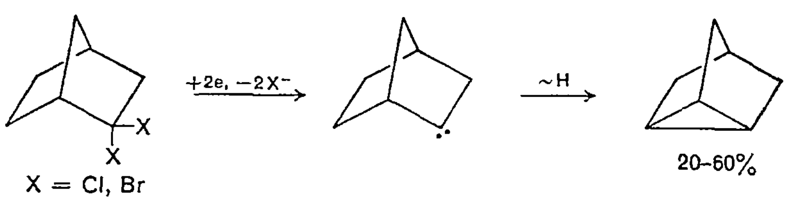
Wawzonek and Duty reported the polarographic behaviour of a large number of chlorocarbons in DMF or acetonitrile solvents[95] and included the noteworthy observation that reduction of carbon tetrachloride appeared to generate dichlorocarbene (equation 23). When carbon



(23)

(26)

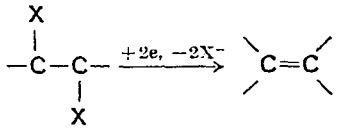
tetrachloride was reduced at a mercury pool in acetonitrile containing tetrabutylammonium bromide at −20° in the presence of tetramethylethylene, an undetermined quantity of product which exhibited the same gas chromatographic behaviour as authentic **26** was obtained. Although the possible formation of carbenes in other *gem*-polyhalo compounds has so far remained unexplored, strong evidence for the intermediacy of an electrochemically generated carbene has been reported in at least one other case[56] (equation 24).



(24)

3. 1,2-Dihalides

A considerable body of data regarding the electroreduction of 1,2-dihalides has accumulated, establishing the generality of the reaction expressed by equation (25). Von Stackelberg and Stracke[24] established



(25)

early that electroreduction of 1,2-dihalides afforded olefinic hydrocarbons in a two-electron process. Závada and coworkers[96] found a marked dependence of the polarographic half-wave potential of the dihedral angle between the C—Br bonds. For a series of 21 1,2-dibromides studied, $E_{\frac{1}{2}}$ varied between −0·82 V and −1·67 V (sce). The less positive potential was obtained for those dibromides for which the *trans* coplanar arrangement of C—Br bonds was conformationally favoured or fixed by a rigid structure. Table 9 illustrates the range of half-wave potentials observed and Figure 2 shows the relation between $E_{\frac{1}{2}}$ and dihedral angle. The large difference in ease of reduction between two isomeric 3,4-dibromo-*t*-butylcyclohexanes (**34** and **35**) is particularly dramatic and supports the contention that the

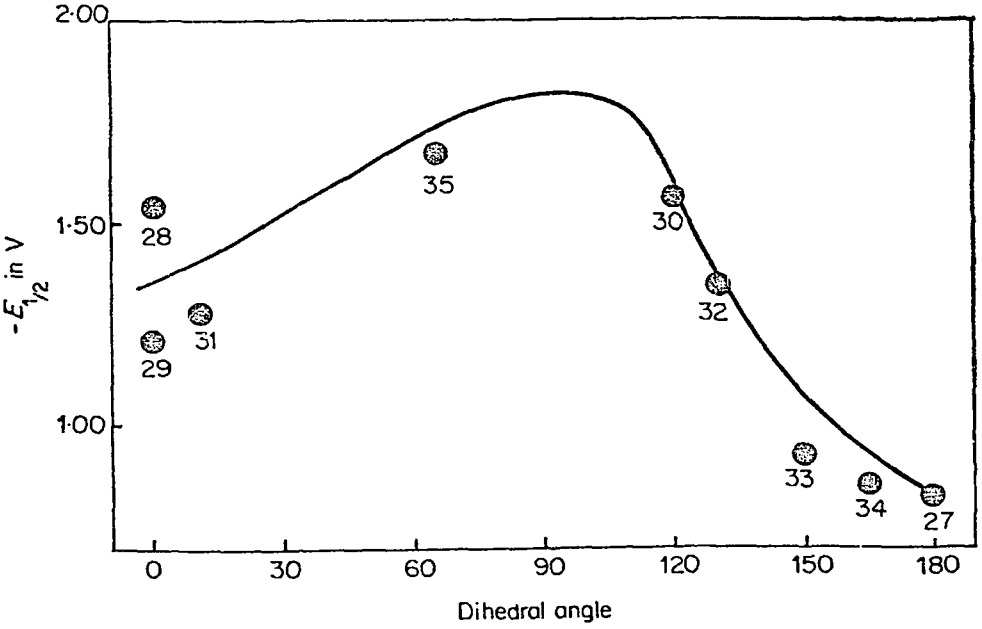
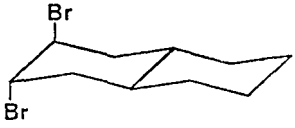
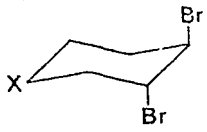
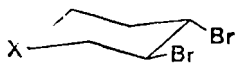


FIGURE 2. Plot of $-E_{\frac{1}{2}}$ of vicinal dibromides versus dihedral angle between the carbon–bromine bonds (Table 9).

TABLE 9. Half-wave potentials for reduction of 1,2-dibromides[96]

No.	Compound	$-E_{\frac{1}{2}}$	Dihedral angle between C—Br bonds
	BuBr	1·90	
	$BrCH_2CH_2Br$	1·23	
(27)		0·82	180°
(28)	*exo-cis*-2,3-Dibromo-bicyclo[2.2.1]heptane	1·53	0°
(29)	*endo-cis*-2,3-Dibromo-bicyclo[2.2.1]heptane	1·21	0°
(30)	*trans*-2,3-Dibromo-bicyclo[2.2.1]heptane	1·56	120°
(31)	*cis*-2,3-Dibromo-bicyclo[2.2.2]octane	1·28	10°
(32)	*trans*-2,3-Dibromo-bicyclo[2.2.2]octane	1·34	130°
(33)	*trans*-1,2-Dibromo-cyclopentane	0·94	150°
(34)		0·86	165°
(35)		1·67	65°

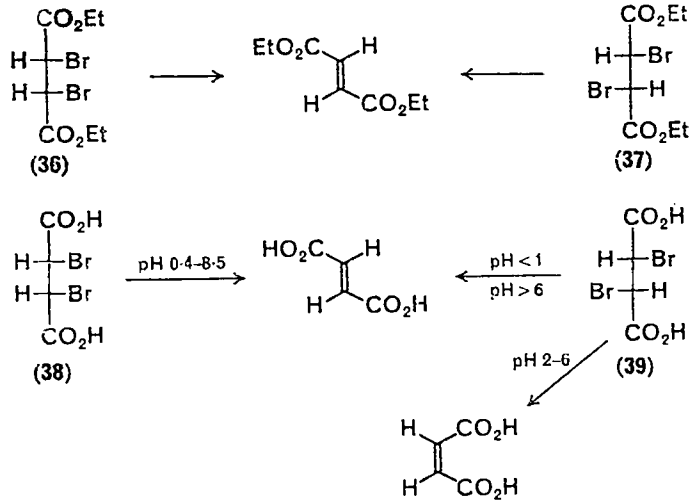
X stands for a *t*-butyl group in the last two compounds.

elimination mechanism is probably a concerted one. Recent studies by Koch and McKeon[97] and Butin and coworkers[98] corroborate this finding. It should be kept in mind, though, that the large difference between **28** and **29** indicates that other factors must be taken into account*. It may be that different products are formed in the two cases, so that different transition states must be considered. Hence product studies are desirable in many of these cases. Preliminary product studies of the controlled potential

* Polarographic data for a number of Diels–Alder adducts of dichloromaleic anhydride which all have rigid *cis* geometry around the Cl—C—C—Cl bond system, also show a large spread in the $E_{\frac{1}{2}}$ values[99].

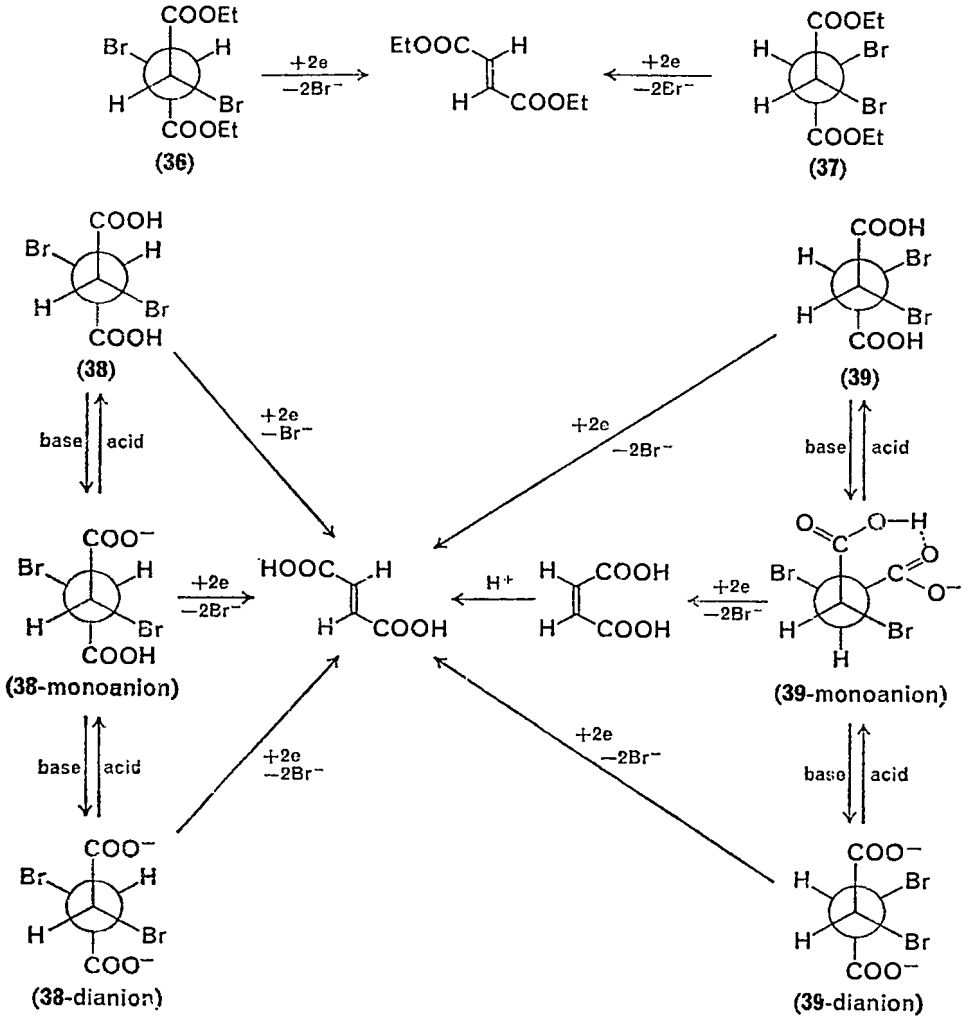
reduction of *meso*- and *dl*-2,3-dibromobutane support the polarographic data of Zavada and coworkers[96]. At $E = -1{\cdot}30$ V (versus s.c.e.) the *meso*-isomer gave a quantitative yield of exclusively *trans*-2-butene, and the *dl*-isomer gave exclusively *cis*-2-butene. This result suggests that at low potential reduction occurs exclusively from the *trans*-coplanar conformation, and promises to introduce a new method for the stereospecific reduction of 1,2-dihalides[202].

Elving, Rosenthal and Martin reported that reduction of both *meso*- (**36**) and *dl*-2,3-dibromosuccinic esters (**37**) gave diethyl fumarate as the only product[100], whereas reduction of the *meso*- (**38**) and *dl*-2,3-dibromosuccinic acids (**39**) gave different products depending on pH. The *meso*-diacid gave only fumaric acid over the entire pH range, but the *dl*-diacid gave maleic acid at intermediate pH range, with a maximum yield at pH ≈ 4. These results are shown in Scheme 8 and can be rationalized by a combination of steric and electronic factors. The rationale is shown in Scheme 9. The *meso*-diester (**36**), diacid (**38**) and dianion (**38**-dianion) all



SCHEME 8

possess a configuration which is both sterically favourable and electronically well suited for concerted reductive elimination in the *trans* bromide orientation. Of the conformations possible for the *dl* system, that which produces *trans* coplanar C—Br bonds is sterically unfavourable for both the diester (**37**) and the dianion (**37**-dianion), in the latter due to charge repulsion. In these cases elimination probably occurs in the *cis* C—Br orientation. However, in the intermediate pH region diacid **39** probably

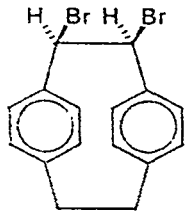


SCHEME 9

exists as its internally hydrogen-bonded monoanion (**39**-monoanion)[101], from which facile reductive elimination can occur to give maleic acid. At very low pH any maleic acid formed is probably isomerized readily to fumaric acid.

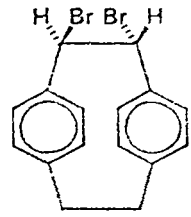
Rifi[102] has reported the polarographic behaviour of the *cis*- and *trans*-[2.2]paracyclophane dibromides (**40** and **41**), results which are in agreement with those of Závada and coworkers for the 2,3-dibromonorbornanes. Again it is apparent that factors other than the C—Br torsional angle are operating to influence the reduction potential.

Feoktistov and coworkers[103, 104] have conducted preparative studies on reductive elimination reactions of 1,2-dihalides. Particularly they have shown[104] that the elimination reaction can be generalized to mixed



$E_{\frac{1}{2}} = -1{\cdot}12$ V (sce)

(40)



$E_{\frac{1}{2}} = -1{\cdot}4$ V (sce)

(41)

halides, such as iodochlorides (equation 26) and bromofluorides (equation 27). The ease of electroreductive 1,2-elimination has very recently been

$$ICH_2CH_2Cl \xrightarrow[+2e,\ -I^-,\ -Cl^-]{\substack{\text{Hg cathode}\\ E_{\frac{1}{2}} = -0{\cdot}9\text{ V (sce)}}} CH_2{=}CH_2 \qquad (26)$$

$$CF_3CHBrCl \xrightarrow[OH^-,\ +2e]{\substack{\text{Pb cathode}\\ 0{\cdot}2\text{ amp/cm}^2}} CF_2{=}CHCl + FC{\equiv}CH \qquad (27)$$

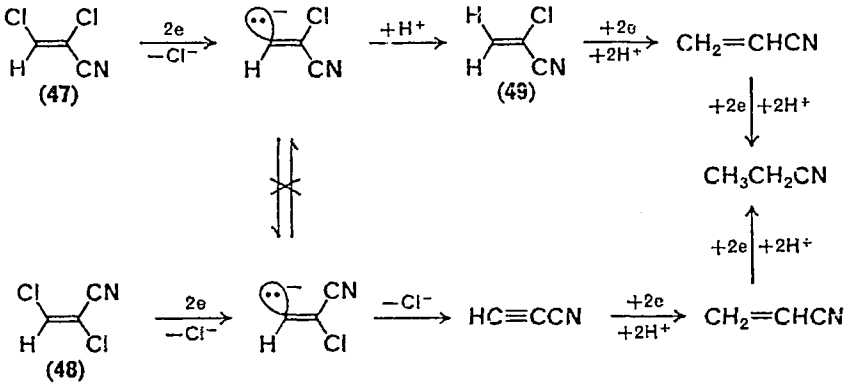
exploited for synthetic purposes. Semmelhack and Heinsolm[201] have found that esters of β-trihaloethanol electroreduce at very favourable potentials, and give excellent yields of the corresponding carboxylic acids, thus providing a novel and selective carboxyl protecting group. Feoktistov and coworkers[105] have further examined the polarographic behaviour of halides **42**–**46**. Whereas **42a** and **42b** produce one two-electron wave in aqueous ethanol, and **42c** produces two two-electron waves, polyhalides **43**–**46** produce one two-electron wave followed by a second

ClF_2CCFCl_2	$BrF_2CCHFCl$	$Br_2CHCHBr_2$
(42a)	(42b)	(42c)
$BrF_2CCFClBr$	BrF_2CCF_2Br	$BrF_2CCHFBr$
(43)	(44)	(45)
	$BrFCHCHFBr$	
	(46)	

wave, the height of which corresponds to a fractional number of electrons. Since the authors established that the second wave involved the consumption of hydrogen ion, they concluded that two products, not one, were

being formed during the first reduction wave of **43–46**. In similar systems it has sometimes been possible to estimate ratios between different conformers from polarographic data[106].

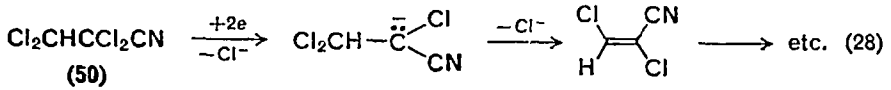
Several reports of the reduction of 1,2-dihaloethylenes have appeared. Feoktistov and collaborators[105] have carried out the reduction of a series of 1,2-dihalogenomaleic and fumaric acids and have concluded that acetylenes are formed in these cases. Mairanovskii and Bergelson[107] had earlier reported the reduction of 1,2-dihaloolefins, and a polarographic study by Jura and Gaul[108] led to some interesting conclusions. These latter authors studied the behaviour of a series of halogen-substituted acrylonitriles. From the values of $E_{\frac{1}{2}}$ for the several stages of reduction of each compound, it was proposed that *cis*- and *trans*-2,3-dichloroacrylonitrile (**47** and **48**) are reduced by different mechanisms. This claim is supported by the isolation of 2-chloroacrylonitrile (**49**) from one isomer (Scheme 10). It is noteworthy

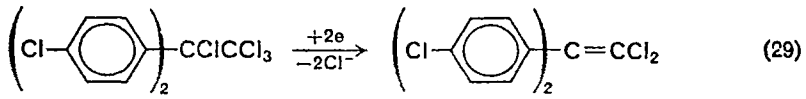


SCHEME 10

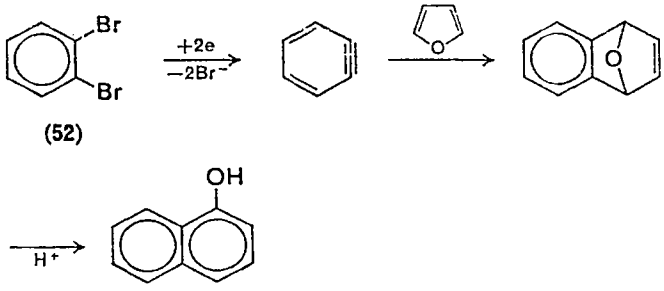
that this mechanism also requires that the intermediate vinyl carbanions undergo proton capture at a rate which greatly exceeds their rate of equilibration. Stereoelectronically, the authors justify their *E1cB* mechanism for **48** and not for **47** on the basis that the *trans*-coplanar orientation of the departing chlorine atom in **48** is more favourable for elimination than proton capture. The claim receives some support from the reduction sequence for 2,2,3,3-tetrachloropropionitrile (**50**), which undergoes a series of two-electron reductions, the first to produce **48**, and the remaining ones identical to those for **48** in Scheme 10 (equation 28). Rosenthal and coworkers[109] had earlier speculated on a similar reduction sequence for the first step in the reduction of 1,1,1,2-tetrachloro-2,2-bis(*p*-chlorophenyl)ethane (**51**) (equation 29).

Comparatively little work has been reported on the reduction of polyhalobenzenes. Wawzonek and Wagenknecht[110] reported that whereas *meta*- and *para*-dihalobenzenes displayed two two-electron polarographic



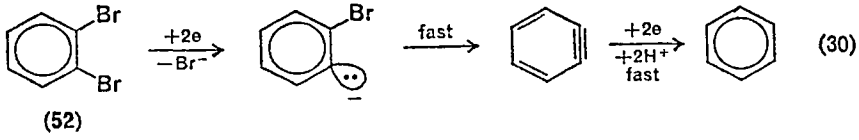


waves, *ortho*-dibromobenzene (**52**) produced a single two-electron wave. The assumption that reductive elimination leading to benzyne took place was corroborated by the isolation of α-naphthol from the reduction of **52** in the presence of furan, albeit in only 1% yield. A probable mechanism for its formation involves benzyne (Scheme 11). The observation that reduction



SCHEME 11

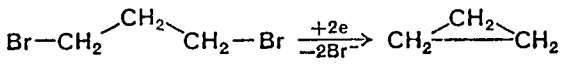
of **52** in the absence of a trapping agent in DMF/acetonitrile gives one four-electron polarographic wave was rationalized by a mechanism in which the second electrochemical step occurs with a rate constant greater than the first (equation 30).



4. ι,ω-Dihalides

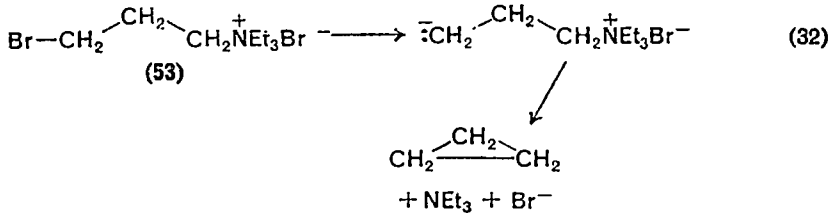
The report by Závada and coworkers[96] that 1,3-dibromopropane is reduced in a single two-electron process led these authors to speculate that '1,3-dibromopropane reduces in one two-electron step followed by a fast

non-electrode process'. Their speculation that this non-electrode process was ring closure to cyclopropane (equation 31) was convincingly demonstrated and extended to several other 1,3-dibromides by Rifi[47,102,111]. A



(31)

carbanion intermediate for this displacement has been demonstrated[111] by the reduction of 3-bromopropyltriethylammonium bromide (**53**), a reaction which occurs at a very anodic potential [$E_{\frac{1}{2}} = -1{\cdot}34$ V (sce)] (equation 32). The reduction of 1,3-dibromides occurs in good yields,



(32)

without interference from a simple reduction reaction and appears to be a general synthetic method. Of particular interest is the use of this reaction to form bicyclobutyl systems (cf. Table 10, compounds **54** and **56**). Rifi has

TABLE 10. Cathodic reduction of 1,ω-dihalides

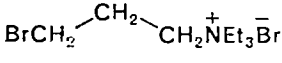
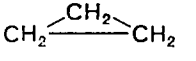
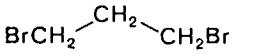
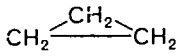
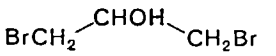
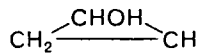
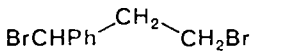
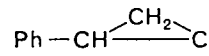
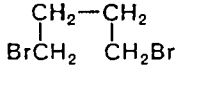
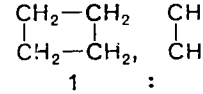
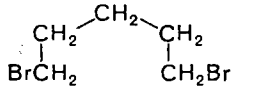
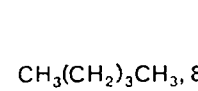
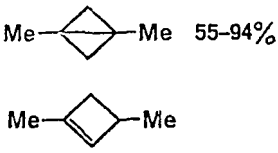
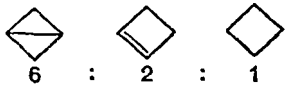
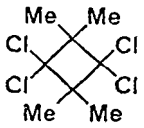
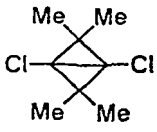
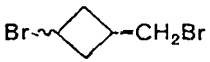
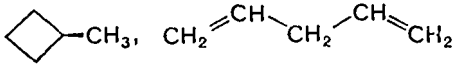
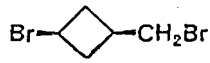
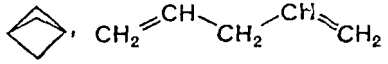
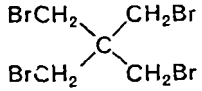
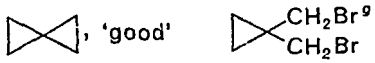
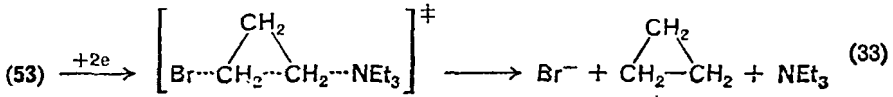
No.	Compound	Products, yield	$-E_{\frac{1}{2}}$[a]	Reference
(53)			1·34	111[b]
			1·93 1·65	111[b] 96[c]
			1·90	102, 113[d]
			—	113[d]
			1·95–1·99 1·65 1·75, 2·03	111[b] 96[c] 112
			2·14, 2·20 1·72, 1·79	111[b] 96[c]

TABLE 10 (*cont.*)

No.	Compound	Products, yield	$-E_{\frac{1}{2}}$[a]	Reference
(54)	 (*cis* and *trans*)	 Me–Me 55–94%; Me–Me	—	111[c]
(55)		 6 : 2 : 1	1·80	111[b]
(56)			—	111[b]
(57)	 (mixture of diasteromers)		—	40[b]
(58)			—	40[f]
(59)		 'good'	—	111[b]

[a] Half-wave potential in volts versus sce.
[b] Hg cathode, DMF, Bu_4NClO_4.
[c] Hg cathode, 95% DMF/5% H_2O, 0·03M Me_4NBr.
[d] Hg cathode, acetonitrile, Et_4NBr.
[e] Hg cathode, DMF, LiBr.
[f] Hg cathode, hexamethylphosphoramide, Bu_4NClO_4.
[g] At −1·4 V.

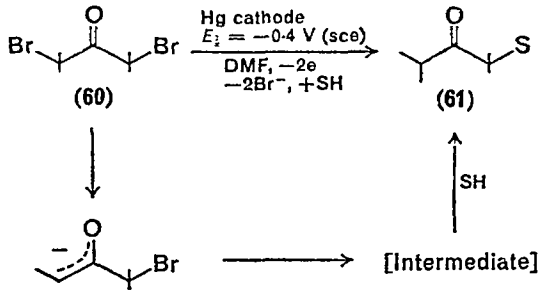
argued that the differences observed in reduction potential between ammonium salt (53) and 1,3-dibromopropane, on the one hand, and long-chain dibromides (e.g. $Br(CH_2)_5Br$, $E_{\frac{1}{2}} = -2{\cdot}14$ V and $Br(CH_2)_6Br$, $E_{\frac{1}{2}} = -2{\cdot}13$ V), on the other hand, can be taken as evidence of the concerted nature of 1,3-eliminations (equation 33). Although the difference



(53) $\xrightarrow{+2e}$ $\left[\text{Br}\cdots\text{CH}_2\cdots\text{CH}_2\cdots\text{NEt}_3\right]^{\ddagger}$ $\longrightarrow$ $\text{Br}^- + \text{CH}_2{-}\text{CH}_2 + \text{NEt}_3$ (33)

is convincingly large in the case of compound **53**, differences of 0·1–0·2 V in the latter cases should be viewed with caution. Fry and Britton[199] have provided clear evidence refuting the possibility of concerted ring closure for 1,3-dibromopropanes. The mixture of *cis*- and *trans*-1,2-dimethylcyclopropanes formed during electroreduction of *meso*- and *dl*-dibromopentanes was essentially the same (*trans* : *cis* = 45 : 41) regardless of the identity of the starting material. Concerted reductive ring closure, as proposed by Rifi, would demand stereospecificity, and such was not observed by these authors. Moreover, the fact that cyclopropanes are the sole products even in the presence of water may only attest to the relative absence of water in the electrode double layer[56] and not to the concerted nature of the reduction reaction. Furthermore, the presence of the positive charge in **53** may have a favourable orientating influence with respect to the negatively charged cathode surface and so even this result should be interpreted with caution. Whichever interpretation one chooses to favour, the general method represents a contribution to synthetic chemistry which merits special attention. Although the optimum orientational relationship for 1,3-elimination in dihalides has been systematically examined with regard to chemical reducing agents[114], data are yet unavailable regarding the stereochemical requirements for electroreduction.

Electroreduction of α,α′-dihaloketones (**60**) has been reported[115] to proceed through an unidentified reactive intermediate which reacted with protonic nucleophile sources to produce compounds **61** (Scheme 12).



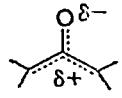
SCHEME 12

Evidence for a reactive intermediate rests on the success of the reaction when electroreduction was carried out at low temperature in the *absence* of SH, followed by the addition of SH and warming. Of the several structures possible for the intermediate (e.g. **62–64**), product evidence predicates in favour of **64** and its *O*-protonated form. A new dimension to this problem has recently been advanced by Fry and Scoggins[200], who claim spectroscopic evidence for the presence of a cyclopropanone from

2,4-dibromo-2-methyl-3-pentanone, and have isolated the methyl hemiketal of **60** in 90% yield by electroreduction of **60** in methanol.

