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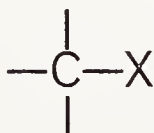
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The chemistry of
the carbon-halogen bond
Part 1

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)
 - The chemistry of the ether linkage (published)
 - The chemistry of the amino group (published)
- The chemistry of the nitro and nitroso group (published in 2 parts)
 - The chemistry of carboxylic acids and esters (published)
- The chemistry of the carbon–nitrogen double bond (published)
 - The chemistry of amides (published)
- The chemistry of the cyano group (published)
- The chemistry of the hydroxyl group (published in 2 parts)
 - The chemistry of the azido group (published)
- The chemistry of acyl halides (published)
- The chemistry of the carbon–halogen bond (published in 2 parts)



The chemistry of the carbon^{//}-halogen bond

Part 1

Edited by

SAUL PATAI

The Hebrew University, Jerusalem

1973

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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 rotatory 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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CHAPTER 1

General and theoretical aspects of the carbon-halogen bond

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Zürich, Switzerland*

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I. GENERAL INTRODUCTION

A. Recent Advances in the Study of Molecular Properties

I. 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* calculations⁵. 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 reactions⁸, 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: CNDO⁹⁻¹¹ (complete neglect of differential overlap), INDO¹² (intermediate neglect of differential overlap), NDDO¹³ (neglect of diatomic differential overlap), PND0¹⁴ (partial neglect of differential overlap), MINDO¹⁵ (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 nucleus¹⁸. 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 Lucken¹⁹.

b. Mössbauer spectroscopy of bonded iodine^{20,21}. The exact frequency of the 57.6 KeV gamma rays emitted by the ¹²⁷I 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* bonding²¹. Though the magnitude of the quadrupole coupling is only determined to an

accuracy of $\sim 0.5\%$ ²⁰, hence less precisely than with n.q.r., Mössbauer spectroscopy has the advantage of also yielding its sign²¹.

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 bonded²². 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 splittings²⁸. Recently a combination of both approaches has been developed, designated as phosphorescence-microwave double-resonance spectroscopy²⁹ (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 octant³¹⁻³³ rule or quadrant³⁴⁻³⁷ 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. curve³⁸. 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 Moscowitz³³ 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 2s, 2p, say) and of the carbonyl n orbital³⁶. 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 century⁴⁰, its systematic application to the study of molecules is recent⁴¹⁻⁴⁵. 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

$$E = h\nu - W \quad (1a)$$

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

$$W = I_A + \Delta E_{\text{vib}} + \Delta E_{\text{rot}} \quad (1b)$$

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}

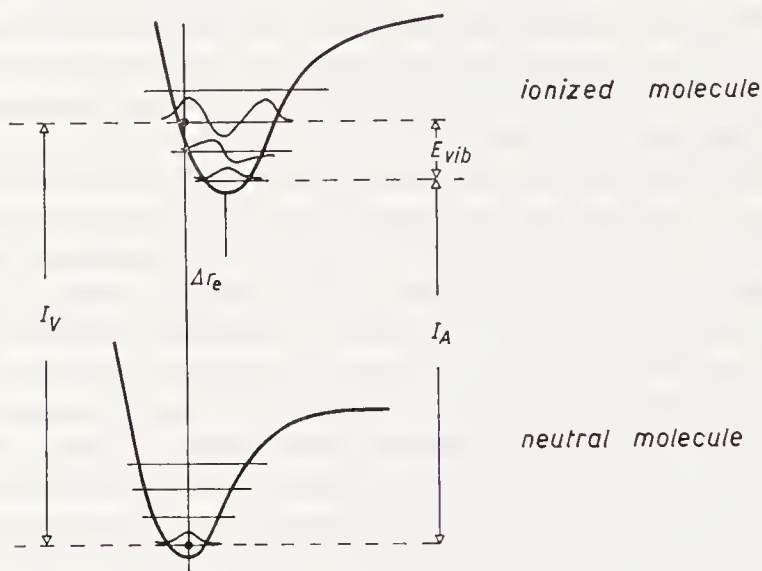


FIGURE 1. Illustration of the vertical and adiabatic ionization potential, I_V and I_A for a diatomic molecule. Δr_e represents the difference in equilibrium geometry between neutral molecule and radical cation.

and ΔE_{rot} are the differences in vibrational and rotational energy. Of course $|I_A| \gg |\Delta E_{\text{vib}}| \gg |\Delta E_{\text{rot}}|$, 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}

$$f_{i\nu, j\mu} = 4.703 \times 10^{29} \cdot \nu_{ij} \cdot |\bar{M}_{ij}|^2 \cdot |S_{\mu\nu}|^2 \quad (2)$$

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 principle⁴⁸. 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 line⁴⁹.

The Franck-Condon principle gives a means of rationalizing ΔE_{vib} in the p.e. spectrum. Koopmans' theorem⁵⁰ 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 orbitals⁵¹⁻⁵³. 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 remark⁵⁴: '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 way⁵⁵ the electronic energy levels of the diatomic halogen molecules may be understood as shown in Figure 2

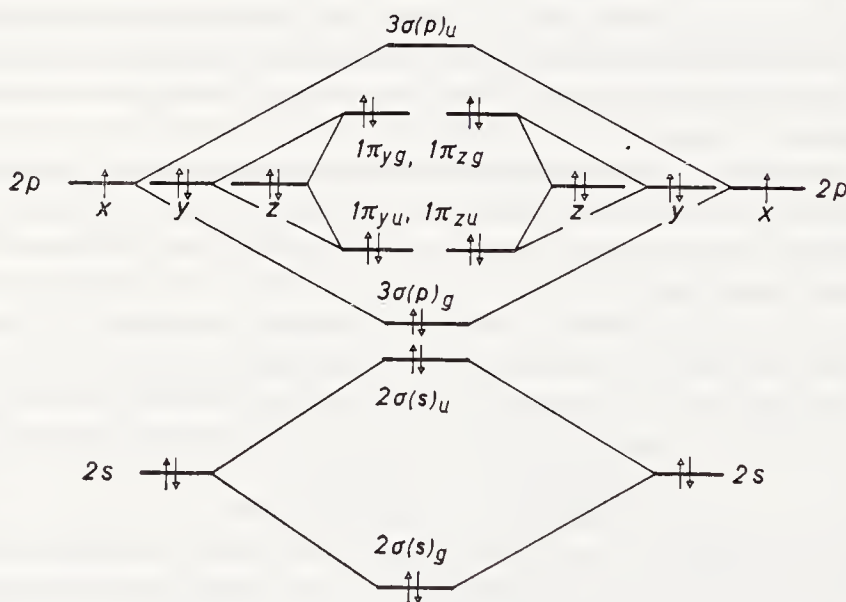


FIGURE 2. The sequence of orbitals in the fluorine atom and molecule, according to a simple energy level scheme.

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' theorem⁵⁰ the ionization potentials are expected to be

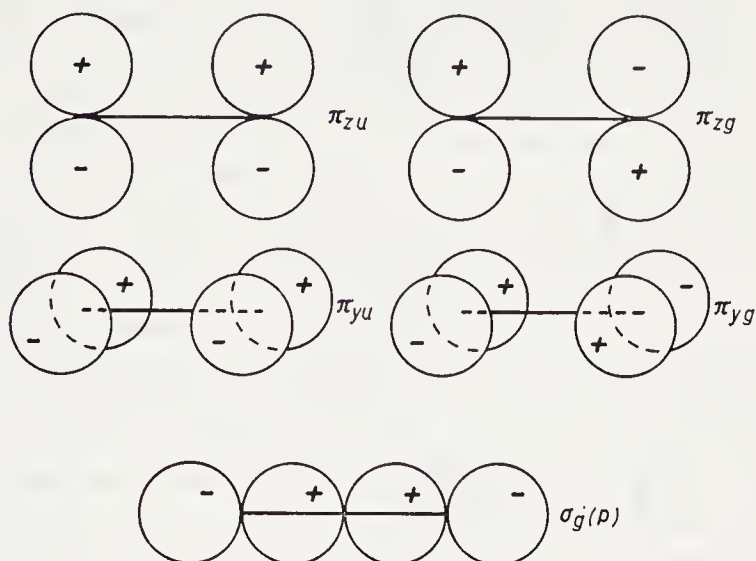


FIGURE 3. A simplified representation of some orbitals of π and σ symmetry.

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 halogens⁵⁶ 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 $X({}^2P_{3/2}) \rightarrow X^+({}^2P_2)$. 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 ^{a, e}
Second ionization potential to ionic state $^2\Pi_u, I_2$ (eV) ^f	18.4 ^c	14.0 ^c	12.5 ^c	10.8, 11.6 ^{c, e}
Electron affinity A (eV)	18.98 ^d	14.43 ^d	13.08 ^d	11.03, 11.82 ^e
Dissociation energy D_e (eV)	3.08 ^f	2.38 ^f	2.51 ^f	2.58 ^f
Vibrational frequency ω_e (cm ⁻¹)	1.65 ^g	2.5143 ^g	1.991 ^h	1.555 ^h
Nuclear quadrupole coupling constants (Mc/s)	892.1 ^a	564.9 ^a	323.2 ^a	214.6 ^a
	—	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 $^2\Pi_g$ and $^2\Pi_u$ 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 chlorine⁵⁷ and, to the author's knowledge at the time of writing, only one calculation has ever been performed on both Br₂ and on I₂⁵⁸.

One notices in the case of F₂ 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 procedure⁵⁹ 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 F₂ obtained by the Hartree-Fock method is −1.37 eV⁶⁰. 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 method⁶¹, positive values for D_e close to the experimental ones are found. The experimental dissociation energy of F₂ 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 hand⁵⁷ and SCF results on the other⁶¹ 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}:

$$D_e(X_2^-) = D_e(X_2) + A(X_2) - A(X) \quad (3a)$$

$$D_e(X_2^+) = D_e(X_2) - I(X_2) + I(X) \quad (3b)$$

By definition in this context:

$$I(X_2) = E_+(r_e^+) - E(r_e) \quad (4a)$$

$$A(X_2) = E(r_e) - E_-(r_e^-) \quad (4b)$$

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

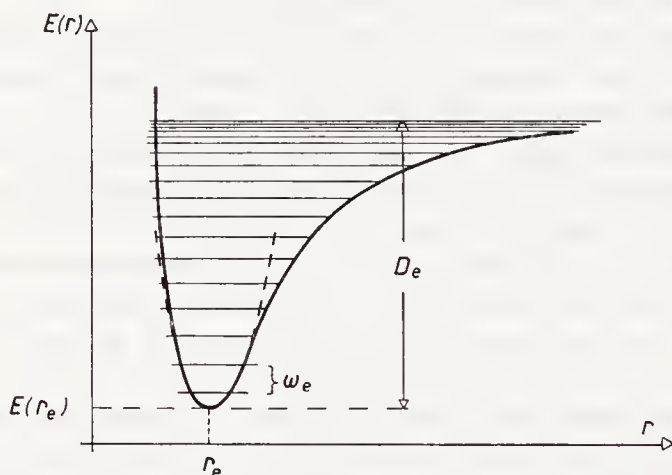


FIGURE 4. Illustration of the binding energy D_e and the vibrational frequency ω_e .

experimentally determined by assessing the charge transfer threshold in halogen ion-halogen molecule⁶⁶ or alkali atom-halogen molecule^{67, 68} collisions of the types



and



* 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 spectra⁷⁰.

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 $D_e(\text{X}_2^+) = D_e(\text{X}_2) - I(\text{X}_2) + I(\text{X})$; see also reference 73.

^e Value for $^2\Pi_{\frac{3}{2}}$ 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 $D_e(\text{X}_2^-) = D_e(\text{X}_2) + A(\text{X}_2) - A(\text{X})$; see also reference 61.

In F_2 one finds only continuous absorption, with a maximum at about $34,500\text{ cm}^{-1}$. Absorption continua set in at $20,850\text{ cm}^{-1}$ in Cl_2 and at $19,580\text{ cm}^{-1}$ 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 Mulliken⁷².

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 $^2\Pi_{3/2}$ and $^2\Pi_{1/2}$ 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 properties⁷⁷ (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 CH₃F 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 CH₃F to CF₄ 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 ₃ F	CH ₂ F ₂	CHF ₃	CF ₄
<i>r</i> (CH)	1.085	1.105	1.091	1.098	—
<i>r</i> (CF)	—	1.385	1.358	1.332	1.317
<i>θ</i> (HCH)	109.47°	109.9°	112.1°	—	—
<i>θ</i> (FCF)	—	—	108.2°	108.8°	109.47°
<i>k</i> _{C—F}	—	5.8	—	8.1	9.2

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

	CH ₃ F	CH ₃ Cl	CH ₃ Br	CH ₃ I
<i>I</i> ₁ (<i>e</i>)	13.04	11.30, 11.32	10.54, 10.86	9.54, 10.16
<i>I</i> ₂ (<i>a</i> ₁)	17.06	14.42	13.49	12.50
<i>I</i> ₃ (<i>e</i>)	17.06	15.40	15.08	14.80
<i>I</i> ₄ (<i>a</i> 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. Δ₁ indicates the spin-orbit splitting in the first p.e. band. Under CH₃Cl, CH₃Br and CH₃I the energies of the resolved ²*E*_½ and ²*E*_½ peaks of this first band are given.

TABLE 3b. First vertical ionization potentials in eV of halo-methanes

	F	Cl	Br	I
CH ₃ X	13.04 <i>e</i>	11.31 <i>e</i>	10.70 <i>e</i>	9.85 <i>e</i>
CH ₂ X ₂	13.29 <i>b</i> ₁	11.40 <i>b</i> ₂ + <i>a</i> ₂	10.61 <i>b</i> ₂	9.46 <i>b</i> ₂
CHX ₃	14.80 <i>a</i> ₁	11.48 <i>a</i> ₂	10.47 <i>a</i> ₂	—
CX ₄	16.23 <i>t</i> ₁	11.69 <i>t</i> ₁	10.54 <i>t</i> ₁	—

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 ₃ F	CH ₂ F 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 ₃ F	CH ₂ F ₂	CHF ₃
Experimental ^a	1.85	1.97	1.65
<i>Ab initio</i> SCF-MO ^a	2.43	2.61	2.21
<i>Ab initio</i> SCF-MO ^b	2.597	2.812	2.245

^a Reference 74.

^b Reference 54.

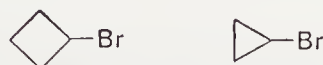
(~ -0.2), at the expense of the carbon atom, which becomes increasingly positive: perfluorination on one carbon centre appears to make that centre very electron deficient.

The p.e. data on the higher halomethanes contrast with those on the fluoromethanes in two interesting ways: the first ionization potentials in CH₃Cl, CH₃Br, CH₃I are not very far from those in Cl₂, Br₂, I₂, respectively (Tables 1b and 3a). In CH₃F, however, it is about 2.7 eV lower than in F₂. Secondly, on going from CH₃Cl to CCl₄ or from CH₃Br to CBr₄ the first ionization potential does not change appreciably, in contrast to the series CH₃F to CF₄ (Table 3b).

To what extent are the electrons in the top-filled e orbitals of CH₃Cl, CH₃Br or CH₃I '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 CH₃F. 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 Heilbronner⁸⁰ 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 atoms⁷⁵. However, none of these atoms lie on a higher ($n \geq 3$) 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 $30,000\text{ cm}^{-1}$ 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 Basch⁵⁴ assign the first and second absorptions in CH_3F , CH_2F_2 and CHF_3 as Rydberg transitions to $3s$ and $3p$ orbitals, respectively. In CF_4 no transition to $3s$ 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 $\text{mdyn}/\text{\AA}$, and characteristic frequencies in cm^{-1} (from reference 78)

	F	Cl	Br	I
$\begin{array}{c} \diagup \\ \text{C}-\text{X} \\ \diagdown \end{array}$	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
$\text{H}_3\text{C}-\text{X}$	-4.00	-2.71	-2.32	-1.85
$\begin{array}{c} \text{H} \\ \\ \text{H}_3\text{C}-\text{X} \end{array}$	-4.23	-3.22	-3.12	-2.97
$\begin{array}{c} \text{H} \quad \text{I} \\ \quad \\ \text{H}_3\text{CH}_2\text{C}-\text{X} \end{array}$	-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 indicate⁸¹ 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. spectra⁸² that the C—Br stretching force constants of CBr_3 are higher than either those of CBr_4 or of HBr . 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 prevails⁸². It seems that in general alkyl radicals are stabilized by chlorine and bromine, in the sense that $\dot{\text{C}}\text{X}_3$ lies energetically less far above CX_4 than $\dot{\text{C}}\text{H}_3$ lies above H_3CX , and $\dot{\text{C}}\text{X}_3$ lies energetically less far above HCX_3 than $\dot{\text{C}}\text{H}_3$ 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 fluoro-methyl 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 resonance⁸⁴. While CH_3 is planar⁸⁵, CF_3 is not⁸⁶. From the magnitude of the coupling constants in e.s.r. spectra one predicts CH_2Cl to be nearly planar⁸⁷, 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 planar⁸² (see also Table 7).

TABLE 7. Properties of halomethyl radicals

	Geometry	Valence angles	Stabilization
CH_3	Planar	120° ^a	
CF_3	Pyramidal	$\sim 115^\circ$ ^{b, c} $> 109^\circ$ ^c	None ^c
CCl_3	Pyramidal	$< 120^\circ$ $> 109^\circ$ ^c	~ 12 kcal/mole ^c
CBr_3	Pyramidal	$< 120^\circ$	~ 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 method⁹⁰, 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 chloroethanes⁹³.

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

$$\phi_{A-B} = a\chi_A + b\chi_B \quad (5)$$

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,

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

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

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 :

$$Q_{\text{H}} = q_{\text{H-C}}, \quad Q_{\text{C}} = 3q_{\text{C-H}} + q_{\text{C-X}}, \quad Q_{\text{X}} = q_{\text{X-C}} \quad (7a)$$

Of course

$$3Q_{\text{H}} + Q_{\text{C}} + Q_{\text{X}} = 0 \quad (7b)$$

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.

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

where s_A stands for Slater's screening constant⁹⁴. The next quantity of importance is the longitudinal polarizability of a given bond, α_{A-B}^l ,

which may be inferred from experiment⁹⁵ 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

$$\mu_{A-B} = \alpha_{A-B}^l \cdot F \quad (9)$$

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

$$\mu_{A-B} = -q_{A-B} \cdot r_{A-B} = \alpha_{A-B}^l \left(\frac{Z_A e}{R_A^2} - \frac{Z_B e}{R_B^2} \right) \quad (10)$$

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_{A-B}^l ($\times 10^{24} \text{ cm}^3$)	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 ₃ F	1.81	1.81	91
CH ₃ Cl	1.86	1.86	91
CH ₃ Br	1.78	1.78	91
CH ₃ I	1.59	1.59	91
CH ₂ F ₂	1.91	1.96	91 ^a
CH ₂ Cl ₂	1.63	1.57	91
CH ₂ Br ₂	1.48	1.43	91
CH ₂ I 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 ₂ H ₅ F	1.95	1.92, 1.96	92
C ₂ H ₅ Cl	2.02	2.00–2.05	92
C ₂ H ₅ Br	1.95	1.99–2.02	92
C ₂ H ₅ I	1.82	1.87–1.93	92
CH ₃ CH ₂ Cl	1.86	1.75–2.09	93 ^b
CH ₃ CHCl ₂	1.79	2.07–3.33	93 ^b
CH ₃ CCl ₃	1.55	1.79–2.03	93 ^b
CH ₂ ClCCl ₃	1.58	1.44 solution	93 ^b
CHCl ₂ CCl ₃	1.09	0.92	93 ^b
CCl ₃ CCl ₃	0.0	0.0	93 ^b
CH ₂ ClCH ₂ Cl	1.03 (25°C)	1.13–1.84	93 ^b
CH ₂ ClCHCl ₂	1.30 (90°C)	1.25–1.42	93 ^b
CHCl ₂ CHCl 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

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

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 Scheraga⁹⁶ have proposed a procedure for calculating barriers to internal rotation⁹⁷ 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

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

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 potential⁹⁸ 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 $i \quad j$	a_{ij}	b_{ij}	c_{ij}	d_{ij}
H...H	9.17×10^3	4.54	45.2	0
H...F	1.69×10^4	4.57	62.7	0
H...Cl	3.90×10^4	4.15	321	0
H...Br	2.18×10^4	3.66	465	0
F...F	6.02×10^4	4.60	118	14.4 ^a
F...Cl	1.47×10^5	4.18	527	4.09 ^a
Cl...Cl	3.14×10^5	3.75	2520	1.16 ^a
Br...Br	3.46×10^4	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 Sutton⁹³ 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 ₃ CH ₃	2.70–3.10 ^a	3.29		2.18
CH ₃ CH ₂ F	3.30 ^c	3.31		2.00
CH ₃ CHF ₂	3.18	3.33		1.88
CH ₃ CF ₃	3.48	3.35		1.76
CF ₃ CH ₂ F	4.58			1.46
CF ₃ CHF ₂	3.51			1.22
CF ₃ CF ₃	3.92	4.35		1.07
CH ₃ CH ₂ Cl	3.7 ^b	3.44	3.0	
CH ₃ CHCl ₂	3.5	3.56	3.1	
CH ₃ CCl ₃	2.8	3.73	3.3	
CCl ₃ CH ₂ Cl	10.0		8.7	
CCl ₃ CHCl ₂	14.2		14.1	
CCl ₃ CCl 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 trend⁹⁹. *Ab initio* SCF calculations have been performed on different conformations of 3-fluoropropene¹⁰⁰ 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 techniques¹⁰¹ have met with some success and the application

of nuclear magnetic resonance appears to gain in importance¹⁰². 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 Sederholm¹⁰³ have studied the fluorine n.m.r. spectra of such molecules as $\text{CFCl}_2\text{—CFCl}_2$, $\text{CF}_2\text{Br—CCl}_2\text{Br}$, $\text{CF}_2\text{Br—CFBr}_2$, $\text{CF}_2\text{Br—CFBrCl}$, CFCIBr—CFCIBr and $\text{CF}_2\text{Br—CHBrCl}$. Applying absolute reaction rate theory¹⁰⁴, 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
$\text{H}_2\text{C=CH}_2$	10.51 ^a	12.38 ^a	45
	10.6	12.85	106
$\text{H}_2\text{C=CHF}$	10.58	13.79	106
<i>cis</i> - HFC=CHF	10.43	13.97	106
<i>trans</i> - HFC=CHF	10.38	13.90	106
$\text{H}_2\text{C=CF}_2$	10.72	14.79	106
$\text{F}_2\text{C=CHF}$	10.53	14.64	106
$\text{F}_2\text{C=CF}_2$	10.52	15.95	106
$\text{F}_2\text{C=CHCl}$	10.04	12.15	105
$\text{F}_2\text{C=CFCl}$	10.24	13.01	105
$\text{F}_2\text{C=CCl}_2$	9.84	12.14	105
$\text{H}_2\text{C=CHCl}$	10.18	11.72	105
<i>cis</i> - HClC=CHCl	9.83	11.71	105
<i>trans</i> - HClC=CHCl	9.81	11.86	105
$\text{H}_2\text{C=CCl}_2$	10.00	11.67	105
$\text{Cl}_2\text{C=CHCl}$	9.65	11.73	105
$\text{Cl}_2\text{C=CCl}_2$	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 $\pi (1b_{3u} = 1b_{zu})^*$ orbital⁴⁵, 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 species¹⁰⁵, 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 bond¹⁰⁵. 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 effect¹⁰⁶. 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