(62)

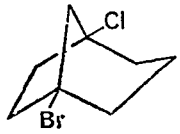
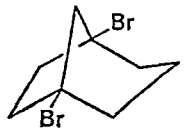
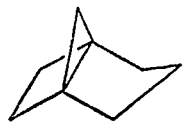
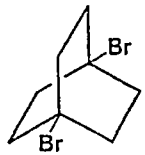
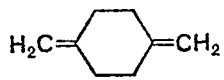
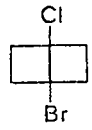
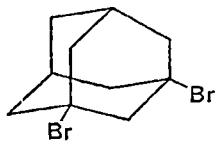
(63)



(64)

Several interesting cases of the reduction of bridgehead bicyclic dihalides have been reported. Such reactions represent a possible route to highly strained tricyclic compounds. The ease of reduction appears to be related to the ring size and not to the stability of intermediate anions (compare **66** and **68** in Table 11). Yet the fragmentation which occurs in **67** takes place

TABLE 11. Cathodic reduction of bridgehead bicyclic dihalides

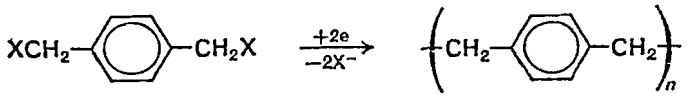
No.	Dihalide	Product	$-E_{\frac{1}{2}}$ [a]	Reference
(65)			2·28	102
(66)			1·99	116
(67)			2·2	102
(68)			2·47	102
(69)		Adamantane	1·97	102

[a] Half-wave potential at a mercury cathode versus sce.

at a surprisingly unfavourable potential for a potentially concerted reaction and is, surprisingly, absent in **66**. Obviously these results suggest fertile ground for further investigations.

5. Vinylogs of vicinal 1,2-dihalides

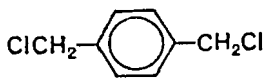
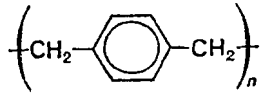
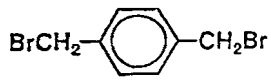
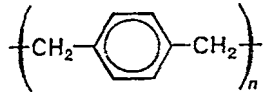
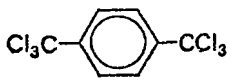
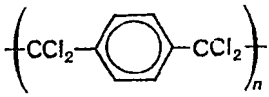
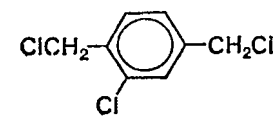
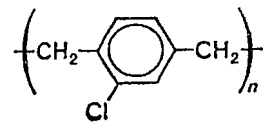
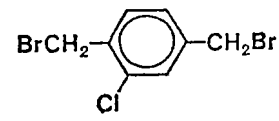
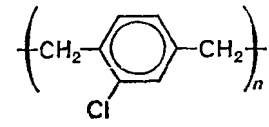
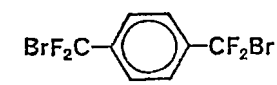
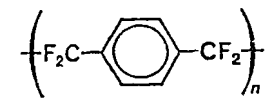
A very interesting and potentially useful example of electroreductive elimination is produced by the case of *ortho-* or *para*-bishalomethylbenzenes. Gilch[117] reported that controlled potential reduction of several 1,4-dihalomethylbenzenes gave polymers (equation 34). A summary of his



(34)

data (Table 12) shows that the yield of polymers is generally good and that some of them, particularly such as the polymer derived from **75**, could be

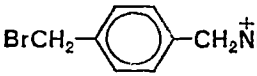
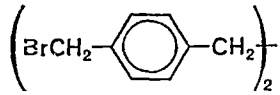
TABLE 12. Cathodic reduction of *p*-bis(halomethyl)benzenes[117]

No.	Compound	Product	$-E$ [a]	Yield (%)
(70)			1·2	35
(71)			1·2	95
(72)			0·7	65
(73)			1·2	90
(74)			1·2	90
(75)			1·1	95

[a] Cpe (V versus sce) using dioxan–water–HCl.

of commercial interest. Covitz[118] reported in the following year similar results for the electroreduction of 1,4-bishalomethylbenzenes which included a number of half-wave potential measurements (Table 13), and

TABLE 13. Cathodic reduction of different bis(halomethyl)benzenes[118]

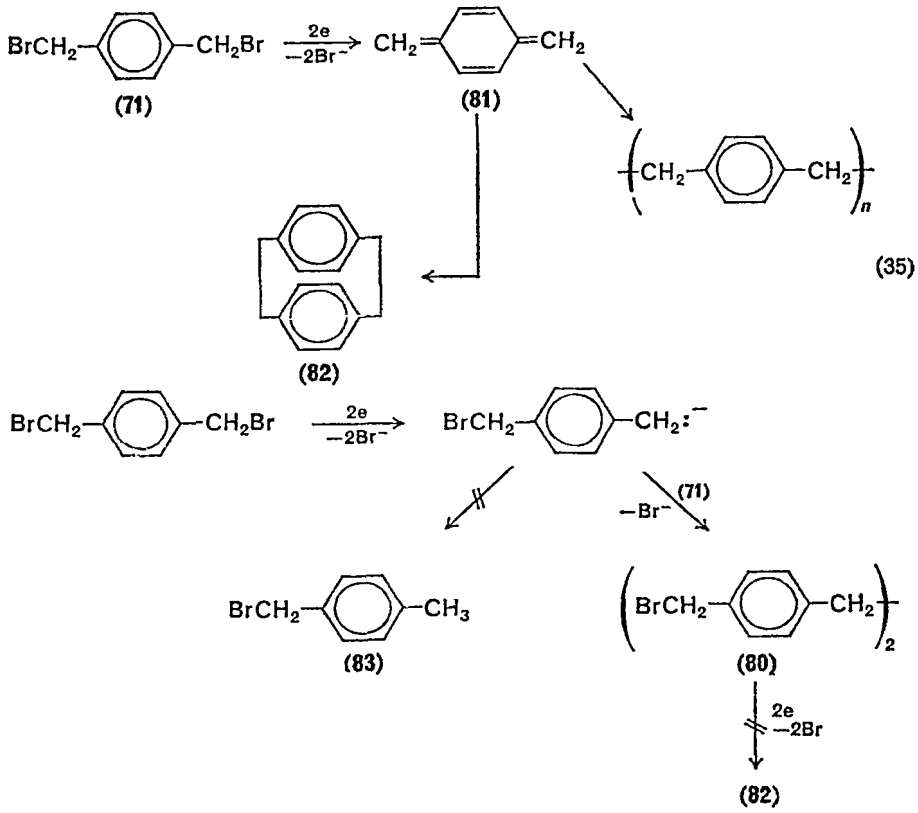
No.	Compound	$-E_{\frac{1}{2}}$ (1)[a]	$E_{\frac{1}{2}}$ (2)[b]
—	Benzyl bromide	1·22[c]	—
(71)	*p*-Bis(bromomethyl)benzene	0·80	1·72
(76)	*m*-Bis(bromomethyl)benzene	1·32	—
(77)	*o*-Bis(bromomethyl)benzene	0·61	1·58
(78)		0·79	1·72
(74)	2-Chloro-1,4-bis(bromomethyl)benzene	0·61	1·59
(79)	2,5-Dichloro-1,4-bis(bromomethyl)-benzene	0·45	1·36
(80)		1·13	—

[a] Half-wave potential in volts, versus sce using DMF, for the first two-electron wave. See reference 95.

[b] Half-wave potential in volts for the second one-electron wave.

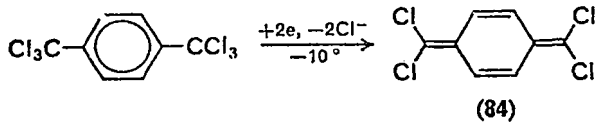
[c] Included for comparison purposes.

the identification of [2.2]paracyclophane (**82**) among the products, a result which provides some insight regarding the mechanism of the reaction. The considerably more anodic reduction potential for the first wave of *ortho*- and *para*-dihalomethyl compounds compared to the *meta* derivative, and to benzyl bromide itself, suggests a concerted process such as is found in vicinal 1,2-dihalides (cf. section III. B. 3. a). Coulometrically this wave corresponds to a two-electron transfer. The obtention of a favourable potential from triethylammonium salt (**78**) is analogous to Rifi's results (cf. Table 10, compound **53**). Furthermore [2.2]paracyclophane was obtained in 5–10% yield from the reduction of the *para*-dibromide (**71**). This suggests that *p*-xylylene (**87**) may be an intermediate in the reaction (equation 35). That the formation of **82** does *not* proceed via **80**, formed from a carbanion in a nucleophilic process (Scheme 13), is clearly demonstrated by the highly negative reduction potential of **80** itself (cf. Table 13), and by the fact that Gilch[117] found that high yields of polymer were obtained even in acid solution and that the intermediate was not diverted to **83**



SCHEME 13

—an observation which is not consistent with carbanion formation. Indeed, when the reduction of **72** (Table 12) was carried out at −10°, a *p*-xylylene (**84**) could be isolated (equation 36). The above data suggest that reduction



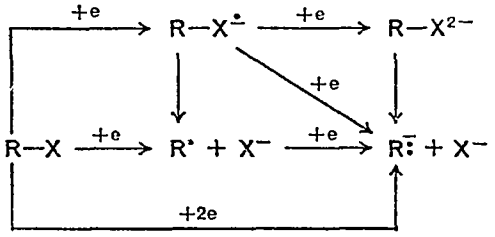
(36)

proceeds via a concerted mechanism to produce a xylylene intermediate, which can then dimerize or polymerize, and that carbanions or radicals are very likely not involved in the reaction (cf. equation 34). This conclusion is supported by the appearance of an unexpected second reduction wave in the case of *ortho*- and *para*-xylylene dihalides (cf. Table 13) which the author attributes to a reduction of the intermediate xylylene system. *meta*-Substituted compounds, for which such a structure is not possible, do not show this second wave.

6. Mechanisms

The very large effort which has been expended towards elucidation of the detailed mechanism of reduction, particularly of saturated monohalides, has failed to produce a commensurate clarification. Problems of mechanism, such as described earlier (section II. A) and outlined in Scheme 1 are discussed separately below. For the most part the discussion will be limited to monohalides attached to tetracoordinate carbon, inasmuch as the evidence for the concerted nature of dihalide reduction mechanisms is rather strong.

a. Sequence of electron-transfers and chemical steps. In principle several possible sequences of electron addition and bond cleavage exist, and these are illustrated in Scheme 14. There have been but few claims that two



SCHEME 14

separate one-electron addition steps have been observed in saturated systems. Feoktistov and Zhdanov[31,119] have observed two one-electron waves during the reduction of β-halopropionitriles, but most other such observations are limited to unsaturated systems[77,120]. While there is a paucity of evidence for discrete one-electron transfer steps, a lack of such evidence does *not* necessarily imply the contrary, since coulometrically only the total number of electrons transferred is observed and polarographically several combinations of mechanisms and rate constants can be conceived that would mask the observation of individual steps. While no serious support exists for the presence of dianions (Scheme 14, path 1), a number of investigators favour formation of the radical anion, a proposal advanced by Streitwieser and Perrin[48]. Fukui and collaborators[121] later have shown that good qualitative correlations exist between the half-wave potential and the calculated LCAO–MO energy level of the lowest unoccupied σ orbital for a series of saturated aliphatic halides and, somewhat surprisingly, also with the lowest unoccupied σ level of conjugated halides (vinyl and aryl systems). The assumption that the radical anion, $(R^{\bullet}—X)^{-}$, is a discrete intermediate in the electrode process

is strongly supported by the fact that this species has a finite lifetime when generated in homogeneous solution by reaction of a halide molecule with a hydrated electron (e^-_{aq})[122]. Generally, there seems to be a parallelism between the electrochemical reactivity of halides and their reactivity towards e^-_{aq}.

Direct observations of anion radicals of halogen-substituted organic compounds by e.s.r. are limited to a few fluorine-containing derivatives[123]. Greig and Rogers[124] studied the electrochemical behaviour of *o*- and *m*-trifluoromethylnitrobenzene and found that a stable anion radical (observable by e.s.r.) is formed in the first polarographic step; the second step is considered to be addition of a second electron to form a dianion. This would seem to contradict the statement made above regarding the possible role of dianions, but in this particular case it does not, since the further reactions of the dianion take place at nitrogen. Anion radicals of a number of fluoronitrobenzenes have been generated (non-electrochemically) and studied by e.s.r.[125]. Obviously, direct observation is possible only in very favourable cases (strong stabilization by another functional group; inefficient leaving group).

On the other hand, it has sometimes been postulated that addition of one or two electrons to the lowest unoccupied σ orbital would occur synchronously with C—X bond cleavage (although it is somewhat difficult to reconcile such a mechanism with the Franck–Condon principle). Hush[126] calculated standard potentials for half-reactions of methyl halides as depicted in equation (37), and used these values for the calculation of the

$$CH_3X + e \longrightarrow CH_3^{\bullet} + X^- \qquad (37)$$

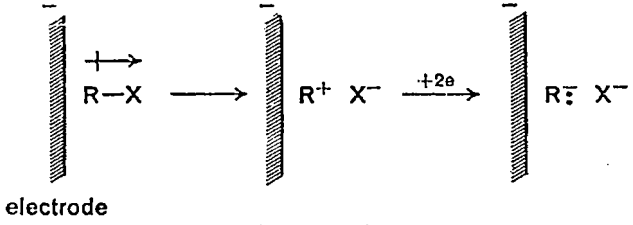
$$X = Cl, Br, I$$

heterogeneous rate constants of this process. Grabowski and coworkers[127] postulated a similar mechanism involving two electrons to explain the stereochemistry of halide reduction (see below).

Beyond this, direct evidence has been sought but not found for the intermediacy of neutral radicals. Indirect evidence is, however, available from product studies (e.g. formation of coupling products), although inferences from such investigations are not wholly unambiguous. Carbanions have been trapped in some cases. Each of these lines of evidence will be examined in detail in section III. B. 6. d.

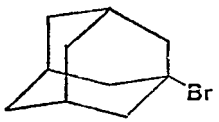
b. Analogy to classical chemical mechanisms. Researchers in the field have frequently drawn direct analogies between the mechanism of carbon–halogen bond reduction and classical displacement mechanisms, and most variants of the S_N1 and S_N2 reaction have been proposed at some time. Elving has devoted attention to summary and classification of reaction

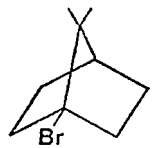
mechanisms on many occasions[19, 20, 43, 128]. Elving and Pullman[20] postulated a stereochemical role for the electrode surface in S_N1-like and S_N2-like reactions. For the former, the strong potential field gradient (ca. 10^7 V/cm in the vicinity of the electrode surface) would induce ionization of the C—X bond. Reduction of the carbonium ion follows (Scheme 15). Such a



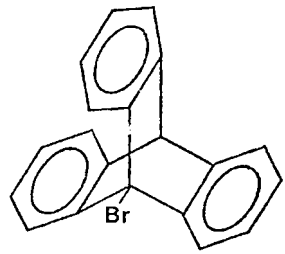
SCHEME 15

scheme requires alignment of the C—X dipole at the electrode surface. The scheme was discussed as a possibility also in earlier studies by Pearson[129]. Lambert and coworkers[36] sought to establish the validity of this mechanism by examination of the reduction potentials of bridgehead bicyclic bromides. If the C—X bond alignment in Scheme 15 is required, then the ability of a bicyclic system to approach closely to the electrode surface is decreased, and the reduction potential should be higher. Data of these authors, of Závada, Krupička and Sicher[96] (cf. Table 4) and of Sease, Chang and Groth[130] concur that such is not the case. Bridgehead bicyclic halides reduce with about the same ease as saturated aliphatic halides [compare 1-adamantyl bromide ($E_{\frac{1}{2}} = -2{\cdot}02$ V) and ethyl bromide ($E_{\frac{1}{2}} = -2{\cdot}22$ V), sce]. Just as convincing is the fact that equally excellent yields of hydrocarbons were obtained from the electroreduction of bridgehead bromides derived from 1-adamantyl (equation 1), 1-norcamphyl (**85**) and 9-triptycyl (**86**) bromides at normal C—Br reduction potentials[37]. The facile reduction





(85)

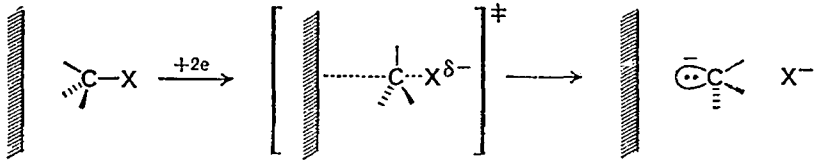


(86)

$-E_{\frac{1}{2}}$	1·96	1·90	1·96 (versus Ag/AgCl)
Yield (%)	77	77	67

of **85** strongly suggests that no carbonium ion could be involved. Sease[130] and Zakharkin[131] have given good arguments for the position that C—X bond scission cannot occur until after electron addition.

Equally unconvincing is the postulate that electroreduction occurs by an S_N2-like path, such as illustrated in Scheme 16. In such a mechanism the



SCHEME 16

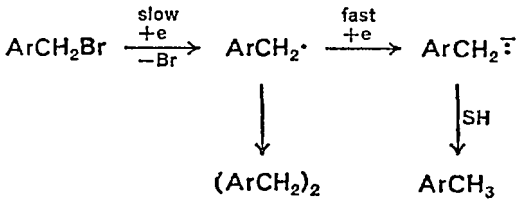
electrode surface plays the role of a nucleophile in the conventional S_N2 reaction, with an electron pair displacing the halide ion from the backside. Lambert and Kobayashi[35] compared half-wave potentials measured in DMF/Et_4NBr with the relative rate of S_N2 displacement by lithium iodide in acetone for a series of alkyl and cycloalkyl bromides. In this study a maximum span in half-wave potentials of 0·24 V was found for bromides whose S_N2 reactivities cover a range of more than 10^7. It was considered that this difference was too small to be compatible with the S_N2 reactivity difference, thus it was concluded that electroreduction is far less sensitive to steric hindrance than is the S_N2 reaction. However, as mentioned in the beginning of this review, 0·24 V is really equivalent to a rate constant ratio of 10^8, provided the *whole* potential difference reflects a ratio between rate constants. Of course this need not be the case, since e.g. adsorption might play an important role in determining half-wave potentials[46,132,133], but it must be emphasized that conclusions based on considerations of $E_{\frac{1}{2}}$ values are less certain in this respect. Krupička, Závada and Sicher[134] have collected data regarding $E_{\frac{1}{2}}$, S_N1 and S_N2 reactivity of a series of alkyl and cycloalkyl halides, and have shown that such cannot provide a unique test for analogy of the electrode reaction with a classical mechanism. These authors are supported in this conclusion by more general reports of Feoktistov[135] and Bauer[136]. In later work Lambert[137] has modified his original proposal and favours a mechanism of stepwise electron addition to the C—X bond while it is perpendicular to the electrode surface. This aspect of the mechanism is discussed in section III. B. 7. a.

c. Linear free energy correlations[16]. Correlations between $E_{\frac{1}{2}}$ and σ values have already been touched upon in the case of aromatic halides (section III. A. 1. d). Generally, these correlations have been moderately successful[138].

Three reports of correlations of aliphatic halide reduction potentials with Taft substituent parameters have been noted. Cizák[139] noted a correlation of $E_{\frac{1}{2}}$ with σ^*, Zuman[140] has reported a similar correlation, and Lambert[137] obtained a good correlation for 24 alkyl bromides using the extended Taft equation (equation 38).

$$E_{\frac{1}{2}}\,(\mathrm{V}) = 0{\cdot}32\sigma^* + 0{\cdot}12E_s - 2{\cdot}16 \qquad (38)$$

Two views exist regarding the effect of substituents on the half-wave potential of substituted benzyl halides. Klopman[49] examined the $E_{\frac{1}{2}}$ of a series of *para*-substituted benzyl halides, and observed that *all* substituents (*p*-OCH_3, CH_3, Br, CO_2Me, NO_2) led to an anodic shift in $E_{\frac{1}{2}}$ relative to the unsubstituted compound. They concluded that this behaviour suggested radical character in the transition state for the rate-determining step and proposed Scheme 17 to account for the result. These results were corroborated by Streitwieser and Perrin[48] who found no satisfactory correlation for $E_{\frac{1}{2}}$ versus σ using a series of substituted benzyl chlorides. The latter



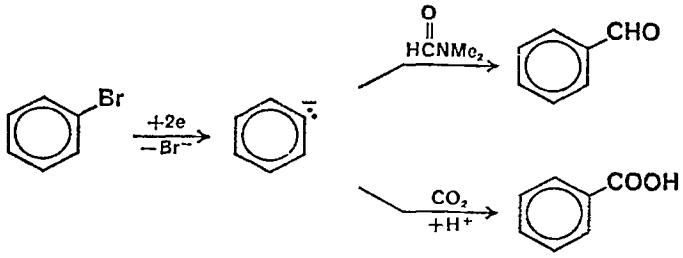
SCHEME 17

authors have interpreted their results in terms of the radical stabilizing effect of substituents. More recent results of Grimshaw and Ramsey[51] using the same systems lead to a satisfactory Hammett σ plot, with $\rho = +0{\cdot}31$ V. However, the value for the *p*-nitro compound deviates greatly from the line in either a σ or σ^- plot and was not included by the authors. In the same year Sease and coworkers[50] published a similar finding for substituted benzyl bromides and calculated a positive value for ρ. These authors conclude that the results suggest a negatively charged potential-determining transition state.

d. Evidence for carbanion and radical intermediates. There have been many reports of the trapping of carbanions in the electroreduction of halides. Wawzonek and collaborators[141] identified phenylacetic acid from the reduction of benzyl chloride in the presence of carbon dioxide (equation 39), a strong indication that the toluenide ion was present.

$$\mathrm{PhCH_2Cl} \xrightarrow[-\mathrm{Cl^-}]{+2e} \mathrm{PhCH_2^-:} \xrightarrow[\mathrm{H^+}]{\mathrm{CO_2}} \mathrm{PhCH_2CO_2H} \qquad (39)$$

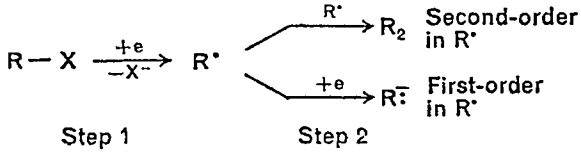
Benzoic acid and benzaldehyde have been reported[142] to form in the reduction of bromobenzene in DMF with carbon dioxide present (equation 40). Moreover, the nature of the most commonly isolated product from



(40)

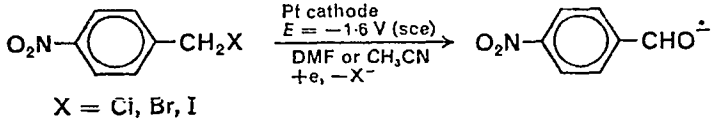
electroreductions of halides, the hydrocarbon, is itself a strong indication of the intermediacy of carbanions, particularly in view of the powerful proton-donating effect of trialkylammonium salts in these reactions[56] (see Scheme 1). Recent studies by Baizer and Chruma[198] provide strong evidence for the formation of carbanions in a host of systems in which the resulting carbanion would be relatively stable, and the subsequent addition, Michael-wise, of these carbanions to a large number of α,β-unsaturated Michael acceptors. The yields of Michael products are good to quantitative, thus providing a powerful new synthetic method for the formation of carbon–carbon bonds.

However, the fact that one can infer the intermediacy of carbanions from such product studies has no bearing on the question of whether or not radicals are present as distinct detectable species, since anions are the ultimate result whether the reduction proceeds stepwise or in a concerted manner. Attempts to detect radicals directly have not been very fruitful. Baizer and Petrovich[22] have questioned claims of Feoktistov and Zhdanov[31,119] regarding the observation of two one-electron reduction waves from β-halopropionitrile reduction (cf. section III. B. 6. a). The validity of the observation notwithstanding, the latter workers reported that radicals could not be detected by means of triangular voltage pulses, even at rates as high as 200 V/second, indicating a very high dimerization rate. The two waves became more separated at higher substrate concentration, a fact which the authors attribute to a difference in order for the two possible reaction paths for the radical (equation 41). Elving and Van Atta[143] have also discussed stepwise addition of electrons in the reduction process.

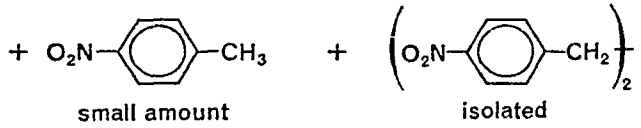


(41)

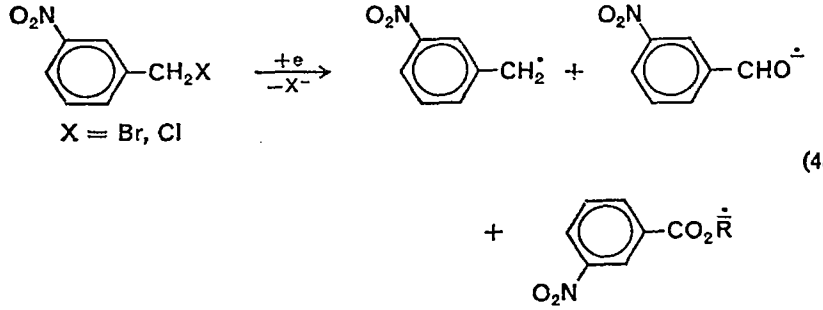
Peterson and collaborators[144] have sought to observe nitrobenzyl radicals from the electroreduction of the corresponding halide by e.s.r. Reduction of the *para* isomers gave a solution which exhibited the e.s.r. spectrum of the *p*-nitrobenzaldehyde anion radical, even with the strictest possible exclusion of oxygen (equation 42). The authors indicate that a very



(42)

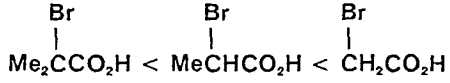


weak signal is detected from the *meta* isomer due to the benzyl radical, but also detect two other oxy radicals (equation 43). *m*-Nitrotoluene was isolated in 40–50% yield from this reaction. The unusual results in this study raise interesting questions which bear further experimentation.



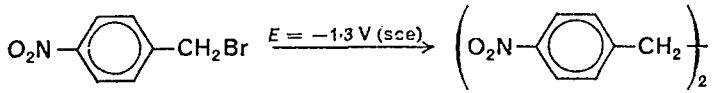
(43)

Although direct evidence for the presence of radicals in these reactions is lacking, possibly due to their absorbed nature on the electrode surface, a surfeit of indirect evidence exists. The reduction potential of substituted benzyl halides[48,49] lends support to the presence of radicals in the potential-determining step. The order of ease of reduction of methyl substituted bromoacetic acids[44] is the same order as the stability of the free radical in



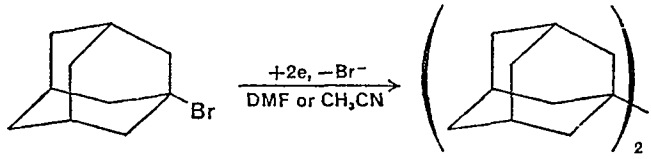
these systems. Many reports of the formation of dimers from halide reduction appear in the literature, and occasionally they constitute the

predominant product[49, 51, 145–151]. 4,4′-Dinitrobibenzyl (**87**) is the sole major product from the reduction of *p*-nitrobenzyl bromide at more negative potentials[49, 51] (equation 44). However, in all these cases, particularly where



(87) (44)

primary or benzylic halides are involved, dimer formation can be explained equally well as arising from S_N2 displacement of a carbanion intermediate on unreacted starting material (cf. Scheme 1). In one case[152], the obtention of low but reproducible yields of 1,1′-biadamantyl (**88**) from the reduction of 1-bromoadamantane (the main product is adamantane) can only be attributed to radical coupling, since S_N2 reaction in this system is not feasible (equation 45). Rearrangement has been observed[153] during the



(88) (45)

Yield
Hg cathode 1%
Al cathode 2%

electroreduction of neophyl chloride (**89**), a system known to undergo free radical rearrangement easily[154] (equation 46). A constant product ratio with

$$\underset{(89)}{PhCMe_2CH_2Cl} \xrightarrow[+2e,\ -Cl^-]{\substack{Hg\ cathode\\ DMF,\ H_2O}} \underset{94\%}{PhCMe_3} + \underset{6{\cdot}3\%}{PhCH_2CHMe_2} + \underset{\sim 0{\cdot}3\%}{(PhCMe_2CH_2)_2} \qquad (46)$$

varying water concentration, and a neophyl chloride rearrangement rate which is much too slow to account for the formation of isobutylbenzene by rearrangement followed by reduction (equation 47), are arguments which

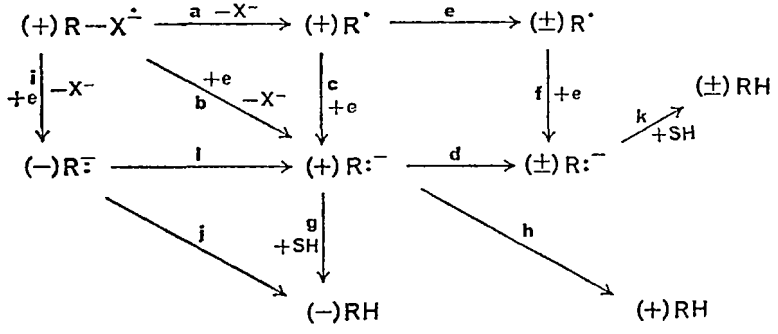
$$PhCMe_2CH_2Cl \not\longrightarrow ClCMe_2CH_2Ph \xrightarrow[\substack{-Cl^-\\ +H^+}]{+2e} Me_2CHCH_2Ph \qquad (47)$$

implicate a radical in the rearrangement step. Hence a radical pathway (Scheme 14, Path 2), probably via the initial formation of the radical anion of the halide, appears to be the view most consistent with experimental details. There is yet, however, little evidence that intermediate radicals are 'free'. Indeed, high yields of dimer in systems which fail to display an e.s.r. spectrum suggest that the radicals are adsorbed at the electrode surface.

7. Stereochemistry[155]

In the last years several reports regarding the stereochemical result of electroreduction of carbon–halogen bonds in optically active compounds have appeared. However, a number of features of this question remain obscure as a result of conflicting evidence. This section is divided into three parts: aliphatic and alicyclic monohalides, cyclopropyl monohalides and cyclopropyl dihalides, because of the large difference in stereochemical behaviour, particularly of carbanions[156], in these three systems. The usual classical study of the stereochemical course of a reaction is greatly complicated in the present case by the role of the electrode. The electrode surface, proximal to an oriented reactive species, may provide a chiral feature to the reaction, as would a reagent molecule in homogeneous reactions. Hence, the orientation of the reacting substrate with respect to the electrode surface will have major stereochemical consequences, particularly if the lifetime of the reactive intermediate is short or if that species remains adsorbed on the surface of the electrode. Interpretation of stereochemical data is further complicated by the presence of the electrical double layer, the composition of which most certainly differs from that of the bulk solvent[56]. The crucial question of the concentration and nature of proton-donating species in the vicinity of the electrode surface, where the reactive intermediate is formed, is still unexplored, yet the answer to this question is important to an understanding of the stereochemistry of carbon–halogen bond reduction.

The other aspect of the stereochemical problem regards whether the stereochemical result is determined largely by the behaviour of the radical or of the carbanion. The question is illustrated in Scheme 18 in detail. If the radical is long-lived and unoriented, racemization can occur via path **aefk**. If the carbanion is formed by C—X scission with retention and is



SCHEME 18

long-lived and unoriented, racemization can occur (path **bdk**). There is some support[127] for the notion that the carbanion is developed with inverted configuration, due to filling of the C—X σ^* orbital. Such a pathway can lead to inversion of configuration (path **ij**) or racemization (path **ildk**). A short-lived or oriented radical would produce a carbanion of retained configuration, which can lead to overall retention (path **ach**), racemization (path **acdk**) or inversion (path **acg**). On the other hand, if the developing carbanion is oriented or short-lived, retention (path **bh**) or inversion (path **bg**), depending on the orientation, can result. Add to this the possibility that organometallic species may intervene (section III. 9) in the reaction sequence, and it becomes fair to say that any single investigation cannot clarify the ambiguities inherent in the problem.

Hush and Segal[157] have examined the relative stabilities of RX and $RX^{\bullet -}$ for various halogen atoms and predicted a trend in the modes of decomposition of the radical ion. Based on semi-empirical SCF–MO calculations, they predict that the stability of the molecular negative ion will increase with increasing atomic number of the halogen atom. Considering only two possible modes of decomposition of the radical anion, the radical path (Scheme 18, path **aefk**) and the S_N2 path (Scheme 18, path **ij**), their stability order of the radical ion predicts that the relative rates of these two reactions will vary with atomic number of X, so as to favour a higher proportion of inversion mechanism (Scheme 18, path **ij**) with increasing atomic number. The authors propose an experimental test for this theory via stereochemical experiments. This prediction suffers from the fact that several reasonable decomposition routes are ignored by the authors in favour of the rather improbable (*vide infra*) S_N2 mechanism. It is by no means clear that the non-radical pathway will lead to inversion.

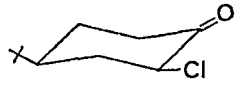
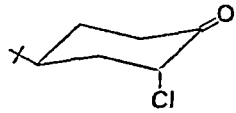
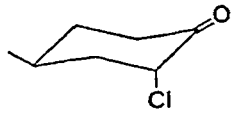
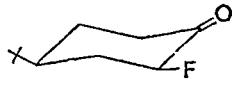
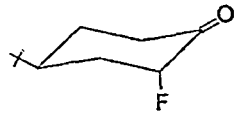
a. Aliphatic and alicyclic monohalides. Polarographic examination of 24 alkyl halides led Lambert[137] to conclude that the reduction proceeds via electron transfer parallel to the C—X bond in the potential-determining step (cf. section III. B. 6. c). This author fitted his data to the modified Taft equation (cf. equation 37) successfully, but the steric parameter ($E_s = 0{\cdot}12$) indicates that the orientational preference may not be important. A comparison of three tertiary bromides of very different bulk shows this to be true (Table 14). However, the greater ease of reduction of benzyl halides (of which **86** is an example)[130] subjects this comparison to some question. Zakharkin and Okhlobystin[131] apparently concur with Lambert in his view. Wilson and Allinger[158] examined the polarographic behaviour of a series of α-haloketones (Table 15) and found a certain orientational preference for the C—Cl bond ($\Delta E_{max} = 0{\cdot}15$ V). This result is consistent with a mechanism involving rate-controlling electron transfer

TABLE 14. Half-wave potentials for reduction of bromides of different bulk

Compound	$-E_{\frac{1}{2}}$
Me_3CBr	2·19[a]
1-Bromoadamantane	2·02[b]
9-Bromotriptycene (86)	2·02[c]

[a] Reference 34.
[b] Reference 96.
[c] Calculated from Reference 37.

TABLE 15. Half-wave potentials for reduction of α-chloroketones[158]

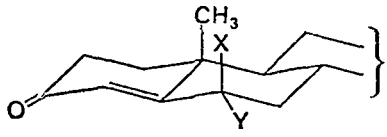
No.	Compound	$-E_{\frac{1}{2}}$[a]
(90)		1·39
(91)		1·57
(92)		1·42
(93)		1·45
(94)		2·08
(95)		1·86

[a] Half-wave potential in volts versus sce, using DMF, 0·1M Bu_4NBr, at a Hg cathode.

to the carbonyl group, followed by rapid protonation) equation 48)[159]. Kabasakalian and McGlotten[160] examined the polarography of twelve α-halosteroids and claimed that differences in $E_{\frac{1}{2}}$ for chloro derivatives permitted the distinction between axial and equatorial isomers (see **96**, for

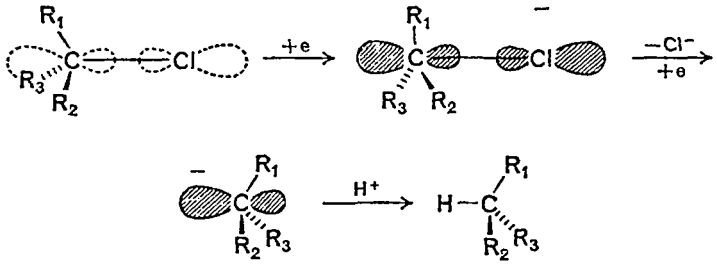
(48)

example). Also in the series of α-brominated ketosteroids[161] there appears to be a difference in $E_{\frac{1}{2}}$ between axial and equatorial C—Br bonds, and again the axial C—Hal bond is easier to reduce.



No.	X	Y	$-E_{\frac{1}{2}}$
(96a)	H	Cl	1·12
(96b)	Cl	H	0·74

Grabowski and coworkers[127] have proposed an interesting mechanistic possibility: since the electrons enter the lowest unoccupied σ* orbital of the substrate molecule, it is possible that electron addition–bond cleavage, with an electron pair in the σ* orbital, could lead to *inversion* at the reaction centre (Scheme 19). The obtention of a product of retained stereochemistry in at least one case[182] suggests, however, a deficiency in the scheme. The former authors note that irrespective of the validity of Scheme 19, the

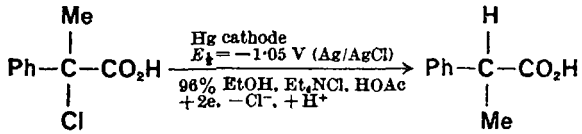


SCHEME 19

theory does not bear on the question of orientation of the substrate molecule with respect to the electrode surface.

Only two results have been published[45,127,162] which deal directly with the stereochemical fate of an aliphatic carbon centre during electroreduction of the carbon–halogen bond and there is good reason to believe

that one of these results may represent a special case of the problem. Czochralska[45, 127, 163] reported the reduction of optically active 2-chloro-2-phenylpropionic acid (**97**) to hydratropic acid (**98**) (equation 49) to



(97) (98) (49)

proceed with 77–92% inversion of configuration. The author established[163] that at this potential C—Cl cleavage must be the primary process by comparing the reduction potential of **97** with mandelic acid (**99**) and **98** (cf. Table 16). Clearly, further reduction occurs at the more negative

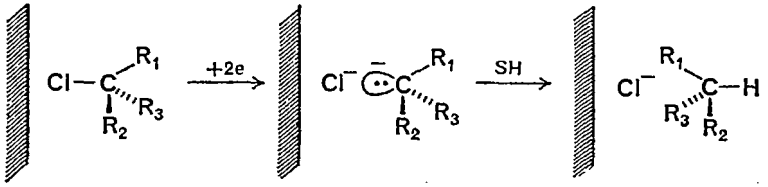
TABLE 16. Half-wave potentials for reduction of compounds of the type $PhC(CH_3)COOH$ [163]
|
X

No.	X =	$-E_{\frac{1}{2}}$ (1)[a]	$-E_{\frac{1}{2}}$ (2)[b]
97	Cl	1·02	1·91[c]
98	H	1·96	—
99	OH	1·81	—

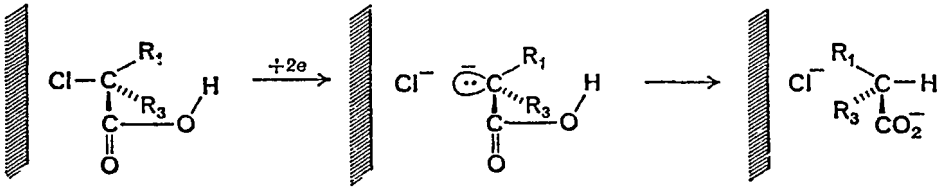
[a] Half-wave potential in volts, versus Ag/AgCl, using 96% EtOH, Et_4NCl, for the first two-electron wave.
[b] Half-wave potential of the second two-electron wave.
[c] In principle this figure and $-E_{\frac{1}{2}}$ (1) for compound **98** should be identical.

second potential (ca. −2·0 V) (assigned as proton reduction by the author). A similar stereochemical result for the dissolving metal reduction of this same compound has been reported[164, 165]. In addition to the rationale advanced by these workers[127] (see Scheme 19), at least two other reasonable interpretations can be accommodated. If reduction to the carbanion occurs while the C—Cl bond is orientated perpendicular to the electrode surface (Scheme 20) the front side of the carbanion may be shielded from direct protonation, provided proton-donating species are not interposed between the carbanion and the electrode surface. In addition, the carboxyl group is ideally located for intramolecular proton transfer to the back of the carbanion, a process which would result in a product of inverted configuration (Scheme 21). It would be very interesting to have stereochemical

studies performed on derivatives of this acid, e.g. an ester or amide to decide about this mechanistic alternative. In a related system without a carboxyl group present, Eberson[162] obtained a very small but reproducible

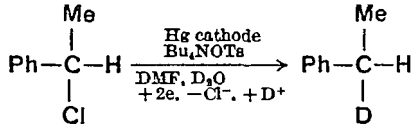


SCHEME 20



SCHEME 21

net retention of configuration. The reduction of optically active α-phenethyl chloride in DMF–D_2O gave [α-D]ethyl benzene of 2% retained configuration (equation 50). This result suggests that the carboxyl group of **97** may

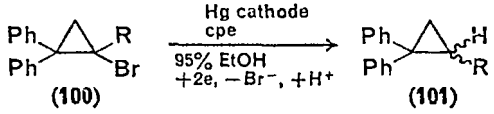


(50)

indeed play an important configuration-determining role in the reduction. Alternative to this, perhaps the electrode does not exert a shielding effect in this case, or racemization may occur at the radical stage of reduction. Clearly, stereochemical results in other systems will be required before the question of stereochemistry of reduction can be resolved.

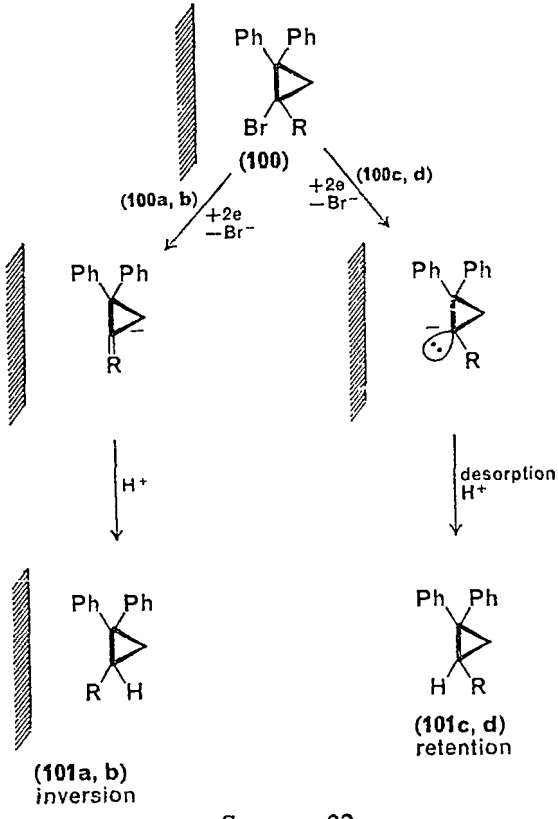
b. Cyclopropyl monohalides. Annino and coworkers[166] carried out an investigation of the reduction of a series of optically active 1-substituted 1-bromo-2,2-diphenylcyclopropanes (**100**), the results of which are particularly instructive. Depending upon the nature of the substituent, the reduction product **101** gave stereochemical results from 56% inversion to 38% retention of configuration (equation 51). A reasonable mechanism to account for these results is shown in Scheme 22. Predominant inversion is observed with those compounds for which the developing carbanion α to a

conjugating group (**100a** and **b**) can stabilize and flatten the carbanion. In these cases protonation occurs from the less hindered side of the molecule, away from the electrode surface. For cases in which conjugative stabilization is not possible (**100c** and **d**), the cyclopropyl carbanion can be desorbed into the bulk of the solution and protonated before inversion has occurred.



(51)

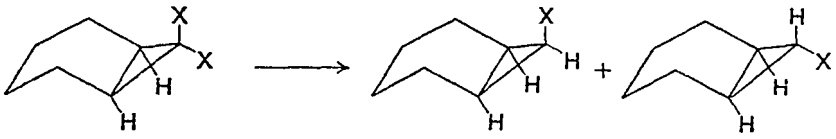
No.	R	Stereochemistry
(100a)	CO_2H	26–35% inversion
(100b)	CO_2Me	30–56% inversion
(100c)	CO_2^-	31–38% retention
(100d)	CH_3	21% retention



SCHEME 22

This result is consistent with the known configurational stability of such carbanions[156,167,168]. It may even provide further understanding to the result observed by Czochralska[45,127] (see equation 48). In this case the presence of acetic acid would repress carboxyl group ionization and give a result analogous to **100a** → **101a**. An earlier report of the reduction of **100d** by Mann, Webb and Walborsky[39] gave essentially the same stereochemical result (21–26% retention) and added some interesting new aspects to the reaction (see section III. B. 9).

c. Cyclopropyl geminal dihalides. Two reports appeared in 1968 which provided new information regarding the mode of formation of the carbanion intermediate. Fry and Moore[90] reduced the first halogen of a series of cyclopropyl geminal dihalides. The thermodynamically less stable *cis* isomer was the major product in all cases, and its amount increased with increasingly protonic solvents (Scheme 23). The same result prevailed

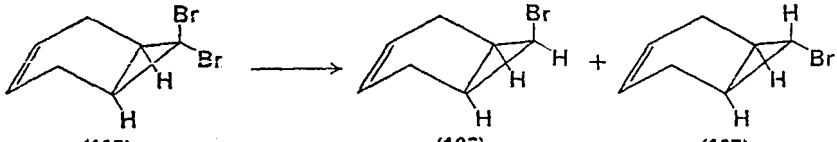


(102) **(103, *cis*)** **(104, *trans*)**

No.	X =	Solvent	Product ratio (**103** : **104**)
(102a)	Br	100% DMF	61 : 39
		90% MeOH, 10% H_2O	84 : 16
(102b)	Cl	100% DMF	81 : 19
		95% MeOH, 5% HCl	100 : 0

SCHEME 23

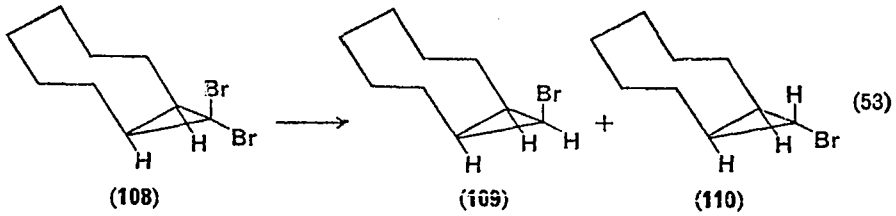
when unsaturation was present in the 3,4-position (**105**) (equation 52) and even in the analogous bicyclononyl system (**108**, equation 53). The



(52)

(105) **(106)** **(107)**

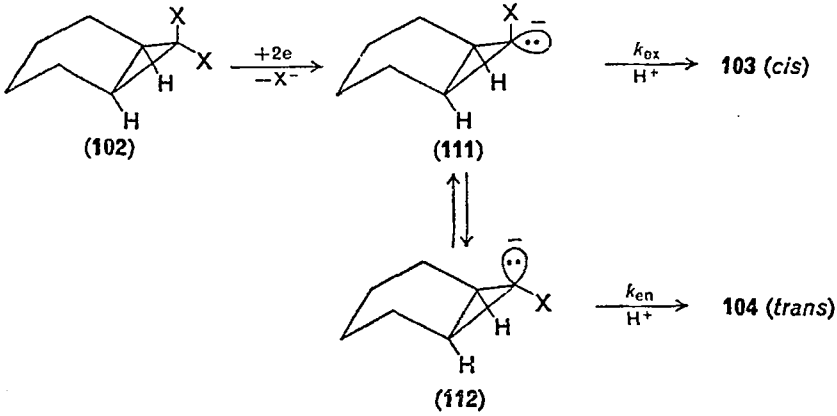
	Product ratio (**106** : **107**)
100% MeOH	73 : 27
90% MeOH, 10% H_2O	91 : 9



(53)

	Product ratio (109 : 110)
100% MeOH	100 : 0

preceding results are easily accommodated by assuming that electron transfer occurs to the more accessible (*exo*) halogen atom to produce the *endo*-halo carbanion (**111**) which diffuses into solution to be protonated before it can become equilibrated (**112**, Scheme 24). The variation of

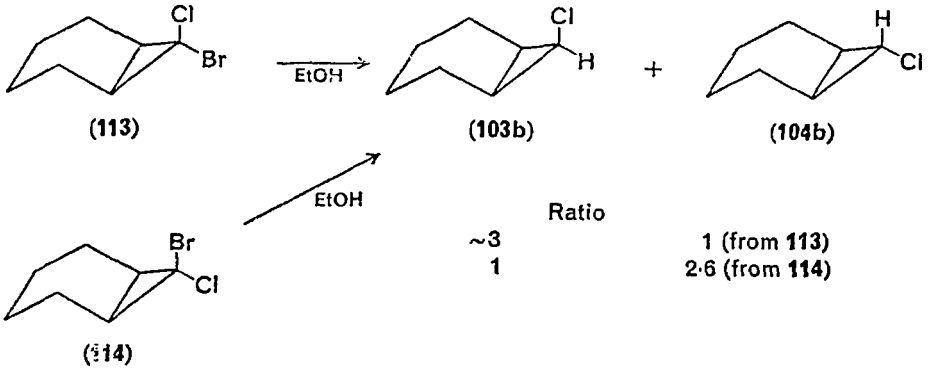


SCHEME 24

product composition with proton concentration appears to preclude the possibility that product composition is a result of kinetic control in the protonation step ($k_{ex} \gg k_{en}$) since, to a first approximation, variation of [H^+] should not affect the ratio of **103** : **104**.

Erickson and coworkers[91] reduced the two possible 7-bromo-7-chloro-bicyclo[4.1.0]heptanes (**113**) and (**114**) (Scheme 25). Their result for the reduction of **102a** (*cis* : *trans* = ≈ 1·3 : 1) corresponded closely to that of Fry and Moore[90] for the same system. The results of Scheme 25 are interpreted by the authors to imply that reduction can occur at either

halogen atom rather than just at the *exo*. However, in mixed halogen compounds the reduction of the carbon–bromine bond would be expected to occur more readily than that of the carbon–chlorine bond, and so the results are neither unexpected nor inconsistent with the study of Fry and Moore.



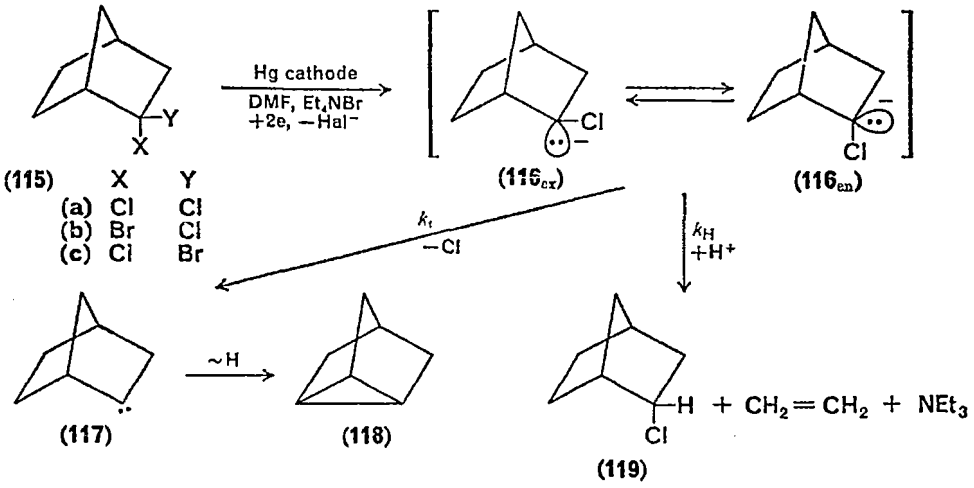
SCHEME 25

8. Proton-donating properties of solvents

One of the more significant developments in recent years in the study of electroorganic chemistry has been an increase in appreciation for the source of protons in the final step of these reductions. Acetonitrile and DMF have been used successfully as anhydrous solvents by many investigators and although a number of investigators have been concerned with the proton-donating ability of these solvents[169,170] a far more important source of protons appears to be from the β-elimination reaction of tetraalkylammonium salts[56,111]. There have also been a few reports of the interference of DMF with electroreduction[171]. It has been appreciated for some time that the bulk concentration of a deliberately added proton source is not necessarily the same as the concentration near the surface of the electrode, where protonation of short-lived species occurs. Indeed, it has been convincingly demonstrated[22,172] that tetraalkylammonium salts effectively exclude water molecules from the double layer and can render highly aqueous solutions rather aprotic at the electrode surface.

A recent paper by Fry and Reed[56] has provided clear evidence that the same conclusion is true in cathodic reduction of halides and that the bulk concentration of protic acids is less important than the type of the proton donor. Phenols and carboxylic acids are good proton donors to radical anions in DMF, but water is not, perhaps due to hydrogen bonding with the solvent. Fry and Reed found that geminal dihalides **115a**, **b** and **c**

(Scheme 26) all underwent reductive elimination of a halide ion to produce a carbanion (**116**), which behaved the same regardless of which dihalide had been its precursor. It underwent two competitive reactions at similar



SCHEME 26

rates: proton transfer (rate k_H), which occurred exclusively to the *exo*, less hindered side of the molecule (see also section III. B. 7. c), and chloride elimination, to produce carbene **117**, which is known[173] to undergo C—H insertion to yield nortricyclene (**118**). The product distribution as a function of added proton sources is shown in Table 17. Although water is somewhat effective in increasing the rate of the proton capture reaction, phenols and acetic acid are quite ineffective. This suggests that the latter are *not*

TABLE 17. Product composition as a function of proton availability in the cathodic reduction of **115**[56]

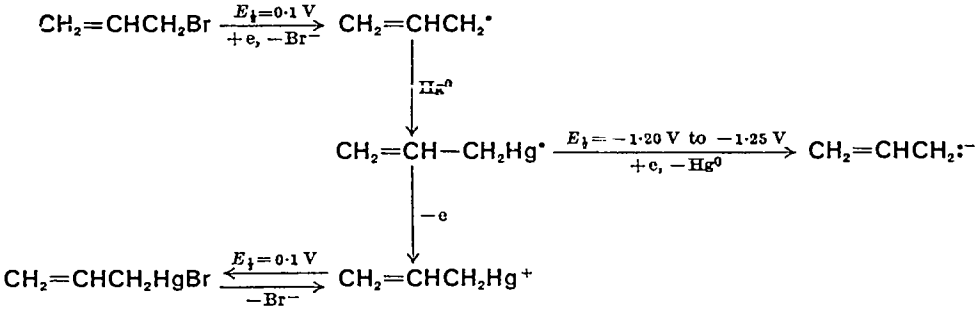
Added proton source[a]	Product composition (%) **119**	**118**
None	38	62
1M H_2O or MeOH[b]	80[c]	20
$MeCO_2H$ or ArOH[d]	~38	~62
$Et_3\overset{+}{N}H\overset{-}{B}r$	92	8

[a] All results are for DMF solvent with Et_4NBr as supporting electrolyte.
[b] Compare with a ratio 60 : 40 for reaction using sodium naphthalenide and 50 millimolar H_2O.
[c] Less ethylene is formed.
[d] Ratio could not be changed even with ten-fold excess of proton source.

incorporated in the double layer at the electrode surface. On the other hand, the cationic triethylammonium ion is apparently effectively incorporated into the layer, serving as a good proton source.

9. Formation of organometallics

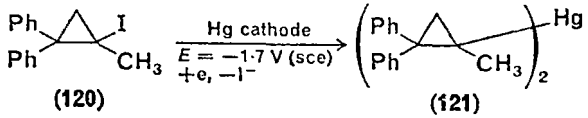
The electrochemical behaviour of carbon–halogen compounds is further complicated by the formation of organometallic compounds formed by reaction with the electrode material. There are many reports of the isolation of organometallics from electroreduction reactions. Although the possibility of a non-electrochemical reaction exists[174–176], it is clear that organometallic compounds are formed during the reduction step. The reduction of ethyl bromide at a Pb electrode yields Et_4Pb[38] and β-iodopropionitrile at Hg, Sn, Pb or Tl cathodes is reported[177] to give, at the potential of the first polarographic wave, $Hg(CH_2CH_2CN)_2$, $Sn(CH_2CH_2CN)_2$, $Pb(CH_2CH_2CN)_2$ and $Tl(CH_2CH_2CN)_2$, respectively. Kirrman and Kleine-Peter[178] confirmed the presence of allyl mercuric bromide during the reduction of allyl bromide in 50% aqueous dioxan. These workers report $E_{\frac{1}{2}} = -1{\cdot}20$ V (sce) for allyl bromide with a prewave at $\sim -0{\cdot}1$ V. For the reduction of allyl mercuric bromide they determined two one-electron reductions, $E_{\frac{1}{2}}$ (1) $= -0{\cdot}1$ V and $E_{\frac{1}{2}}$ (2) $= -1{\cdot}25$ V. These results can be interpreted as shown in Scheme 27. Diallyl mercury was found to



SCHEME 27

be reduced only with great difficulty and probably is not involved in the reaction. On the other hand, Sease and Reed[179] reported the isolation of dihexyl mercury from the large-scale reduction of hexyl bromide at a mercury cathode. This result is interpreted as evidence for the presence of radicals, as was also done from analogous findings in the reduction of allenic halides[180]. The current–time curve during reduction of 1-bromo-1-methyl-2,2-diphenylcyclopropane was not exponential[39], indicating the presence of an intermediate. The dialkylmercury compound was judged to

be the best candidate for the intermediate. Analysis of the electrolyte during electrolysis showed that soluble mercury compounds were present, and from the reduction of 1-iodo-1-methyl-2,2-diphenylcyclopropane (**120**) at −1·7 V (sce) the dialkylmercury compound (**121**) could actually be isolated (equation 54). Whereas in 1960 Marple and coworkers[151] found no



(120) (121) (54)

evidence for mercury compounds in the electroreduction of monohalides, Grimshaw and Ramsey[51] isolated several dibenzylmercury derivatives following preparative scale reduction of substituted benzyl halides. It is noteworthy that in the cases in which a bibenzyl is a significant product dibenzylmercury derivatives are also found. *p*-Nitrobenzyl bromide forms the dimer exclusively upon preparative electroreduction. Benzyl bromide and benzyl bromides substituted in the ring with a group of negative σ value all yielded the corresponding dibenzylmercury compounds; 3-bromo and 3,4-dichlorobenzyl bromide, with groups of intermediate values of σ, gave a mixture of substituted dibenzylmercury and bibenzyl; and 4-nitrobenzyl bromide, with a group of a large positive value of σ, gave only 4,4′-dinitrobibenzyl. For the intermediate examples in which both products were found, the relative yield of each was strongly dependent on both the supporting electrolyte and the electrode potential (for an example, see Table 18). From these data the authors conclude that all products are formed from the benzyl radical and that it is not possible to reduce the benzyl radical to the benzyl carbanion at a mercury cathode in aqueous or alcoholic solution in these systems. However, the trapping of benzyl carbanions in DMF by carbon dioxide[111] (see section III. B. 6. d) to produce phenylacetic acid shows that, at least under anhydrous conditions,

TABLE 18. Product distribution from the cathodic reduction of 3,4-dichlorobenzyl bromide in methanol solution as a function of electrode potential[51]

	Product ratio	
$-E$ [a]	Bibenzyl	Dibenzylmercury
0·94	5	95
1·05	48	52
1·30	82	18

[a] Cpe was conducted at this potential.

carbanions must be present. Also, a recent investigation[181] demonstrates that toluene is formed in the reduction of benzyl bromide under anhydrous conditions and that the ratio dibenzylmercury/toluene is strongly dependent on the electrode potential, toluene being the only product at the more negative potentials (see Table 19).