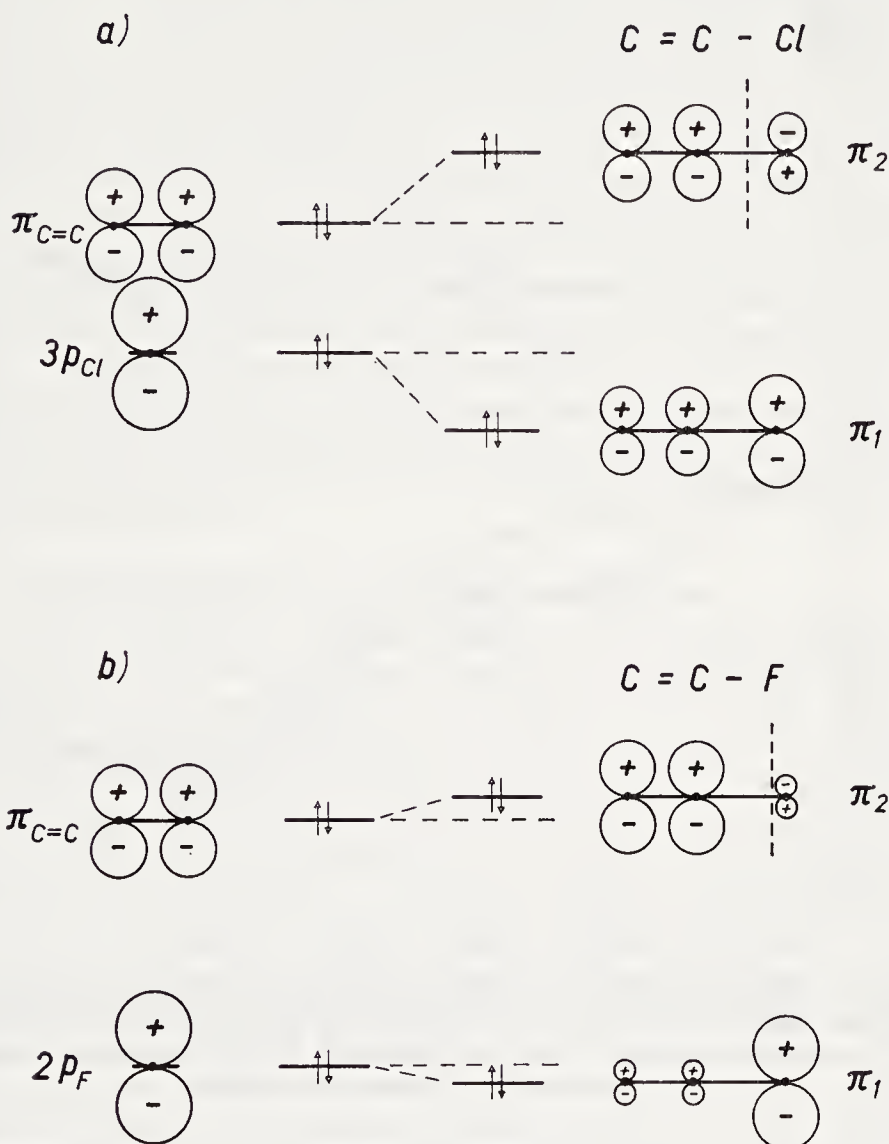


FIGURE 5. (a) The destabilizing influence of chlorine by conjugation with the highest filled π orbital of ethylene. Note the node bisecting the C—Cl bond in π_2 . (b) Because of the higher ionization potential of fluorine, i.e. its lower $2p$ level, the conjugative effect is much less pronounced. The 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.

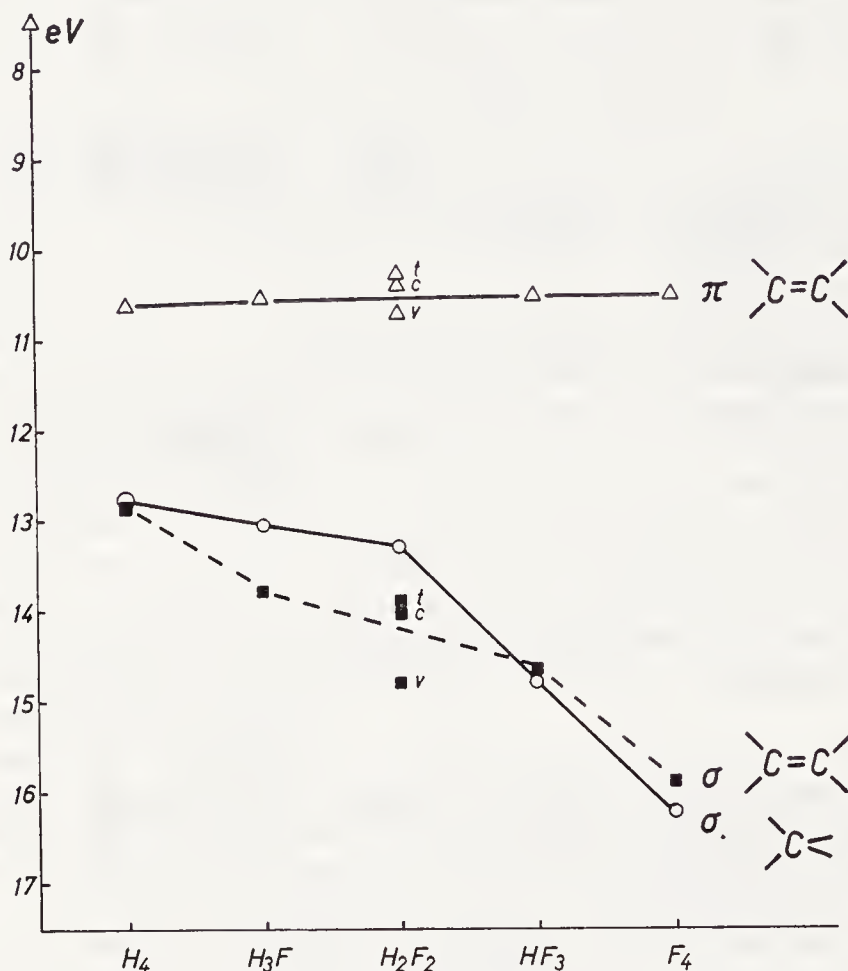


FIGURE 6. The perfluoro effect: \circ , the first ionization potential of the fluoromethanes; \blacksquare , the second ionization potential of the fluoroethylenes; \triangle , the first ionization potential of the fluoroethylenes, which is scarcely affected; t, c, v mean *trans, cis, vicinal*, respectively.

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 Warsop¹⁰⁷ 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 $+(0.11 \pm 0.01 \text{ \AA})$ for the change of the C—C bond lengths and $-(0.03 \pm 0.015 \text{ \AA})$ 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 Luz¹⁰⁸ 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 ($f \approx 0.3$) starting at or above 2150 Å and attaining a maximum at about 1620 Å, is the $\text{V} \leftarrow \text{N}$ transition, corresponding to $\pi_z \rightarrow \pi_z^*$ excitation, of symmetry ${}^1\text{B}_{gu}$ 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 ($f \approx 0.03$). 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 Kammer¹¹²⁻¹¹⁴ have, from *ab initio* calculations, come to a somewhat modified interpretation of the broad 2150–1620 Å $\text{V} \leftarrow \text{N}$ 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 account¹¹⁵. 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 state¹¹³. The $V_g \leftarrow N$ transition, though magnetic dipole allowed and electric dipole forbidden for $\theta = 0$, gains electric dipole allowedness for $0^\circ < \theta < 90^\circ$, 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 Sandorfy¹¹⁶. 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	$V_u \leftarrow N$	≤ 1620	$V_g \leftarrow N$	≥ 1620
$H_2C=CHF^c$	$3R \leftarrow N$	1776	$V \leftarrow N$	Max. 1665	$3R' \leftarrow N$	1532
<i>cis</i> -HFC=CHF		1910		Max. 1585		1586
<i>trans</i> -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
<i>trans</i> -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 ethylene¹¹⁷⁻¹¹⁹. 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 $3R \leftarrow N$ 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 Sandorfy¹¹⁶ 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 calculations¹²¹ 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 $V \leftarrow N$ maximum is encountered, as compared to ethylene. Of interest is a recent study of the vacuum u.v. spectra of several chlorofluoroethylenes¹²³. An attempt is made to correlate the $V \leftarrow N$ 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 Russell¹²³: 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 coworkers¹²⁸⁻¹³⁰ 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 $\pi, \pi, \sigma, \sigma \dots$, while in the dihalogen species of symmetry $D_{\infty h}$ one finds $\pi_u, \pi_g, \pi_u, \sigma_g, \sigma_u \dots$. 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:

$$\Delta_i = I_{\frac{3}{2}i} - I_{\frac{1}{2}i} \quad (12)$$

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

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

Theoretically, the magnitude of Δ_i is roughly equal to¹²⁸

$$\Delta_i \approx \zeta' \sum_p Z_p^2 c_{ip}^2 \quad (14)$$

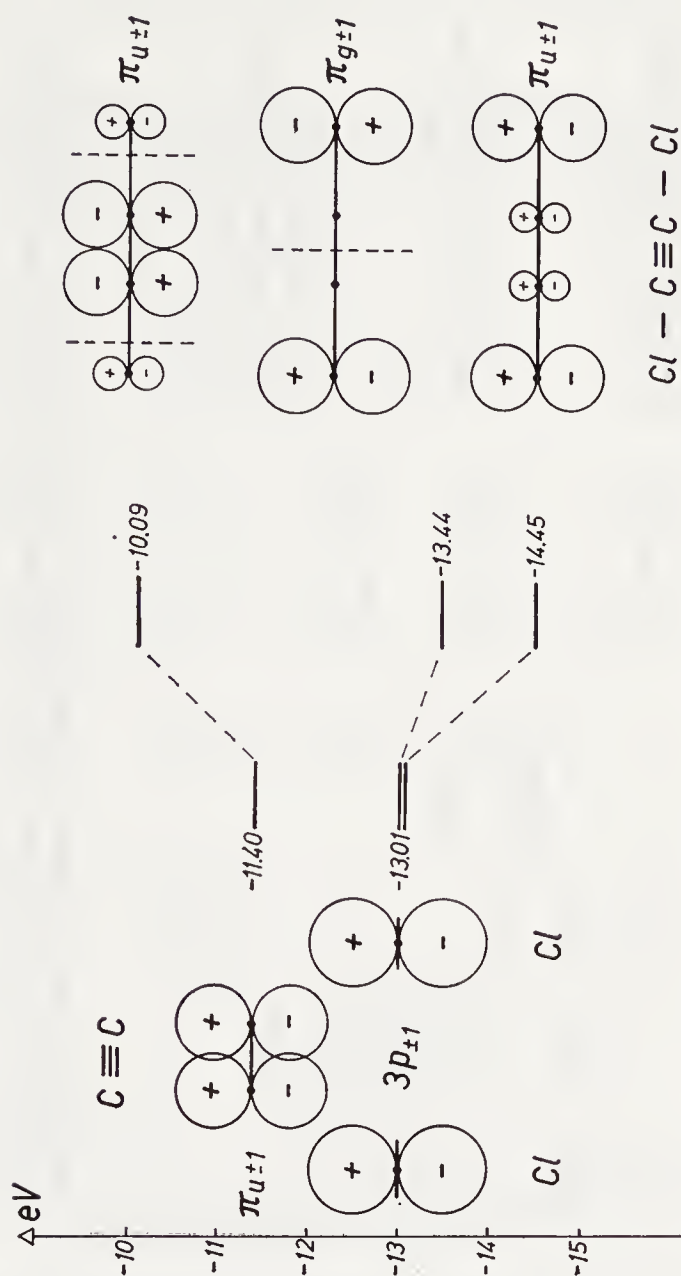


FIGURE 7a. The filled π orbitals in dichloroacetylene. Each level is doubly degenerate. The highest orbital contains a relatively small chlorine contribution. Note the node across both C-Cl bonds. (See also reference 128.)

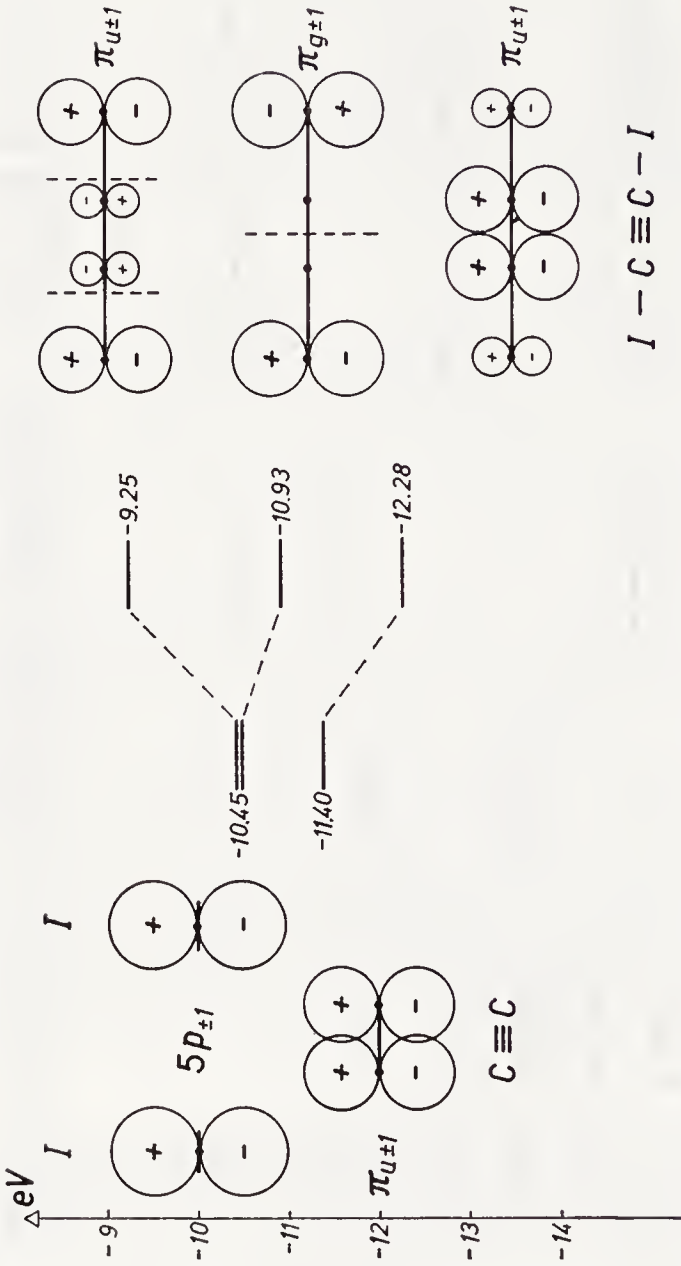


FIGURE 7b. The filled π orbitals in diiodoacetylene. Because of the low ionization potential of iodine the highest π orbital shows a relatively large iodine contribution. (See also reference 128.)

where Z_p is the nuclear charge of the p th 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*:

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

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

Each orbital is doubly occupied in the ground state of the neutral molecule. In all molecules $X-C\equiv C-X$ 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 $^2\Pi_{\frac{3}{2}}$ and $^2\Pi_{\frac{1}{2}}$ states—data on halogenated acetylenes are from Heilbronner and coworkers^a; Δ_i refers to i th 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 \equiv CCl ^a	—	~ 0.08	
ClC \equiv CCl	—	~ 0.10	
Br ^b	0.46		
Br ₂ ^c	0.35	~ 0.26	
HBr ^b	0.32		
HC \equiv CBr ^a	0.14	0.13	
BrC \equiv CBr	0.20	0.29	0.13
I ^{a, b}	0.94		
I ₂ ^c	0.64	~ 0.79	
HI ^b	0.66		
HC \equiv CI ^a	0.41	0.23	
IC \equiv 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 Schäublin¹³⁰ 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 Warsop¹³¹ 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 factors¹³² 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 are¹³⁰: $\Delta r_{\text{C-F}} = -0.062 \text{ \AA}$, $\Delta r_{\text{C-Cl}} = -0.067 \text{ \AA}$, $\Delta r_{\text{C-I}} = -0.078 \text{ \AA}$. On the other hand, the C \equiv C bond length increases by the respective amounts $+0.053 \text{ \AA}$, $+0.026 \text{ \AA}$, $+0.025 \text{ \AA}$.

Ab initio SCF calculations on HC \equiv CF and HC \equiv CCl have been performed by McLean and Yoshimine (cited in reference 133) and on the dihalogenated species by Straub¹³⁴. 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 effect¹³⁶. 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 ago¹³⁷ 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 therefrom¹³⁷, 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 perturbation¹³⁸. 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 nucleus¹³⁹⁻¹⁴². On this basis Petruska¹⁴⁰, for instance, distinguishes between the following¹⁴¹: (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 :

$$-\Delta\nu = \sum_m l_m + \left| \sum_m v_m \exp(2\pi im/3) \right|^2 - 0.2 \left| \sum_m v_m (-1)^m \right|^2 \quad (16)$$

where l_m and v_m are parameters characteristic of the substituent attached to carbon atom m in the benzene ring ($m = 1, \dots, 6$). 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's¹⁴⁰ parameters for benzene substitution

Substituent	l (cm ⁻¹)	v (cm ⁻¹)
F	50	17.0
Cl	935 (840 <i>ortho</i>)	11.0
Br	975	11.0
I	1000	15.0
CH ₃	560 (405 <i>ortho</i>)	8.0
NH ₂	3550	21.0

Values of l and v for halogen substitution as obtained by Petruska¹⁴⁰ are given in Table 16. They reflect the following relative influences.

Second-order inductive effect: $\text{NH}_2 > \text{F} > \text{I} > \text{Cl}, \text{Br} > \text{CH}_3$

Resonance or conjugative* effect: $\text{NH}_2 > \text{I} \gtrsim \text{Cl}, \text{Br} > \text{CH}_3 > \text{F}$

* 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 basis¹⁴⁵. 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

Turner¹⁵⁰ 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 Kuebler¹⁵¹ 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 calculations⁷. 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 $^{-1}$)
	(37,850 cm $^{-1}$)	0	16+0	(48,780 cm $^{-1}$)	0	(54,050 cm $^{-1}$)	0
C ₆ H ₆	2640			2050		1850	
C ₆ H ₅ F	2660	270	17+70	2060	200	1840	-300
1,3-C ₆ H ₄ F ₂	2655	200	17+68				
1,4-C ₆ H ₄ F ₂	2735	1290	17+205				
C ₆ H ₅ Cl	2715	1030	18+12	2165	2500	1910	1700
1,2-C ₆ H ₄ Cl ₂	2772	1850	20+20	2220	3700	1965	3200
1,3-C ₆ H ₄ Cl ₂	2780	1900	20+18	2215	3600	1975	3400
1,4-C ₆ H ₄ Cl ₂	2815	2340	20+42	2285	5000	1945	2600
C ₆ Cl ₆	3035	4920	24+0	2450	8000	2190	8400
C ₆ H ₅ Br	2720	1070	18+10	2210	3500	1920	2000
1,2-C ₆ H ₄ Br ₂	2775	1850	20+14				
1,3-C ₆ H ₄ Br ₂	2785	1950	20+24				
1,4-C ₆ H ₄ Br ₂	2825	2450	20+32				
C ₆ H ₅ I	(2730)	(1200)	20+30	2300	5300	1960	3000
C ₆ H ₅ CH ₃	2685	610	21+10	2110	1400	1900	1400
C ₆ H ₅ NH ₂	2955	4000	20+224	2395	7000	1980	3600

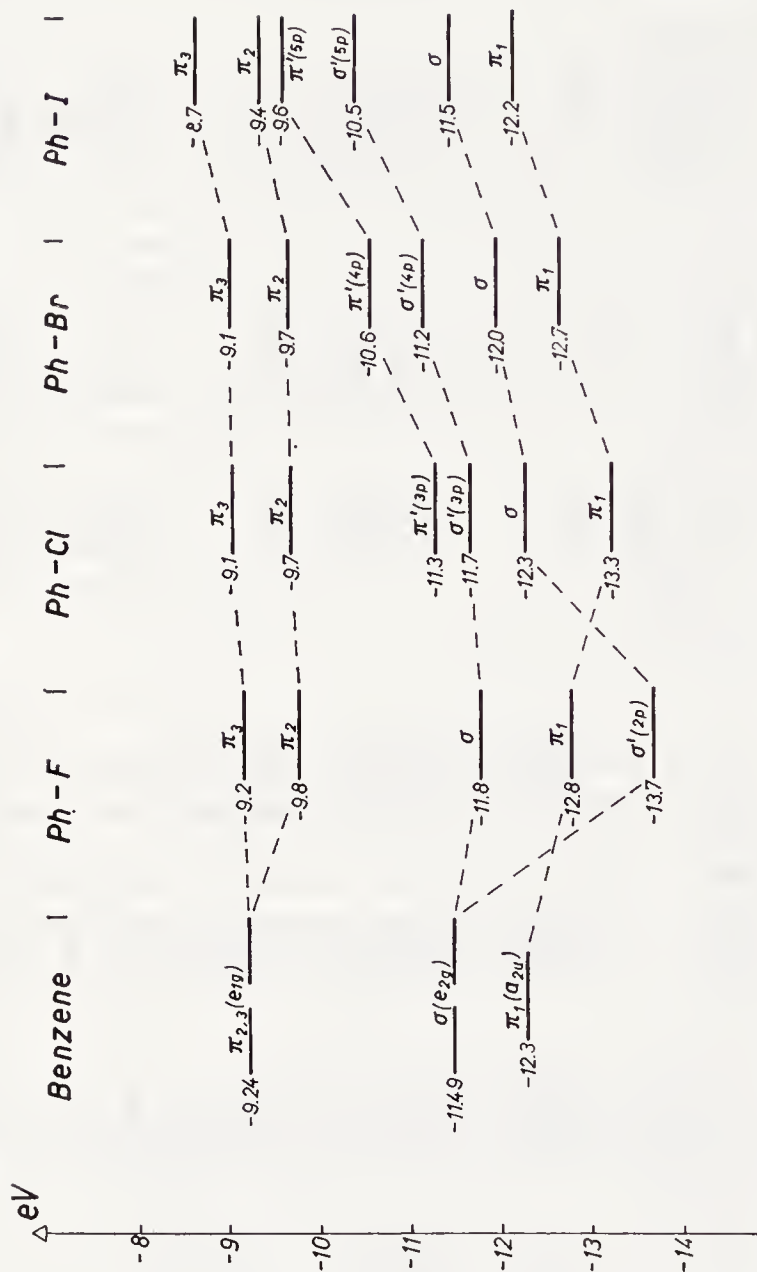


FIGURE 8. Orbital energy levels in benzene and monohalogenated benzenes. The data on benzene stem mainly from reference 150, those on the substituted benzenes from reference 151. The interpretation and assignments are based partly on reference 150, partly on reference 151, and are, for the rest, somewhat 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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CHAPTER 2

Structural chemistry of the C—X bond

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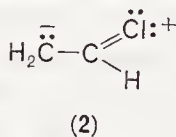
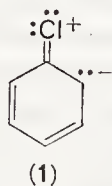
I. INTRODUCTION

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 compounds¹. 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, $\text{CH}_2=\text{CH}-\text{CH}=\text{CH}_2$ (1.48 Å) and butadiyne, $\text{HC}\equiv\text{C}-\text{C}\equiv\text{CH}$ (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 $C(sp^3) = 0.77 \text{ \AA}$, $C(sp^2) = 0.74 \text{ \AA}$, $C(sp) = 0.69 \text{ \AA}$ 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 summarized⁸.