TABLE 19. Product distribution from the cathodic reduction of benzyl bromide in acetonitrile solution as a function of electrode potential[181]

$-E$ [a]	Current yield (%)		
	Dibenzylmercury	Toluene	Bibenzyl
1·35[b]	60	Trace	—
1·80	46	44	3
2·1[c]	0	99	Trace

[a] Cpe versus $Ag/AgClO_4$ reference electrode.
[b] At the foot of the single polarization curve.
[c] At the plateau.

In at least one other case[182] the fully reduced product (C—X → C—H) accompanies a substantial isolated yield of organomercurial in the presence of a protonic solvent (equation 55). It is implied here that either

$$ICH_2CH_2CN \xrightarrow[0\cdot5N\ H_2SO_4]{Hg\ cathode} CH_3CH_2CN + Hg(CH_2CH_2CN)_2 \qquad (55)$$

the two products are formed from competitive reaction of carbanion (with solvent) and radical (with mercury), respectively, or that the carbanion is precursor to both products. Independent of the formation of organomercurials at the electrode, reactions may be complicated by the formation of amalgams between the supporting electrolyte and the electrode. Such cases have been reported[183] for tetrabutylammonium salts at mercury.

IV. ANODIC REACTIONS

Although electroorganic preparation of compounds containing carbon–halogen bonds is not within the scope of this chapter, it should be mentioned that a recent exhaustive review with extremely useful tables covers this topic[1a]. A more specialized review covering electrochemical fluorination has also appeared[184]. A paucity of reports dealing with electrochemical oxidation of carbon–halogen compounds is due to the fact that among these compounds only iodides appear to be oxidized readily in the region of accessible potentials (see section II. B), although the oxidation

of bromides has been observed (*vide infra*). A discussion of halide electrooxidation has recently appeared[1b].

The oxidation of aliphatic and aromatic halides follows a different course, the former giving rise to products derived from a carbonium ion, while the latter undergo coupling reactions (Scheme 2). The difference in behaviour may reflect the difficulty in producing aromatic carbonium ions. Controlled potential oxidation of aliphatic iodides in acetonitrile[185] gives a Ritter-type reaction[186,187] (equation 56) to produce acetamides upon

$$RI \xrightarrow[-\frac{1}{2}I_2]{-e} R^+ \xrightarrow{MeCN} \left[R-\overset{+}{N}\equiv C-Me \leftrightarrow R-N=\overset{+}{C}-Me \right] \xrightarrow[-H^+]{H_2O} RNHC(=O)Me \qquad (56)$$

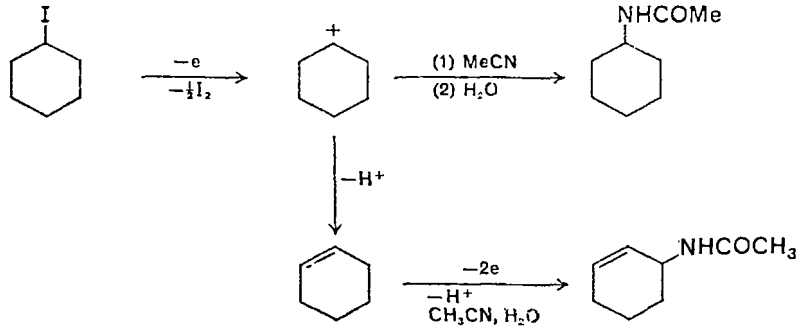
hydrolysis. The electrochemical Ritter reaction has been observed during oxidation reactions conducted in acetonitrile solution[188], a result thought to imply the intermediacy of carbonium ions. Further evidence of the carbonium ion nature of this reaction is found in the observation that neopentyl iodide produces *N*-*t*-pentylacetamide, via a skeletal rearrangement[185].

The preparative potential of this reaction is suggested by the work of Laurent and Tardivel[189] who reported excellent isolated yields of substituted acetamides from aliphatic and arylaliphatic iodides (Table 20).

TABLE 20. Anodic oxidation of aliphatic iodides in acetonitrile[189]

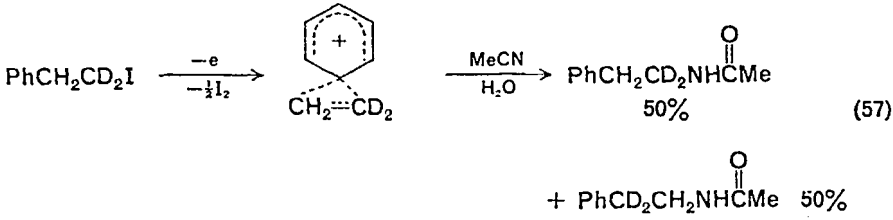
R in RI	Overall yield (%)	*N*-Substituted acetamide product composition	
		RNHCOMe	R¹NHCOMe
Pr	70	60	40 (*i*-Pr)
Bu	70	58	42 (*s*-Bu)
i-Bu	84	0	12 (*s*-Bu) 88 (*t*-Bu)
s-Bu	54	100	0
	79	~100	Trace
$PhCH_2CH_2-$	93	100	0
$PhCH_2\underset{\displaystyle Me}{\underset{\vert}{CH}}-$	97	95	Trace $\left(\begin{array}{c} Et \\ \vert \\ PhCH- \end{array}\right)$
			Trace $\left(\begin{array}{c} Me \\ \vert \\ PhCHCH_2- \end{array}\right)$

The extensive rearrangement encountered by these workers is further evidence of the cationic nature of this reaction. Oxidation of cyclohexyl iodide produced a mixture of *N*-cyclohexylacetamide and *N*-cyclohex-3-enylacetamide, a result which the authors ascribe to elimination of a proton from the cation to produce cyclohexene, which in turn is oxidized to the allylic acetamide (Scheme 28). This postulate is supported by the experimental results of Shono[190] on the electrooxidation of cyclohexene in acetonitrile.

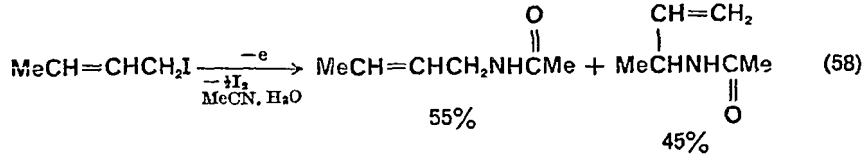


SCHEME 28

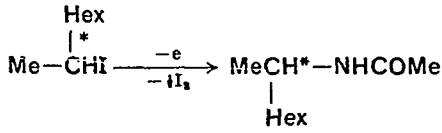
In a more recent paper Laurent and Tardivel[191] present clear evidence for a Wagner–Meerwein rearrangement during the oxidation of β-phenethyl iodide-α,α-d_2. For this example the authors report 50% rearrangement and postulate phenyl participation (equation 57), via a phenonium ion. It is



interesting that no hydride migration to form derivatives of the α-phenylethyl system was observed in this reaction. Crotyl iodide under the same conditions showed extensive rearrangement (equation 58). However, the



interesting observation that optically active 2-iodooctane gave unrearranged product (70%) with 25% *inversion* of configuration (in addition to 30% of

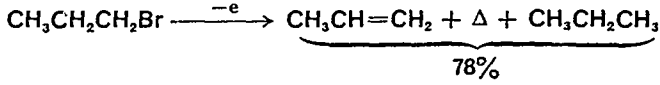


(59)

70% yield 25% inversion

rearranged products) (equation 59) clearly suggests that a simple, symmetrically solvated carbonium ion cannot be involved. Again, either the electrode surface or the departing halide atom must play a role in determining the stereochemistry of this reaction.

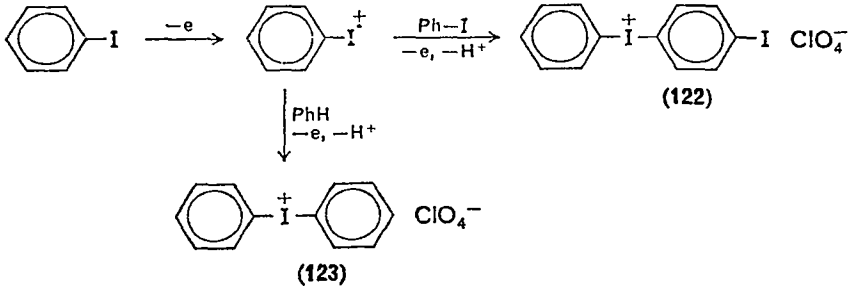
Oxidation of propyl bromide is reported to produce an excellent yield of a mixture of propylene, cyclopropane and propane[192] (equation 60). The



(60)

former two products appear to be derived from a carbonium ion intermediate, but the origin of the saturated hydrocarbon is unclear.

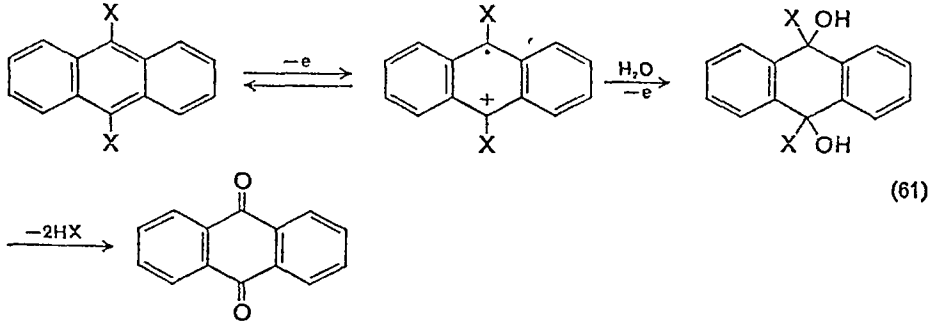
By contrast, no carbonium ion products are formed from aryl iodides with acetonitrile. Iodobenzene in acetonitrile with lithium perchlorate as supporting electrolyte yields 4-iododiphenyliodonium perchlorate (**122**) (Scheme 29). In the presence of benzene, diphenyliodonium perchlorate (**123**) is formed[185].



SCHEME 29

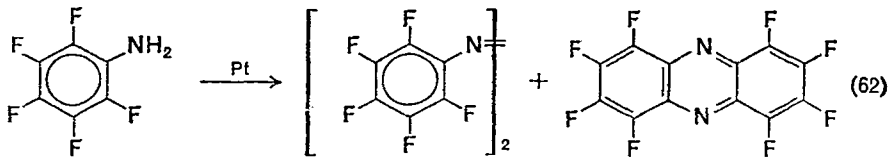
Aryl bromides normally undergo reactions at other positions than halogen (section B), but a few cases of anodic replacements of halogen in easily oxidized bromoarenes are known. 9,10-Dihaloanthracenes undergo initial one-electron transfer upon oxidation in acetonitrile to form

moderately stable cation radicals[193]. In the presence of water these react further in an overall two-electron process to form anthraquinone, possibly via a bis-geminal halohydrin (equation 61). In the presence of lutidine a nucleophilic displacement on bromine has been observed in 9,10-dibromoanthracene[194].



(61)

Some interesting synthetic applications have been found in the anodic oxidation of perfluorinated aromatic compounds[195–197]. Anodic oxidation of, e.g. perfluoroaniline in acetone–water/potassium acetate at 1·5–1·6 V (sce) gave a mixture of (the expected) decafluoroazobenzene (18%) and octafluorophenazine (8%) with loss of two fluorine atoms (equation 62).



(62)

The formation of the latter compound was thought to involve free radical displacement of fluorine (by the $C_6F_5NH^{\bullet}$ radical).

The scant work which has been reported so far for anodic halide oxidation reactions suggests synthetic applications of this reaction, particularly in aliphatic systems and further research in this area should be fruitful.

V. ACKNOWLEDGMENTS

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VI. REFERENCES

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The Chemistry of The Carbon–Halogen Bond
Edited by Saul Patai

CHAPTER 16

Thermochemistry of organic halides

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'A man who does not know what has been taught by those that have gone before him is sure to set an undue value on his own ideas.'
MARK PATTISON

I. INTRODUCTION

When Professor Patai wrote the letter of invitation for this chapter, he asked that lengthy tabulated data be excluded and that 'the emphasis should be put on the explanation of how thermochemical results and principles may help the chemist in understanding and in prediction and on the presentation of recent and novel results'. It is always difficult for a thermochemist to follow such advice, because his main activity is usually compiling tables of data and he is interested in a couple of kcal/mole here or a few cal/(mole-K) there. At the same time, the task has been made very

much easier by the publication in the last year or so of some extensive and critical monographs and reviews. These are discussed in more detail in the next section.

Currently, fluorine gets the lion's share of attention in halogen chemistry, a fact reflected in the contents of the present chapter. The selection of topics will also be influenced by the author's early training in gas-phase thermochemistry. Although gas-phase data are probably better understood at the moment than their liquid counterparts, it seems likely that liquid-phase thermochemistry will receive relatively more attention in the future.

The thermochemical quantities under consideration are heat of formation ΔH_f^0, entropy S^0 and heat capacity C_p^0. Although the joule will soon replace the kilocalorie as the unit of energy, English-speaking chemists and English language chemical journals still predominantly use the kilocalorie. The units used throughout will therefore be kcal/mole for ΔH_f^0 and cal/(mole-K) for S^0 and C_p^0.

There is a minor inconsistency in the current use of the word thermochemistry. It is sometimes used, as in the present chapter, to include entropy and heat capacity and is, therefore, synonymous with the term chemical thermodynamics. However, authors occasionally use the term thermochemistry to mean heats of formation or heats of reaction and do not include S^0 or C_p^0.

Those interested in the detailed application of thermochemistry to kinetics should read the chapter by Egger and Cocks on the pyrolysis of carbon–halogen bonds, in the present volume.

II. TYPES OF THERMOCHEMICAL DATA AND WHERE TO FIND THEM

A. Group Additivity Values

Group additivity is used to estimate thermochemical data that are lacking, to check measured data for consistency with those for chemically related compounds and to point out where further experiments are needed. The group additivity method is simple, fast and accurate and is quickly gaining wide acceptance as the best method for estimation of gas-phase data. For example, *ASTM Committee E-27 on the Hazard Potential of Chemicals* has adopted Group Additivity as the method to estimate the thermochemical properties of the air pollutants peroxyacetyl nitrate (PAN) and peroxybenzoyl nitrate (PBN).

Group additivity postulates that chemical thermodynamic properties of molecules are made up of contributions from the individual groups that comprise the molecule. Group additivity is therefore an extension of the

series atom additivity, bond additivity, . . . and turns out to be an excellent compromise between simplicity and accuracy. For a detailed treatment of the additivity principle as applied to thermochemistry, see an early paper by Benson and Buss[1], and a more recent *Chemical Review* article[2]. The latter contains all the group values that could be derived from gas-phase thermochemical data for organic halogen compounds up to 1969. The group values permit the estimation of S^0 to an accuracy of ± 1 cal/(mole-K) and C_p^0 to an accuracy of $\pm 0{\cdot}5$ cal/(mole-K). For most organic compounds—for example, hydrocarbons, oxygen-containing, nitrogen-containing and so forth—group additivity allows ΔH_f^0 to be estimated to within ± 1 kcal/mole. However, there is evidence that, for very polar compounds, even group additivity is insufficient to predict ΔH_f^0 adequately. The accuracy for haloalkenes, such as $CF_2{=}CH_2$ and $CCl_2{=}CH_2$, may be as poor as ± 5 to ± 10 kcal/mole. Group additivity predicts that the heats of reaction in equations (1) and (2) are zero, whereas the experimental values[3] are more than 7 kcal/mole exothermic. The *Chemical Review* group values are reproduced together with a few additional groups for halogenated free radicals in two recent monographs by Benson[4] and by Benson and O'Neal[5].

$$H_3CCH_3 + Cl_3CCCl_3 \longrightarrow H_3CCCl_3 \qquad (1)$$

$$H_3CCH_3 + F_3CCF_3 \longrightarrow H_3CCF_3 \qquad (2)$$

The Benson and Buss[1] paper contains bond contributions that permit estimation for organic halogen compounds of ΔH_f^0 to ± 6 kcal/mole, S^0 and C_p^0 at 25°C to ± 3 cal/(mole-K). The accuracy of bond additivity is, therefore, not as good as that of group additivity, but it is often good enough for a first-order approximation. Even atom additivity can be used for S^0 and C_p^0 at 25°C and has about the same accuracy as bond additivity. The Benson and Buss paper has the atom contributions.

Group additivity has recently been extended[6] to the estimation of the heat capacities of liquids at 25°C with an improvement in precision from about ± 4 to better than 1·5 cal/(mole-K). There are only a few data for halogenated organics, therefore only a few halogen-containing groups could be derived. However, if the groups are not available, then C_p^0 of the liquid can be estimated to within a few cal/(mole-K), if the C_p^0 of the ideal gas is known, from ΔC_p^0 (liquid minus gas) = 12 cal/(mole-K).

B. Critically Evaluated Reviews

The last few years have seen the publication of two independent monumental efforts in extracting from the literature, critically evaluating

and compiling thermochemical data. I had not thought it possible that the work could have been done by so few people, gifted and experienced though they be. The books are Stull, Westrum and Sinke's *The Chemical Thermodynamics of Organic Compounds*[7] and Cox and Pilcher's *The Thermochemistry of Organic and Organometallic Compounds*[8]. These books will be invaluable to physical organic chemists for many years to come.

In Stull, Westrum and Sinke's book, the two features most relevant to the present task are the chapter on the chemical thermodynamics of halogen compounds and the computer print-out table towards the end of the book listing selected values of ΔH_f^0 and S^0 of organic compounds at 298K, arranged by empirical chemical formula. The chapter on halogen compounds contains tables of data in the JANAF format[9] from 298K to 1000K for the ideal gas state. Care should be exercised in using these tables, because there is no clear distinction between measured and estimated values. The methods of estimation are based on what is essentially bond additivity and may, therefore, be off by 2 or 3 cal/(mole-K) for S^0 and C_p^0. The tables show the lack of data in the aromatic series; there are data for only three aromatic chlorides, one aromatic bromide and one aromatic iodide.

Cox and Pilcher's book is complementary to that of Stull, Westrum and Sinke. Cox and Pilcher give no data on S^0 or C_p^0 but have done an extraordinarily thorough job on ΔH_f^0. The heart of the book is a table of thermochemical data. To the user who wants an answer rather than to find out how the answer was obtained, the most useful columns in the table are ΔH_f^0 (l or c) and ΔH_f^0 (g). For the specialist, there is a rundown on how the data were obtained. The ordering of compounds is different from that of most texts and requires a little study.

In 1961, Patrick[10] wrote an interesting review of the thermochemistry of organic fluorine compounds. Although some of the heats of formation differ from current thinking by about 5–10 kcal/mole, much of the discussion is still valid, particularly on the thermal decomposition of polymers.

The generally accepted source of data for the halogen atoms, hydrogen halides and small organic compounds is the *JANAF Thermochemical Tables*[9]. These tables list thermochemical properties up to 6000K.

Lacher and Skinner[3] have critically examined heats of formation of fluorocarbons and fluorohalogenated hydrocarbons. Golden and Benson[11] have thoroughly reviewed the hydrocarbon radical thermochemistry derived from iodine-atom reactions, much of it their own work. Furuyama, Golden and Benson[12] have summarized the thermochemical properties of halomethanes and halomethyl radicals.

C. Original Data

No single journal contains a majority of original thermochemical data, but about half the field is covered by the *Journal of Chemical Thermodynamics*, the *Journal of Chemical Physics*, the Chemical Society (London) journals and the American Chemical Society journals (i.e. the *Journal of Chemical Engineering Data*, the *Journal of Physical Chemistry* and the *Journal of the American Chemical Society*). A vitally important key to the current literature is the *Bulletin of Thermodynamics and Thermochemistry* published annually by IUPAC. Most of the *Bulletin's* content is now on tape for mechanized searching. The Substance–Property Index is a good place to start a search. For each compound, this index gives the type of chemical thermodynamic property measured and a reference to another part of the *Bulletin*. This *Bulletin* reference is either a literature reference in the Bibliography of Recent Papers section or an abstract of work in progress at one of the 2000 worldwide laboratories that contribute information to the *Bulletin*. The literature reference is usually both to the original paper and a *Chemical Abstracts* reference.

III. THERMOCHEMISTRY AND KINETICS

Most elementary chemical reactions obey the Arrhenius law, and therefore their rate constants can be broken down into pre-exponential Arrhenius A-factors (or entropies of activation) and activation energies (or heats of activation).

$$k = A\exp(-E/RT)$$
$$= \frac{\kappa T}{h}\exp(\Delta S^{+}/R)\exp(-\Delta H^{+}/RT)$$

where k is the rate constant, A is the Arrhenius A-factor, E is the activation energy, R is the gas constant, T is absolute temperature, κ is Boltzmann's constant, h is Planck's constant, ΔS^{+} is the entropy of activation, and ΔH^{+} is the heat of activation.

Considerable progress has been made in understanding and predicting Arrhenius A-factors of gas-phase reactions using transition-state theory and estimates of thermochemical properties of free radicals and transition states. Benson and O'Neal have shown[5] that, for over 120 unimolecular reactions, the Arrhenius A-factor can be estimated to within the average experimental uncertainty of a factor of 2. For example, they have calculated that the A-factor for the elimination of HCl from ethyl chloride should be $10^{13.6}$ s^{-1} compared with the observed A-factor of $10^{13.6\pm0.5}$ s^{-1}. Benson

and Haugen[13] have used a simple, self-consistent electrostatic model to predict activation energies for four-centre reactions such as,

$$X_2 + Y_2 \rightleftarrows 2\,XY \quad (3)$$

$$X_2 + \text{olefin} \longrightarrow \text{product} \quad (4)$$

$$HX + \text{olefin} \longrightarrow \text{product} \quad (5)$$

where X, Y = H, F, Cl, Br and I. For most of the reactions, the calculated and experimental results agreed to within $\pm 1{\cdot}3$ kcal/mole, and the maximum deviation was 3·2 kcal/mole.

There is another useful relation between Arrhenius parameters and thermochemistry. For the reaction

$$A + B \rightleftarrows C + D \quad (6)$$

it can be shown that the overall entropy change for the reaction (6), that is ΔS^0_6, is related to the A-factor of the forward reaction A_6 and the A-factor of the reverse reaction A_{-6}, by $\exp(\Delta S^0_6/R) = A_6/A_{-6}$. Similarly, the heat of reaction ΔH^0_6 is related to the activation energy of the forward reaction, E_6, and the activation energy of the back reaction E_{-6}, by $\Delta H^0_6 = E_6 - E_{-6}$. Therefore, if the Arrhenius parameters of the forward reaction are known, the Arrhenius parameters for the back reaction can be calculated exactly from the known or estimated thermochemical properties of the reactants and products with no assumption necessary for transition state properties.

The application of thermochemical kinetic principles to the pyrolysis of organic halogen compounds is treated in more detail by Egger and Cocks in this volume.

IV. SOME CURRENT TOPICS IN ORGANIC HALOGEN THERMOCHEMISTRY

A. The F—F Bond Strength

The bond dissociation energy of the fluorine molecule is one of the most important thermochemical quantities in halogen chemistry. Part of the interest stems from theories of bonding, which have sought to explain the anomalously low F—F bond strength. Perhaps more relevant to organic fluorine thermochemistry, the F—F bond strength gives the heat of formation of the fluorine atom, so that it in turn is used to calculate R—F bond dissociation energies:

$$\Delta H^0_f(F) = \tfrac{1}{2}\,D(F{-}F)$$

where D is the bond strength or bond dissociation energy.

$$D(R{-}F) = \Delta H^0_f(R) + \Delta H^0_f(F) - \Delta H^0_f(RF)$$

Up to 1950, the widely accepted value of D(F—F) was 63 kcal/mole. Then Evans, Warhurst and Whittle[14] led the change to D(F—F) ~ 37 kcal/mole, a value made easier to accept by the effusion measurements of Wise[15] which gave D(F—F) = 39·9 kcal/mole. The JANAF value is based on the experiments of Wise[15] and is D(F—F) = 37·9 ± 0·6 kcal/mole, which gives ΔH_f^0(F) = 18·9 kcal/mole.

However, the whole subject has been reopened recently. Dibeler, Walker and McCulloh have studied the photoionization of F_2 [16] and ClF [17], and have concluded that D(F—F) = 30·9 ± 0·7 kcal/mole. The ClF results use an unpublished value, ΔH_f^0(ClF) = −14·4 ± 0·8 kcal/mole, obtained by Nuttale and quoted by Dibeler, Walker and McCulloh[17]. In support of their 'low' value for D(F—F), Dibeler, Walker and McCulloh refer to a Birge–Sponer extrapolation by Stricker and Krauss[18] that gives D(F—F) = 33·2 ± 1·1 kcal/mole.

On the other side of the coin from Stricker and Krauss are Iczkowski and Margrave[19] whose Birge–Sponer extrapolation gave 37·5 ± 2 kcal/mole. Dibeler, Walker and McCulloh's photoionization experiments have recently been questioned by Berkowitz, Chupka, Guyon, Halloway and Spohr[20] who have also made photoionization studies on F_2 and report D(F—F) = 37·7 ± 0·2 kcal/mole, that is, in excellent agreement with the old 'high' value.

The conclusion to be drawn at this stage is that there is insufficient evidence to justify changing the present widely accepted value of D(F—F) = 37·9 kcal/mole, but that the issue of the 'low' value is still lurking around the corner.

B. Rotating-bomb Calorimetry

Rotating-bomb combustion calorimetry is a widely used method for determining heats of combustion of organic chlorine and bromine compounds. Laynez, Ringner and Sunner[21] have made a very important contribution to organic halogen thermochemistry by comparing the rotating-bomb combustion method with reaction calorimetry. They studied the reactions

$$\text{tris}(c) + \text{HBr}(g) \longrightarrow \text{tris.HBr}(c) \quad \text{and} \quad \text{tris}(c) + \text{HCl}(g) \longrightarrow \text{tris.HCl}(c)$$

where tris is tris(hydroxymethyl)aminomethane by both methods, and found the results to be in agreement. The base tris has been extensively studied as a standard in reaction calorimetry. The reaction, tris + HX → tris.HX, is very clean and is capable of being studied to a high precision. A conservative estimate is about ±0·2%, or ±0·05 kcal/mole.

The main objection to this study is that, to obtain complete combustion of the salts (no soot or CO), it was necessary to add much paraffin oil (in amounts corresponding to 50–60% of the total energy change). However, the foregoing seems to be a minor objection and does not vitiate the conclusion that there is no serious systematic error in the rotating-bomb combustion calorimetric method.

C. The Heat of Formation of Carbon Tetrachloride

There is a surprisingly wide range of values for $\Delta H_f^0(CCl_4)$ in the gaseous state. Hu and Sinke[22] have recently obtained $-22{\cdot}9$ kcal/mole by rotating-bomb combustion calorimetry. At the other end of the range, Lord and Pritchard[23] report $-27{\cdot}4$ or $-29{\cdot}8$ kcal/mole from a study of the reaction $CO_2 + CCl_4 = 2\,COCl_2$. Lord and Pritchard's two values are based on Bodenstein and Plaut's value[24], $\Delta H_f^0(COCl_2) = -52{\cdot}3 \pm 0{\cdot}1$ or Tachoire's value[25] of $\Delta H_f^0(COCl_2) = -53{\cdot}5 \pm 0{\cdot}3$ kcal/mole. Support for $\Delta H_f^0(CCl_4) = -27{\cdot}4$ kcal/mole comes from Lord and Pritchard's finding[26] that $\Delta H_f^0(COCl_2) = -52{\cdot}4 \pm 0{\cdot}1$ kcal/mole in excellent agreement with Plaut and Bodenstein's value of $-52{\cdot}3$ kcal/mole. Between the extremes reported by Hu and Sinke ($-22{\cdot}9$) and by Lord and Pritchard ($-27{\cdot}4$) are $-24{\cdot}0$ kcal/mole recommended by Stull, Westrum and Sinke[7] and $-25{\cdot}2 \pm 1{\cdot}2$ kcal/mole favoured by Cox and Pilcher[8]. It has not been possible for the author to decide which of the above values is the best one. This is unfortunate, because carbon tetrachloride is a cornerstone of the chlorofluoromethane series that is considered later. I have, therefore, taken the easy way out by choosing an intermediate value of $\Delta H_f^0(CCl_4) = -26$ kcal/mole. Clearly, more work is needed on this important molecule. (**Note added in proof:** A recent (May, 1973) measurement at SRI indicates that $\Delta H_f^0 = -22$ kcal/mole.)

D. The Chlorofluoromethanes

The thermochemistry of the chlorofluoromethanes $CClF_3$, CCl_2F_2, CCl_3F and CCl_4 has been an active field of research. Many equilibria between the chlorofluoromethanes have been studied so the heats of formation are all linked together. To obtain absolute values for the heats of formation, it is important to obtain results that are independent of the others. A good example of this is the value for CCl_4 obtained from CO_2 and $COCl_2$, discussed in the previous section. $CClF_3$ is the only other member of the series for which independent determination is possible. Lord, Goy and Pritchard[27] and Coomber and Whittle[28] have studied four such reactions. The results are summarized in Table 1. The agreement is so good that a value of $\Delta H_f^0(CClF_3) = -169$ kcal/mole seems to be an almost inescapable conclusion.

TABLE 1. Heat of formation of $CClF_3$

Reaction	Reference	$\Delta H_f^0(CClF_3)$ (kcal/mole)
$CClF_3 = \underset{(-140\cdot8)}{CF_3I} + \underset{(+4\cdot2)}{ClI} - \underset{(-14\cdot9)}{I_2} - \underset{(-17\cdot3)}{17\cdot3}$	27	$-168\cdot8$
$CClF_3 = \underset{(-166\cdot4)}{CHF_3} - \underset{(-2\cdot4)}{2\cdot4}$	27	$-168\cdot8$
$CClF_3 = \underset{(-155\cdot0)}{CBrF_3} + \underset{(+3\cdot5)}{BrCl} - \underset{(-7\cdot4)}{Br_2} - \underset{(-10\cdot5)}{10\cdot5}$	28	$-169\cdot4$
$CClF_3 = \underset{(-155\cdot0)}{CBrF_3} - \underset{(-3\cdot5)}{BrCl} + \underset{(0)}{Cl_2} - \underset{(-10\cdot7)}{10\cdot7}$	28	$-169\cdot2$
Value selected		-169

The values of ΔH_f^0 for the chlorofluoromethanes recommended by Stull, Westrum and Sinke[7] and by Cox and Pilcher[8], are in Table 2, along with a third set of values as a result of the present selection. The reasons for selecting the numbers for $CClF_3$ and CCl_4 have already been discussed, and we proceed now to a discussion of the interrelation between $CClF_3$, CCl_4 and CCl_2F_2 and CCl_3F.

TABLE 2. Selected values of heats of formation of chlorofluoromethanes

	ΔH_f^0/(kcal/mole) Reference 7	Reference 8	Preferred values
$CClF_3$	$-166\cdot0$	$-169\cdot0 \pm 1\cdot0$	-169
CCl_2F_2	$-115\cdot0$	$-114\cdot8 \pm 1\cdot3$	-118
CCl_3F	$-68\cdot0$	$-64\cdot0 \pm 2$	-70
CCl_4	$-24\cdot0$	$-25\cdot2 \pm 1\cdot5$	-26

Sciponi, Gambaretto and Vecchio[29] have studied the catalysed equilibria between $CClF_3$, CCl_2F_2, CCl_3F and CCl_4. Their results agree reasonably well with those derived by Benson and Buss[1] from the work of Peterson and Pitzer[30], but are significantly different from the earlier results of Mears and Stahl[31]. The heats of reaction obtained are arranged in the form of equations for $CClF_3$ in Table 3, for Cl_2F_2 in Table 4 and for CCl_3F in Table 5. In this way, each equilibrium is used several times to give a value of a heat of formation of a different chlorofluoromethane. In the right half of Tables 3, 4 and 5, the arithmetical result for each equilibrium is worked

TABLE 3. Heat of formation of $CClF_3$ calculated from equilibria with other chlorofluoromethanes (all values in kcal/mole)

Equilibrium reference	Equilibrium	Values of $\Delta H_f^0(CClF_3)$ calculated from right-hand side of equilibrium using Table 2		
		Reference 7	Reference 8	Preferred values
31	$CClF_3 = 2\,CCl_2F_2 - CCl_3F - 3{\cdot}7$	−165·7	−169·3	−169·7
1, 30	$CClF_3 = 2\,CCl_2F_2 - CCl_3F - 1{\cdot}5$	−163·5	−167·1	−167·5
29	$CClF_3 = 2\,CCl_2F_2 - CCl_3F - 2{\cdot}14$	−164·1	−167·7	−168·1
29	$CClF_3 = 3\,CCl_3F - 2\,CCl_4 - 10{\cdot}17$	−166·2	−151·8	−168·2
29	$CClF_3 = CCl_2F_2 + CCl_3F - CCl_4 - 6{\cdot}15$	−165·2	−159·8	−168·2
	Compare value selected	−166	−169 ± 1	−169

TABLE 4. Heat of formation of CCl_2F_2 calculated from equilibria with other chlorofluoromethanes (all values in kcal/mole)

Equilibrium reference	Equilibrium	Values of $\Delta H_f^\circ(CCl_2F_2)$ calculated from right-hand side of equilibrium using Table 2		
		Reference 7	Reference 8	Preferred values
31	$CCl_2F_2 = 2\,CCl_3F - CCl_4 - 2{\cdot}6$	−114·6	−105·4	−116·6
1, 30	$CCl_2F_2 = 2\,CCl_3F - CCl_4 - 4{\cdot}4$	−116·4	−107·2	−118·4
29	$CCl_2F_2 = 2\,CCl_3F - CCl_4 - 4{\cdot}0$	−116·0	−106·8	−118·0
31	$CCl_2F_2 = \frac{1}{2}(CClF_3 + CCl_3F + 3{\cdot}7)$	−115·2	−114·7	−117·7
1, 30	$CCl_2F_2 = \frac{1}{2}(CClF_3 + CCl_3F + 1{\cdot}5)$	−116·2	−115·8	−118·8
29	$CCl_2F_2 = \frac{1}{2}(CClF_3 + CCl_3F + 2{\cdot}14)$	−116·0	−115·5	−118·5
29	$CCl_2F_2 = CClF_3 - CCl_3F + CCl_4 + 6{\cdot}15$	−115·8	−124·0	−118·8
	Compare value selected	−115·0	−114·8 ± 1·3	−118

TABLE 5. Heat of formation of CCl_3F calculated from equilibria with other chlorofluoromethanes (all values in kcal/mole)

Equilibrium reference	Equilibrium	Values of $\Delta H_f^0(CCl_3F)$ calculated from right-hand side of equilibrium using Table 2		
		Reference 7	Reference 8	Preferred value
31	$CCl_3F = \frac{1}{2}(CCl_2F_2 + CCl_4 + 2{\cdot}6)$	−68·2	−68·7	−70·7
1, 30	$CCl_3F = \frac{1}{2}(CCl_2F_2 + CCl_4 + 4{\cdot}4)$	−67·3	−67·8	−69·8
29	$CCl_3F = \frac{1}{2}(CCl_2F_2 + CCl_4 + 4{\cdot}0)$	−67·5	−68·0	−70·0
31	$CCl_3F = -CClF_3 + 2\,CCl_2F_2 - 3{\cdot}7$	−67·7	−64·3	−70·7
1, 30	$CCl_3F = -CClF_3 + 2\,CCl_2F_2 - 1{\cdot}5$	−65·5	−62·1	−68·5
29	$CCl_3F = -CClF_3 + 2\,CCl_2F_2 - 2{\cdot}14$	−66·1	−62·7	−69·1
29	$CCl_3F = \frac{1}{3}(CClF_3 + 2\,CCl_4 + 10{\cdot}27)$	−67·9	−69·7	−70·4
29	$CCl_3F = CClF_3 - CF_2Cl_2 + CCl_4 + 6{\cdot}15$	−68·8	−73·2	−70·8
	Compare value selected	−68·0	−64 ± 2	−70

out using the values in Table 2. For example, in Table 3, the first equilibrium is $CClF_3 = 2\,Cl_2F_2 - CCl_3F - 3{\cdot}7$. If Stull, Westrum and Sinke's values[7] for CCl_2F_2 and CCl_3F are used, the equation is $CClF_3 = -230 + 68 - 3{\cdot}7 = -165{\cdot}7$. That is, $\Delta H_f^0(CClF_3) = -165{\cdot}7$ kcal/mole. Similarly, if Cox and Pilcher's values[8] for CCl_2F_2 and CCl_3F are used, the equation gives $\Delta H_f^0(CClF_3) = -169{\cdot}3$ kcal/mole and so on. Tables 3, 4 and 5, therefore, provide consistency checks for the interrelations between the heats of formation selected by the two previous reviews[7,8] and the present work. In Table 3, the values of $\Delta H_f^0(CClF_3)$ that result from Stull, Westrum and Sinke's work range between $-163{\cdot}5$ and $-166{\cdot}2$ kcal/mole, which is a reasonably close spread and averages out about -165 kcal/mole, only slightly more positive than their selected value of -166 kcal/mole. Similarly, the values of $\Delta H_f^0(CClF_3)$ that result from the present selection range from $-167{\cdot}5$ to $-169{\cdot}7$ kcal/mole, compared with the selected value of -169. However, in the case of Cox and Pilcher's numbers, the values of $\Delta H_f^0(CClF_3)$ that result from their numbers for the other chlorofluoromethanes range from $-151{\cdot}8$ to $-169{\cdot}3$ kcal/mole, rather a large spread compared with their selected value of -169 ± 1 kcal/mole. The picture is much the same for CCl_2F_2 in Table 4 and for CCl_3F in Table 5. The biggest spread is in Cox and Pilcher's values for CCl_2F_2 that range from $-105{\cdot}4$ to $-124{\cdot}0$ kcal/mole.

These equilibria, therefore, provide a very sensitive consistency check on the heats of formation of the chlorofluoromethanes. The sensitivity is at first sight a little surprising, because there is not so large a difference in the absolute values for any chlorofluoromethane as shown by Table 2.

E. Bis-trifluoromethyl Peroxide and the Trifluoromethoxy Radical

The equilibrium $CF_3OOCF_3 \rightleftarrows CF_3OF + CF_2O$ was first reported by Porter and Cady[32] at temperatures in the region of 300°C. Levy and Kennedy[33] have recently measured the equilibrium constant for this interesting reaction from 222 to 337°C, giving (corrected to 25°C) a heat of reaction of $24{\cdot}5 \pm 0{\cdot}7$ kcal/mole and an entropy change of $38{\cdot}5 \pm 1{\cdot}2$ cal/(mole-K). From the known[9] thermodynamic properties of CF_3OF and CF_2O, Levy and Kennedy then obtain $\Delta H_f^0(CF_3OOCF_3) = -360{\cdot}2 \pm 3$ kcal/mole and $S^0(CF_3OOCF_3) = 97{\cdot}0 \pm 1{\cdot}2$ cal/(mole-K). There are no other known values of the heat of formation of the peroxide. However, as regards the entropy, Levy and Kennedy[33] quote unpublished calculations by Durig of 93·9 (assuming that all frequencies are harmonic) and 95·7 (assuming that CF_3 torsions are anharmonic), in good agreement with the observed values.

Levy and Kennedy also calculate that $\Delta H_f^0(CF_3O) = -159{\cdot}8 \pm 2{\cdot}5$ kcal/mole based on Czarnowski, Castellano and Schumacher's[34] activation energy of $43{\cdot}5 \pm 0{\cdot}5$ kcal/mole for the reaction $CF_3OF \rightarrow CF_3O + F$. In turn, they calculate that the O—O bond strength in $CF_3O—OCF_3$ is $40{\cdot}6 \pm 5$ kcal/mole, a very reasonable value in view[35] of the O—O bond strength of about 38 kcal/mole in dialkyl peroxides and 44 kcal/mole in alkyl hydroperoxides.

It would be interesting to know the thermochemical properties of the related peroxides CF_3OOH[36], CF_3OOF[37], CF_3OOCF_2OF[37] and $(CF_3OO)_2CFOF$[37].

F. Chlorooolefins

Alfassi, Golden and Benson[38] have recently studied the iodine-catalysed thermal equilibrium between 1-chloro-1-propene and 3-chloro-1-propene. Abell and Adolf[39] had previously studied the same equilibrium by HBr-photocatalysis. Alfassi, Golden and Benson made a combined plot of both sets of results to give a wider temperature range and therefore a better equilibrium constant and found that

$$\text{3-chloro-1-propene} = \text{1-chloro-1-propene}(cis) + (2{\cdot}9 \pm 0{\cdot}4)\ \text{cal/(mole-K)} + (3{\cdot}4 \pm 0{\cdot}2)\ \text{kcal/mole}$$

$$\text{3-chloro-1-propene} = \text{1-chloro-1-propene}(trans) + (2{\cdot}6 \pm 0{\cdot}3)\ \text{cal/(mole-K)} + (2{\cdot}5 \pm 0{\cdot}2)\ \text{kcal/mole}$$

The previously measured[7] ΔH_f^0(3-chloro-1-propene) = 0·2 kcal/mole gives ΔH_f^0(1-chloro-1-propene, *cis*) = −3·2 kcal/mole and ΔH_f^0(1-chloro-1-propene, *trans*) = −2·3 kcal/mole.

Mansson, Ringner and Sunner[40] have measured the heat of formation of 1,1-dichloroethene to be 0·5 kcal/mole, in excellent agreement with the previous value[7] of 0·3 kcal/mole.

G. Recent Thermochemical Results

Some recent results for ΔH_f^0, S^0 and C_p^0 at 25°C are listed in Table 6. Where more than one value is given, no attempt has been made to choose between them, or to give an alternative. The arrangement of the table follows closely that used by Stull, Westrum and Sinke[7] because, of all the forms used by various authors, theirs was the form found easiest to use. All the compounds listed contain at least one carbon atom. Curiously, nobody did any work on C_5 compounds.

TABLE 6. Thermochemical properties at 25°C of organic halogen compounds

Formula	Name	State	ΔH_f^0 (kcal/mole)	Ref.	S^0 (cal/mole-K)	Ref.	C_p^0 (cal/mole-K)	Ref.
$CBrN_3O_6$	Bromotrinitromethane	*l*	−8·19	41				
$CBrN_3O_6$	Bromotrinitromethane	*g*	3·22	41				
CBr_2O	Carbonyl bromide	*l*	−34·7 ± 0·2	42				
CCl	CCl radical	*g*	108·5	43				
$CClF_2$	Chlorodifluoromethyl radical	*g*	−64·3 ± 2	44				
$CClN_3O_6$	Chlorotrinitromethane	*l*	−16·43	41				
$CClN_3O_6$	Chlorotrinitromethane	*g*	−5·57	41				
CCl_2	CCl_2 radical	*g*	59·8	43				
CCl_2O	Phosgene	*g*	−52·37 ± 0·14	26				
CCl_4	Carbon tetrachloride	*l*	−30·69	22				
CCl_4	Carbon tetrachloride	*g*	−28·6	23				
CF	CF radical	*g*	58 ± 1	45				
CFN	Cyanogen fluoride	*g*			53·6	46	9·98	46
CFN_3O_6	Fluorotrinitromethane	*l*	−60·16	41				
CFN_3O_6	Fluorotrinitromethane	*g*	−51·99 ± 0·48	41				
CF_2	Difluoromethylene radical	*g*	−39·3 ± 3	47				
CF_2	Difluoromethylene radical	*g*	−41·7 ± 0·4	45	58·9 ± 1·2	45		
CF_3O	Trifluoromethoxy radical	*g*	−160 ± 2·5	33				
$CHClF_2$	Chlorodifluoromethane	*g*					13·5	48
$CHCl_3$	Chloroform	*l*	−32·10	22				
CHI_2	Diiodomethyl radical	*g*	79·9 ± 2·3	12				
CH_2Br	Bromomethyl radical	*g*	38·9	49				
CH_2Cl	Chloromethyl radical	*g*	30·0	49				
CH_2Cl_2	Dichloromethane	*l*	−29·70	22				
CH_2I	Iodomethyl radical	*g*	52·4	49				
CH_2I	Iodomethyl radical	*g*	55·0 ± 1·6	50				

TABLE 6. (*cont.*)

Formula	Name	State	ΔH_f^0 (kcal/mole)	Ref.	S^0 (cal/mole-K)	Ref.	C_p^0 (cal/mole-K)	Ref.
CH_2I_2	Diiodomethane	*g*	29·2	50				
C_2ClF_5	Chloropentafluoroethane	*g*					26·3	48
C_2F_3N	Trifluoroacetonitrile	*g*	−118·7	51				
$C_2F_6O_2$	Bis-trifluoromethyl peroxide	*g*	−360 ± 3	33	97·0 ± 1·2	33		
$C_2HCl_3O_2$	Trichloroacetic acid	*g*			90·77	52	38·30	52
$C_2H_2ClF_3$	Chlorotrifluoroethane	*g*					21·2	48
$C_2H_2Cl_2$	1,1-Dichloroethene	*l*	−5·8	40				
$C_2H_2Cl_2$	1,1-Dichloroethene	*g*	0·5	40				
$C_2H_2Cl_2F_2$	1,1-Difluoro-2,2-dichloroethane	*g*			83·29	53	24·68	53
$C_2H_3ClO_2$	Chloroacetic acid	*g*			83·15	52	32·51	52
$C_2H_2Cl_2O_2$	Dichloroacetic acid	*g*			88·45	52	35·41	52
$C_2H_3Cl_3$	1,1,1-Trichloroethane	*l*	−40·87	22				
$C_2H_3Cl_3$	1,1,1-Trichloroethane	*l*	−41·8	40				
$C_2H_3Cl_3$	1,1,1-Trichloroethane	*g*	−30·0	40				
C_2H_3F	Fluoroethylene	*g*			60·4	54		
$C_2H_4Cl_2$	1,2-Dichloroethane	*l*	−40·55	22				
$C_3Cl_3F_3$	Trichlorotrifluoroethane	*g*					28·9	48
$C_3F_2N_2$	Difluoromalononitrile	*g*			81·93	55	23·15	55
$C_3H_2Cl_3F_3$	1,1,1-Trifluoro-3,3,3-trichloropropane	*l*	−198·5	56				
$C_3H_3Cl_3$	1,2,3-Trichloropropene	*l*	−24·37	22				
$C_3H_3F_5O$	2,2,3,3,3-Pentafluoropropan-1-ol	*l*	−319·90	57				
$C_3H_4ClF_3$	1,1,1-Trifluoro-3-chloropropane	*l*	−191·0	56				
$C_3H_4Cl_2$	2,3-Dichloropropene	*l*	−17·56	22				
$C_3H_4Cl_2$	1,1-Dichlorocyclopropane	*g*			72·5	58	19·9	58

$C_3H_4Cl_4$	1,2,2,3-Tetrachloropropane	*l*	−60·25	22				
$C_3H_4F_4O$	2,2,3,3-Tetrafluoropropan-1-ol	*l*	−263·38	57				
C_3H_5Cl	Chlorocyclopropane	*g*			69·4	58	17·2	58
C_3H_5Cl	1-Chloro-1-propene, *cis*	*g*	−3·2	38, 39				
C_3H_5Cl	1-Chloro-1-propene, *trans*	*g*	−2·3	38, 39				
$C_3H_5F_3O$	3,3,3-Trifluoropropan-1-ol	*l*	−229·41	57				
C_3H_5IO	Iodoacetone	*g*	31·0	59	85·7	59		
C_3H_7Cl	2-Chloropropane	*g*	−34·6	60				
C_3H_7I	1-Iodopropane	*g*	−7·4	61	81·0	61		
C_3H_7I	2-Iodopropane	*g*	−9·4	61	77·6	61		
C_4HBr	Bromobuta-1,3-diyne	*g*			62·19	62	21·19	62
C_4HCl	Chlorobuta-1,3-diyne	*g*			63·98	62	21·37	62
C_4HI	Iodobuta-1,3-diyne	*g*			65·38	63	21·53	63
C_4H_9I	2-Methyl-2-iodopropane	*g*			76·02	63	28·15	63
$C_4H_{11}BrNO_3$	Tris(hydroxymethyl)amino-methane HBr	*c*	−213·3	21				
$C_4H_{11}ClNO_3$	Tris(hydroxymethyl)amino-methane HCl	*c*	−223·9	21				
C_6BrF_5	Bromopentafluorobenzene	*g*			100·82	64	38·89	64
$C_6Br_2Cl_4$	1,2-Bromochlorobenzene	*g*			86·58	64	28·85	64
$C_6Br_2F_4$	1,2-Bromofluorobenzene	*g*			83·59	64	27·28	64
C_6ClF_5	Chloropentafluorobenzene	*s*	−203·3	65				
C_6ClF_5	Chloropentafluorobenzene	*g*	−193·6	65				
C_6ClF_5	Chloropentafluorobenzene	*g*			97·90	64	38·37	64
$C_6Cl_2F_4$	1,2-Chlorotetrafluorobenzene	*g*			80·74	64	26·46	64
$C_6Cl_2F_4$	1,3-Chlorotetrafluorobenzene	*g*			81·02	64	26·30	64
$C_6Cl_2F_4$	1,4-Chlorotetrafluorobenzene	*g*			76·90	64	25·19	64
C_6Cl_6	Hexachlorobenzene	*g*			104·13	64	41·90	64
$C_6F_2I_4$	1,2-Fluorotetraiodobenzene	*g*			85·60	64	27·19	64
C_6F_5I	Iodopentafluorobenzene	*g*			102·94	64	39·15	64
C_6F_6	Hexafluorobenzene	*s*	−237·0	65				

TABLE 6. (*cont.*)

Formula	Name	State	ΔH_f^0 (kcal/mole)	Ref.	S^0 (cal/mole-K)	Ref.	C_p^0 (cal/mole-K)	Ref.
C_6F_6	Hexafluorobenzene	*l*			65·65	66	52·62	66
C_6F_6	Hexafluorobenzene	*g*	−228·5	65				
C_6F_6	Hexafluorobenzene	*g*			91·54	64	37·40	64
C_6HCl_5	Pentachlorobenzene	*g*			101·65	64	38·24	64
C_6HF_5	Pentafluorobenzene	*s*	−201·3	65				
C_6HF_5	Pentafluorobenzene	*g*			89·63	64	34·29	64
C_6HF_5	Pentafluorobenzene	*g*	−192·6	65				
C_6HF_5O	Pentafluorophenol	*g*	−228·8	65				
C_6HF_5O	Pentafluorophenol	*s*	−244·9	65				
$C_6H_2Cl_4$	1,2,3,4-Tetrachlorobenzene	*g*			94·91	64	34·46	64
$C_6H_2Cl_4$	1,2,3,5-Tetrachlorobenzene	*g*			95·50	64	34·60	64
$C_6H_2Cl_4$	1,2,4,5-Tetrachlorobenzene	*g*			94·03	64	34·61	64
$C_6H_2F_4$	1,2,3,4-Tetrafluorobenzene	*g*			83·91	64	30·47	64
$C_6H_2F_4$	1,2,3,5-Tetrafluorobenzene	*g*			85·29	64	31·08	64
$C_6H_2F_4$	1,2,4,5-Tetrafluorobenzene	*g*			84·59	64	31·62	64
$C_6H_3Br_3$	1,3,5-Tribromobenzene	*g*			95·30	64	32·21	64
$C_6H_3Cl_3$	1,2,3-Trichlorobenzene	*g*			88·47	64	30·77	64
$C_6H_3Cl_3$	1,2,4-Trichlorobenzene	*g*			89·94	64	30·88	64
$C_6H_3Cl_3$	1,3,5-Trichlorobenzene	*g*			86·64	64	30·80	64
$C_6H_3F_3$	1,2,4-Trifluorobenzene	*g*			82·61	64	28·85	64
$C_6H_3F_3$	1,3,5-Trifluorobenzene	*g*			78·75	64	28·33	64
$C_6H_4Br_2$	1,2-Dibromobenzene	*g*			86·43	64	27·99	64
$C_6H_4Br_2$	1,3-Dibromobenzene	*g*			87·69	64	28·04	64
$C_6H_4Br_2$	1,4-Dibromobenzene	*g*			86·33	64	28·94	64
$C_6H_4Cl_2$	1,2-Dichlorobenzene	*g*			81·66	64	27·14	64
$C_6H_4Cl_2$	1,3-Dichlorobenzene	*g*			82·07	64	27·21	64

$C_6H_4Cl_2$	1,4-Dichlorobenzene	*g*			80·46	64	27·22	64
$C_6H_4F_2$	1,2-Difluorobenzene	*g*			76·94	64	25·45	64
$C_6H_4F_2$	1,3-Difluorobenzene	*l*			53·50	66	38·03	66
$C_6H_4F_2$	1,3-Difluorobenzene	*g*			76·83	66	25·49	66
$C_6H_4F_2$	1,3-Difluorobenzene	*g*			76·50	64	25·50	64
$C_6H_4F_2$	1,4-Difluorobenzene	*g*			75·30	64	26·06	64
C_6H_5Br	Bromobenzene	*g*			77·76	64	23·82	64
C_6H_5Cl	Chlorobenzene	*g*			75·04	64	23·42	64
C_6H_5F	Fluorobenzene	*g*			72·32	64	22·54	64
C_6H_5I	Iodobenzene	*g*			79·85	64	24·09	64
$C_7HF_5O_2$	Pentafluorobenzoic acid	*s*	−296·3	65				
$C_7HF_5O_2$	Pentafluorobenzoic acid	*g*	−274·5	65				
$C_7H_3H_5$	Methylpentafluorobenzene	*s*	−211·3	65				
$C_7H_3F_5$	Methylpentafluorobenzene	*g*	−201·6	65				
C_7H_5ClO	Benzoyl chloride	*l*	−38·31	22				
C_7H_5IO	Benzoyl iodide	*g*	2·6 ± 1·0	67				
$C_8H_6Cl_4$	2,3,5,6-Tetrachloro-*p*-xylene	*s*	−41·64	22				
C_8H_9Cl	α-Chloroethylbenzene	*l*	−13·92	22				

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The Chemistry of The Carbon–Halogen Bond
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CHAPTER 17

Rearrangements involving halides

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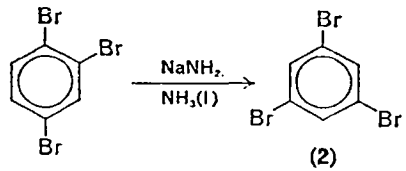
I. INTRODUCTION

Halides are very useful in organic preparative work. In addition to substitution and elimination reactions they are also prone to undergo rearrangements, in some of which the net reaction is an isomerization or a substitution with or without a rearrangement of the carbon skeleton. A large group of complicated rearrangements is considered to involve a three-membered ring either as starting material, product or intermediate and most of the interest in this chapter is devoted to these rearrangements. Allylic isomerization reactions and rearrangements are not discussed because they receive extensive coverage in another volume in this series[1,2].

II. ISOMERIZATIONS WITHOUT SKELETAL REARRANGEMENT

A. Isomerization of Aryl Halides

Halobenzenes and other aryl halides are known to be stable and unreactive with nucleophiles and they are very often used as solvents when working at high temperatures. Recent investigations have shown that migration of halogen takes place when aryl halides are treated with nucleophiles. In 1959 Wotiz and Huba discovered that when 1,2,4-tribromobenzene (**1**) was treated with $NaNH_2$, the product recovered was the 1,3,5-isomer (**2**)[3]. This rearrangement has been carefully studied by Bunnett and coworkers, and Bunnett recently has written an excellent summary of

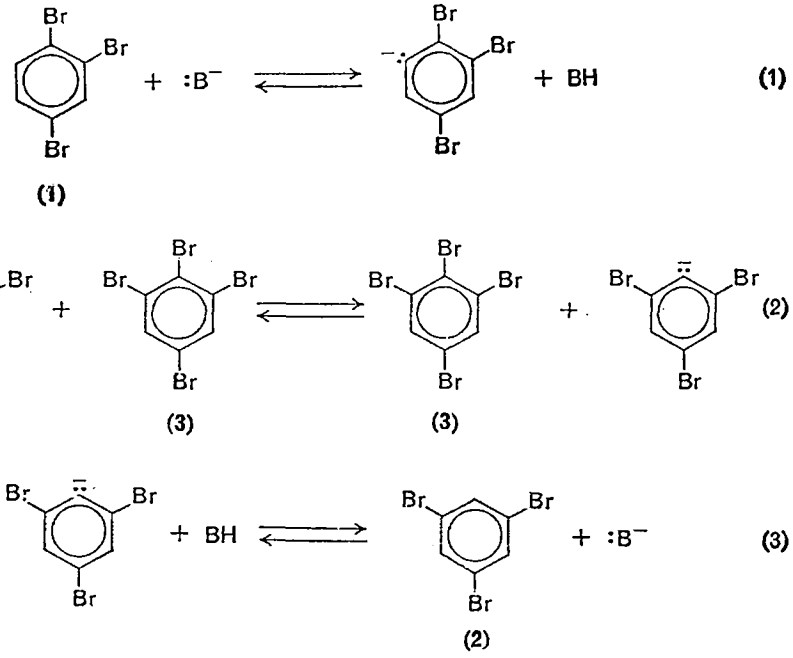


(1) (2)

his work concerning 'the base-catalysed halogen dance' including the mechanism of the reaction[4].

Bunnett and Moyer found that potassium anilide was a more efficient catalyst than $NaNH_2$ for this type of rearrangement[5]. They were able to isolate up to 60% of **2** and in addition to starting material, **1**, and dibromoanilines they also discovered small amounts of the disproportionation products *p*- and *m*-dibromobenzene, 1,2,3,5- and 1,2,4,5-tetrabromobenzene.