Similar bond length variations are found for carbon-halogen bonds¹, with ranges $1.38-1.32 \text{ \AA}$ for $C-F$, $1.78-1.64 \text{ \AA}$ for $C-Cl$, $1.94-1.79 \text{ \AA}$ for $C-Br$ and $2.14-1.99 \text{ \AA}$ for $C-I$. Decreases in the $C-Cl$ bond distances in chlorobenzenes (given as 1.70 \AA in reference 1, but see section II, B) and chloroalkenes (1.72 \AA), in comparison with similar bonds in saturated aliphatic chlorine compounds (1.77 \AA), have been interpreted in terms of about 10–20% double-bond character for the $C-Cl$ bonds², resulting from conjugation of an unshared pair of electrons of the chlorine atom with the double bond or aromatic nucleus:



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 (\AA)

	% <i>s</i> - 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 atom⁷, 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

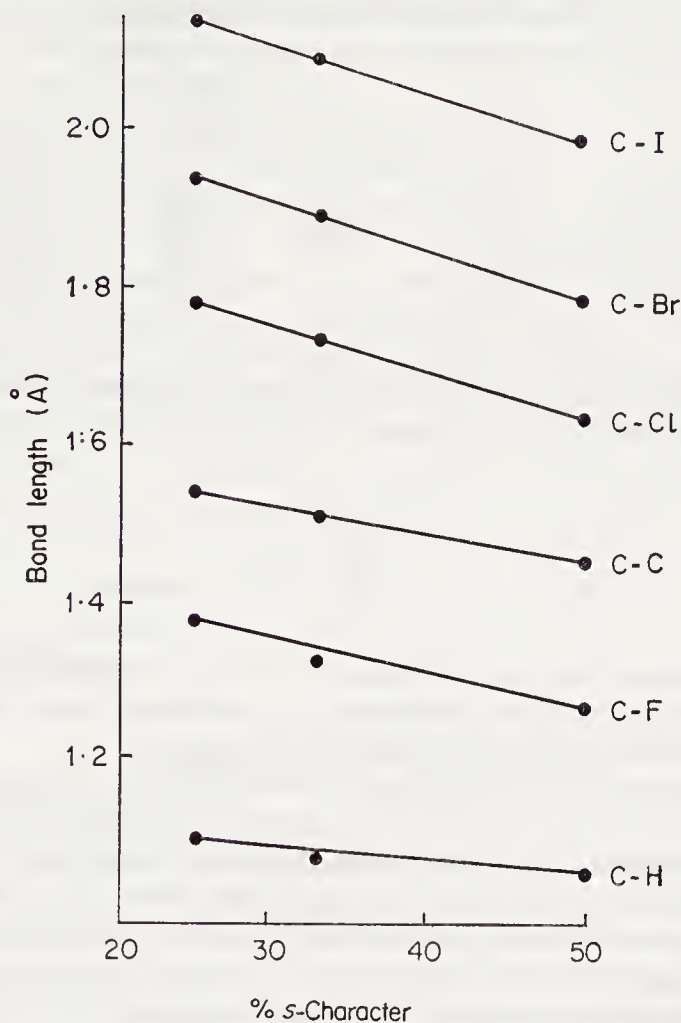


FIGURE 1. Relation between C—X bond distance and % *s*-character of the carbon atom.

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 orbitals⁷.

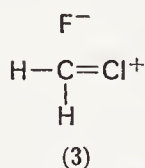
Further lesser variations in C—X bond lengths have been related to the electronegativities of the other atoms bonded to the carbon atom¹¹. Thus (Table 2), the C—F bond length decreases from 1.385 Å in CH₃F to

1.323 Å in CF₄; the C—Cl distance from 1.781 Å in CH₃Cl to 1.751 Å in CF₃Cl and to 1.766 Å in CCl₄. The effect is most marked with the strongly electronegative fluorine atom. The effect has again been attributed to

TABLE 2. Dependence of C(sp³)—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 ₂ CH—X	1.332	—	1.762	1.798
R ₃ C—X	1.323	1.751	1.766	1.803

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



atom, in this case small second-order effects¹¹: 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 CH₃Cl to *t*-BuCl is consistent with increasing ionic character, but it is difficult to place the arguments on a quantitative basis¹³.

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

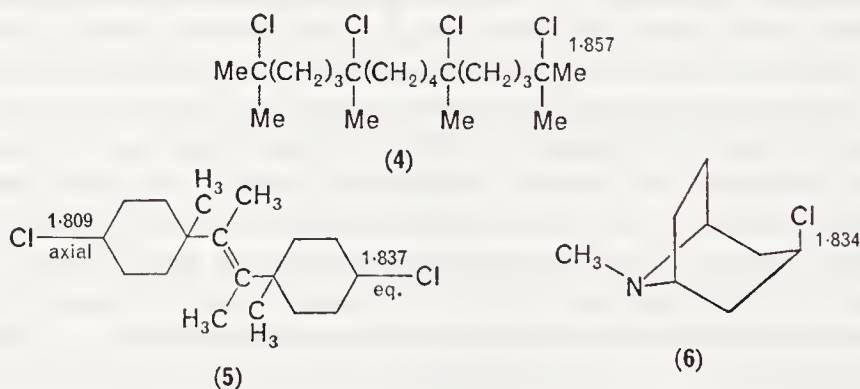
A. Saturated Compounds

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

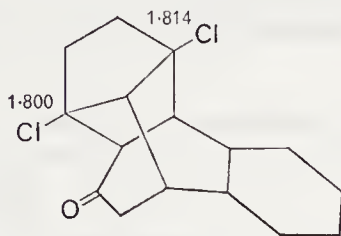
Compound	C—Cl	Reference
2,6,11,15-Tetrachloro-2,6,11,15-tetramethylhexadecane (4)	1.857 (7)	14
<i>trans</i> -2,5-Dichloro-1,4-dioxan	1.845 (6)	15
2,3-Bis-(<i>cis</i> -4-chloro-1-methylcyclohexyl)- <i>trans</i> -2-butene (5)	1.837 (7) 1.809 (9)	16
α -Chlorotropane (6)	1.834 (3)	17
<i>cis</i> -2,3-Dichloro-1,4-dioxan	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
<i>t</i> -Butyl chloride	1.803	12
<i>iso</i> -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 ₂ C(CONH ₂) ₂	1.781 (2)	21
8,8-Dichloro-4-phenyl-3,5-dioxabicyclo[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.

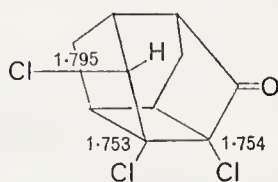


Two of the compounds in Table 3 each contain one axial and one equatorial chlorine atom. In *cis*-2,3-dichloro-1,4-dioxan the C—Cl distances are 1.819 and 1.781 Å for the axial and equatorial chlorines respectively, while in **5** the distances are 1.809 and 1.837 Å for axial and equatorial C—Cl bonds. 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.

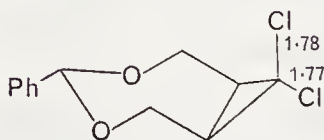
The long C—Cl distance of 1.857 Å in **4** has been ascribed to molecular packing forces in the crystal, which contains relatively short Cl···H intermolecular contacts, the shortest being 2.7 Å, in comparison with the



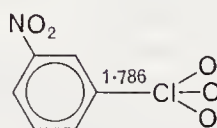
(7)



(8)



(9)



(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 observed²⁵. 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 bond²⁶.

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
<i>N</i> -Methyl- <i>p</i> -chlorobenzaldoxime	1.768 (7)	28
2-Chloro-4-nitroaniline	1.766 (9)	29
1,3-Di- <i>p</i> -chlorophenyl-2-triethyl-carbinyl-4-ethyl-5,5-diethyl-1,3-diaza-2,4-diborolidine	1.764 (6)	30
Bis-(5-chlorosalicylaldoximate)copper(II)	1.762 (11)	31
<i>N</i> -5-Chlorosalicylideneaniline	1.752 (6)	32
2-Chloro-5-nitrobenzoic acid	1.753 (6)	33
<i>p</i> -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
<i>N</i> -(<i>p</i> -Chlorophenyl)- α -isopropyl- β -phenyl- β -lactam	1.741 (3)	38
Ammonium chloranilate monohydrate	1.741 (6)	39
<i>p</i> -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- <i>N</i> -salicylideneaniline	1.737 (3)	44
<i>trans-pp'</i> -Dichloroazobenzene	1.737 (4)	45
<i>o</i> -Chlorobenzoic acid	1.737 (7)	46
4,4'-Dichlorodiphenylsulphone	1.736 (7)	47
Di- <i>p</i> -chlorophenyl hydrogen phosphate	1.736 (13)	48
<i>o</i> -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
<i>syn-p</i> -Chlorobenzaldoxime	1.728 (6)	53

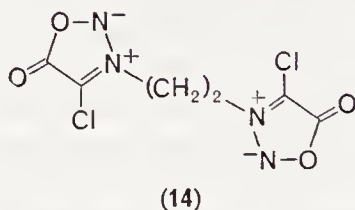
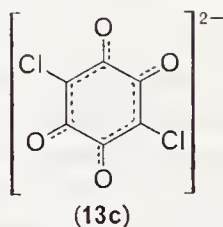
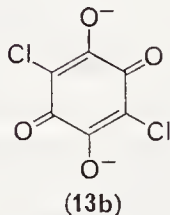
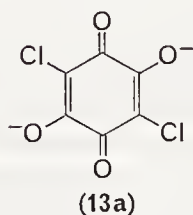
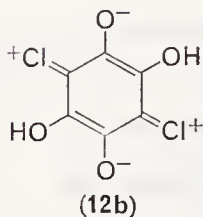
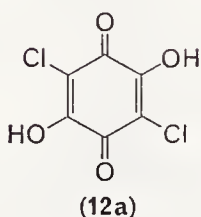
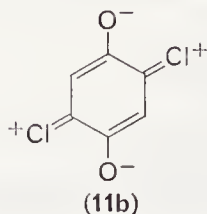
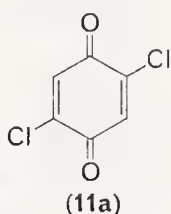
TABLE 4 (*cont.*)

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)	
<i>N,N,N',N'</i> -Tetramethyl- <i>p</i> -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- <i>n</i> -propylcalicene	1.705 (7)	67
1,2,3,4-Tetrachlorobenzo[<i>g</i>]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 quoted⁷ 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 substitution²⁷. 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



the shorter C—Cl bonds have *ortho* chlorine substituents, and the shortening may result from some type of interaction between the chlorine atoms⁶⁶. 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 atom⁶⁹.

C. Ethylenic and Acetylenic Compounds

Olefinic C—Cl bonds average 1.72 \AA and at acetylenic carbon atoms the C—Cl distances are about 1.64 \AA . 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 \AA in saturated compounds, 1.73 – 1.74 \AA in cyclopropane derivatives, 1.74 \AA in most aromatic molecules, but about 1.71 \AA in chlorobenzoquinones and some other polychlorinated molecules, 1.72 \AA at ethylenic carbon atoms, and 1.64 \AA 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 \AA in saturated molecules, about 1.89 \AA at ethylenic carbon atoms, and about 1.79 \AA at acetylenic carbon atoms. The quoted average C—Br bond distance in aromatic molecules¹ is 1.85 \AA , but this value seems low in the light of recent work, a length of about 1.89 \AA having been found in several compounds, e.g. 1.886 – $1.896 (16) \text{ \AA}$ in 2,4,6-tribromoaniline⁷⁰, $1.91 (3) \text{ \AA}$ in the *O-p*-bromobenzoate of batrachotoxinin A⁷¹, $1.905 (15) \text{ \AA}$ in the *p*-bromobenzoyl derivative of ϵ -caesalpin⁷², 1.892 and $1.904 (10) \text{ \AA}$ in 5-(6'-bromo-3'-ethyl-2'-methylbenzimidazolium) barbiturate⁷³, and $1.897 (18) \text{ \AA}$ in the bromoindole derivative of 3β -methoxy-21-keto- Δ^{13} -serratene⁷⁴.

The C—I bond distance has been observed as 2.14 – 2.21 , 2.09 , 2.05 and 1.99 \AA 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 \AA (Table 5), although

one distance as long as 1.43 ± 0.02 Å has been reported, for *t*-butyl fluoride⁷⁷. 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(<i>sp</i> ³)—F	1.39	1.33
C(<i>sp</i> ²)—F	1.34	1.31
C(<i>sp</i>)—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 Å¹; a recent X-ray study⁷⁸ 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 halides⁵. 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 molecule⁶.

(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 emphasized⁹. 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 industries⁸.

(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. <i>Chemical methods</i>	
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. <i>Physical methods</i> ^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 applicability³¹. 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 elements³²

Element	Edge	Wavelength (Å)	Energy (keV)
H	None		
C	<i>K</i>	43.68	0.2838
N	<i>K</i>	~ 31.2	~ 0.397
O	<i>K</i>	23.32	0.5317
P	<i>K</i>	5.784	2.1435
S	<i>K</i>	5.0185	2.47048
F	<i>K</i>	~ 18	~ 0.69
Cl	<i>K</i>	4.3971	2.8196
	<i>M_I</i>	417	0.0297
Br	<i>K</i>	0.9204	13.470
	<i>L_I</i>	6.959	1.781
	<i>N_I</i>	399	0.0311
I	<i>K</i>	0.37381	33.1665
	<i>L_{II}</i>	2.5542	4.8540
	<i>M_{IV,V}</i>	19.66	0.6161
	<i>N_{IV,V}</i>	224	0.0552
	<i>O_I</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 content³⁴. Based on the same principle, a method has been proposed for controlling the thickness of polyvinylchloride sheet continuously³⁴.

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 applications³⁵. Three types of spectra can be distinguished³⁶.

Photoelectron spectra measure the energy of electrons emitted after a photon of known energy impinged on the sample³⁷. 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 obtained³⁸.

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* lines³⁹, arising from the transition of an *L* shell electron to a *K* shell vacancy³² (for example bromine-containing drug traces in serum excreta, and tissues can be determined at the level of a few p.p.m. or less⁴⁰). However, other lines can now be used³⁵. 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 silver⁴¹. 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 line⁴².

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 $1\ \mu$) and the X-ray emission is measured and recorded. For the halogens the limits of detectability are about 10^8 atoms. A particle of $1\ \mu$ diameter should contain at least about 2% of F, 0.2% of Cl or Br and 0.07% of I⁴⁵.

The use of the microprobe analyser for organic and biological samples has also received some attention³¹. 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 explored⁴⁶.

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 analysed⁴⁷, thus converting the method into a destructive one. Nuclear activation is a very convenient method for trace analysis²⁸ of organic compounds and of biological matter⁴⁸⁻⁵⁰.

Losses of halogen by volatilization are observed on irradiation of biological samples, which necessitates special containers for long irradiation times⁵¹. 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 3⁵². The background

TABLE 3. Detection limits (p.p.m.) of the halogens in various matrices⁵²

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

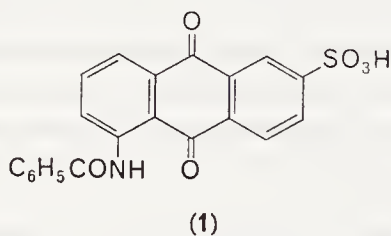
activities limit the use of neutron activation coupled with paper or thin-layer chromatography in the trace analysis of chlorine and bromine derivatives in drugs⁵³. The activation of paper chromatograms has been reviewed⁵⁴.

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 example⁵⁵, 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 $^{19}\text{F}(\gamma, n)^{18}\text{F}$ and $^{81}\text{Br}(\gamma, n)^{80}\text{Br}$ are respectively -10.4 and -10.0 MeV, while the other nuclides need higher energies to become activated.

The pre- and post-treatment of samples are necessary in many cases⁴⁷ 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



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 contaminants⁹⁰.

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

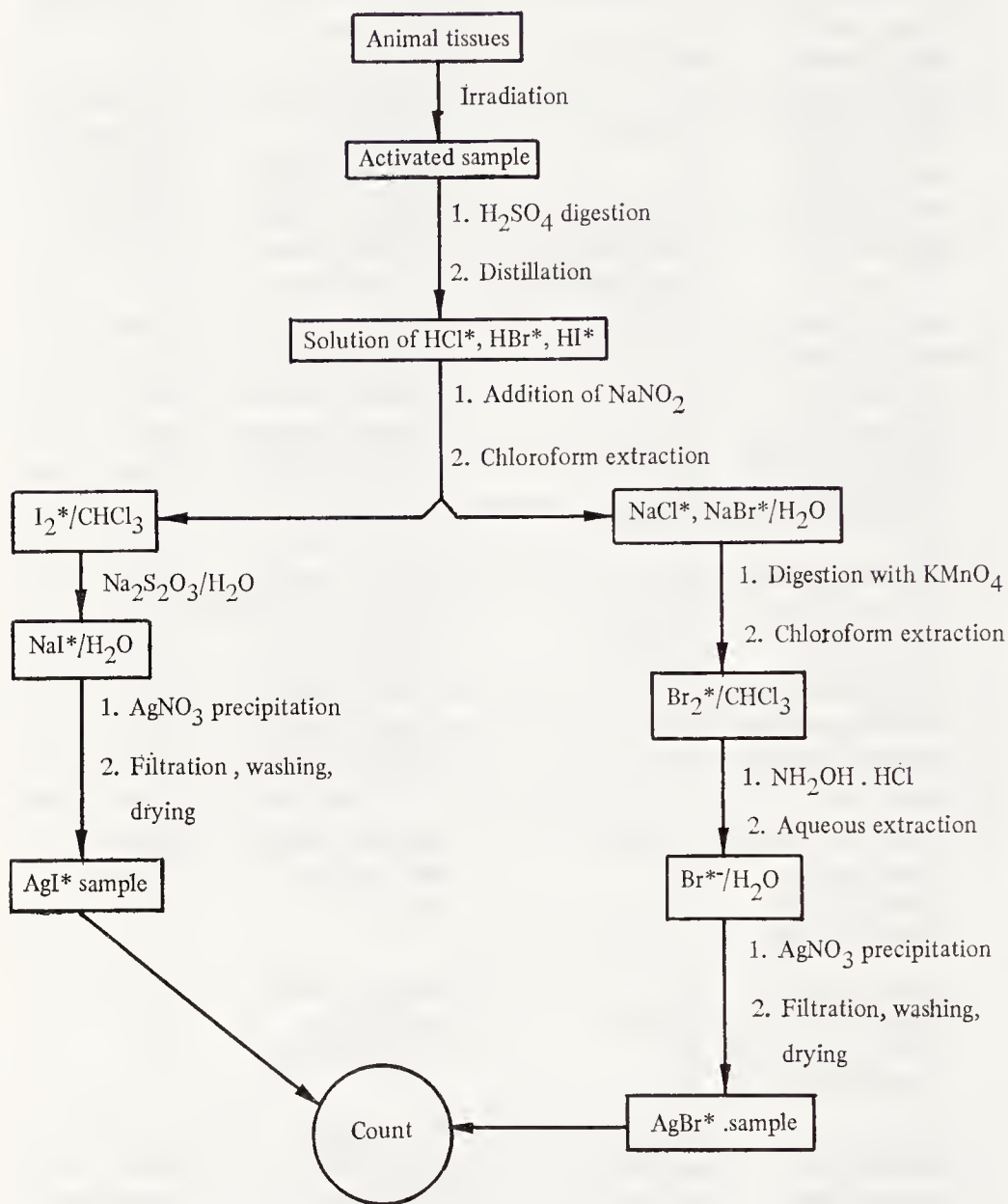


FIGURE 1. Determination of Br and I in animal tissues by nuclear activation⁸⁹.

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	
^{124m1} Sb	93 s	β^-	IT	A few γ 's	
^{124m2} 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

I. 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 nm¹⁰³.

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 selectivity¹⁰⁵. Similar studies were also reported for argon plasmas¹⁰⁶.

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 explored¹⁰⁹.

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 markedly¹¹⁰. Airborne organic fluorine has been determined by the SrF excitation in a flame with detection limits of about 50 $\mu\text{g/l}$ ¹¹¹.

The time-consecrated Beilstein test¹¹² 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 range¹¹³.

Sensitizing with indium seems to give better results: organochloro¹¹⁴, organobromo^{115,116} and organoiodo¹¹⁷ 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 distinctive 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 matter¹¹⁹.