Bunnett and Scorrano have found that 1,2,3,5-tetrabromobenzene (**3**) acts as a co-catalyst and a three-step mechanism was proposed (equations 1–3)[6]. Experiments with 1,2,4-triiodobenzene showed that this compound

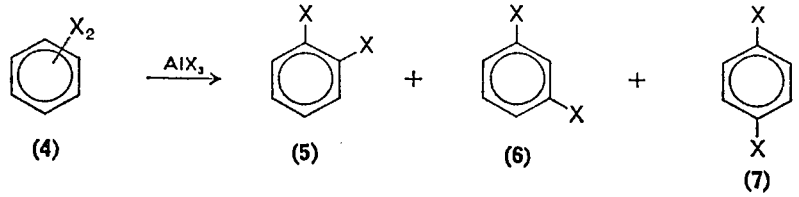


underwent the same type of rearrangement, but 1,2,4-trichlorobenzene, on the contrary, did not react[6]. Base-induced isomerization has also been found among bromine derivatives of thiophene[7] and isothiazoles[8].

It has been known for a long time that Friedel–Crafts catalysts such as $AlCl_3$ and $AlBr_3$ can cause isomerization and disproportionation of halobenzenes[9,10]. These reactions have been frequently investigated and a review of earlier work was given by Thomas[11].

The isomerization of dihalobenzenes has been studied by Olah and coworkers[12–15], Kooyman and coworkers[16,17] and by Koptyug and coworkers[18]. The dihalobenzenes studied include the dibromo-, dichloro-, difluoro-, bromochloro-, bromofluoro- and chlorofluoro compounds, **4**. In

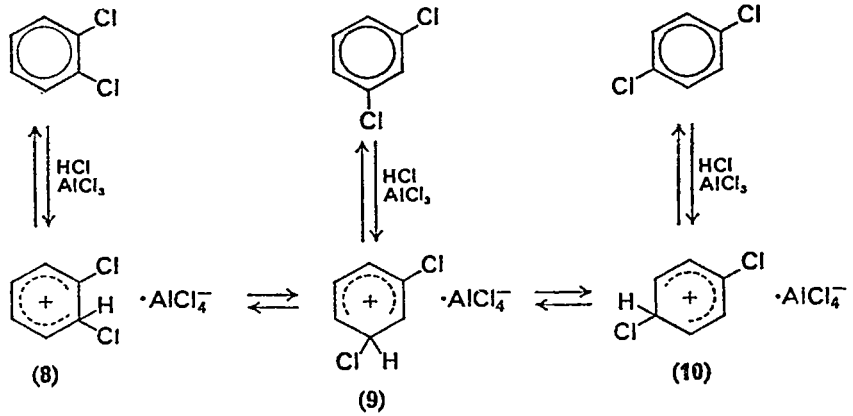
all cases the thermodynamically controlled equilibrium had the same composition: 5% of the *ortho* (**5**), 62% of the *meta* (**6**) and 33% of the *para*



(4) (5) (6) (7)

(**7**) isomer. Small amounts of the disproportionation products mono- and trihalobenzenes were also present. With chlorofluorobenzenes the equilibrium could not be reached from the *ortho* isomer and halogen exchange yielded a considerable amount of dichlorobenzenes[13].

The mechanism for the rearrangement has been studied using ^{14}C-labelled compounds. When the isomerization of *o*-dichlorobenzene was performed in the presence of ^{14}C-chlorobenzene, a very small amount of the initial radioactivity was found in the dichloro compounds. This observation was interpreted in terms of an intramolecular migration of chlorine atoms, suggesting an equilibrium of the σ-complexes **8**, **9** and **10**[18].

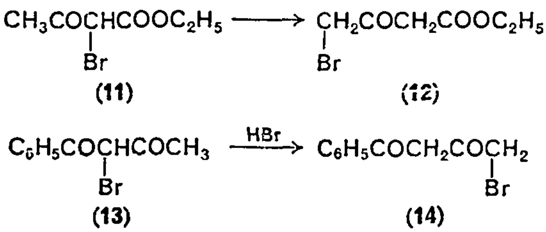


(8) (9) (10)

B. *Isomerization of α-Haloketones*

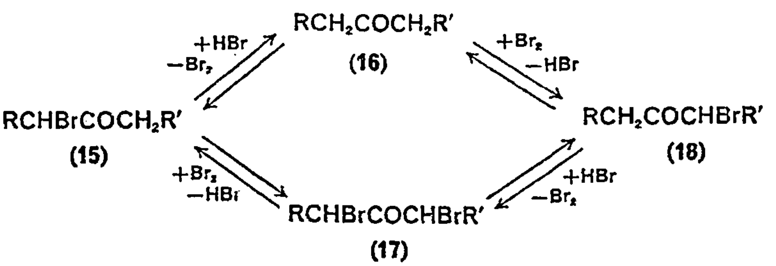
The first example of a halogen migration in α-haloketones was reported in 1894 by Hantzsch, who found that ethyl α-bromoacetoacetate (**11**) rearranged to the γ-isomer **12**[19]. Another example of this type of bromine migration was studied by Kröhnke and Timmler, who reported that hydrogen bromide in acetic acid catalysed the rearrangement of 1-bromo-1-benzoylacetone (**13**) to the 3-bromo isomer **14**[20]. It should be pointed out

that halogen migration can have synthetic use, since the starting bromo ketones **11** and **13** form the kinetically controlled product. Although



comparatively little attention has been paid to it, bromine migration in bromo ketones seems to be quite common.

3-Bromolaevulic acid, **15a**, heated with hydrobromic acid in a sealed tube, was rearranged to the 5-bromo isomer **18a**. In addition to **15a** and **18a** chromatography also showed detectable amounts of laevulic acid, **16a**, and 3,5-dibromolaevulic acid (**17a**). The same four components were obtained from **18a** and HBr. This behaviour was explained in terms of a disproportionation, and a four-component scheme was proposed (equation 4). The reactions are all reversible and lead to an equilibrium[21].



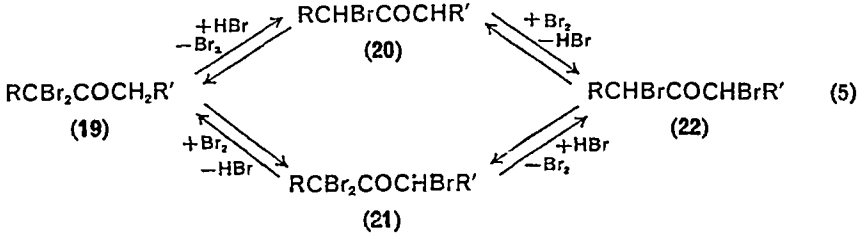
(4)

a $R = CH_2COOH$ $R' = H$
b $R = CH_3$ $R' = H$
c $R = C_2H_5$ $R' = H$
d $R = CH_3$ $R' = CH_3$

A series of aliphatic monohaloketones was found to behave in the same way[22]. When **15b–d** and **18b–d** were treated with a small amount of hydrobromic acid and kept at 30°C, bromine migration started and the progress of the reaction could be followed continuously by ^{1}H-n.m.r. until equilibrium was reached. The composition at equilibrium was the same whether started with pure **15** or **18** or with equimolar amounts of **16** and **17**.

Dibromoketones were found to undergo the same rearrangements as monobromoketones. In this case, it was found that the reactions could also be catalysed by HCl. For simple ketones a four-component scheme

illustrates the situation (equation 5). In the case of acetone (**a**) the composition at equilibrium was the same whether started from **19a**, **22a** or equimolar amounts of **20a** and **21a**[23]. In attempts to prepare 2,2-dibromopentanone-3



a R = R' = H
b R = R' = CH_3

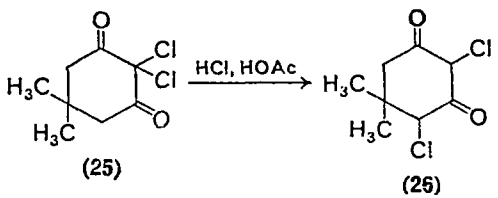
(**19b**) it was found that this compound rearranged according to equation (5) and could not be isolated[24]. Turning to mixed ketones, the situation is more complex, seven compounds being detected[23]. Only a few examples of halogen migration in chloroketones have been reported, and in these cases far more vigorous conditions are needed than in the rearrangement of bromoketones. Iodoketones, however, are extremely unstable under acidic conditions. One drop of hydrochloric acid caused an immediate disproportionation of monoiodoacetone to several unidentified products[25].

In 1914 Blaise reported that heating 3,3-dichlorobutanone-2 (**23**) in acetic acid and hydrogen chloride at 100°C for several hours resulted in rearrangement to the 1,3-dichloro isomer **24**[26]. Later it could be established

$$\underset{\textbf{(23)}}{CH_3CCl_2COCH_3} \xrightarrow[100°C]{HCl,\ HOAc} \underset{\textbf{(24)}}{CH_3CHClCOCH_2Cl}$$

by ^{1}H-n.m.r. that about 20% of **23** was isomerized to **24** under the conditions given[27]. In contrast, one drop of hydrobromic acid caused a complete rearrangement[23] of 3,3-dibromobutanone-2 into a variety of products within a few hours at 30°C.

Voitila reported that 2,2-dichlorodimedone (**25**) in a solution of hydrogen chloride in acetic acid after five weeks at room temperature was completely rearranged to the 2,4-dichloro isomer **26**[28]. Schamp found that the same



(25) (26)

isomerization took place when **25** was refluxed in HCl–DMF (155°C)[29]. The isomerization of the 2,2-dibromo compound occurred at a much lower temperature (55°C)[30].

In special molecules a spontaneous rearrangement of a chloroketone can take place. A recrystallized sample of the chlorodiketone **27** kept a few days in the air at room temperature was completely rearranged to the enol **28**[27].

(27) **(28)**

The first step in the halogen migration discussed in this section is a replacement of the halogen by hydrogen. It is known that α-halogeno and especially α-bromoketones can be reduced by a variety of nucleophiles, but at present the accepted theory involves a polar mechanism, which is in fact the exact reversal of the acid-catalysed halogenation of a ketone[31].

III. ISOMERIZATIONS WITH SKELETAL REARRANGEMENT

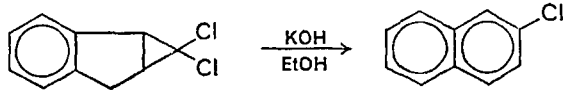
Addition of a carbene to a monocyclic C_{n+2}-alkene yields a bicyclo[*n*.1.0]-alkane. These bicyclo[*n*.1.0]alkanes can easily be rearranged to monocyclic alkanes with $n+3$ carbon atoms in the ring. A combination of these two reactions results in a ring-expansion sequence, which has recently been reviewed by Gutsche and Redmore[32]. In several examples of this general ring-expansion sequence the carbene is generated by the action of base on haloforms, thus yielding *gem*-dihalobicyclo[*n*.1.0]alkanes. Reese and coworkers have studied the thermal rearrangement of a series of dihalocarbene adducts, one example of which is 6,6-dihalobicyclo[3.1.0]hexanes (**29**), which are completely converted into 2,3-dihalocyclohexenes (**30**). It is

(29) **(30)**

a X = Cl 170 °C, 1·5 hr
b X = Br 120 °C, 1·0 hr

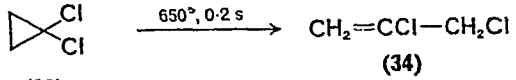
generally found that the dibromocarbene adducts (**b**) rearrange more readily than the dichlorocarbene adducts (**a**)[33]. In some cases the rearrangement is

accompanied by a dehydrohalogenation, which generates an aromatic system. The dichloro compound **31** obtained from the addition of dichlorocarbene to indene is found to decompose in refluxing alkaline ethanol to 2-chloronaphthalene (**32**) in a 98% yield[34]. It has also been found that



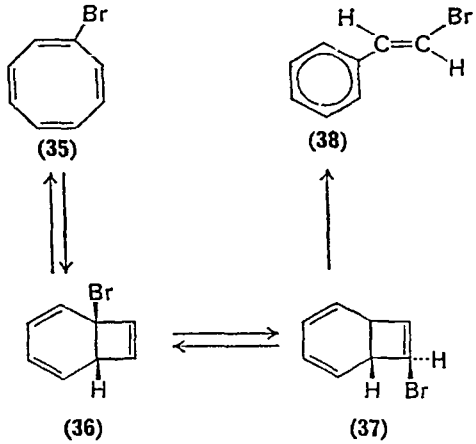
(**31**) (**32**)

heating 1,1-dichlorocyclopropane (**33**) results in ring opening and halogen migration to 2,3-dichloropropene (**34**)[35].



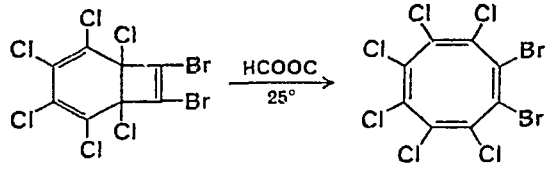
(**33**) (**34**)

Another interesting example of an isomerization with skeletal rearrangement is the conversion of bromocyclooctatetraene (**35**) to *trans*-β-bromostyrene (**38**), first described by Cope and Burg in 1952[36]. Recently the mechanism of this rearrangement was studied by Huisgen and coworkers. The reaction sequence suggested by these authors involves a valence tautomerization of **35** to 1-bromobicyclo[4.2.0]octatriene (**36**), which by an



allylic rearrangement affords the cyclobutene derivative **37**. A conrotatory ring opening of **37** leads to **38**[37]. The reversal of the first step in this reaction sequence (**35**→**36**) has been studied by Roedig and coworkers.

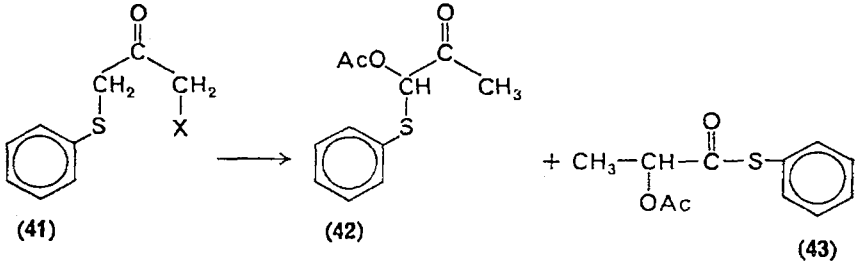
When the halogenated bicyclo[4.2.0]octatriene **39** was dissolved in formic acid the halogenated cyclooctatetraene **40** could be isolated in 60% yield[38].



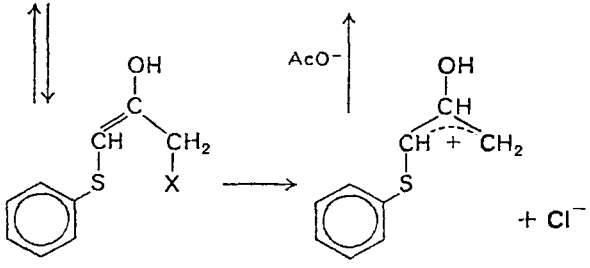
(39) (40)

IV. REARRANGEMENTS DURING SUBSTITUTION WITHOUT SKELETAL REARRANGEMENT

Rosnati and coworkers have studied the substitution of some α-chloroketones bearing in the α′-position a heteroatom with a lone pair of electrons, such as oxygen or sulphur[39]. An example of such a compound is 1-chloro-3-phenylthiopropanone-2 (**41**), which in refluxing acetic acid in the presence of KOAc gives a mixture of 1-acetoxy-1-phenylthiopropanone-2 (**42**) and the thiolacetate **43**. The mechanism of this rearrangement is



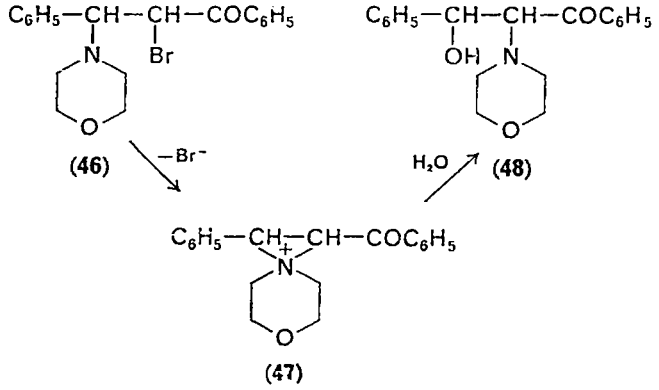
(41) (42) (43)



(44) (45)

suggested to involve an enolization to the conjugated α′-enol **44** followed by formation of the cation **45**, which in a nucleophilic attack by the acetate yields **42**. The mechanism of the formation of the thiolacetate **43** will be discussed in section V.

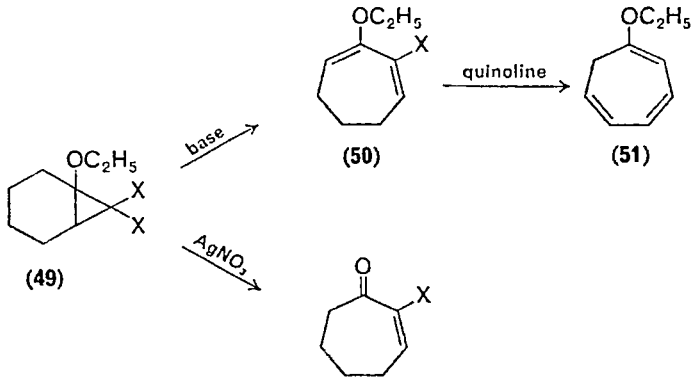
A similar rearrangement was studied by Southwick and Walsh who reported in 1955 that on heating the β-morpholino-substituted α-bromoketone **46** with aqueous acetone it was converted into the α-morpholino-β-hydroxyketone **48**. The process is believed to be a result of the displacement of bromine followed by a rearrangement in which the ethylene-immonium salt **47** is suggested to be an intermediate[40].



V. REARRANGEMENTS DURING SUBSTITUTION WITH SKELETAL REARRANGEMENT

The thermal ring-expansion isomerization of *gem*-dihalobicyclo[*n*.1.0]-alkanes was discussed in section III. Under basic conditions the rearrangement is accompanied by substitution, which is also valid for silver ion-catalysed rearrangements.

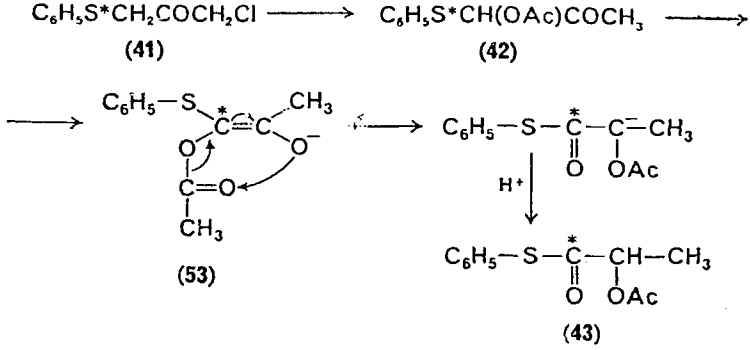
Parham and coworkers have studied the rearrangement of 1-ethoxy-7,7-dihalobicyclo[4.1.0]heptane (**49**). Treatment of the dichlorocarbene



a X = Cl
b X = Br

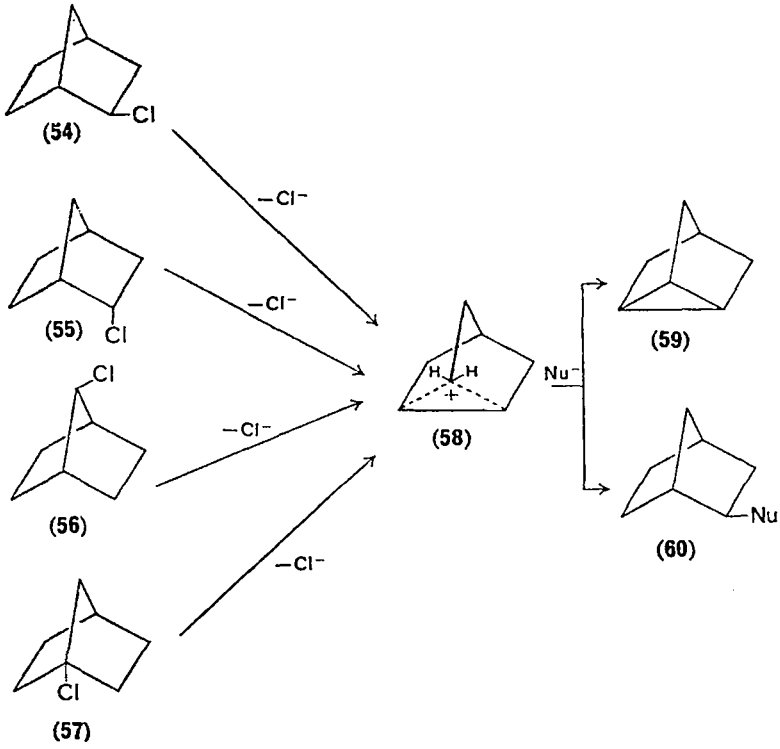
adduct **49a** with boiling pyridine yielded 83% chlorodiene **50a**. Heating **49a** in quinoline for 15 min at 170°C resulted in the formation of **51** in a 38% yield. The dibromo derivative **49b** heated in quinoline at 110°C for 30 min gave **51** in a 32% yield. The dibromo compound treated with silver nitrate in methanol at room temperature yielded 87% 2-bromo-2-cycloheptene-1-one (**52a**), but only recovered starting material could be detected[41] from the experiment with the chloro analogue with silver nitrate.

The rearrangement of the chloro ketone **41** to the acetoxy ketone **42** reported by Rosnati and coworkers[39] was discussed in section IV. In addition to **42** the thiolactate **43** can also be isolated and it has been found that the acetoxy ketone **42** is a precursor to **43**[42]. Experiments with ^{14}C-labelled compounds have shown that a rearrangement of the carbon skeleton takes place, the interesting step being an intramolecular oxidation–reduction of the intermediate enolate **53**.



Substitution of halides often results in rearrangements, especially when a carbenium ion is involved as intermediate (S_N1 conditions). In the case of bicyclic norbornyl derivatives, considerable effort has been directed during the past two decades towards the elucidation of the structure of the intermediate norbornyl cation[43–45]. A number of physical techniques have now become available for the direct observation of the intermediate cation derived from norbornyl derivatives. Olah and coworkers have generated the norbornyl cation **58** from *exo*-2-norbornyl chloride (**54**) in a solvent prepared from SbF_5, SO_2ClF and SO_2F_2 kept at −78°C. Other starting materials for the same carbenium ion are from the *endo* isomer **55**, from 7-chloro-(**56**) or from 1-chloronorbornane (**57**). Quenching the solution with a nucleophile such as pyridine or methanol gives nortricyclene (**59**) and/or an *exo*-2-norbornyl derivative (**60**) depending on conditions and the nucleophile[46].

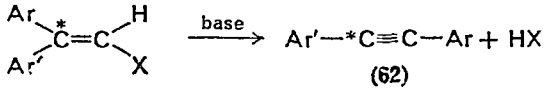
The 'frozen-out' intermediate cation was studied by means of ^{1}H-n.m.r., ^{13}C-n.m.r. and Raman spectroscopy. All evidence clearly demonstrates that the 2-norbornyl cation, under stable ion conditions, is non-classical and its structure corresponds to corner-protonated nortricyclene **58**[46].



VI. REARRANGEMENTS WITH ELIMINATION OF HYDROGEN HALIDE

A. The Fritsch–Buttenberg–Wiechell Rearrangement

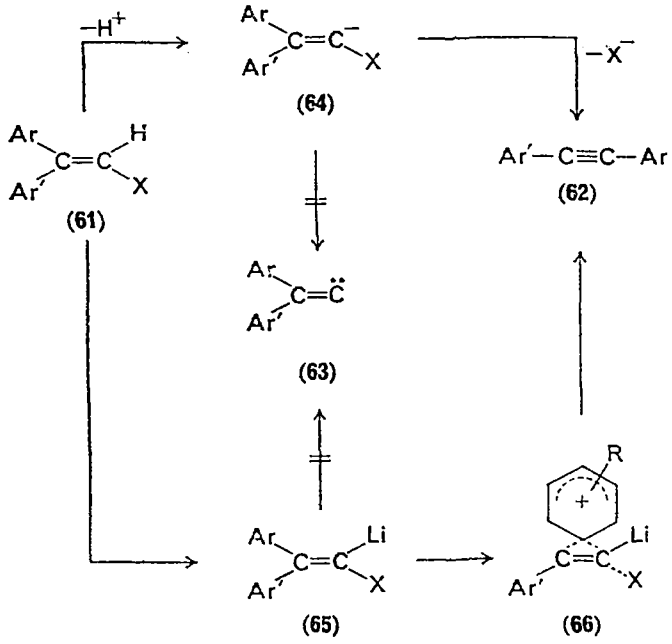
In 1894 it was discovered that 1,1-diaryl-2-haloethylenes (**61**) under the influence of strong bases rearrange to diarylacetylenes, **62**. This reaction is called the Fritsch–Buttenberg–Wiechell rearrangement. Alkoxides, alkali amides and lithium-organic reagents have been used as bases, the best



(61) (62)

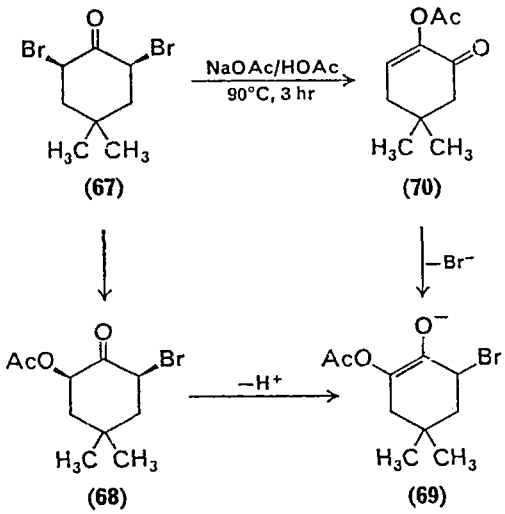
yields being obtained with alkali amides in liquid ammonia and lithium-organic reagents in ether. The order of halogen reactivity is Br > I ≫ Cl. The reaction has recently been reviewed by Köbrick and Buck[47].

The net reaction of the Fritsch–Buttenberg–Wiechell rearrangement is removal of a hydrogen and a halogen from the same carbon: an α-elimination. A carbene intermediate, **63**, can be disproved by the observation that the reaction is stereoselective, where the preferred migrating group is the one *trans* to the halogen[48]. At present the generally accepted view of the mechanism is that in a protic polar medium the intermediate is the carbanion **64**, while in an aprotic medium with an organolithium base, the substrate is metalated to an α-halovinyllithium compound **65**, which rearranges via a 'Beckmann-like' intermediate **66** to the acetylene **62**[48].



B. The Bordwell–Wellman Rearrangement

In 1963 Bordwell and Wellman reported that the reaction of *cis*-2,6-dibromo-4,4-dimethylcyclohexanone (**67**) with sodium acetate in acetic acid gave **70** as the major product[49]. The mechanism of the reaction has been studied and is believed to involve the displacement of a bromine atom to form the *cis*-2-acetoxy-6-bromocyclohexanone (**68**) followed by 1,3-elimination of hydrogen bromide accompanied by acyl migration[50].

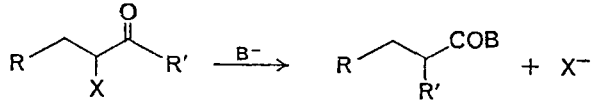


VII. REARRANGEMENTS INVOLVING THREE-MEMBERED RINGS

A. The Favorsky Rearrangement

1. Introduction

The Favorsky rearrangement is the skeletal rearrangement of α-halogenated ketones **71** in the presence of bases. Various derivatives of carboxylic acids **72** containing the same number of carbon atoms as in the initial ketone can be formed depending on the base used. The most frequently used are hydroxides and alkoxides, which give carboxylic acid salts and esters, respectively, but amines can also be used. In this case the product is an amide.



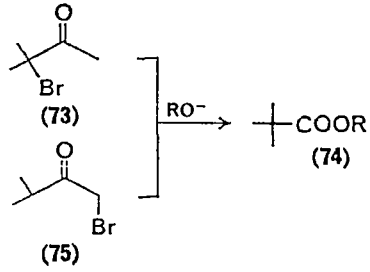
The yields from the Favorsky rearrangement vary greatly, depending on the structure of the parent ketone, the number and nature of halogen atoms, the base used and other experimental conditions. No general recommendation can be made on the choice of optimal conditions for the reaction, as they must be selected separately for each type of reaction.

It is well known that both chloro- and bromoketones can be used as starting materials in the Favorsky rearrangement, and chloroketones are normally favoured over bromoketones, due to unwanted side-reactions in the case of the latter. However, since the purification of the products from the chlorination of ketones is often quite laborious, bromoketones are preferred in these cases. A few examples of the rearrangement of α-iodoketones have recently been reported[143,144]. The α-haloketones are reactive compounds and in the presence of bases they can yield products in which the halogen atom is substituted or eliminated. The first example of a skeletal rearrangement of an α-haloketone was reported in 1880 and in 1894 Favorsky described this rearrangement as a general reaction. There have been several reviews of the Favorsky rearrangement, covering the literature up to 1969[51–53].

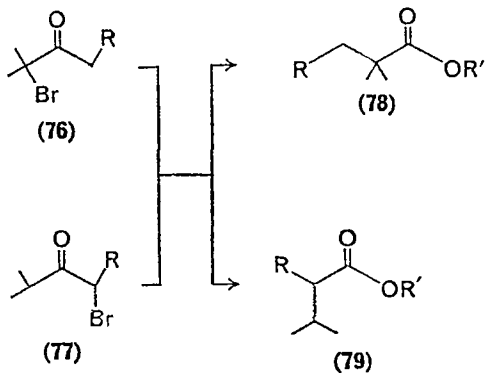
2. Synthetic use of the Favorsky rearrangement

The Favorsky rearrangement is a preferred route to branched carboxylic acids. Applied to alicyclic systems it provides a direct method for ring contraction. The rearrangement of polyhaloketones is in several cases a stereoselective reaction resulting in the thermodynamically less stable isomer.

a. Aliphatic monohaloketones. In 1940 Aston and Greenburg reported[54] that treatment of 3-bromo-3-methyl-2-butanone (**73**) by various alkoxides yielded esters of trimethylacetic acid **74**. Since then it has been observed

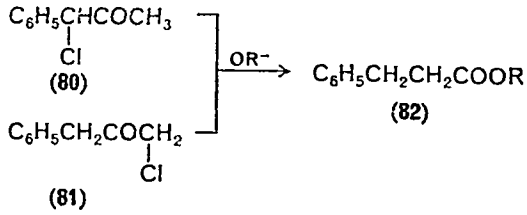


that this is the only ester formed and that the isomeric 1-bromo derivative **75** also yielded only the same ester[55]. Higher homologues, **76** and **77**, were found[55,56] to give mixtures of the two isomeric esters **78** and **79**. The ratio of the two esters was found to be the same whichever of the two isomeric haloketones was used, but it was found to vary with the substituent R and, surprisingly, also with the base used[56,57]. In all cases studied, the main component was the ester **78**.



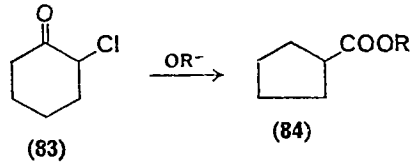
R = Me, Et, Pr, *i*-Pr and *t*-Bu

Bordwell and coworkers[58] found that 1-chloro- (**80**) and 3-chloro-1-phenyl-2-propanone (**81**) both yielded the same product, 3-phenylpropionic acid (**82**). The same reaction took place starting from various *meta*- and *para*-subsituted derivatives of **80** and **81**.



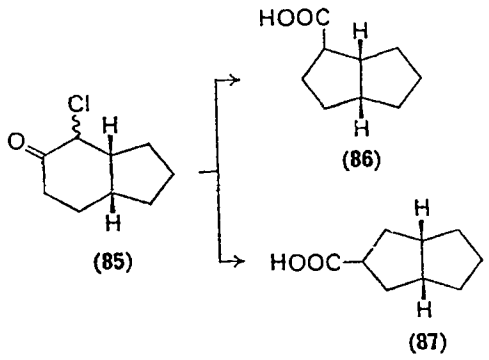
b. Alicyclic monohaloketones. In alicyclic ketones the halogen atom can either be attached directly to the ring or to a side-chain containing the keto group. The cyclic system can be monocyclic, bicyclic or polycyclic, including steroids.

The rearrangement of 2-chlorocyclohexanone **83** has been very carefully studied. In this reaction a ring contraction occurs to produce cyclopentanecarboxylic acid derivatives, **84**. A review concerning ring con-



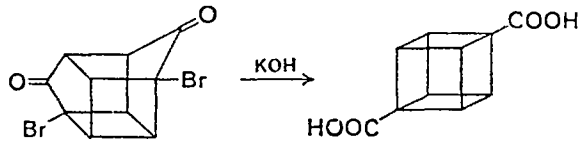
traction by Favorsky rearrangement has recently been published[59]. This method is a useful general method for ring contraction in cyclo-C_6 and

higher ring systems. α-Haloketones in fused systems behave in the same way as their monocyclic analogues. The rearrangement of 4-chloro-*cis*-5-hydrindone (**85**) yields a mixture of the two bicyclic esters **86** and **87**[60–62].



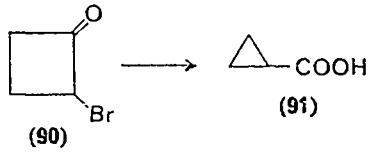
The rearrangement of halogenated steroid ketones provides a method of modifying the steroid. However, the product mixture is in several cases quite complex and the rearrangement of 2-α-bromocholestan-3-one has been found to yield three esters[63,64].

In general, α-halogenated cyclopentanones do not undergo this ring contraction and the only examples reported are rearrangements of polycyclic ketones. In 1964 Eaton and Cole reported[65] the first successful synthesis of a cubane compound, in which the key step was a Favorsky rearrangement of the dibromo dione **88** to cubanedicarboxylic acid **89**[65].

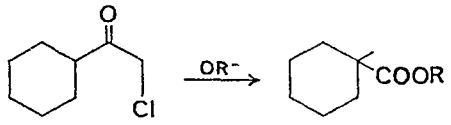


Conia and coworkers[66,67] have studied the rearrangement of α-halocyclobutanones (**90**), a reaction which yields cyclopropanecarboxylic acid (**91**). It has been observed[67] that this ring contraction occurs in aqueous solution in the absence of base, even at pH 1–3. A review of ring contractions in the cyclobutanone ring system has recently been published[68].

An α-haloketone with the halogen in the side-chain is cyclohexyl chloromethyl ketone (**92**). This ketone yields ester **93** when treated with alkoxide[69].

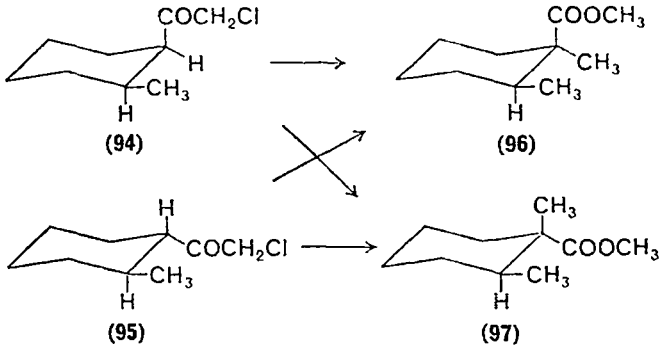


(90) (91)



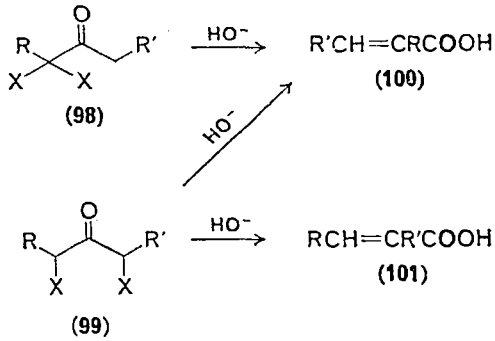
(92) (93)

House and Richey have studied the rearrangement of the *cis* and *trans* isomers of 2-methylcyclohexyl chloromethyl ketone (**94** and **95**) in methanol and in 1,2-dimethoxyethane. In all cases the major products are the two esters **96** and **97**, which are formed in approximately equal amounts by a non-stereospecific Favorsky rearrangement[70].



(94) (96) (95) (97)

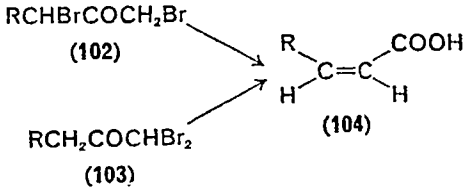
c. Dihaloketones. The general reaction for the rearrangement of α,α-(**98**) and α,α′-dihaloketones (**99**) can be written as



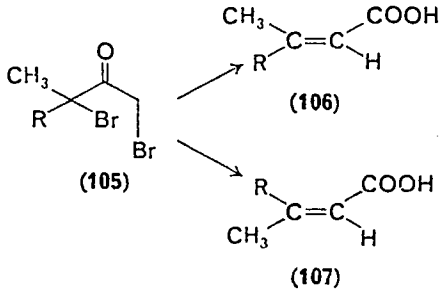
(98) (100) (99) (101)

Depending on the nature of R and R′ in **99**, either ester **100** or **101** or both are formed.

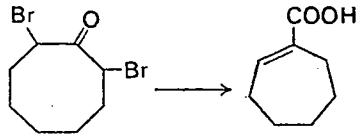
The 1,3-dibromo- (**102**) and 1,1-dibromo-2-ones (**103**) have been found to undergo a stereospecific Favorsky rearrangement yielding the thermodynamically less stable *cis*-2-enoic acid (**104**)[71,72]. The method seems to



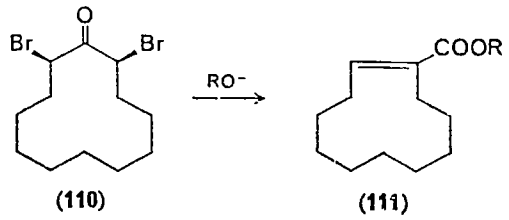
have general applicability, and the optimal yields were obtained with weak bases such as potassium bicarbonate[73]. 1,3-Dibromo-2-ones (**102**) are the preferred starting material since they can be obtained in good yields from direct bromination of the parent ketone[74]. The dibromo derivatives of α-branched methyl ketones (**105**) have also been studied, but in this case no stereoselectivity was found, the two isomers **106** and **107** being formed in nearly equal amounts[75].



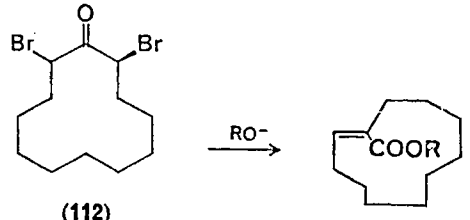
Alicyclic α,α'-dihaloketones with the two halogen atoms in the ring react with bases under ring contraction. Treatment of 2,7-dibromocyclooctanone (**108**) with sodium hydroxide is reported to yield 96% of the



unsaturated acid **109**[76]. Garbisch and Wohllebe[77] separated the *cis*- and *trans*-isomers of 2,12-dibromocyclododecanone. They found that the *cis*-isomer **110** yielded exclusively the *trans*-ester **111** while the *trans*-isomer **112** yielded the *cis*-ester **113**. The dibromo derivatives of undecanone behaved in the same way[77].

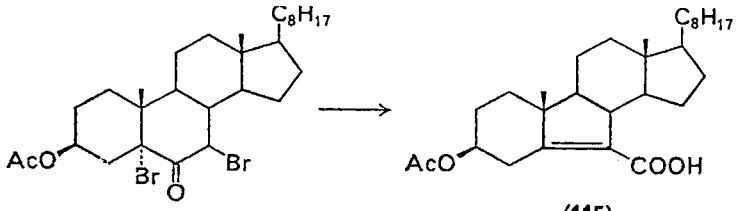


(110) (111)



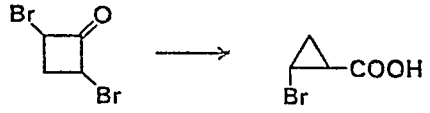
(112) (113)

Examples are found where the Favorsky rearrangement has been applied to polycyclic α,α'-dibromoketones. In the steroid series Woodward and Clifford studied the rearrangement of the dibromocholestanone **114**; this compound, boiled with pyridine, was found to yield the B-nor unsaturated acid **115**[78,79].

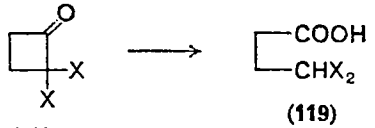


(114) (115)

The dihalo derivatives of cyclobutanone did not behave in the same way as the higher homologues. The 2,4-dibromo compound **116** yielded the bromosubstituted acid **117**. The isomeric 2,2-dihalocyclobutanone (**118**) underwent a ring cleavage to 4,4-dihalobutyric acid (**119**)[80].

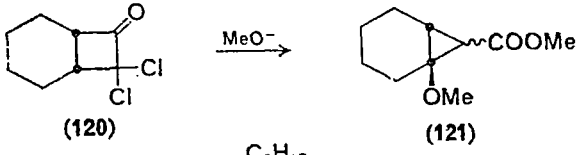


(116) (117)

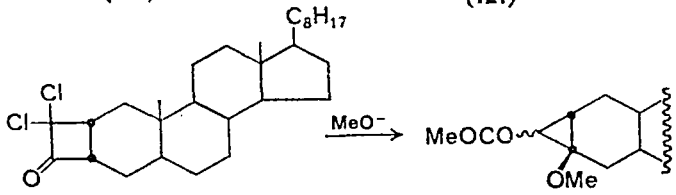


(118) (119)

Olefins treated with dichloroketene yield *cis*-fused α,α-dichlorocyclobutanones. Fletcher and Hassner have found that when compounds **120** and **122** are treated with methoxide, the products are the methoxysubstituted esters **121** and **123**[81].

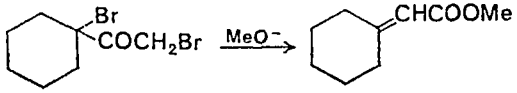


(120) (121)



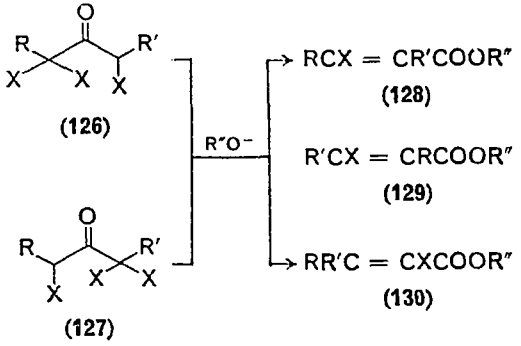
(122) (123)

Cyclic dihaloketones with only one halogen in the ring do not undergo a ring contraction. Wagner and Moore found[82] that the rearrangement of **124** resulted in the unsaturated acid **125**.



(124) (125)

d. Polyhaloketones. The general equation for the Favorsky rearrangement of trihaloketones can be written:

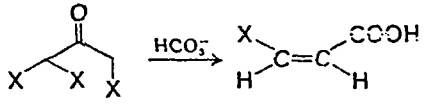


(126)

(127)

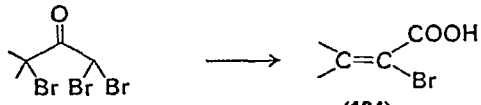
In general, it is not possible to separate the two isomers **126** and **127**, which are both formed in the direct halogenation of the parent ketone[74] and consequently the reaction product can be rather complex with three possible *cis–trans* pairs (**128–130**)[145]. In some cases, mainly where symmetric ketones were used (R = R′), only one acidic product has been isolated.

Trihaloketones and higher substituted ketones with a CX_3CO group are cleaved by a haloform reaction. The rearrangement of 1,1,3-trihaloacetones (**131**) was found to be stereospecific, yielding only *cis*-3-haloacrylic acid (**132**)[83].

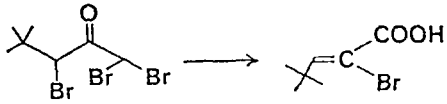


(131) (132)

On the other hand, in the case of 1,1,3-tribromo-3-methyl-2-butanone (**133**) the product **134** is an α-halosubstituted acid, type **130**[84], and the rearrangement of the crowded tribromoketone **135** also yielded an α-bromo-substituted acid (**136**)[85].



(133) (134)



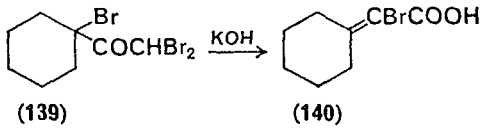
(135) (136)

A ring contraction occurs as expected when alicyclic trihaloketones are treated under Favorsky conditions. One example is the reaction **137** → **138** studied by Hesse and Krehbiel[86]. In this case the product is a β-halogenated

(137) (138)

unsaturated acid and evidently bromine is a more efficient leaving group than chlorine. The same conclusion could be drawn from experiments with 1,3-dichloro-1-bromoacetone[87].

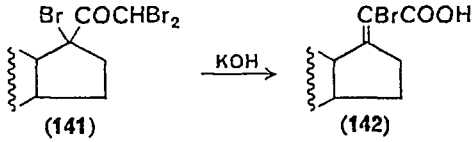
Wagner and Moore[84] have also studied the cyclic ketone **139** where two halogens are in the side-chain. In this case no ring contraction occurs: the Favorsky product is the unsaturated acid **140**.



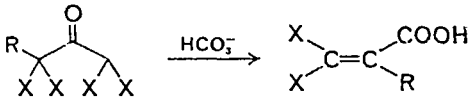
(139) (140)

An analogous reaction occurred[84] when the steroid tribromoketone **141** was treated with ethanolic potassium hydroxide under formation of **142**.

Good yields of 3,3-dihalo-2-alkylsubstituted acrylic acids (**144**) could be isolated from the reaction between 1,1,3,3-tetrahalo-2-ones (**143**) and an aqueous solution of a bicarbonate or a carbonate[88].



(141) (142)



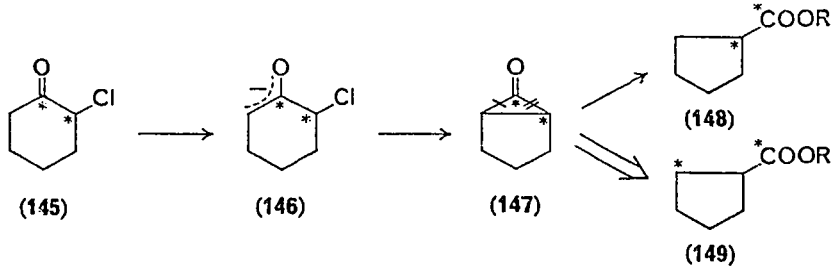
(143) (144)

3. The mechanism of the Favorsky rearrangement

Considerable interest has been shown in the mechanism of the Favorsky rearrangement. Nevertheless, no mechanism has yet been suggested which is suitable for all structural types of α-haloketones and for all experimental conditions. At present the accepted view is that different mechanisms are working in the rearrangement depending on the structure of the initial ketone and the conditions used. Good reviews of the historical background are given in references 52 and 53.

a. The cyclopropanone mechanism. In 1951 Loftfield presented his elegant proof that a symmetric intermediate is involved in the Favorsky rearrangement of 2-chlorocyclohexanone[89]. This investigation disproved the generality of the unsymmetric mechanisms previously suggested by Favorsky, Richard and Tchoubar[102,146,147]. Loftfield[89] prepared ^{14}C-labelled 2-chlorocyclohexanone, in which the isotope was equally distributed between carbon atoms 1 and 2 (**145**). When this ketone was treated with less than one equivalent of sodium isoamyloxide in isoamyl alcohol, the main product was isoamyl cyclopentanecarboxylate together with some recovered chloroketone. Degradation of haloketone and ester established

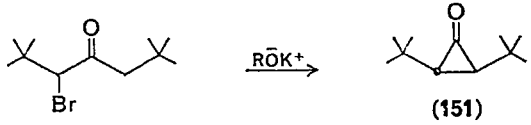
that the recovered chloroketone had the same labelling as the starting material and that the ^{14}C in the ester was distributed 50% on the carboxyl carbon atom, 25% on the ring α-carbon atom and 25% on the two ring β-carbon atoms together. These data clearly show that the reaction proceeds via an intermediate in which the α- and α′-positions of the cyclohexanone are formally equivalent, and Loftfield proposed that this intermediate was a *cyclopropanone*[89]. The initial step is the removal of a proton from the α′-position to form the enolate anion **146**. Concerted or subsequent ejection of halide leads to a cyclopropanone **147**, which is rapidly cleaved by alkoxide to give the esters **148** and **149** in a 1 : 1 ratio.



(145) (146) (147) (148) (149)

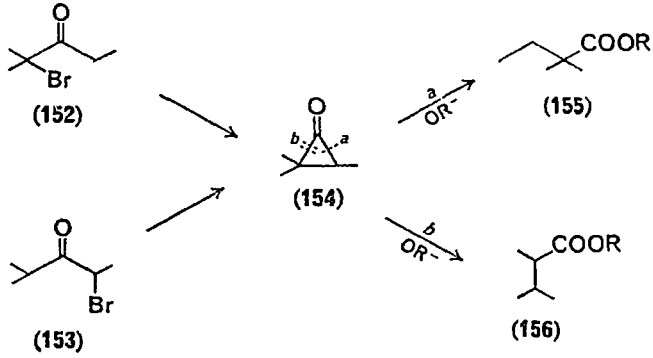
At the present time the cyclopropanone mechanism is generally accepted for the Favorsky rearrangement of α-haloketones having at least one α′-proton. α-Haloketones lacking α′-protons undergo a quasi-Favorsky rearrangement, see section VII.A.4.a. However, Warnhoff, Wong and Tai have reported[90] that a series of bicyclic α-bromoketones (with one α′-proton) can rearrange to a single product by either a cyclopropanone or a 'benzilic acid-like' mechanism (see section VII.A.3.b).

One of the main arguments against the cyclopropanone mechanism was that no cyclopropanones had been synthesized. Now these compounds are available and their chemistry has been investigated, providing additional indication for a cyclopropanone intermediate. (For good reviews of cyclopropanone chemistry, see references 91 and 92.) Of particular interest is the observation that a cyclopropanone can be isolated under Favorsky conditions. Pazos and Greene found[93] that the reaction of α-bromodineopentyl ketone (**150**) with the potassium salt of *p*-chlorophenyldimethylcarbinol resulted in the formation of *trans*-2,3-di-*t*-butyl-cyclopropanone (**151**).



(150) (151)

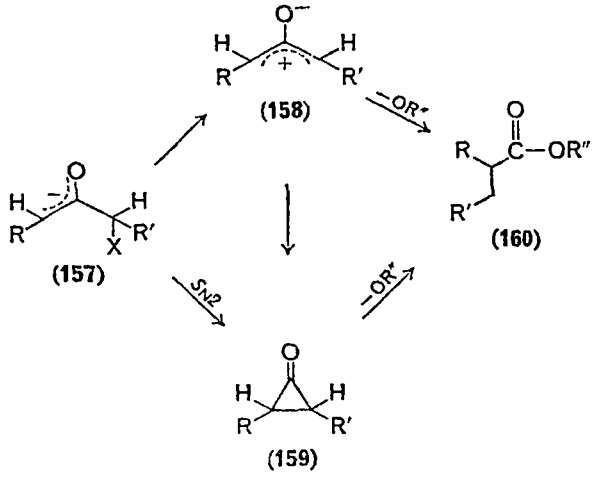
The two isomeric monobromoketones **152** and **153** have been found[57] to give the same ratio of rearranged ester **155** and **156**. This ratio was found to vary significantly with the base used.



The postulated intermediate cyclopropanone **154** was found to behave identically[56].

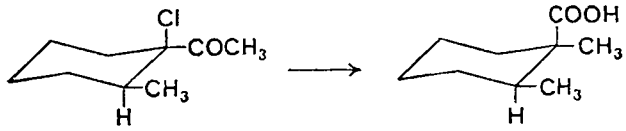
Analyses (n.m.r., m.s.) of products and recovered α-haloketones from rearrangements run in deuterating solvents show that for most ketones both α- and α′-protons have been more or less completely exchanged prior to rearrangement. Investigations by Sachs[94] and by Jullien and Lai[95] show that in an α-haloketone the exchange in the α-position in general is much faster than in the α′-position.

Considerable interest has been devoted to the formation of the cyclopropanone **159** from the enolate anion **157**. It can be formed in an internal



S_N2 attack, but also in a two-step reaction, in which the open zwitterion **158** is an intermediate. It has also been suggested that the products **160** are formed directly from **158**.

Stork and Borowitz have studied the rearrangement of the two epimeric 1-acetyl-1-chloro-2-methylcyclohexanes, using alkoxide in ether[96]. They found this rearrangement (**161**→**162**) to be stereospecific and that the

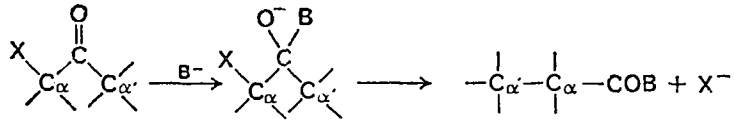


(161) **(162)**

resulting new carbon–carbon bond has the opposite configuration to that of the departing halogen. This clearly demonstrates that in this rearrangement the cyclopropanone is formed in a direct internal S_N2 attack. However, House and Gilmore found that the stereospecificity is lost when a polar solvent such as methanol is used. In view of these data an open zwitterion intermediate seems most likely[97].

In a series of publications Bordwell and coworkers discuss the possibility of distinguishing between an internal S_N2 attack and a two-step mechanism from a study of the Hammett constants[58]. However, it seems to be an overvaluation of the small differences in the Hammett correlation to draw any definite conclusions from this approach. Bordwell and Scamehorn also discuss a rapid equilibrium between a cyclopropanone and its open zwitterion[98]. However, the successful resolution and racemization of *trans*-2,3-di-*t*-butylcyclopropanone (**151**) studied by Greene and coworkers[99], shows that, for this cyclopropanone, the two forms are separated by an energy barrier of more than 30 kcal/mole. Recent calculations using the MINDO/2 and INDO method predict that unsubstituted cyclopropanone is more stable than the corresponding zwitterion. The MINDO/2 calculation gives a difference of 78 kcal/mole[100] and the INDO calculation 220 kcal/mole[101].

b. The 'benzilic acid-like' mechanism. The rearrangement of 2-bromocyclobutanone **90** to **91** has been studied in deuterating solvents. Analyses revealed that in this case no cyclopropanone or zwitterionic intermediate can be involved, and in this case a 'benzilic acid-like' mechanism has been suggested[66, 67]. Unlike the cyclopropanone mechanism this is an unsymmetric mechanism. It involves the addition of nucleophile to the carbonyl carbon atom, followed by a concerted displacement of the halide ion by an anionotropic 1,2-migration of the $C_{\alpha'}—C_{C=O}$ bond in the intermediate **163**.

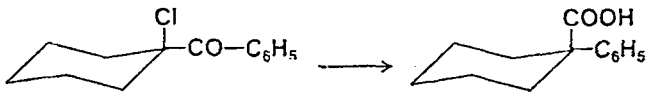


(163)

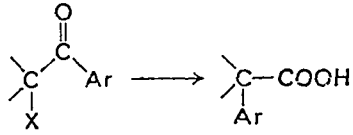
As mentioned above, Warnhoff and collaborators have found that a 'benzilic acid-like' mechanism is also valid in the rearrangement of a few bicyclic α-bromoketones[90].

4. Miscellaneous Favorsky-like rearrangements of α-haloketones

a. The quasi-Favorsky rearrangement. In 1939, Tchoubar and Sackur reported the base-catalysed rearrangement of α-chlorocyclohexyl phenyl ketone **164** to the acid **165**[102]. Ketone **164** is an α-haloketone lacking α′-protons, and in this respect is different from the other ketones discussed in sections VII.A.1–3. The base-induced rearrangement of this type of α-haloketone is called the quasi-Favorsky rearrangement. Later, Stevens and Farkas investigated the conditions for the reaction **164**→**165** and found that optimal yields were obtained when the reaction was run in refluxing xylene using dry sodium hydroxide[103]. These seem to be the general conditions used in the quasi-Favorsky rearrangement. The general scheme for a quasi-Favorsky rearrangement can be written **166**→**167** and

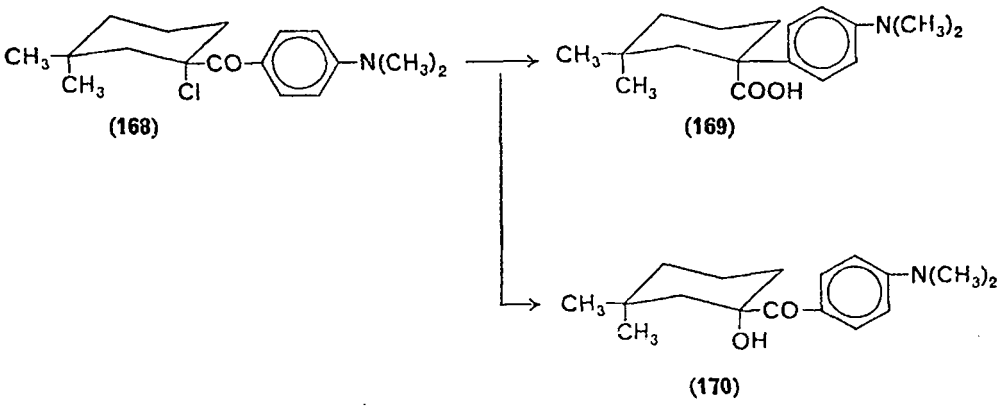


(164) (165)

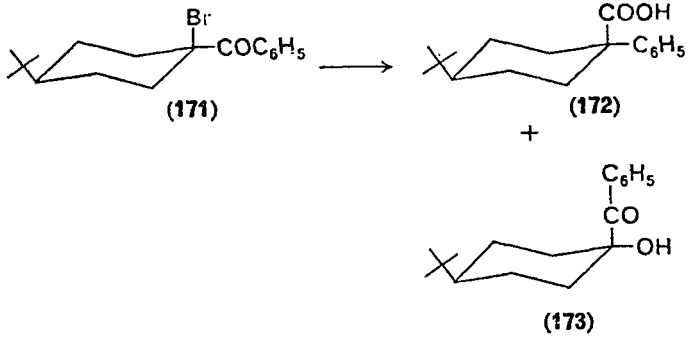


(166) (167)

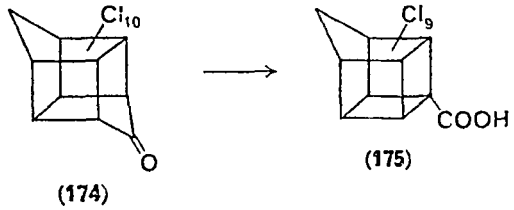
a limited number of examples are reported. Smissman and coworkers[104] have studied the rearrangement using nitrogen-substituted ketones; one example is the rearrangement of the ketone **168**, which yields the acid **169** and the hydroxyketone **170**. Smissman and coworkers have also studied the mechanism of this reaction. Starting with optically active ketone (−) **168** they found racemic acid **169** and racemic hydroxyketone **170**.