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 $\text{Cl} < \text{Br} < \text{I}$ and the discrimination from non-halogen matter was excellent, as is dramatically illustrated in Figure 2, where both photometric and ionization responses

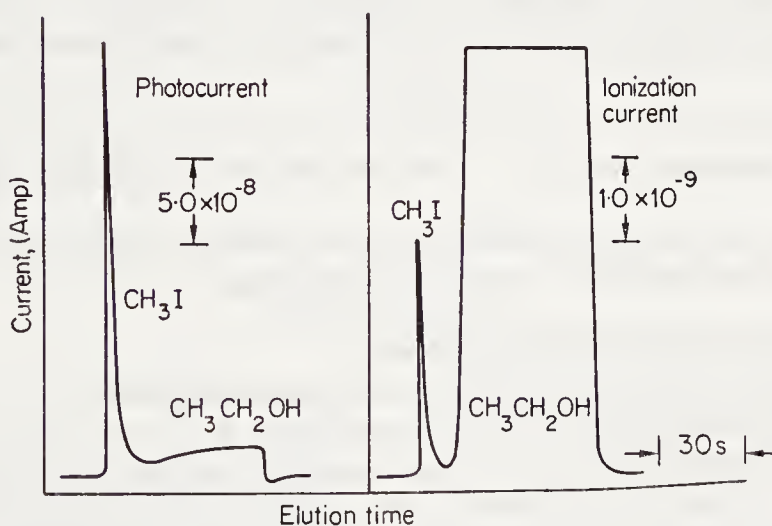


FIGURE 2. Comparison of photometric and ionization current response in a detector fitted with a sodium sulphate pellet. Sample: 5 μl of 0.0010% methyl iodide in ethanol¹²⁰. Reproduced by permission of the American Chemical Society from A. V. Novak and H. W. Malmstadt, *Anal. Chem.* **40**, 1108 (1968).

were measured for the same sample¹²⁰. 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 compounds¹²¹.

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,

$$M = \sum_i n_i m_i \quad (1)$$

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

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_i s 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>I</i>) ^c	Quadrupole moment (<i>Q</i>) ^d
¹ H	1.007825	99.985	1/2	—
² H	2.01410	0.015	1	2.77 × 10 ⁻³
¹² C	12.000000	98.89	—	—
¹³ C	13.00335	1.11	1/2	—
¹⁴ N	14.00307	99.63	1	7.1 × 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 × 10 ⁻²
³⁴ S	33.96786	4.22	—	—
³⁶ S	35.96709	0.014	—	—
³⁵ Cl	34.96885	75.53	3/2	-7.97 × 10 ⁻²
³⁷ Cl	36.96590	24.97	3/2	-6.21 × 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 ¹²C, in the physical scale.^c In units $h/2\pi$.^d In units of 10⁻²⁴ cm².TABLE 7. The statistical weights (w_j) of the quintet corresponding to an ion containing Cl₂Br₂

z_i	Terms with equal z_k	m/e	w_j	
			Approximate	Precise ^a
	$(3\ ^{35}\text{Cl} + ^{37}\text{Cl})_2(^{79}\text{Br} + ^{81}\text{Br})_2 =$ $(9\ ^{35}\text{Cl}_2 + 6\ ^{35}\text{Cl}^{37}\text{Cl} + ^{37}\text{Cl}_2)$ $(^{79}\text{Br}_2 + 2\ ^{79}\text{Br}^{81}\text{Br} + ^{81}\text{Br}_2) =$			
4	$9\ ^{35}\text{Cl}_2\ ^{79}\text{Br}_2 +$	M	9	9.82
6	$18\ ^{35}\text{Cl}_2\ ^{79}\text{Br}^{81}\text{Br} + 6\ ^{35}\text{Cl}^{37}\text{Cl}^{79}\text{Br}_2 +$	$M + 2$	24	25.61
8	$9\ ^{35}\text{Cl}_2\ ^{81}\text{Br}_2 + 12\ ^{35}\text{Cl}^{37}\text{Cl}^{79}\text{Br}^{81}\text{Br} +$	$M + 4$	22	22.95
	$\ ^{37}\text{Cl}_2\ ^{79}\text{Br}_2 +$			
10	$6\ ^{35}\text{Cl}_2\ ^{37}\text{Cl}^{81}\text{Br}_2 + 2\ ^{37}\text{Cl}_2\ ^{79}\text{Br}^{81}\text{Br} +$	$M + 6$	8	8.17
12	$\ ^{37}\text{Cl}_2\ ^{81}\text{Br}$	$M + 8$	1	1.00

^a Computed by developing

$$\left(\frac{75.53}{24.47}\ ^{35}\text{Cl} + ^{37}\text{Cl}\right)_c \left(\frac{50.54}{49.46}\ ^{79}\text{Br} + ^{81}\text{Br}\right)_b = \sum_{i=1}^I a_i\ ^{35}\text{Cl}_{\alpha_i}\ ^{37}\text{Cl}_{\beta_i}\ ^{79}\text{Br}_{\gamma_i}\ ^{81}\text{Br}_{\delta_i}$$

instead of equation (3).

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

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

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

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 be²⁷ 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.

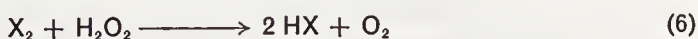
(v) *Equipment*: The existence in a laboratory of obsolete equipment in good working condition may often dictate the analytical procedure, especially if an alternative choice is expensive.

(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.

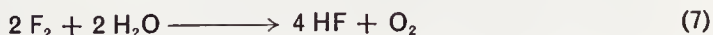
The mineralization step of an organic elementary analysis and the finishing steps have been reviewed^{11-15, 20-23, 125}.

I. Combustion tube

a. *Oxygen combustion*. A series of variations of the classical semimicro combustion method of Pregl²⁰ 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-



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



Reduction of the combustion gases by sodium bisulphite has also been applied¹²⁶. 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 samples¹²⁹.

Among the variations proposed are empty tube combustions¹³⁰, platinum catalysed combustions¹³¹, alumina plates¹³², sintered quartz plates¹³³, etc. Determinations at the submicro level has been carried out¹³⁴.

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 phosphine¹³⁶. 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 century¹³⁷, 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

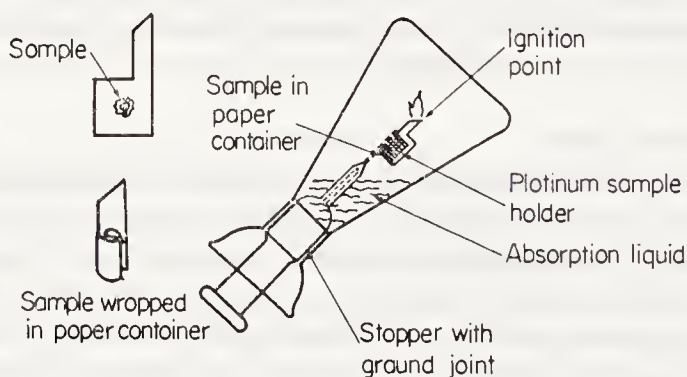


FIGURE 3. Oxygen combustion flask. Reproduced by courtesy of A. H. Thomas Co.

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 reviewed¹⁴¹. Some variations are summarized in Table 8.

TABLE 8. Modifications of the oxygen flask combustion method

Type of variation	Remarks	Reference
1. <i>Sample size</i>		
(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. <i>Accuracy and applicability</i>		
(a) Micro	Using potentiometric finish	22
(b) Submicro	Using chemical and potentiometric finish	21, 23
3. <i>Special handling of samples</i>		
(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. <i>Modifications due to the halogen content</i>		
(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 recommended¹⁴¹.

^c Although peroxide is not strictly necessary¹⁶³ it is useful in converting nitrogen and sulphur combustion products into nitrate and sulphate respectively¹⁴¹.

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

^e $\text{Br}_2 + 5 \text{ClO}^- + \text{H}_2\text{O} \rightarrow 2 \text{BrO}_3^- + 5 \text{Cl}^- + \text{H}^+$. 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 size¹⁶⁹⁻¹⁷¹. Thus, determination of chlorine traces in petroleum¹⁷², various halogens in viscous polybutylene fraction¹⁷³ and general organic halogen microanalysis¹⁷⁴ 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 reviewed¹⁵.

*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 samples¹¹⁻¹⁵. 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 doubted¹⁷⁶, it is the authors' experience that bromine can be adequately determined in organic samples, e.g. in routine determination of brominated wood¹⁷⁷⁻¹⁷⁹, where Schöniger's method failed because of the low combustibility of the samples¹⁷⁹. Activation analysis⁸⁰ 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 peroxide¹⁹⁵. 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 digestion¹².

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 medium¹⁹⁶, treatment with the sodium diphenyl reagent¹⁹⁷ 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 ammonia²⁰¹, amines (see end of section IV. A) or potassium hydroxide²⁰². Detection by the use of alcoholic silver nitrate¹¹⁻¹⁵ 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 titration²⁰³.

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}.

I. 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 digestion²⁰⁴.

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}.



(X = Cl, Br)

After oxygen combustion and absorption in water, hydrogen fluoride can be determined by acidimetry²⁰⁶ 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

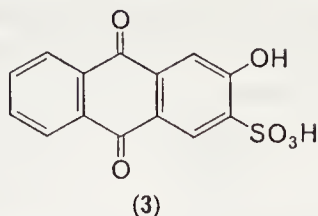
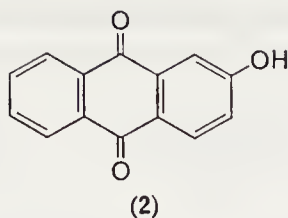
a. Fluoride. Micro and semimicro determinations of this halide can be performed by precipitating as lead chlorofluoride^{161, 207}. The composition of the precipitate is variable and therefore a strict routine of analysis is advised, and either expulsion of interfering ions¹⁶¹ or volatilization of the fluorine might be advisable²⁰⁸. These procedures are, however, cumbersome and titrations with lanthanum(III) nitrate are recommended. Quantitative precipitations of fluoride with lanthanum(III) are also possible⁴². The precipitation methods for fluoride ions have been reviewed²⁰⁹.

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 poor²¹⁰. 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 century²¹¹ 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 proposed²¹⁴. These methods are of advantage only when simultaneous elementary analyses including the halides have to be performed in the same combustion train.

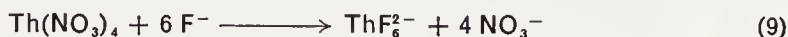
3. Detection and determination of halides with the aid of colour indicators

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



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



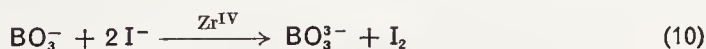
(ii) Sodium alizarinsulphonate is also an acid-base indicator changing its colour from yellow in acidic solution to violet in alkaline solution. Therefore the appropriate buffer should be used to allow a good end-point in fluoride titration (change from yellow to red).

(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) nitrate²¹⁸, zirconium(IV) chloride²¹⁹ and aluminium chloride²²⁰. The visual methods for detection and titration of fluoride have been reviewed²⁰⁹.

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 colour²⁰⁹.

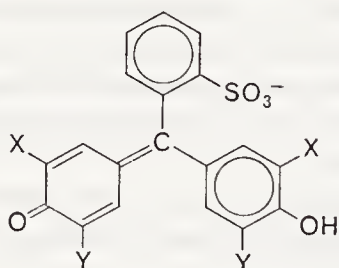
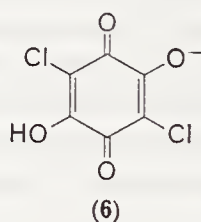
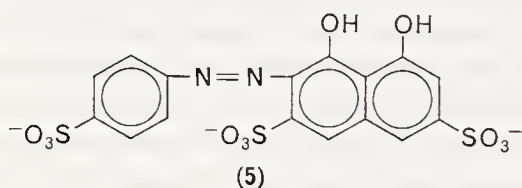
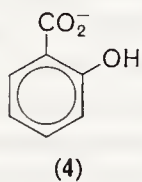
Fluoride ion in the $\mu\text{g/l}$ range inhibits the rate of reaction (10), catalysed by Zr^{IV} ion, thus affording a sensitive kinetic method of fluoride determination²²⁸.



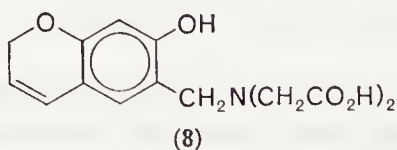
b. Chloride, bromide and iodide. The direct colorimetric determination of halides has been paid scarce attention. Nile blue sulphate or chloride

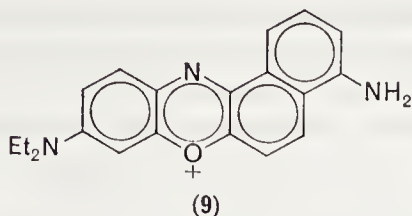
TABLE 10. Reagents for spectrophotometry of fluoride ion

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
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

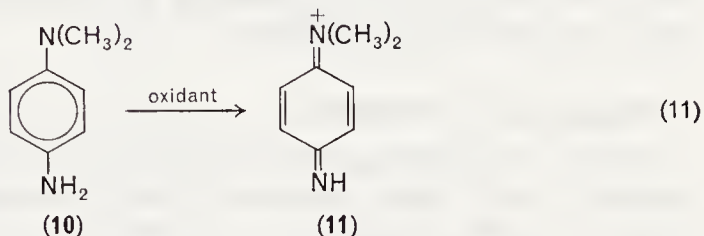


(7a, X = CO₂⁻; Y = CH₃)
 (7b, X = CH₂N(CH₂CO₂)₂; Y = CH₃)
 (7c, X = Br; Y = Cl)



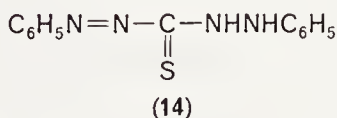
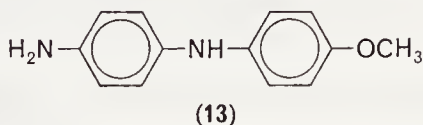
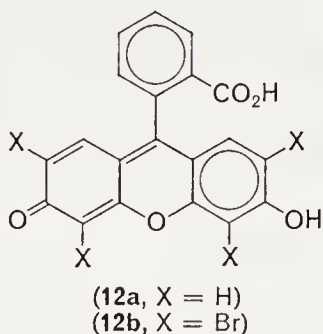


(9) forms salts with bromide or iodide which can be extracted into organic solvents and determined spectrophotometrically²²⁹. The spectrophotometric measurement of hexachloroferrate ions²³⁰ may be developed into a general colorimetric method for chlorides. Iodide catalyses the formation of Prussian blue, 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

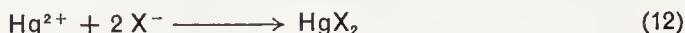


reaction is inhibited, however, by the copper(I) produced, unless halides or pseudohalides are present, as these anions combine strongly with copper(I). This reaction system has been developed into a semiquantitative indicator method²³¹.

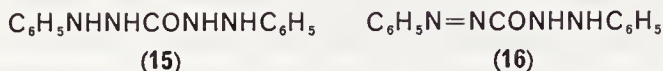
Argentometry by Mohr's method²³², although still in use after more than a century, is not suitable for micro scale analysis. Addition of organic adsorption indicators is made in order to facilitate the end-point observation: fluorescein (12a) is long in use²³³, variamine blue B (13) was used in micro-titrations²³⁴ and dithizone (14) in aqueous acetone titrations²³⁵. The subject has been reviewed²³³.



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)



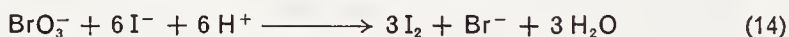
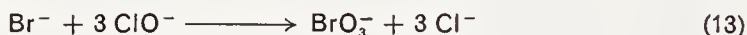
or diphenylcarbazone (16)²³⁶. The reaction is pH-dependent and good results are obtained only within rather narrow limits, e.g. in water at pH 1.5–2²³⁷.



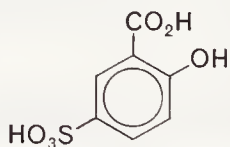
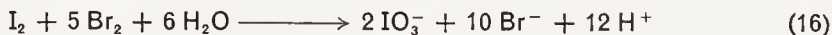
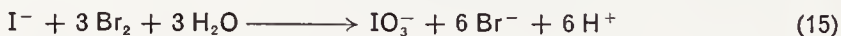
The method is suitable for finish after most mineralization procedures. A convenient modification is to carry out the titration in 80% ethanol²³⁸. Many adaptations have been proposed in the micro scale^{126, 239, 240}. The subject has been reviewed^{233, 241–243}.

4. Amplification reactions

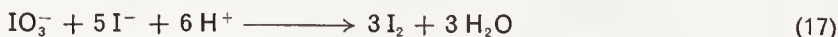
Bromide and iodide may be oxidized to the corresponding halates, thus enlarging sixfold their conversion factor. Bromide is oxidized with sodium hypochlorite at pH 5–7 (equation 13), the excess reagent is destroyed with sodium formate, iodide and acid added (equation 14) and the iodine titrated. This is the classical van der Meulen method, which has been modified for semimicro work²⁴⁴. Iodide interferes in the method.



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.



(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	$\text{Cl}_2, \text{Br}_2, \text{I}_2$	Colourless to blue	246
Thio-Michler's ketone (18)	$\text{Cl}_2, \text{Br}_2, \text{I}_2$	Brown-yellow to blue	12
<i>N,N</i> -Dimethyl- <i>p</i> -phenyl- ene-diamine (10)	$\text{Cl}_2, \text{Br}_2, \text{I}_2$	Colourless to red	12
Diphenylamine	$\text{Cl}_2, \text{Br}_2, \text{I}_2$	Colourless to blue ^a	12
Congo red (19)- H_2O_2	Cl_2	Red to blue	192
<i>o</i> -Tolidine (19') ^e	$\text{Cl}_2 + \text{Br}_2$ 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

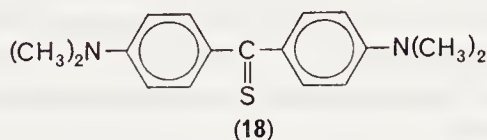
^a Under certain conditions the method becomes specific for chlorine.

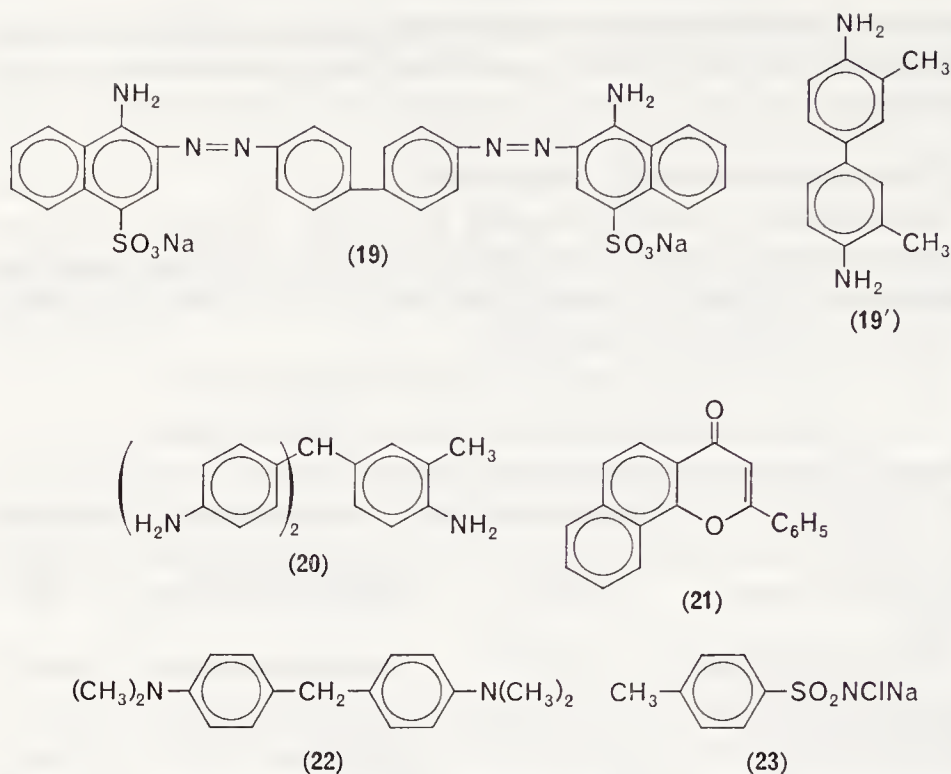
^b The reaction entails conversion to eosin (12b). Iodine interferes by yielding the tetraiodo analogue (erythrosine). See section II. D. 8. b.

^c The other halogens interfere. However, freshly prepared chloramine-T (23) solutions transform iodide to iodine²⁵¹ 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.





6. Chromatography of the halide anions

Halide ion separation has been effected on thin layers made of ion exchange resins²⁵², keratin²⁵³ 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 solvents²⁵³ or with amine-containing alcoholic solvents²⁵⁴. The R_f values found in the latter case follow the order



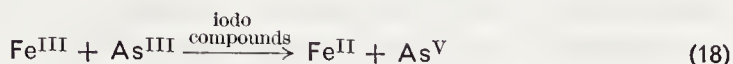
Spot visualization can be done by any of the following reagents²⁵⁴:

(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 halides²⁵⁶.

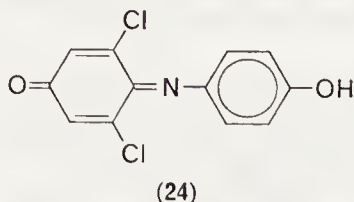
(ii) Ammoniacal silver nitrate-fluorescein spray will show the halide spots after u.v. irradiation²⁵⁴.

(iii) Zirconium-alizarin complex decolorates in the presence of fluoride showing a pale spot²⁵⁷.

(iv) A ferricyanate–arsenite spray will reveal iodide as a blue spot, as iodide catalyses reaction (18) leading to the formation of Prussian blue¹⁹². In fact this principle has been developed into a very sensitive colorimetric method for iodide determination (0.01–0.10 $\mu\text{g/ml}$ range)²⁵⁸.



(v) 'Dichlorophenolindophenol' (24)–silver nitrate shows pink spots on a pale blue background. The spots turn to brown on exposure to sunlight²⁵⁹.



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

7. Electrometric halide determinations

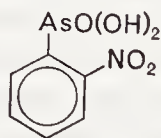
a. General comments. A great variety of instrumental methods have been applied to halide determinations which include the photometric methods of section II. G. 3. However, of more extended application are the various electrometric methods due to their accuracy, specificity, simplicity and adaptability to the requirements of routine analysis²¹. 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 reviewed²⁰⁹.

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.
<i>1. Fluoride^a</i>			
Potentiometry (null-point)	Titration with Ce^{IV} . The Ce^{IV} – Ce^{III} redox potential is lowered by fluoride complex formation	> 5 mM	260, 261
Potentiometry	Titration with $\text{AgNO}_3 + \text{Th}(\text{NO}_3)_4$, Pt and calomel electrodes, optimum results at pH 7.2. All four halides can be determined	Semimicro	317
High frequency titration	Titration with La^{III} or Sr^{II}	Semimicro	216
Polarography	Displacement by F^- of <i>o</i> -nitrobenzene-arsonic acid (25) from its complex with Th^{IV} ; the reduction of 25 is measured	2–10 μg	264
Amperometry	Titration with $\text{Th}(\text{NO}_3)_4$, rotating Al electrode		265
<i>2. Chloride, bromide and iodide^a</i>			
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. $\log [\text{Hal}^-]$ 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

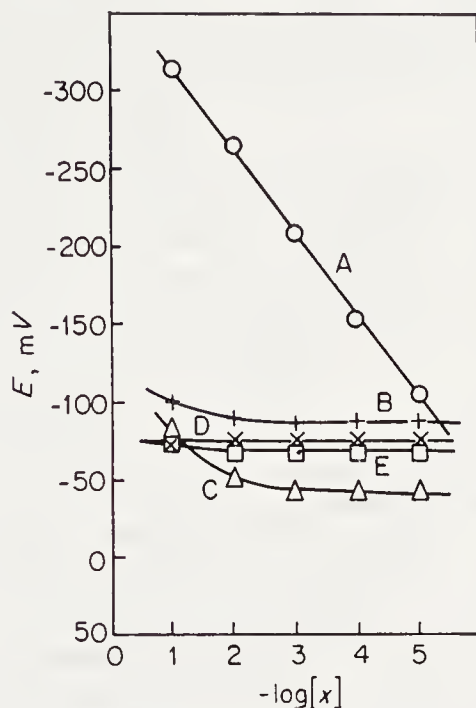


FIGURE 4. Potentiometric selectivity of a Pungor-type I^- membrane electrode to I^- in I^- — Cl^- and I^- — Br^- binary mixtures. Reference electrode Ag — AgCl (0.1) electrode with KNO_3 salt bridge: A, calibration graph for I^- electrode; B, 10^{-5}M KI in Br^- solution; C, 10^{-6}M KI in Br^- solution; 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 design²⁷⁷. 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 agents²⁷⁸.

Since some of the theoretical approaches²⁷⁴ and some phenomena are not yet fully understood²⁷², the classification of the types of ion-specific electrodes is still contradictory. However, according to their construction they can be divided into three main classes²⁷⁴:

(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.

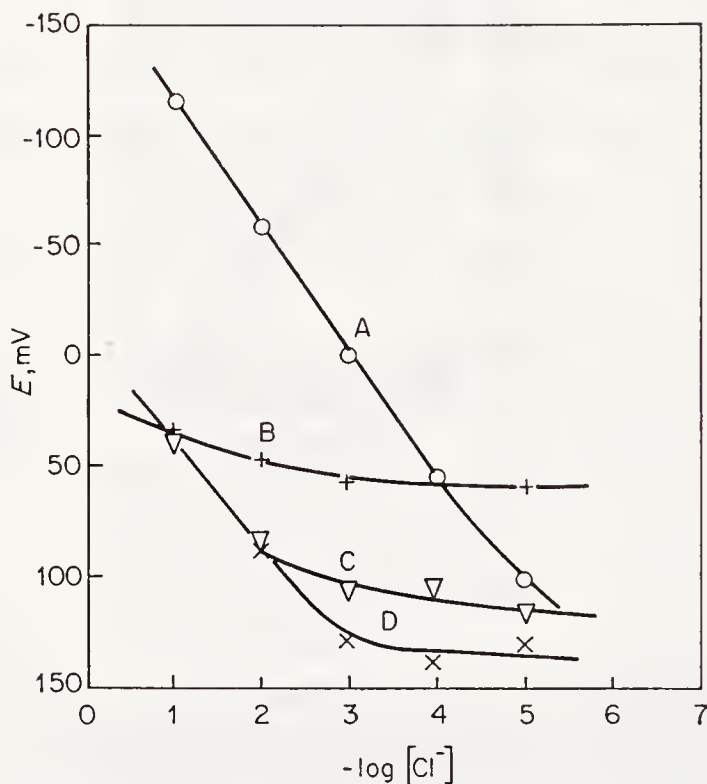


FIGURE 5. Potentiometric selectivity of a Pungor-type Br^- membrane electrode to Br^- in Br^- — Cl^- binary mixtures. Reference electrode Ag — AgCl (0.1) with KNO_3 salt bridge: A, calibration graph for Br^- electrode; B, 10^{-4}M Br^- in Cl^- solution; C, 10^{-5}M Br^- in Cl^- solution; D, 10^{-6}M Br^- in Cl^- solution²⁷⁴. 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 coworkers²⁷⁴ 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 chloride²⁸⁰ and chloride alone was studied²⁸¹.

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 membrane²⁷². Thus, the silver iodide membrane electrode gives the Nernstian 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 examined²⁸². 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 purposes²⁷². Among them, the iodide-selective electrode was studied in detail²⁸³. The single crystal rare earth fluoride electrodes²⁸⁴ 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 Nernstian behaviour with fluoride concentrations as low as 10^{-5} M and a useful non-Nernstian response at least at 10^{-6} M, at the proper pH²⁷². 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 modified²⁸⁷ for measurements of $10\ \mu\text{l}$ 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 type²⁸⁸ 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 results²⁸⁹. Successive titration of chloride, bromide and iodide with silver nitrate using Pungor²⁷⁹ and homogeneous²⁹⁰ electrodes were performed.

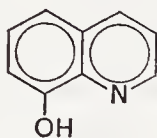
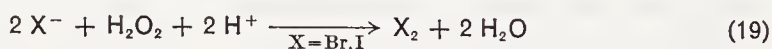
Some applications of ion-selective electrodes to end determinations of halogens in organic compounds are listed in Table 13.

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 occur³⁰⁹.

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 test³¹⁰ (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 precipitation³¹¹. 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 consumed²⁶².



(26)

Bromide can be detected after oxidation with sulphochromic mixture by the fuchsin-bisulphite method²⁴⁹ (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 ₂ S 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	≥ 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	≥ 10 ⁻⁶ M	304
Cl ⁻ , Br ⁻ , I ⁻	Standard solutions	Heterogeneous	Direct reading	≥ 10 ⁻⁶ M I ⁻ , ≥ 10 ⁻⁵ M Br ⁻ , ≥ 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 titrations	Micro	290
Cl ⁻ , Br ⁻ , I ⁻	Standard solutions	Ag ₂ S 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 test³¹² (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 iodide²⁴⁴.

Iodide is converted to iodine by fresh chloramine T (23) and detected by reaction with tetrabase³¹³ (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 potentiometry³⁰⁹. At a very early stage³¹⁴ 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 discussed³¹⁵. 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-point³¹⁵.

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 ions³¹⁶.

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 nitrate²⁶⁶ or by potentiometry with a mixed titrant containing thorium and silver nitrate at a platinum electrode³¹⁷.

Amperometric titrations with silver nitrate with rotating platinum electrode¹⁶⁷ or at a quiet mercury pool at +0.15 V were tried¹³¹. 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 used³¹⁸ 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 devices³¹⁹ 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 level¹³⁶. An extensive bibliography of applications of this instrumentation is available³²².



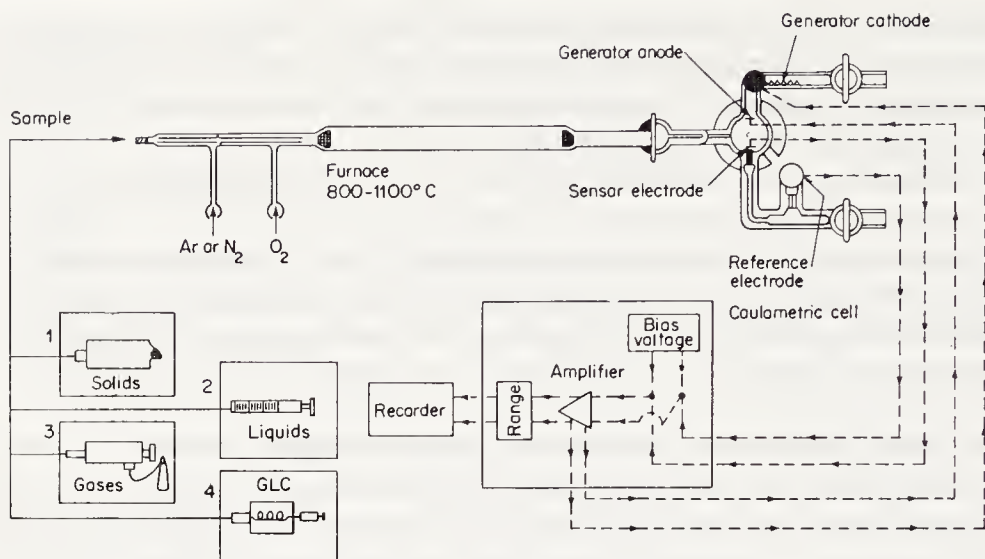


FIGURE 6. Automatic microcoulometric titration system for organic halides³²². Reproduced by courtesy of Dohrmann Instruments Co.

Another variation of automated analysis coupled with gas chromatographic separation is also commercially available³²³. 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 detector³²⁴ where the solution is measured. The system, which is capable of measuring halogen in the $<10^{-7}$ g range³²⁵, is shown schematically in Figure 7.

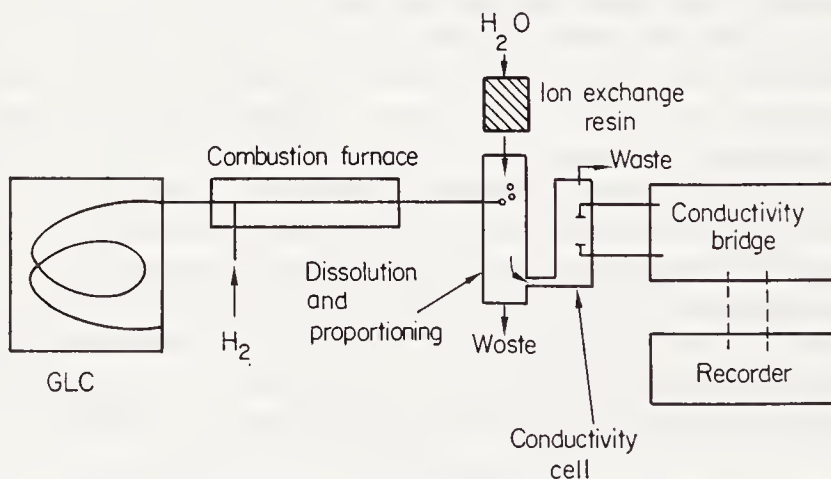


FIGURE 7. Electrolytic conductivity detector for automatic analysis of organic halides³²³. By courtesy of Tracor Inc.

III. MOLECULAR ANALYSIS

A. Distribution Properties

I. Thin-layer chromatography

This separation technique³²⁶ 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 gel³²⁶; 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 development³⁵³. Thus, Δ^5 -3 β -hydroxysterols (33) are converted to the corresponding dibromides which migrate faster, while sterols with the double bond at another position remain near the start³⁵⁷, e.g. small amounts of 5 α -cholestan-3 β -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

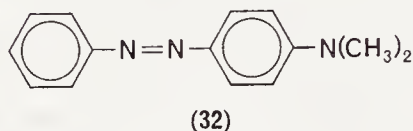
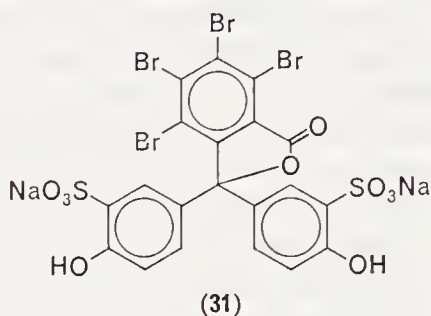
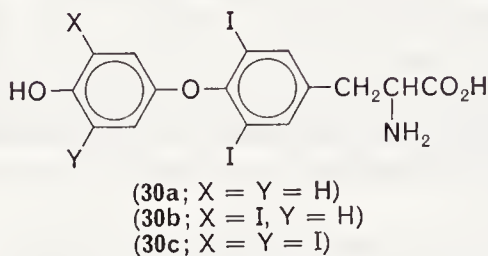
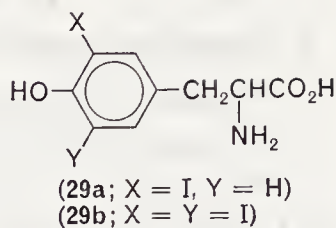
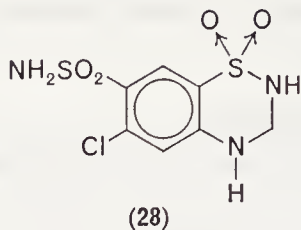
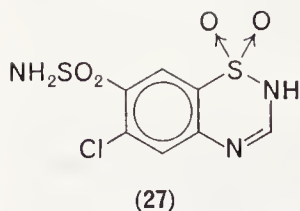
Type of compound	Visualization reagents ^a	Reference
Monohalogenated anilines ^b		329
Halogenated pyridines		330
Halogenated bactericides	1	331
Bromoureides ^c and their metabolites	7, 9	332-335
Chlorothiazide (27) and hydrochlorothiazide (28) derivatives ^d		334, 336, 337
Iodinated amino acids (29a, 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.

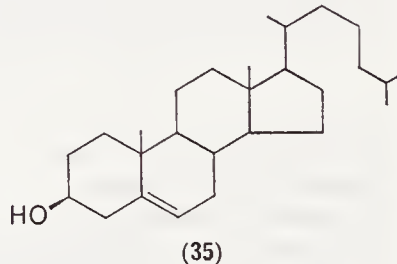
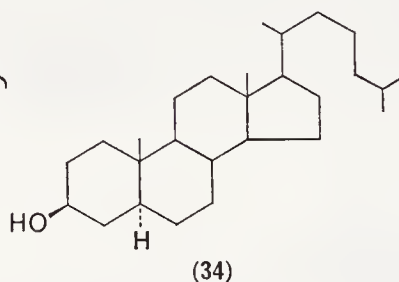
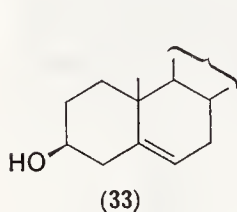
^c Used as hypnotics.

^d Used as diuretics.



(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 foodstuffs³⁴⁸.

Cumulative bibliography on the subject has been compiled³⁶³⁻³⁶⁵.



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 rule³⁶⁸. For instance³⁶⁹, 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	<i>o</i> -Tolidine (19') followed by u.v. irradiation (254 nm)	Green spots after 1 min with chlorinated pesticides. Detection limit 0.5–1 μ g	358
3	Starch mixed in the layer, and u.v. irradiation (254 nm)	After a few minutes iodo compounds yield blue spots	339
4	$\text{FeCl}_3 + \text{K}_3[\text{Fe}(\text{CN})_6] + \text{As}_2\text{O}_3$	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	$\text{Ce}(\text{SO}_4)_2 + \text{H}_2\text{SO}_4$	Iodo compounds	346
7	<i>N,N</i> -Dimethyl- <i>p</i> -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 procedure³⁴⁶.

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 investigated³⁷². 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 separations³⁷⁴. 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 compounds³⁷⁵.

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
Apiezon ^d (non-polar)	300	High-boiling compounds
Tricresyl phosphate ^e		Alkyl iodides

^a From reference 375.

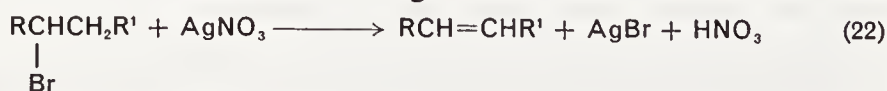
^d High molecular weight hydrocarbons.

^b Nonylphenoxypolyethyleneoxyethanol.

^e From reference 64.

^c Polyethyleneglycols.

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 example³⁷⁷, 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



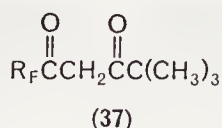
columns respectively. This leaves primary and tertiary alkyl bromides for the chromatography.

An interesting general technique also applicable to organic halides is the so-called carbon skeleton chromatography³⁷⁸⁻³⁸⁰. 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 compounds³⁶⁷. These detectors have long been used in pesticide trace analysis³⁸¹. 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 8³⁸². 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 derivatives³⁸³. 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	<i>N</i> - or <i>O</i> -chloroacetyl	386, 387
Alcohols, phenols, amino acid <i>n</i> -butyl esters	<i>N</i> - or <i>O</i> -pentafluoropropionyl	387-389
Amines, alcohols, phenols	<i>N</i> - or <i>O</i> -chlorodifluoroacetyl	387
Amino acid <i>n</i> -butyl esters	<i>N</i> -trifluoroacetyl	386, 388, 389
Amphetamine and ephedrines	<i>N</i> -pentafluorobenzoyl	390
Phenethylamine, catecholamines	<i>N</i> -perfluoroacyl and <i>N</i> -perfluoro- alkylidene	391, 392
Carbamate pesticides	<i>N</i> -Trifluoroacetyl	393



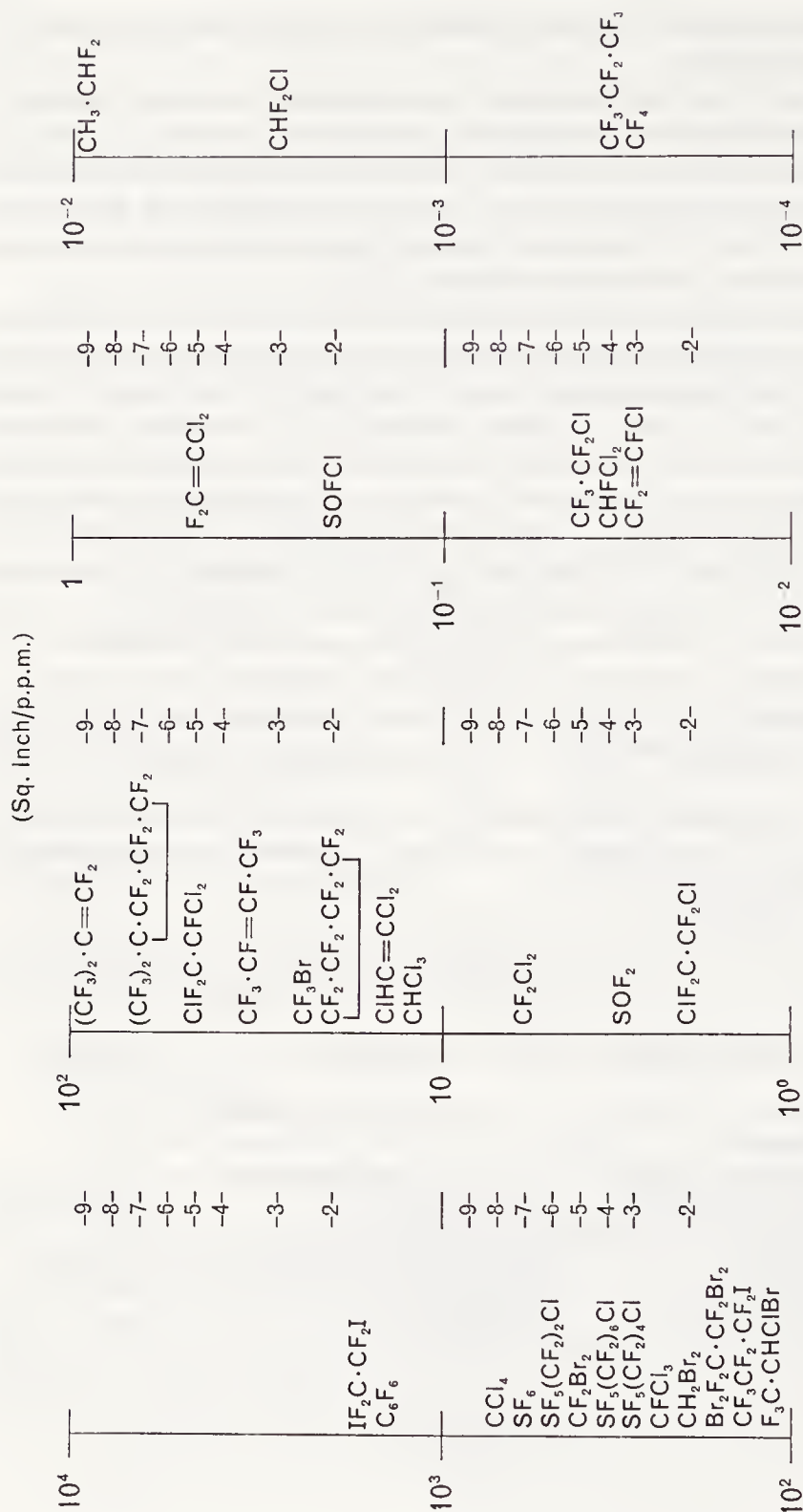


FIGURE 8. The dependence of electron-capture detector response on the structure of organic fluoro compounds³⁸². Reproduced by permission of the American Chemical Society from C. A. Clemons and A. P. Altschuler, *Anal. Chem.*, 38, 133 (1966).

Flame ionization detectors can be modified so that they become especially sensitive to organic halogens (not fluorine), phosphorus, nitrogen, arsenic and sulphur compounds³⁹⁴⁻³⁹⁶ with sensitivity in the nanogram region³⁹⁵. 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

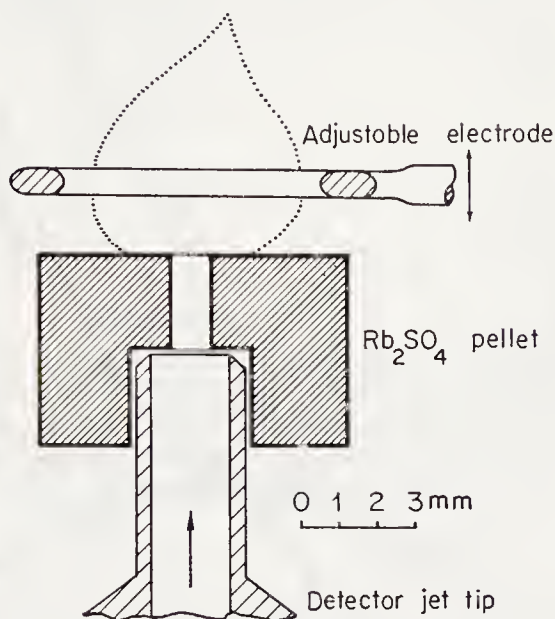


FIGURE 9. Alkali flame detector modification for attaining selective response with various hetero-elements³⁹⁷. Reproduced by permission of Elsevier Publishing Co. from S. Lakota and W. A. Aue, *J. of Chromatogr.*, **44**, 472 (1969).