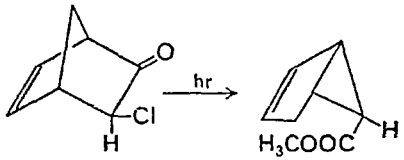
These data led them to suggest a two-step carbenium ion-pair mechanism[104,105]. However, this mechanism seems to be valid only in the rearrangements of nitrogen-substituted ketones. Baudry and Charpentier-Morize have studied the rearrangement of ketone **171**, which yielded the acid **172** and the hydroxyketone **173**, both formed in an inversion. This is interpreted in terms of a 'benzilic acid-like' mechanism (see section VII.A.3)[106].



An unusual example of a quasi-Favorsky rearrangement has been reported by Scherer and coworkers. They found that the perchlorinated cage ketone **174** reacted with potassium hydroxide in refluxing xylene to yield the cage acid **175** in 85% yield[107].

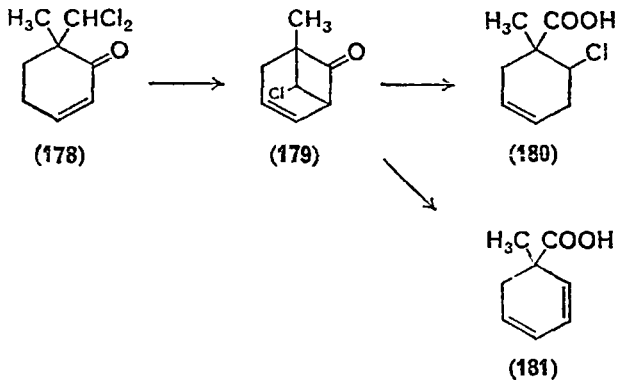


b. The photo-Favorsky rearrangement. In 1970 Kaplan and Hartwig reported that when the bicyclic chloroketone **176** in methanol was photolysed the *endo* acid **177** was formed in a 95% yield. This is an example of a photochemical Favorsky rearrangement[108].



(176) (177)

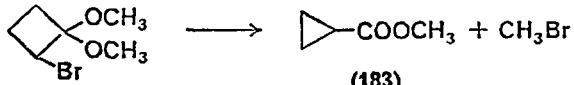
c. The homo-Favorsky rearrangement. In 1971 Wenkert and coworkers[109] reported that β-haloketones can undergo a base-induced dehydrochlorination to carboxylic acid, and they called this a homo-Favorsky rearrangement. In order to avoid an elimination the starting β-haloketone should not contain any α-hydrogens (but one or more α′ hydrogens). An example of a homo-Favorsky rearrangement is the reaction of base with the ketone **178** yielding the two acids **180** and **181**. In analogy with the Favorsky rearrangement the homo-Favorsky rearrangement was found to involve a cyclobutanone intermediate **179**.



(178) (179) (180) (181)

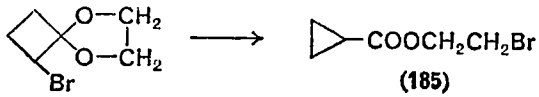
5. Rearrangement of α-haloketals

In 1968 Salaun and Conia reported that 2-bromocyclobutanone dimethyl ketal **182** when heated rearranged to **183** and methyl bromide[110]. This



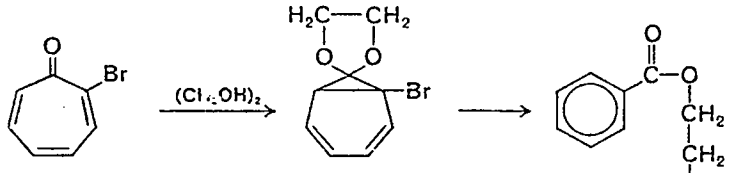
(182) (183)

rearrangement is very similar to the ring contraction of 2-bromocyclobutanone **90** (see section VII.A.2.b). However, it was also found that the dioxolane **184** gave the 2-bromoethyl ester **185**[110].



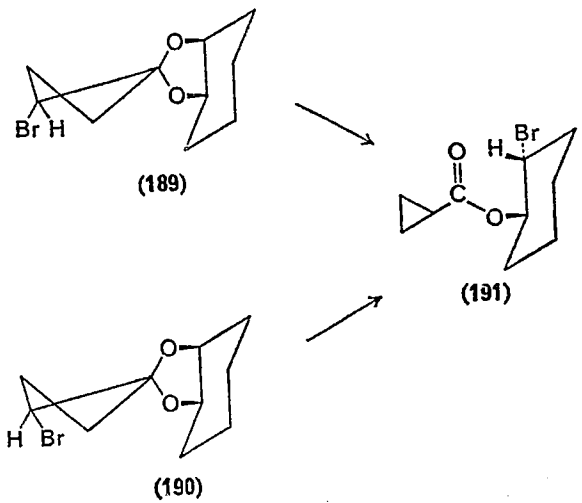
(184) **(185)**

A similar reaction has been described by Baldwin and Gano[111]. They found that 2-bromotropone **186** when heated with ethylene glycol in benzene yielded 2-bromoethylbenzoate, **188**. The norcaradiene valence tautomer **187** is discussed as a likely intermediate. When the reaction was studied for



(186) **(187)** **(188)**

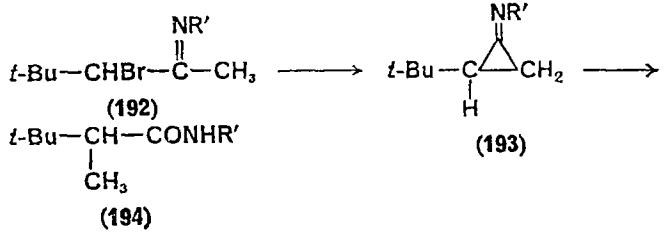
the rearrangement of the *syn–anti* pair **189** and **190** to the 2-bromocyclohexyl ester **191**, it was found that the thermal ring contraction involved inversion at the C atom undergoing bromine substitution. For an ionic mechanism orbital symmetry predicts inversion of configuration, but, for a concerted thermally allowed reaction, orbital symmetry predicts retention at this carbon atom[110, 111].



(189) **(191)** **(190)**

6. Rearrangement of α-halketimines

Recently Quast and coworkers reported that the α-bromoketimine **192** can undergo a base-induced rearrangement very similar to the Favorsky rearrangement[112]. When treated with potassium *t*-butoxide in THF **192** yields the cyclopropanoneimine **193** in more than 90% yield. Hydrolysis (KOH dioxan/water at 100°C for 24 hr) of the ketimine causes ring cleavage and the molecule undergoes a rearrangement to the amide **194**.

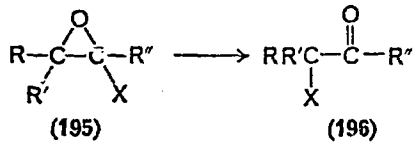


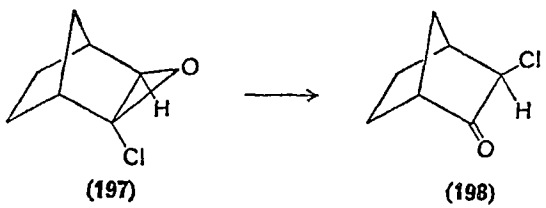
B. Rearrangement of α-Haloepoxides

1. Saturated α-haloepoxides

α-Haloepoxides are a class of reactive compounds liable to undergo thermal and acid-catalysed rearrangements. In these rearrangements the halogen is found to be the migrating species. A good review of this reaction and its mechanism has recently been published[113].

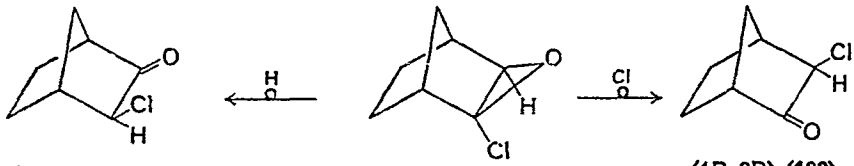
Monohaloepoxides **195** yield α-haloketones **196** and numerous examples of α-chloroepoxide rearrangements can be found, including aliphatic as





well as cyclic and polycyclic compounds. A few examples of rearrangement of α-bromo-[113] and α-iodoepoxides are also found in the literature[114]. McDonald and Steppel have studied the mechanism of the rearrangement[115]. The main product from the rearrangement of the bicyclic epoxide

197 was the *exo*-chloroketone **198**. A careful examination of the process reveals that this result can be explained by either a chlorine or a hydrogen migration. In order to distinguish between these two possibilities the optically active (1R, 3R)-α-chloroepoxide **197** was prepared. If the rearrangement is a chlorine migration, the rearrangement yields only the (1R,3R)-**198** enantiomer, while a hydride shift produces the other



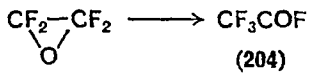
(1S, 3S)-(198) (1R, 3R)-(197) (1R, 3R)-(198)

(1S,3S)-**198** enantiomer. The experiment established that >90% of the rearrangement proceeds by a chlorine migration[115]. A few reports concerning the rearrangement of polyhaloepoxides can be found. One example is epoxide **199**, obtained by direct oxidation of 2,3-dibromo-2-butene, which yielded 3,3-dibromobutanone **200**[116].

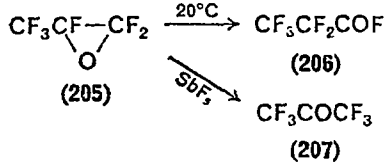
(199) (200)

The rearrangement of 1,1-dihalogeno-substituted epoxides **201** yields, in general, acid halides **202**[112].

(201) (202)



(203) (204)

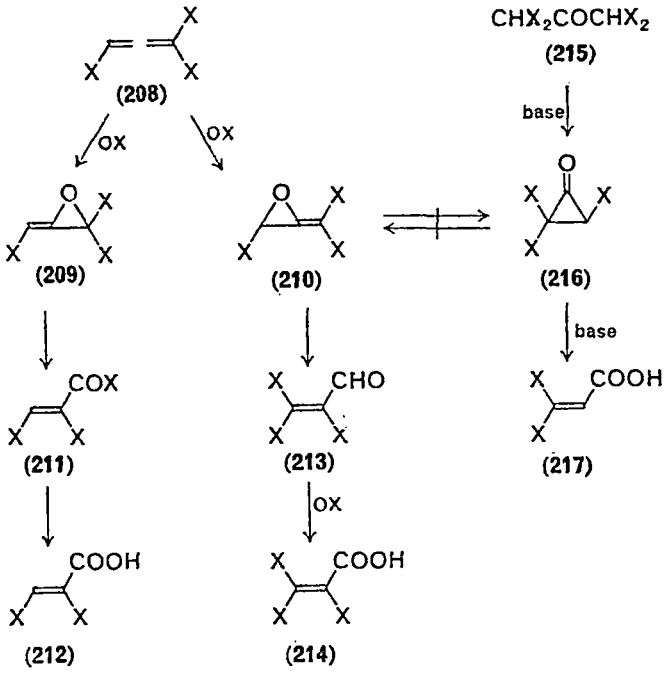


(205) (206) (207)

The rearrangement of the two perfluoroepoxides **203** and **205** has been of industrial importance. The tetrafluoroepoxide **203** below room temperature[117] rearranges to trifluoroacetyl fluoride **204**. Hexafluoropropylene oxide **205** has been found to rearrange to perfluoropropionyl fluoride **206** when heated to about +20°C[118], but in the presence of catalytic amounts of antimony pentafluoride the product is hexafluoroacetone **207**[119]. Data available from rearrangements of fluorochloro- and fluorobromoepoxides indicate that the tendency for migration decreases in the series Br > Cl > F.

2. Halogenated allene oxides

Since allene oxides can isomerize to cyclopropanones, it is possible that halogenated allene oxides isomerize to halogenated cyclopropanones, which are supposed to be intermediates in the Favorsky rearrangement of polyhaloketones (see section VII.A). Kai and Seki[120] and Andersson and Kumar[121] have studied the oxidation of tribromo- and triiodoallene (**208**), which probably results in a mixture of the two allene oxides **209** and **210**. The rearrangement of the 1,1-dihaloepoxide **209** yields an acid halide **211**, which is in analogy with the rearrangement of other 1,1-dihalogenated epoxides (see section B.1). After hydrolysis the halide could be identified as *Z*-2,3-dihaloacrylic acid (**212**), and it is interesting to notice that no



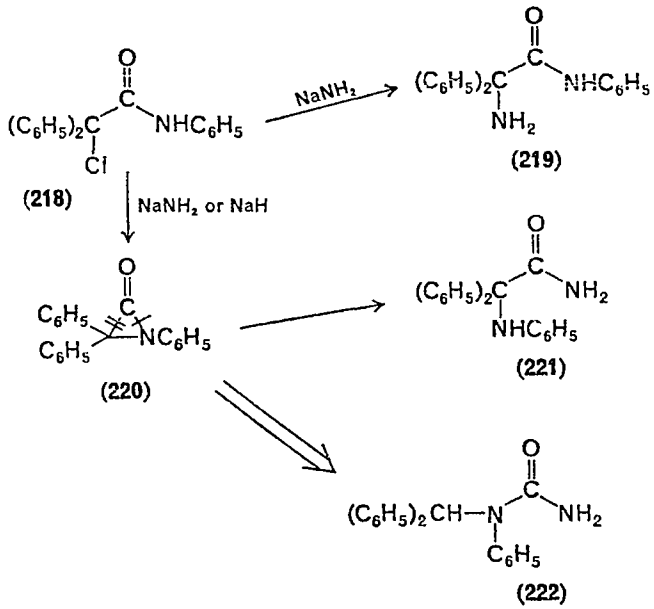
E-isomer could be detected. The rearrangement of the other allene oxide **210** yielded **213**, which could be isolated as its oxidation product trihaloacrylic acid **214**.

The corresponding trihalocyclopropanone **216** is the postulated intermediate in the Favorsky rearrangement of 1,1,3,3,-tetrahaloacetones (**215**). The product from this reaction is 3,3-dihaloacrylic acid (**217**)[88]. Therefore no rapid isomerization of the allene oxides **209** and **210** to the cyclopropanone **216** seems to take place in this case.

C. Rearrangement of α-Haloamides

In a series of papers Sarel and coworkers have studied the reactions of α- and β-halogenated amides. In 1958 Sarel and Greenberger reported that α-chloro-α-phenylacetanilide reacted with sodium amide and sodium hydride yielding a complex mixture of products[122]. In subsequent papers base-induced reactions of other α-chloroamides were studied, the products identified and the mechanism of the reactions discussed.

The reaction of α-chloro-α,α-diphenylacetanilide (**218**) with sodium amide in liquid ammonia has been studied in detail[123]. One of the products was found to be the α-aminoanilide **219**, which is formed in a displacement



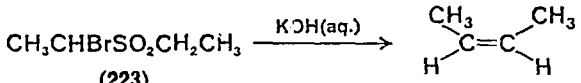
reaction. Two other products were the α-amino-substituted amide **221** and the urea derivative **222**. Sarel and coworkers suggest that these compounds are formed via the aziridinone (α-lactam) **220**. This ring compound can be

isolated in 85% yield when the α-chloroanilide **218** reacts with sodium hydride in benzene[124]. Ring opening along the keto–nitrogen bond results in the formation of **221** and when the keto–carbon bond opens up the product is **222**[123].

D. The Ramberg–Bäcklund Rearrangement

1. Introduction

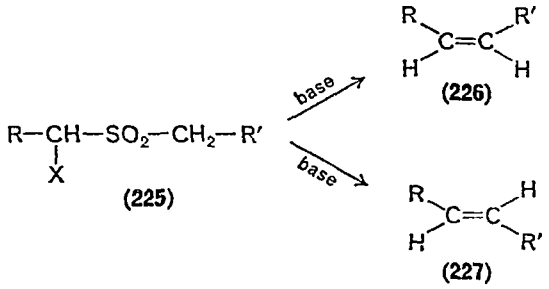
In 1940 Ramberg and Bäcklund reported that α-bromoethyl ethyl sulphone **223** when treated with 2N KOH was readily converted in good yield to 2-butene, the *cis*-isomer (**224**) of which predominated[125,126]. This



reaction, which has come to be known as the Ramberg–Bäcklund rearrangement, is of current interest, not only because of its synthetic applications but also because of its interesting mechanism. The main contribution to our knowledge of this reaction originates from the work of Paquette and Bordwell and their groups. Quite recently both Paquette and Bordwell have written good review articles covering the literature up to 1968[127–129].

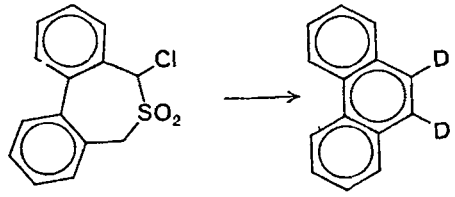
2. Synthetic use of the Ramberg–Bäcklund rearrangement

The Ramberg–Bäcklund rearrangement of α-monohalosulphones (**225**) with at least one α′-proton was shown to be a quite general method of preparing olefins. Usually the product is a *cis–trans* mixture, and usually the thermodynamically less stable *cis*-isomer **226** dominates. The *cis–trans*



ratio, however, is found to be dependent on the starting sulphone and the base used. One example is reported where the *trans*-isomer **227** was the only product[130].

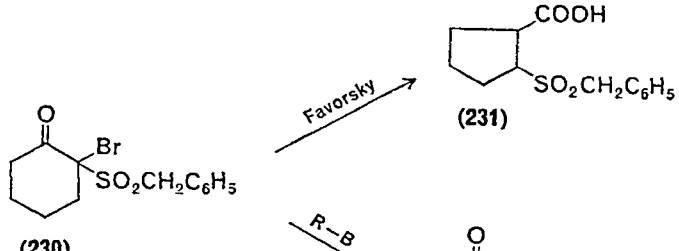
The halosulphones studied include aliphatic, cyclic and benzylic sulphones. Rearrangements of α-chloro- and α-bromosulphones are general, and a few examples of the reactions of α-iodosulphones are also reported. The order of reactivity is I > Br ⩾ Cl[131]. Reactions performed in deuterating solvents yield deuterated olefins in good yields. One example is the successful preparation of 9,10-d_2-phenanthrene (**229**) from the α-chlorosulphone **228**[132].



(228) (229)

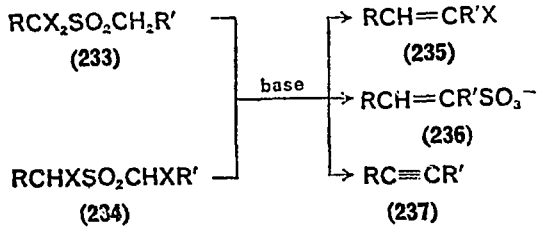
Meyers and coworkers found that CCl_4 in the presence of KOH reacts rapidly with unhalogenated sulphones leading to the Ramberg–Bäcklund product in high yields[133].

Shahak and Bergmann have studied a system where an interesting competition between a Ramberg–Bäcklund and a Favorsky rearrangement is possible. 2-Benzylsulphonyl-2-bromocyclohexanone (**230**) is an α-bromosulphone as well as an α-bromoketone. Examination of the products showed that only the Ramberg–Bäcklund product **232** was formed[134].

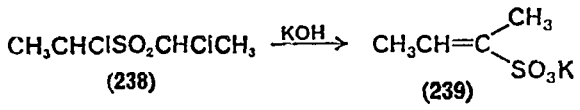


(230) (231) (232)

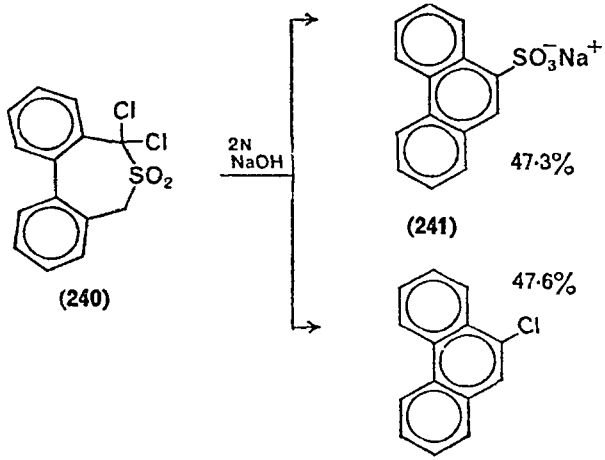
The rearrangement of α,α- (**233**) or α,α′-dihalosulphones (**234**) with at least two α- and α′-protons gives rise to three types of products, vinyl chlorides, **235**, α,β-unsaturated sulphonic acids, **236**, and acetylenes, **237**[127–129]. The proportion of these products depends on the structure of the sulphone used.

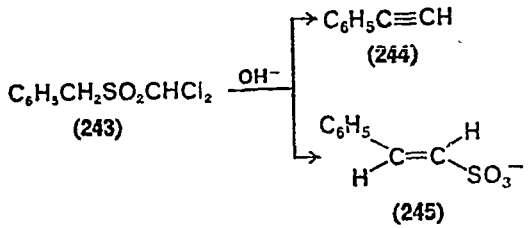


Ramberg and Bäcklund reported that α,α′-dichlorodiethyl sulphone (**238**) gave potassium-2-butene-2-sulphonate (**239**) in 80% yield[125,126]. Paquette

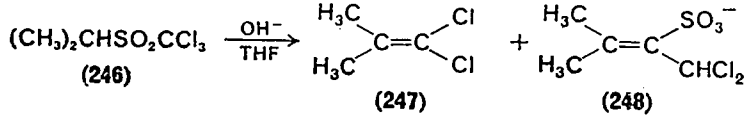


has reported that treatment of the α,α-dichlorosulphone **240** with base yielded the two substituted phenanthrenes **241** and **242**[135]. Phenylacetylene **244** is the main product (about 60% yield) from the rearrangement of dichloromethyl benzyl sulphone (**243**). The other product is *trans*-β-styrenesulphonic acid (**245**), about 30%[136].





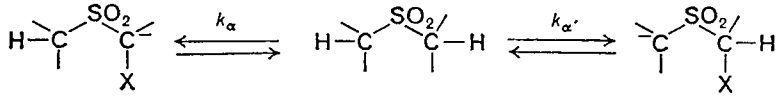
Paquette and Wittenbrook have studied the rearrangement of trichloromethyl sulphones. The reaction of the trichlorosulphone **246** with hydroxide in THF resulted[137] in the vinyl dichloride **247** (14%) and the sulphonic acid **248** (72%).



(246) **(247)** **(248)**

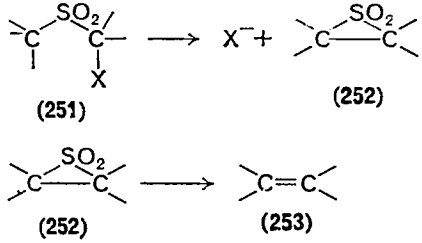
3. The mechanism of the Ramberg–Bäcklund rearrangement

The mechanism of the Ramberg–Bäcklund rearrangement has been carefully studied. It was originally proposed by Bäcklund that an episulphone might be formed as an intermediate in the reaction[126]. The now accepted view is in accordance with a three-step mechanism for the rearrangement of a monohalosulphone[127–129]. Step 1 is a rapid preequilibrium between the sulphone **250** and its α-anion **249** and α′-anion **251**. Deuterium labelling has shown that the incorporation is much faster



(249) **(250)** **(251)**

in the α-position than in the α′-position ($k_\alpha > k_{\alpha'}$)[138]. Step 2 is a slow intramolecular 1,3-displacement of chloride ion in the α′-anion **251** yielding to an episulphone intermediate **252**. Step 3 is a rapid loss of sulphur dioxide from the episulphone intermediate **252** yielding the olefin **253**.

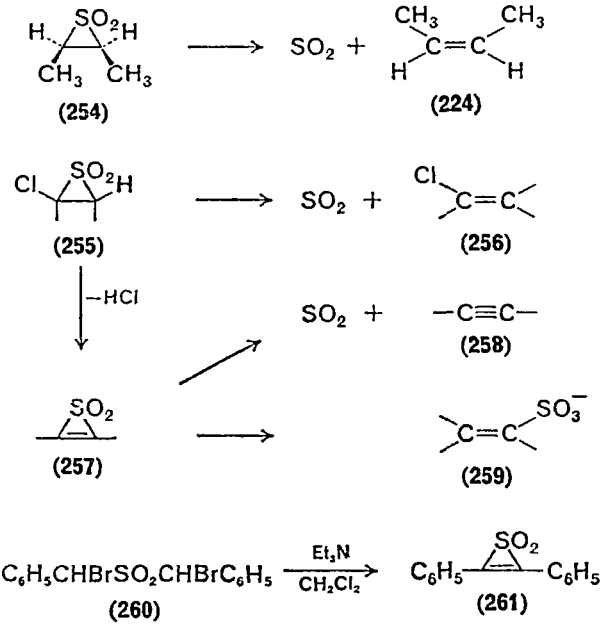


(251) **(252)** **(252)** **(253)**

Episulphones have not been isolated from any Ramberg–Bäcklund rearrangements. However, they can readily be prepared from the reaction of diazoalkanes with sulphur dioxide. Neureiter found that when the *cis*-episulphone **254** was treated with base the product was *cis*-2-butene (**224**) of more than 99% purity[139]. Thus the elimination of sulphur dioxide from

episulphones occurs stereospecifically. Furthermore, since the *cis*-alkane is the main product from the Ramberg–Bäcklund rearrangement, the predominating intermediate must be the *cis*-episulphone.

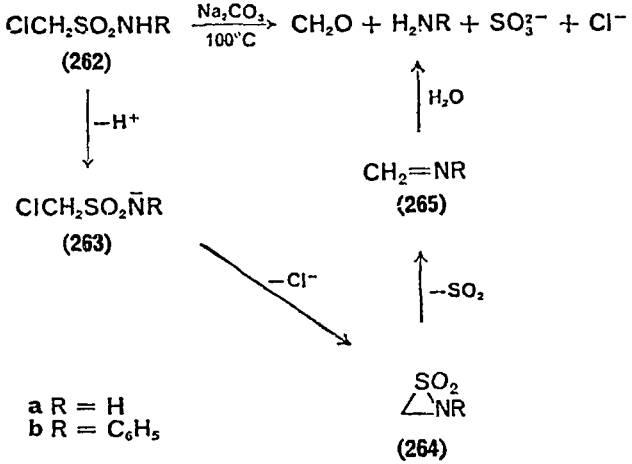
In the case of α,α- and α,α′-dihalosulphones steps 1 and 2 yield a chloroepisulphone intermediate **255**. This intermediate may either undergo loss of sulphur dioxide, resulting in the production of vinyl chloride **256**, or yield a thiirene dioxide intermediate **257** by the base-induced elimination of HCl. Compound **257** can lose sulphur dioxide to yield acetylenes **258** or rearrange to vinyl sulphonic acids **259**[127]. For products **256** and **259** geometric isomerism is possible. No chloroepisulphone (**255**) or thiirene dioxide (**257**) has been isolated from Ramberg–Bäcklund rearrangements. However, Carpino and coworkers have prepared 2,3-diphenylthiirene dioxide (**261**) from α,α′-dibromodibenzyl sulphone (**260**) and triethylamine[140].



E. Rearrangements of α-Halosulphonamides

In 1941 it was reported by Johnson and Douglass that chloromethanesulphonamide (**262a**) and chloromethanesulphonanilide (**262b**) react rapidly in alkaline solution to give amine, formaldehyde, chloride and sulphite. It was also observed that *N*,*N*-disubstituted derivatives did not react[141]. The mechanism of this reaction was studied by Bordwell and

Cooper, who suggested a 'Ramberg–Bäcklund-like' mechanism[130]. In the first step in this reaction the *N*-proton is lost. The intermediate anion **263** undergoes an internal S_N2 attack, yielding a three-membered α-sultam intermediate, **264**. Expulsion of sulphur dioxide yields an aldimine, **265**,



which is hydrolysed to formaldehyde and amine. Later, Farrar studied other examples of this reaction. He found that primary and secondary α-iodo-, α-bromo- and α-chlorosulphonamides are decomposed by hot dilute alkali, while the α-fluoro-substituted ones did not react[142].

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