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 possibilities⁴⁰¹. For coupling to slow-scanning instruments the interrupted elution gas chromatography technique has been developed⁴⁰¹. The most

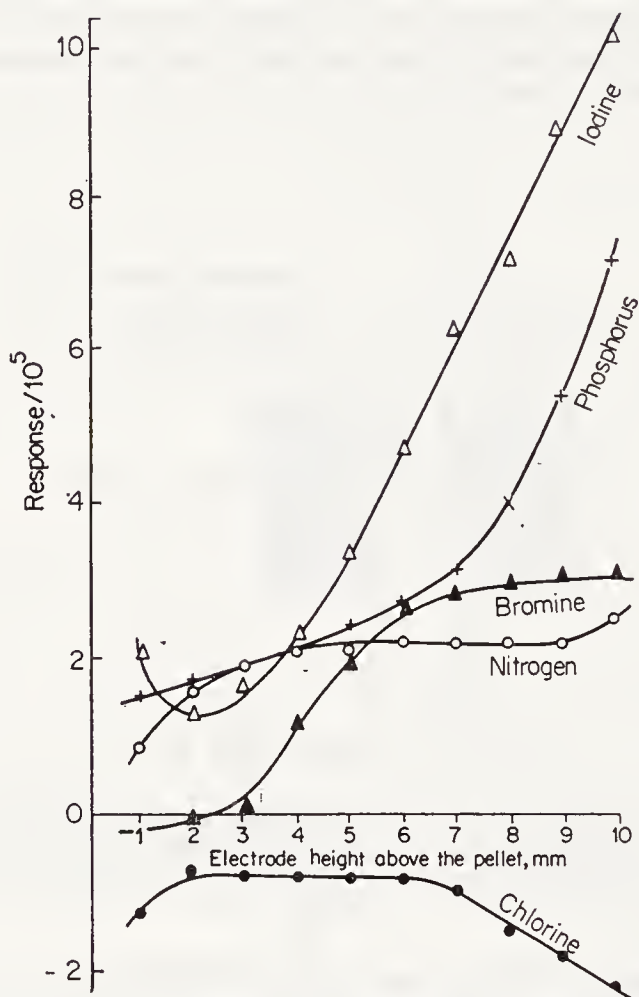


FIGURE 10. Effect of electrode height (in Figure 9) on the response of the alkali flame detector³⁹⁷. Reproduced by permission of Elsevier Publishing Co. from S. Lakota and W. A. Aue, *J. of Chromatogr.*, **44**, 472 (1969).

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 cells⁴⁰³, u.v. spectrophotometers (for example, the alkyl iodides with less than six carbon atoms have been distinguished³⁷⁹) and nuclear magnetic resonance spectroscopy with multiple scanning⁴⁰⁴.

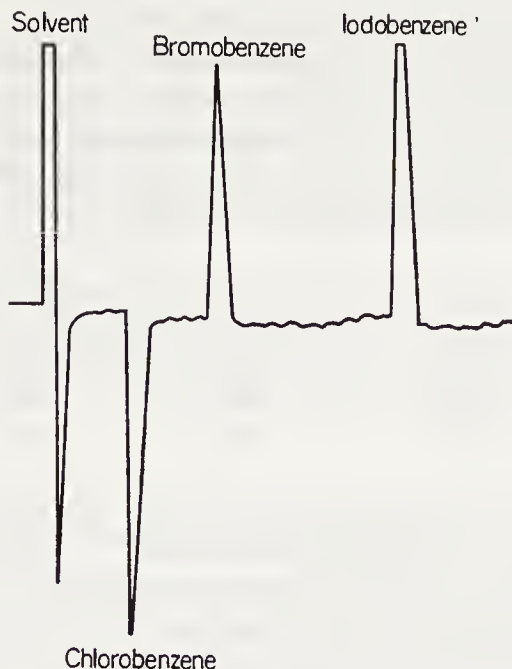


FIGURE 11. A typical chromatographic trace for a mixture of organic halides using the alkali flame detector of Figure 9. The sign of the bromobenzene peak can be inverted by narrowing the electrode gap (Figure 10)³⁹⁷. Reproduced by permission of Elsevier Publishing Co. from S. Lakota and W. A. Aue, *J.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

3. Phase solubility titrations

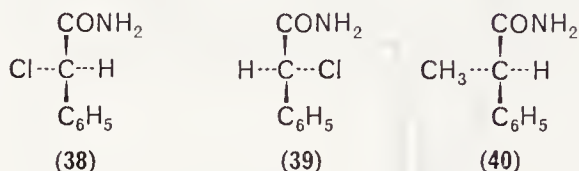
This technique⁴⁰⁵ is of practical importance for determining the composition of liquids containing specific organic halogen compounds, as these are usually much less soluble in hydroxylic solvents and water. For example⁴⁰⁶, mixtures of alcohols with bromobenzene, 1,2-dibromoethane, chloroform⁴⁰⁶, dichloromethane and allyl bromide⁴⁰⁷ 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 compound⁴⁰⁸, 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 nature⁴⁰⁹.



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 elsewhere⁴¹⁴.

(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 state⁴¹⁶. 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

<i>A. Elementary reagents</i>	
Chlorine: ox (205), (206)	Nickel: red ^d ; nhr (76)
Copper: red (175)	Palladium: red (154), (177)
Devarda's alloy (Cu—Al—Zn): red (174)	Platinum: nhr (86)
Hydrogen: nhr (76), (86); red (154), (157), (158), (177)	Sodium: red ^b (161), (170)
Lithium: red ^b (144), (169), (173); d2x (184)	Sulphur: nhr ^e
Lithium-sodium alloy: met (88)	Zinc: d2x (178)–(183); red (154), (159)
Magnesium: d2x (184), (197); met (87), (89), (91)–(95), (97), (98), (139), (184); red ^{e, d} (139), (167); dhx (167)	Zinc-copper couples: d2x (195); red (146), (147)
<i>B. Acids, oxides, hydroxides and alkoxides</i>	
Anion exchange resins (OH ⁻ form): c-c (65); dhx (106)	Potassium hydroxide: c-s (37); dhx (99), (122), (123), (126); ns ^h (26), (32)
Chlorosulphonic acid: nhr (207)	Silver oxide: c-c (119); dhx (114); ns (32)
Chromium trioxide: ox (198)	Sodium 2- <i>n</i> -butylcyclohexanolate: dhx (103)
Nitric acid: nhr ^f (208)	Sodium ethoxide: dhx (104)
Potassium bicarbonate: dhx (122)	Sodium hydroxide: c-c (26); c-o (33); c-s (35), (38); dhx ^g (99), (102); ns (25)
Potassium <i>t</i> -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)	
<i>C. Metal amides, carbonyls and hydrides</i>	
Dicobalt octacarbonyl: c-c (96)	Potassium amide: dhx (115); c-c (131)
Lithium aluminium hydride: red (145)	Sodamide: dhx (116)–(118), (128)– (130)
Lithium dicyclohexylamide: dhx (105), (197)	Sodium hydride: nhr (46)
Lithium diethylamide: dhx (120)	Sodium borohydride: red (143)
Nickel tetracarbonyl: red (141), (160)	
<i>D. Salts</i>	
Ammonium thiocyanate: ns (85)	Formaldehyde sodium sulfoxylate: red (157)–(158)
Benzyltrimethylammonium mesitoate: dhx (134)	Lead tetraacetate: c-o (43)
Calcium carbonate: dhx ⁱ	Lithium bromide: dhx ⁱ
Chromium(II) salts: d2x (186), (187); red (148)–(150), (156), (187); c-c (187)	Lithium carbonate: dhx (133)
	Magnesium iodide: ns ^j
	Mercury(II) halides: met (95)

TABLE 18 (*cont.*)*D. Salts (cont.)*

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

E. Organometallic compounds

Allylsodium: c-c (76)	Methyl lithium: c-c (168); dhx (166), (167); red (166)–(168)
Butyllithium: dhx (165); red (165)	Methylmagnesium bromide: red (142)
Dimethylcopperlithium: c-c (69)–(71)	Phenylthiomethyl lithium: c-c (73)
Disodium naphthalene: d2x (189)	Sodium methylsulphonyl methide: d2x (188); red (162)–(164)
Disodium phenanthrene: d2x (189)	Tri- <i>n</i> -butyltin hydride: red (140), (155), (171); dhx^o
3-Lithio-1-(trimethylsilyl)propyne: c-c (68)	
Lithium acetylide: c-c (72)	
Lithium diphenylamide: dhx (105)	

F. Amines, amides, hetarenes and hydrazine derivatives

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

TABLE 18 (*cont.*)*G. Organophosphorus compounds*

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

H. VIth group element compounds

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

I. Miscellaneous organic compounds

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

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

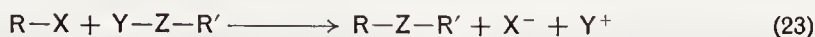
as: aromatic substitution;
c-b: reaction leading to a C—B bond formation;
c-c: reaction leading to a C—C bond formation;
c-n: reaction leading to C—N bond formation;
c-o: reaction leading to a C—O bond formation;
c-p: reaction leading to a C—P bond formation;
c-s: reaction leading to a C—S bond formation;

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.



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 ring⁴²¹, to the extent that they become useful as derivating reagents for the amines⁴²².

The kinetics and steric behaviour of displacement reactions⁵ 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.

I. 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

^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.

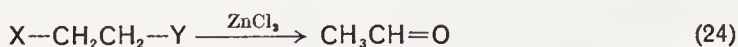
ⁿ See Table 19.

^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 structures¹².



(X, Y = halogen, OR, NR₂, SR)

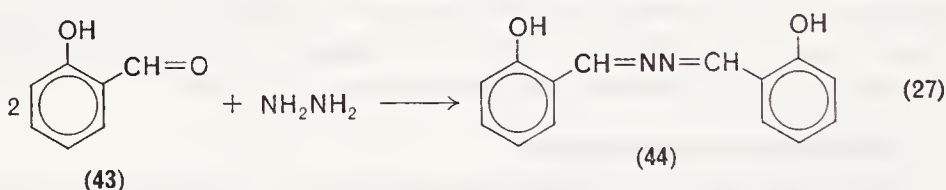
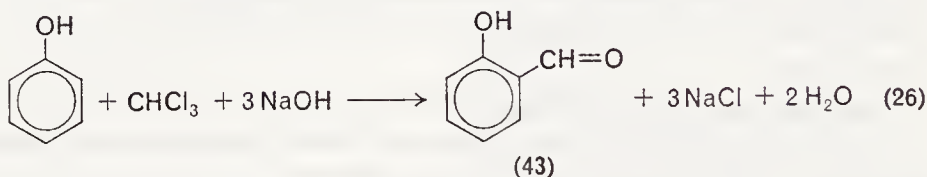


(41)

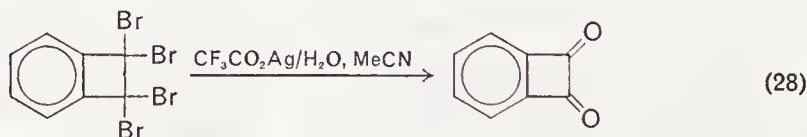
Some highly halogenated compounds undergo the haloform reaction (25), which can be followed by salicylaldehyde (43) formation if carried out in the presence of phenol (reaction 26). Reaction (27) yields fluorescent salicylaldazine (44) when salicylaldehyde is treated with hydrazine¹². For example, chloral (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-fluoromethane⁴²⁵.



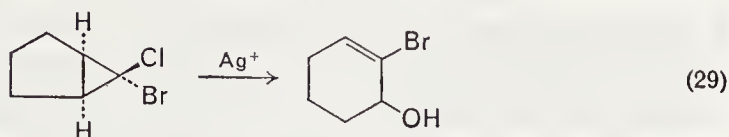
(42)



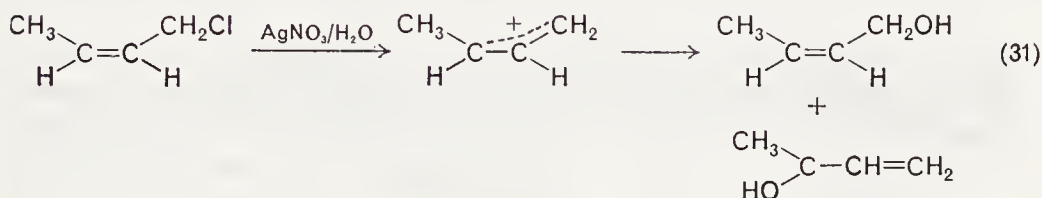
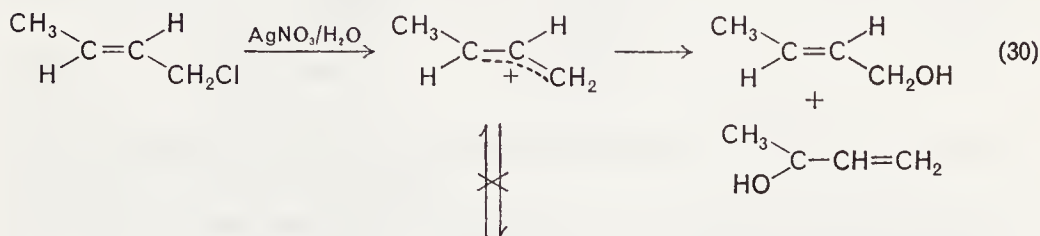
gem-Dibromides are hydrolysed to the ketones in the presence of silver trifluoroacetate (reaction 28)⁴²⁶ or a base such as potassium hydroxide⁴²⁷.



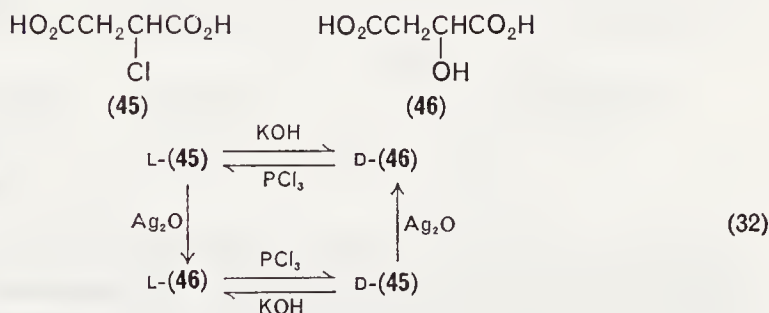
Silver ions catalyse the hydrolysis of the *endo* halogen in *gem*-dihalo-cyclopropanes bringing about a rearrangement (reaction 29)⁴²⁸.



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



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



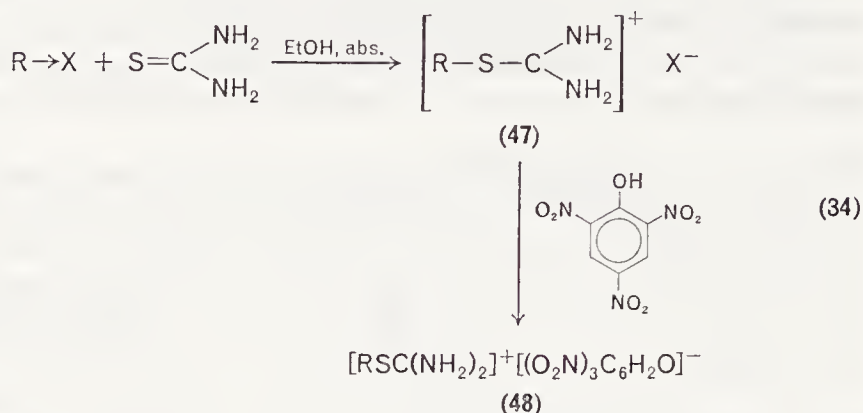
2. Ether formation

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 triiodophenol⁴³², *p*-hydroxybenzoic acid⁴³³, *p*-hydroxydiphenylamine⁴³⁴ and β -naphthol^{11, 14, 19} have been proposed for this purpose.

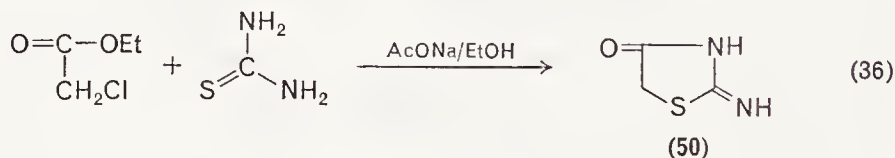
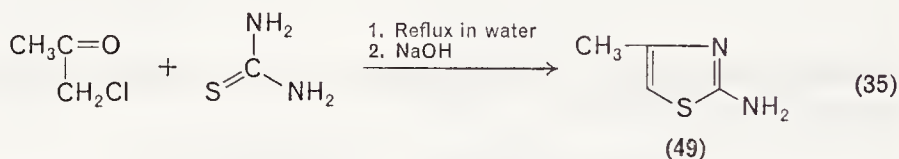


3. Thioethers and similar derivatives

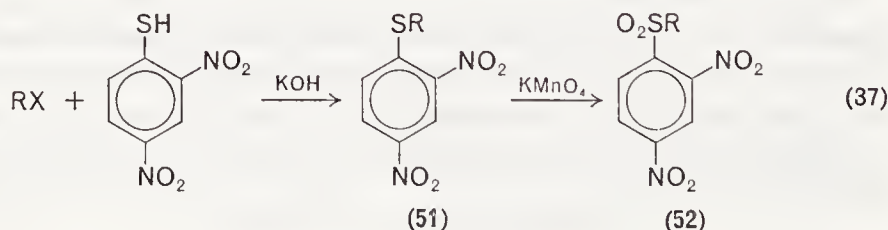
Alkyl halides combine with thiourea^{11,14,19,435} to give *S*-alkylthiuronium salts (47) which on addition of picric acid yield the corresponding picrates (48) (reaction 34). α -Haloketones yield with thiourea substituted



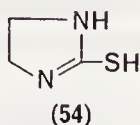
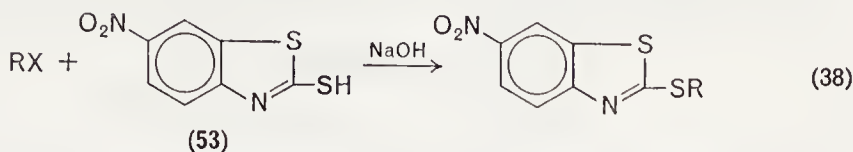
2-aminothiazoles (49) as shown in reaction (35)⁴³⁶. Similarly, α -halo esters yield pseudohydantoins (50), with loss of the alcoholic moiety of the ester (reaction 36)⁴³⁷.



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}.

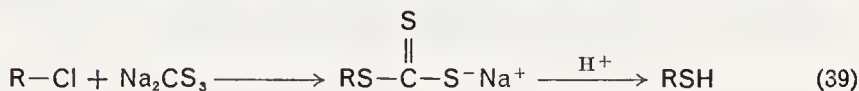


Alkyl halides can be derivatized with 6-nitro-2-mercaptobenzothiazole (53) as shown in reaction (38). This reagent is recommended for dihalides^{14, 19, 440, 441}. The picric acid complex of the thioether formed from



an alkyl halide and 4,5-dihydro-2-mercaptoimidazole (54) has been also proposed for derivatization⁴⁴².

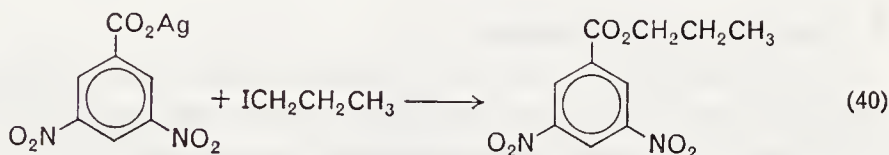
Alkyl halides heated with sodium thiocarbonate yield the corresponding



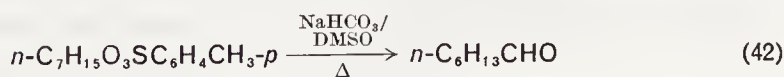
thiols (reaction 39)⁴⁴³. Dithioethers are formed from primary alkyl halides with thiosulphate (see reactions 77-78).

4. Ester formation

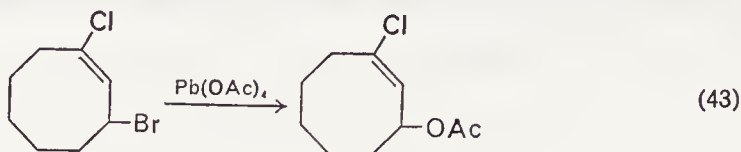
3,5-Dinitrobenzoates are formed from alkyl iodides as shown in reaction (40), but results are unsatisfactory with alkyl chlorides and bromides^{14, 444}.



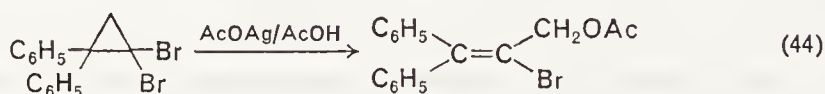
Primary alkyl halides yield with silver *p*-toluenesulphonate the corresponding tosylate (reaction 41) which can be further oxidized to an aldehyde on heating with dimethyl sulfoxide (reaction 42, similar to reaction 200)⁴⁴⁵. Secondary and tertiary alkyl halides yield olefins under the same conditions of esterification⁴⁴⁶, unless the reaction is carried out at very low temperatures⁴⁴⁷.



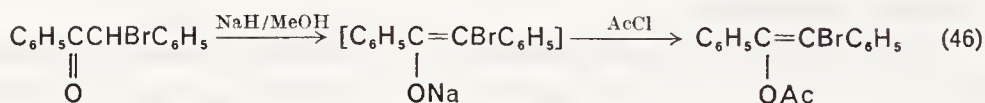
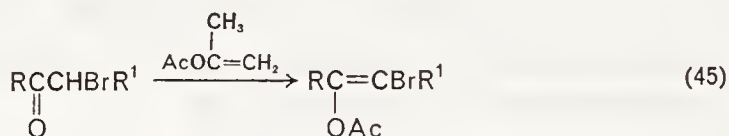
Lead tetraacetate displaces bromine preferentially, forming acetates (reaction 43), and is better than silver acetate for this purpose⁴⁴⁸.



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

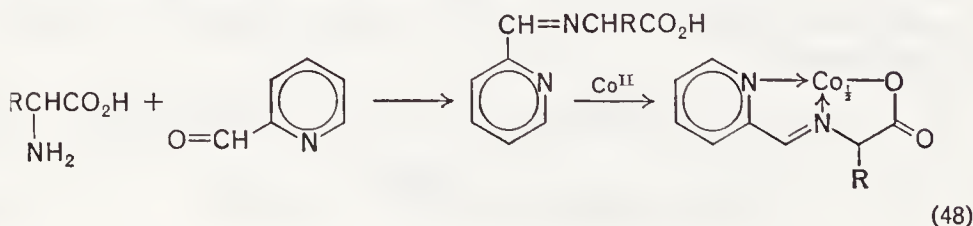
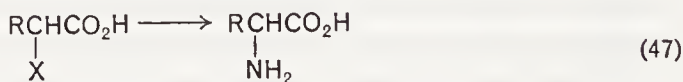


It is possible to convert an α -haloketone to the corresponding enol ester without touching the halogen by treating either with isopropenyl acetate (reaction 45)¹ or with sodium hydride (reaction 46)⁴⁵⁰.

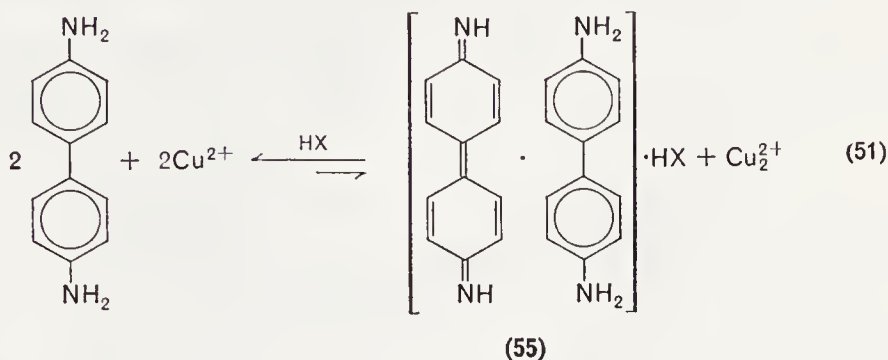
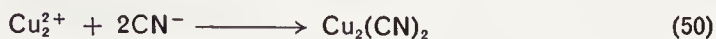
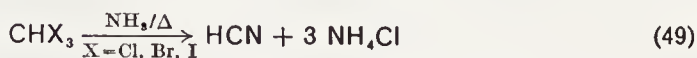


5. N-Substitution of amines

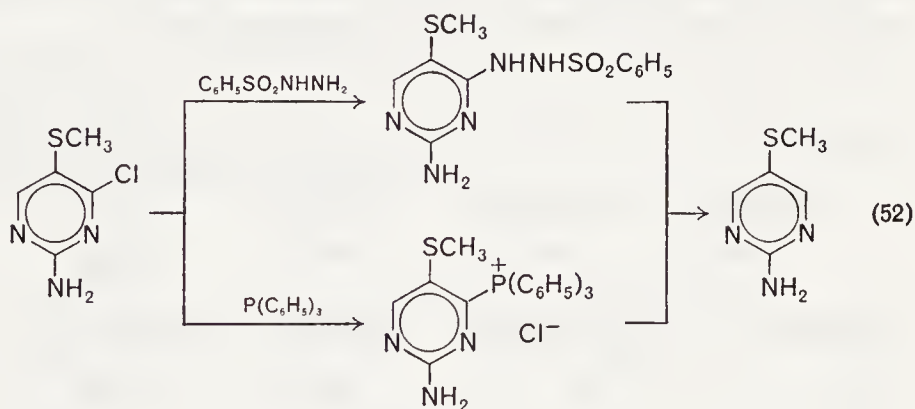
α -Halo acids are converted by ammonia to the corresponding amino acid (reaction 47) which can be detected as the cobalt(II) complex of the Schiff base with 2-pyridinecarboxaldehyde (reaction 48)^{192, 247}.



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.

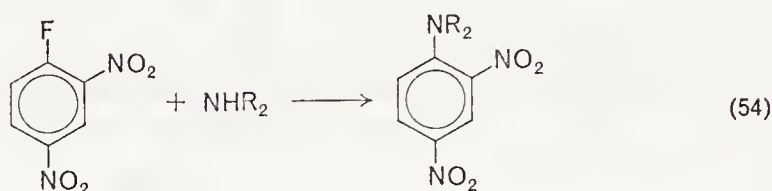
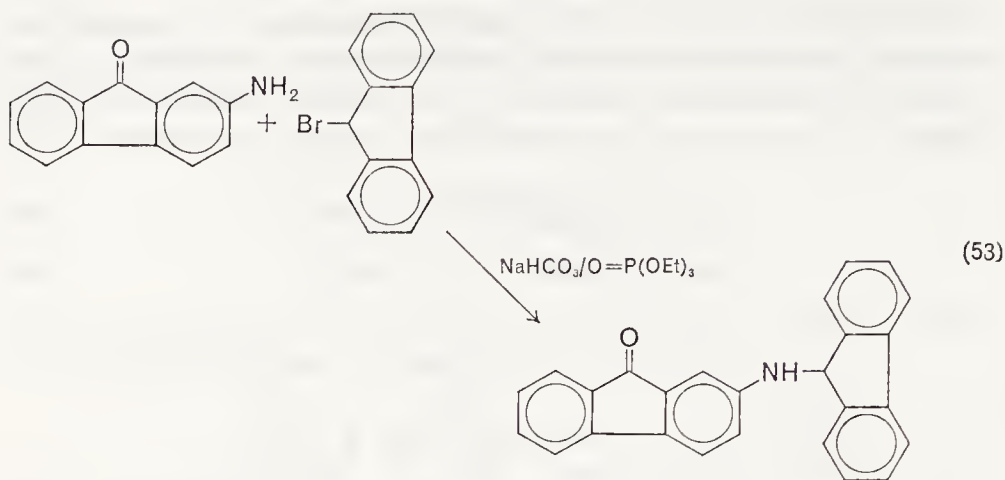


Benzenesulphonhydrazide with certain heterocyclic halogen compounds yields the corresponding *N*-aryl derivative which, on heating with alkali, releases the reduced heterocyclic system (reaction 52)⁴⁵¹. Alternatively the same reduction can be carried out with triphenylphosphine (reaction 52).

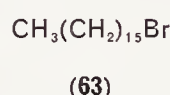
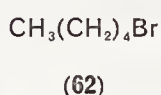
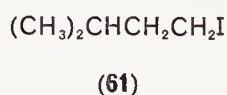
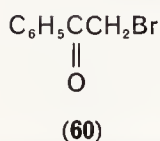
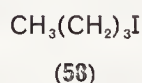
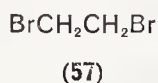
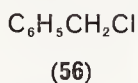


Alkyl and aryl bromides or iodides alkylate weakly basic amines in the presence of triethyl phosphate, as shown in reaction (53)⁴³⁴.

Aromatic halides substituted with electronegative groups combine with primary and secondary amines^{421, 422} (reaction 54).



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 reflux⁴⁵². A modification for the higher alkyl iodides has also been proposed⁴⁵³.



6. N-Substitution of amides

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

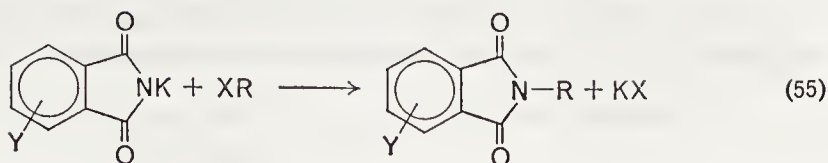
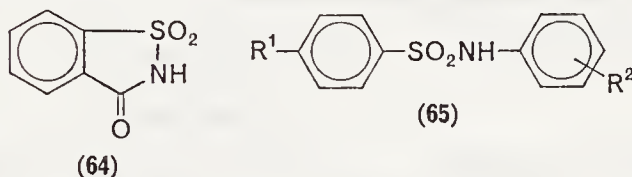


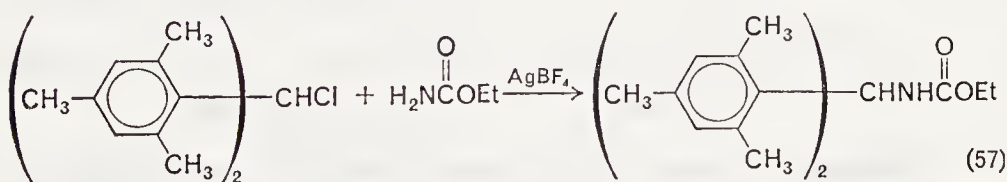
TABLE 19. Imides and sulphonamides recommended for derivatizing alkyl halides

Reagent	Reference
3-Nitrophthalimide	14, 19, 454
4-Nitrophthalimide	14, 19, 455
Tetrachlorophthalimide	14, 19, 456
Saccharin (64)	14, 457
<i>p</i> -Bromobenzenesulphon- <i>p</i> -aniside (65, R ¹ = Br; R ² = <i>p</i> -OCH ₃)	14, 458
<i>p</i> -Toluenesulphotoluidides (65, R ¹ = CH ₃ ; R ² = <i>o</i> -, <i>m</i> -, <i>p</i> -CH ₃)	14, 459



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

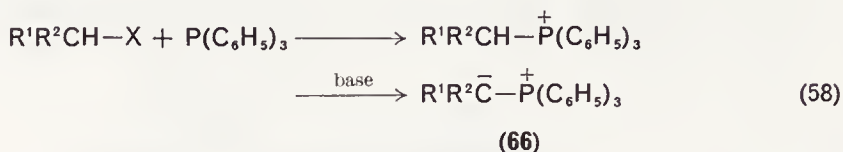
Benzhydryl halides can react with ethyl carbamate in the presence of silver tetrafluoroborate (reaction 57)⁴⁶⁰.



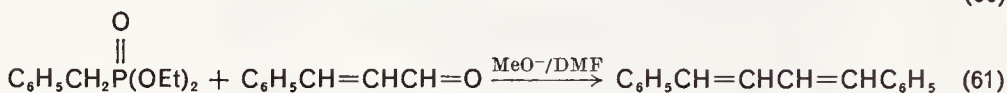
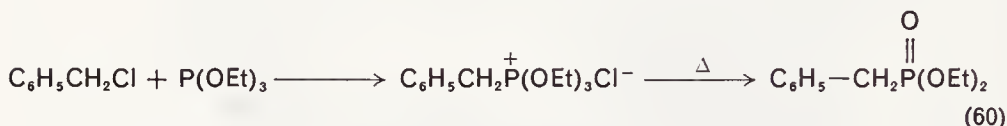
7. Derivatization via *P*-alkylation (Wittig-type reactions)

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

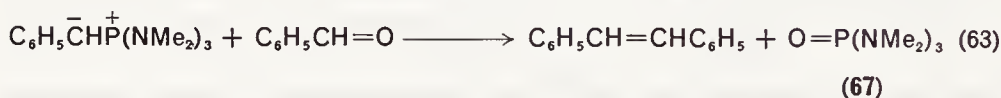
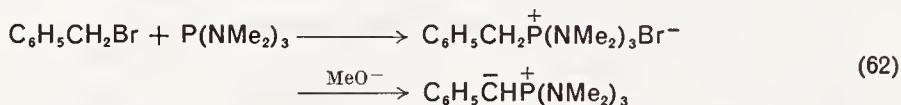
in reactions (58–59) and the reductive dehalogenations discussed in section IV. D. 2. a. The usual reactivity for the halides is $I > Br > Cl$.



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

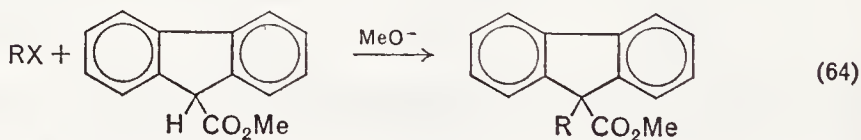


triamide (reactions 62–63)⁴⁶⁴. The latter reagent yields hexamethylphosphoric triamide (67) which is water-soluble.

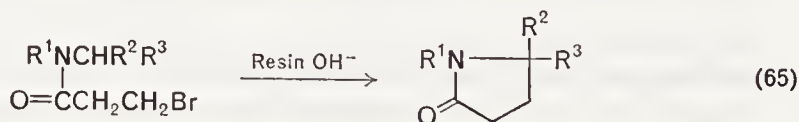


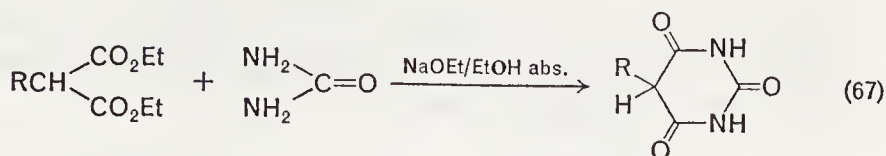
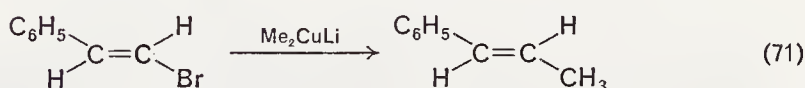
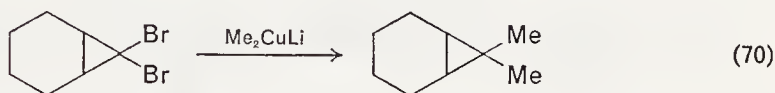
8. C-Alkylation of carbanions

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



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

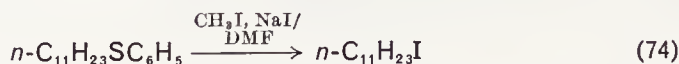


$$\text{Cyclopentene-1-CH}_2\text{Cl} + \text{CH}_2(\text{CO}_2\text{Et}) \xrightarrow{\text{NaOEt/EtOH abs.}} \text{Cyclopentene-1-CH}(\text{CO}_2\text{Et})_2 \quad (66)$$

$$\text{R-I} + \text{LiCH}_2\text{C}\equiv\text{CSi}(\text{CH}_3)_3 \longrightarrow \text{RCH}_2\text{C}\equiv\text{CSi}(\text{CH}_3)_3 \xrightarrow{\text{Ag}^+/\text{EtOH}} \text{RCH}_2\text{C}\equiv\text{CH} \quad (68)$$
$$\text{C}_6\text{H}_5\text{I} \xrightarrow{\text{Me}_2\text{CuLi}} \text{C}_6\text{H}_5\text{CH}_3 \quad (69)$$


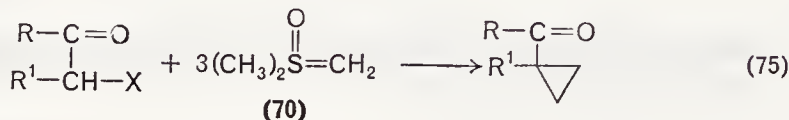
(72)

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 phenylthiomethyl lithium. If

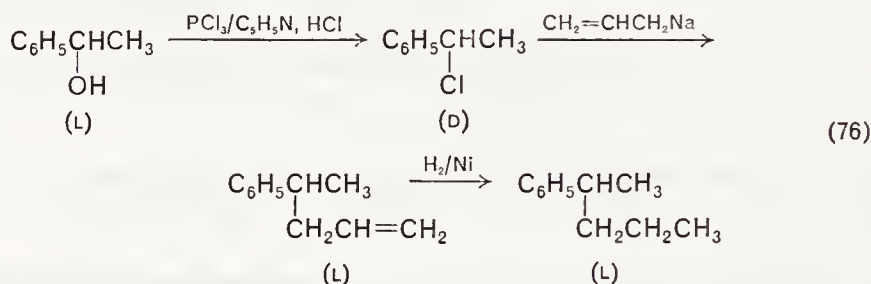
the halide happens to be allylic the reaction becomes easier, but suitable acceptors of HI and I₂ have to be added to the reaction mixture in order to avoid double-bond migrations⁴⁷².



Dimethyloxosulphonium methylyde (70) yields acylcyclopropanes with α -halo carbonyl compounds (reaction 75)⁴⁷³.

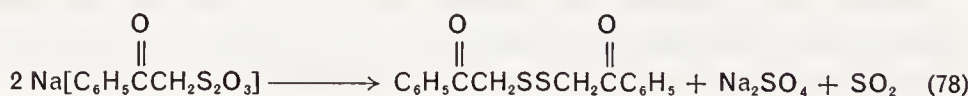
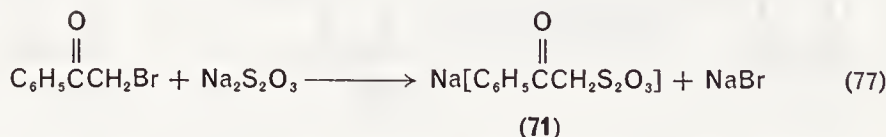


Alkyl alkali metals produce the halogen displacement usually accompanied by Walden inversion, a fact which may be helpful in assigning absolute configurations (see, however, reference 474). For example, the configuration of 2-phenylpentane was correlated with that of α -phenethol via a halogenated intermediate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

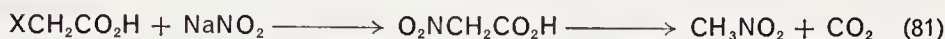
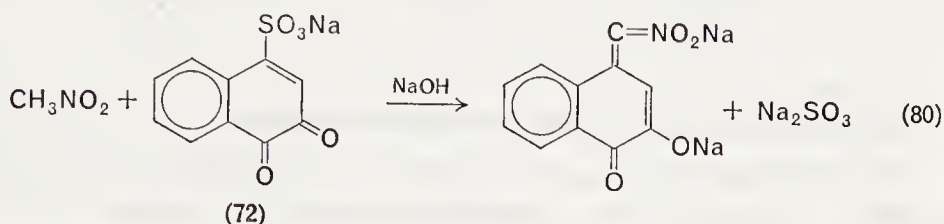
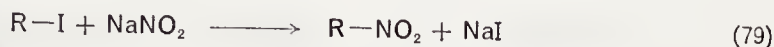


9. Miscellaneous nucleophilic substitutions

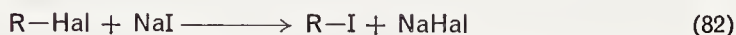
Primary alkyl halides yield Bunte salts (71) on treatment with thio-sulphate (reaction 77). These derivatives undergo further decomposition, releasing sulphur dioxide (reaction 78) that may be detected by its smell or reductive properties^{12, 192, 476}.



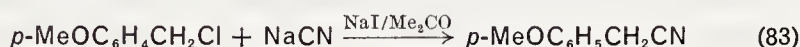
Alkyl iodides treated with sodium nitrite yield the corresponding nitroalkanes (reaction 79). Methyl iodide can thus be detected if its product is further treated with sodium 1,2-naphthoquinone-4-sulphonate (**72**) in alkaline medium, yielding a coloured compound (reaction 80)¹⁹². The same method may 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 halides⁴⁷⁸.



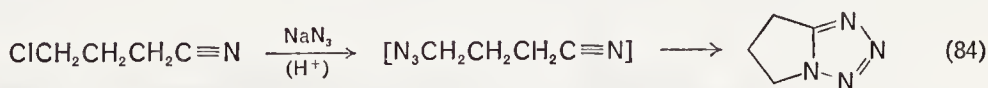
Alkyl and aryl halides that are susceptible to nucleophilic substitution can be converted to the corresponding iodides by treatment with sodium iodide in various solvents, as shown in reaction (82)⁴⁷⁹⁻⁴⁸¹. Sodium iodide



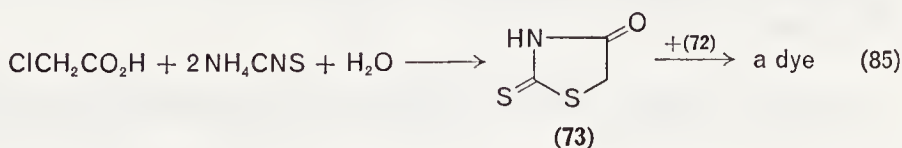
is a helpful catalyst in the conversion of benzyl chlorides to their corresponding cyanides (reaction 83)⁴⁸².



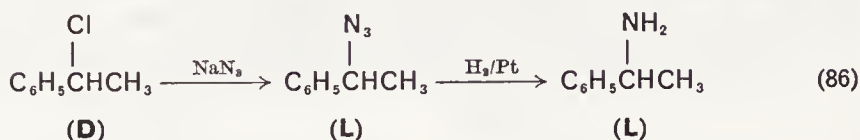
The azide ion is similar to iodide, but usually more effective, in displacing organic halogen (including iodine)⁴⁸³. An additional advantage is that the organic azido group may undergo thermal rearrangements and cyclizations involving other properly situated groups in the molecule^{483, 484}, yielding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



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

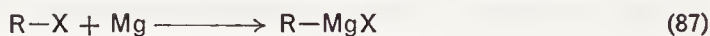


Displacement by strong nucleophilic electrolytes usually involves a Walden inversion⁵. This fact may be helpful in correlating the absolute configuration of an alkyl halide with that of a known compound. For example, α -phenethyl chloride was correlated with α -phenethylamine⁴⁸⁵ as shown in reaction (86).

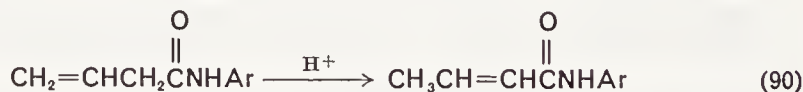
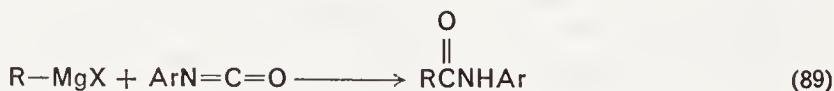


B. Displacement via Organometallic Intermediates

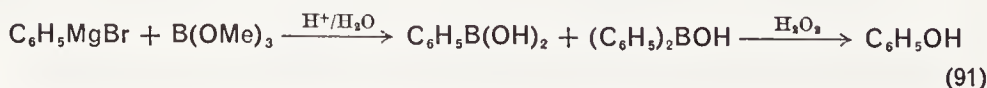
The formation of Grignard reagents is the first step for multiple possibilities of derivatization. Although reaction (87) constitutes the most widely used method for organometal intermediate formation, treatment of alkyl or aryl halides with lithium, lithium-sodium alloys or butyllithium yields the corresponding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



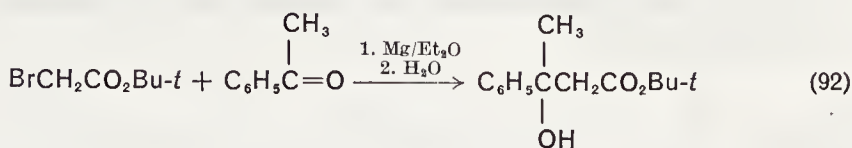
Among the derivatives recommended for organic halides^{11, 14, 19} are conversions into anilides^{486, 487}, toluides and α -naphthalides⁴⁸⁶. These are prepared by reacting the organometallic intermediate with the corresponding aryl isocyanate, as shown in reaction (89). The anilides resulting from allyl halides can be converted into crotonic anilides by treatment with acid (reaction 90)⁴⁸⁷.



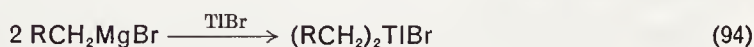
Aromatic Grignard reagents may be converted into phenols by means of methyl borate (reaction 91)⁴⁸⁸.



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.



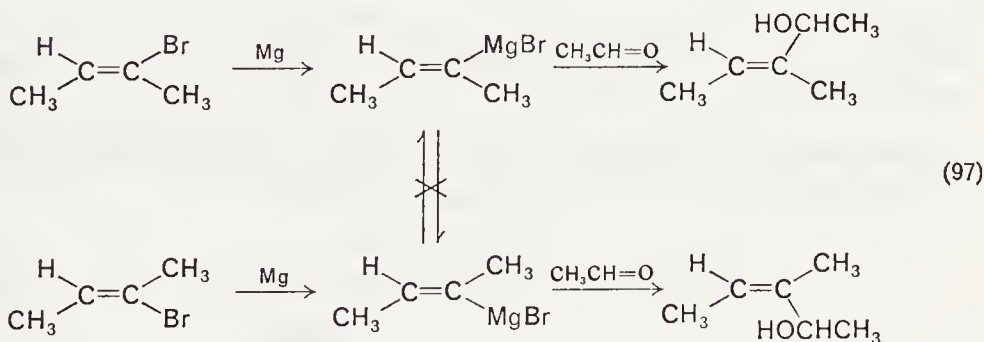
Aryl Grignard reagents with no *ortho* substituents undergo high yield biaryl formation on treatment with thallium(I) bromide (reaction 93). Secondary alkyl Grignard reagents give a similar reaction in about 50% yield and primary alkyl or *ortho* substituted aryl Grignard reagents give dialkylthallium(III)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



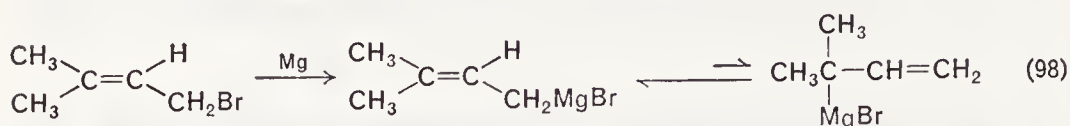
Other organometallic derivatives obtained via Grignard reagents are halomercury compounds (reaction 95), which have been recommended for identification purposes^{11, 14, 19}. The organomercury halides can be further reacted in the presence of dicobalt octacarbonyl to yield a ketone (reaction 96)⁴⁹¹.



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



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 magnesium⁴⁹².

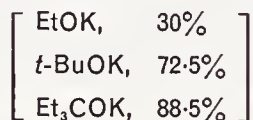
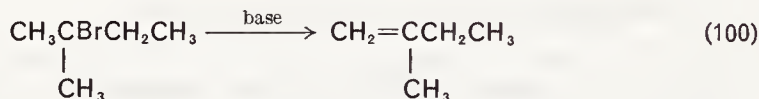
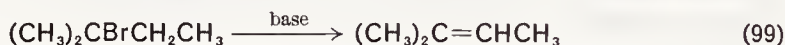


C. Elimination of Hydrogen Halide

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.

I. Alkyl halides

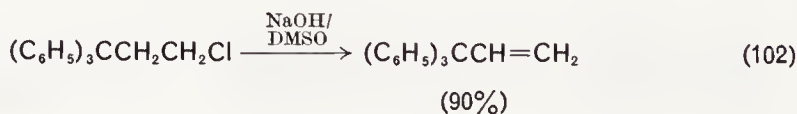
Alkali hydroxides and alkoxides bring about dehydrohalogenation under various conditions depending on the substrate. When two elimination products are possible, hydroxides tend to obey Saytzeff's rule (reaction 99); however, the yield of the anti-Saytzeff products varies with the nature of the base,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



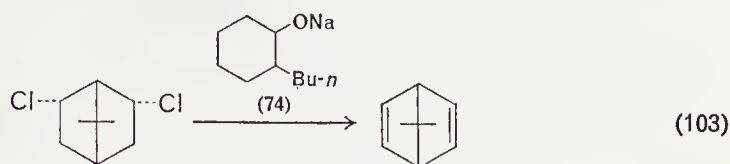
Dehydrohalogenations with potassium *t*-butoxide proceed smoothly in dimethyl sulphoxide solvent, e.g. reaction (101)⁴⁹⁹.



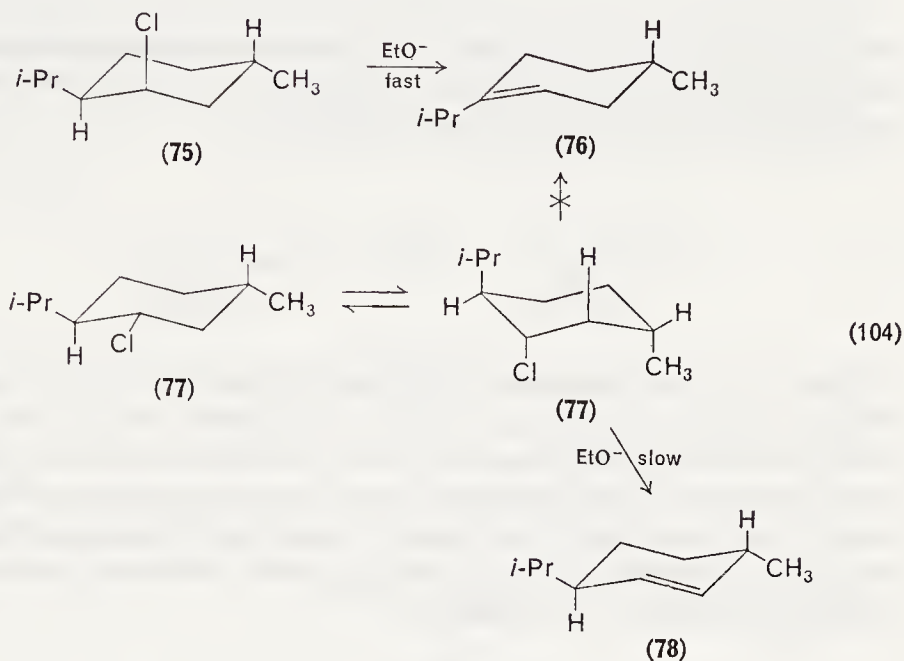
Good yields are obtained in the same solvent in dehydrochlorinations with sodium hydroxide or ethoxide (reaction 102)⁵⁰⁰.



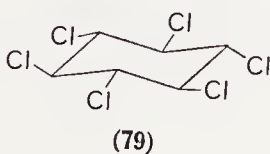
Sodium 2-*n*-butylcyclohexanolate (**74**) is effective in dehydrohalogenating compounds even in cases where potassium *t*-butoxide and lithium diethylamide (see below) fail, e.g. reaction (103)⁵⁰¹.



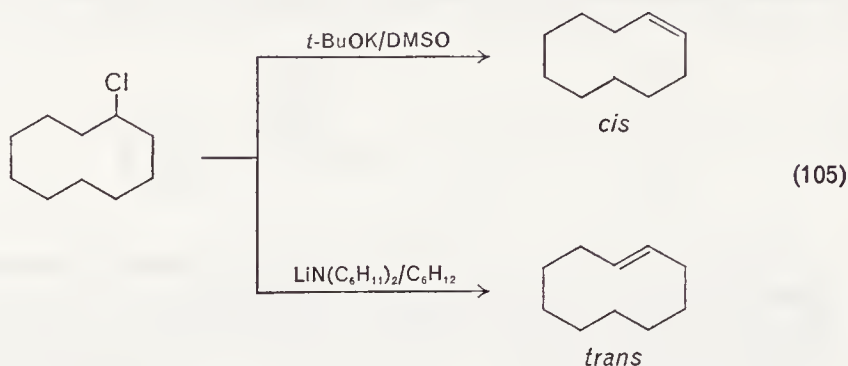
In cyclic compounds *trans*-diaxial eliminations are favoured, especially if they conform to the Saytzeff rule and a *t*-hydrogen is eliminated; on the other hand, axial-equatorial or diequatorial eliminations are very sluggish. Reaction (104) illustrates the production of 3-menthene (**76**) from neo-



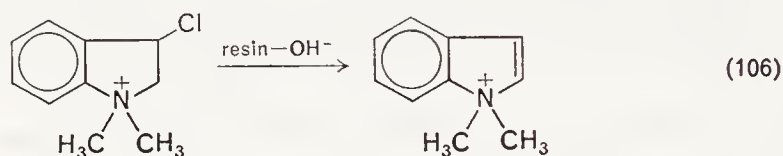
menthyl chloride (**75**) according to Saytzeff's rule, while the anti-Saytzeff product 2-menthene (**78**) is produced from the anomeric menthyl chloride (**77**)⁵⁰². Similarly, the all-equatorial isomer of hexachlorocyclohexane (**79**), is by far the most resistant to alkaline solvolysis⁵⁰³.



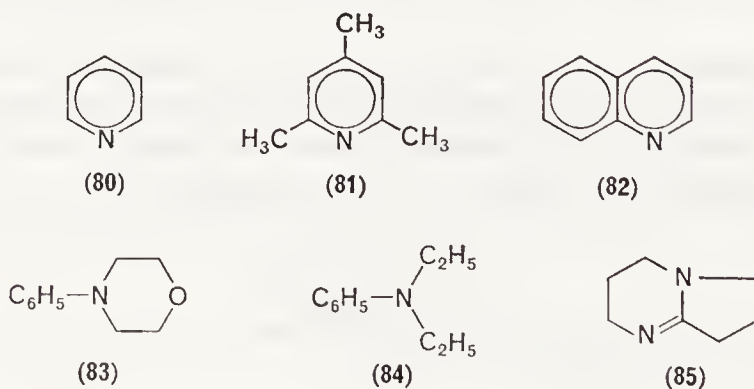
The stereochemistry of the resulting olefins depends on the dehydrohalogenation reagent^{497, 498, 504}, as shown, for example, in reaction (105).



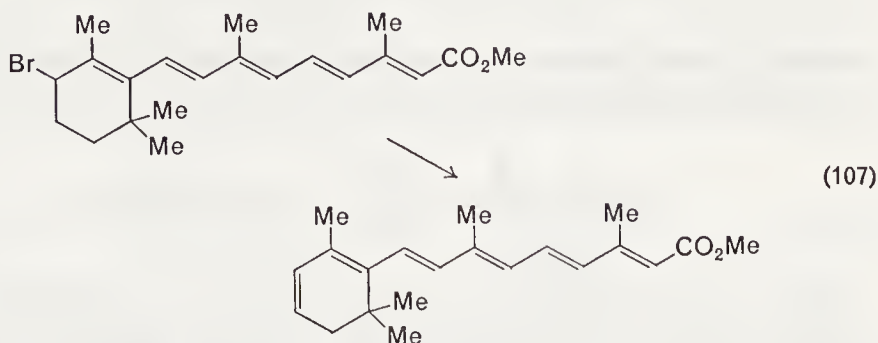
Organic halides containing the quaternary ammonium moiety can be dehydrohalogenated by treatment with strongly basic resins (reaction 106). Treatment with bases in solution brings about elimination reactions involving the quaternary ammonium function⁵⁰⁵.



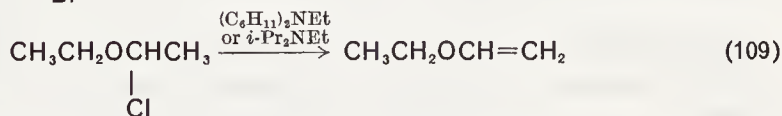
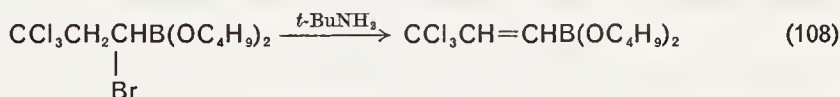
Amines and nitrogen-containing aromatic heterocycles can be used for effecting dehydrohalogenations. These are mild bases which need either harsh conditions or the presence of easily removable proton or halogen in the substrate. These properties allow selective removal of halogen atoms in polyhalogenated compounds. Heating in the presence of heterocyclic compounds such as pyridine (80), *s*-collidine (81) and quinoline (82) has long been used for this purpose¹.



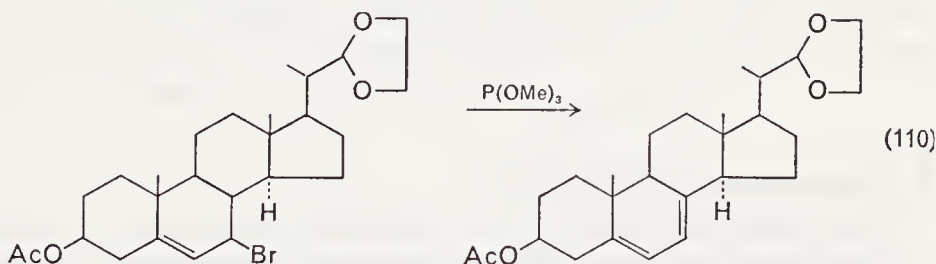
N-Phenylmorpholine (**83**) acts like *N,N*-diethylaniline (**84**) but is purified more easily. They can both be used for allylic halides (reaction 107)⁵⁰⁶. A very effective dehydrohalogenating reagent is 1,5-diazabicyclo[4.3.0]non-5-ene (**85**)⁵⁰⁷.



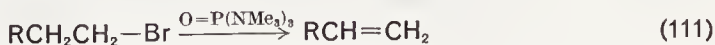
Other useful amine bases for alkyl halide dehydrohalogenation are *t*-butylamine (e.g. reaction 108⁵⁰⁸), dicyclohexylethylamine, diisopropylethylamine (e.g. reaction 109⁵⁰⁹) and triethylamine¹. α -Haloketones, on the other hand, are reduced in the presence of dialkylanilines (see section IV. D. 1. b).



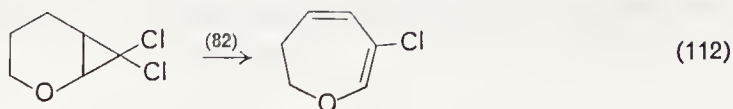
Trimethyl phosphite catalyses dehydrohalogenation on refluxing in xylene (reaction 110)⁵¹⁰.



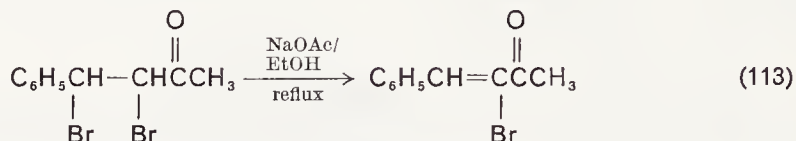
Primary alkyl bromides undergo dehydrobromination on heating with hexamethylphosphoric triamide, yielding terminal alkenes (reaction 111)⁵¹¹. *gem*-Dihalocyclopropanes undergo elimination-rearrangement



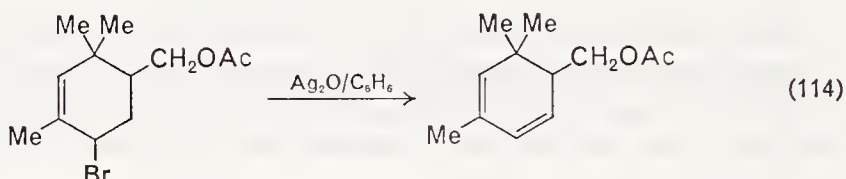
via vinyl halide intermediates on heating with bases such as pyridine (80) or quinoline (82)^{512, 513}, e.g. reaction (112)⁵¹².



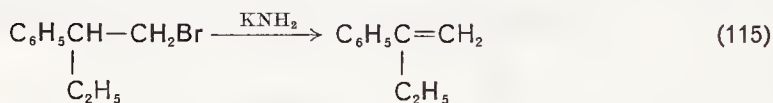
Refluxing *vic*-dibromides in the presence of ethanolic sodium acetate yields vinyl bromides (reaction 113)⁵¹⁴.



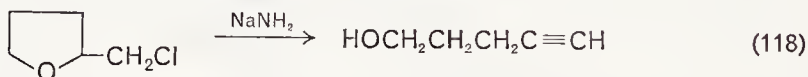
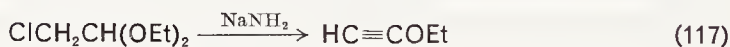
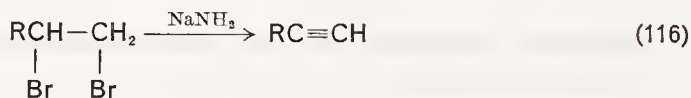
Silver oxide converts allylic halides slowly into conjugated dienes (reaction 114)⁵¹⁵. Alkali amides cause dehydrohalogenations, but no



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

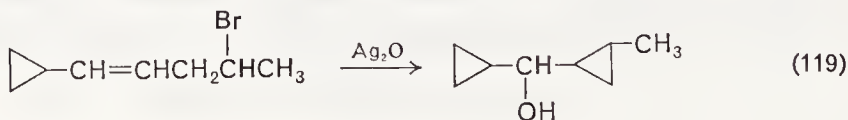


vic-Dibromides are converted to the corresponding acetylenes (reaction 116)⁵¹⁷. Similarly, β -haloethers also yield acetylenes (reactions 117⁵¹⁸ and 118⁵¹⁹).

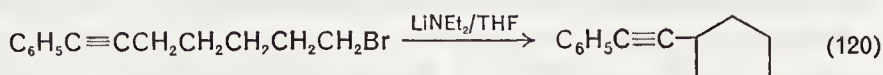


2. Cyclization of alkyl halides

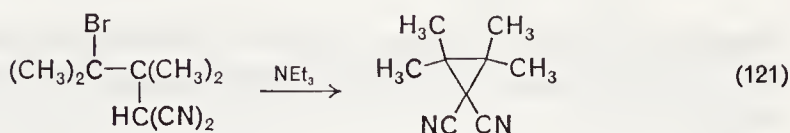
Unsaturated alkyl halides and halogenated compounds containing suitable functional groups dehydrohalogenate forming cyclic compounds on treatment with various reagents. Homoallylic halides yield cyclopropanes with silver oxide or potassium carbonate (reaction 119)⁵²⁰.



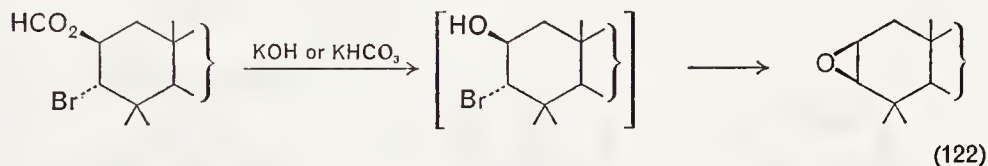
Lithium diethylamide has been used to cyclize acetylenic halides as shown in reaction (120)⁵²¹. Tri-*n*-butyltin hydride gives similar results⁵²².



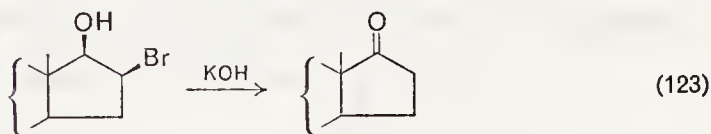
Triethylamine also is capable of causing cycloalkyl formation, if both the halogen and the departing proton are sufficiently activated, as in reaction (121)⁵²³ (see also section IV. A. 8).



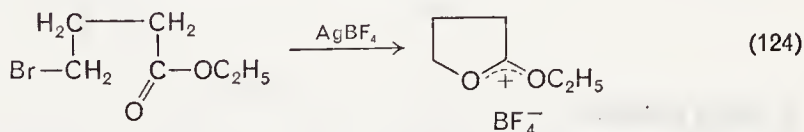
Halohydrins or their formates in the *trans*-diaxial conformation yield epoxides with bases (reaction 122)⁵²⁴⁻⁵²⁶. The stereoselectivity of this reaction is high⁴²⁸. *Trans*-diequatorial halohydrins may also undergo this cyclization⁵²⁴.



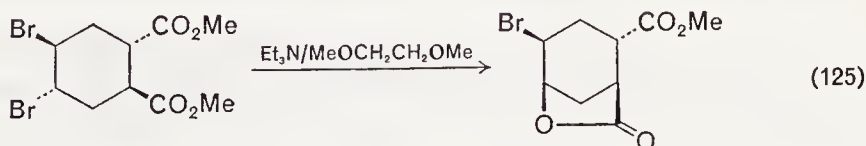
Halohydrins with the *cis* configuration yield carbonyl compounds (reaction 123)^{524, 527}.



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.

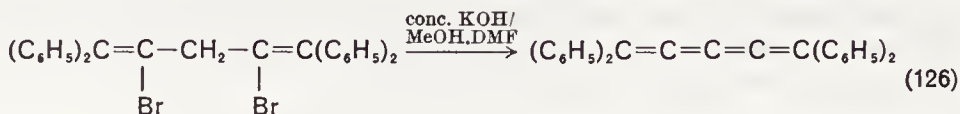


Triethylamine may cause the lactonization of γ -bromo acids (reaction 125)⁵²⁹.

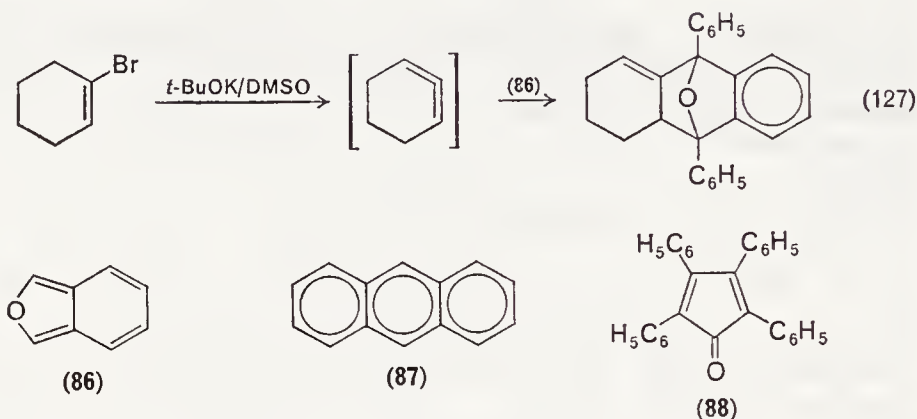


3. Vinyl halides

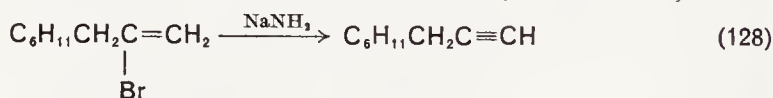
Displacement and elimination reactions are more difficult to carry out with these compounds than with alkyl halides and more drastic treatment is therefore required. Treatment with hydroxide or alkoxide yields allenes (reactions 126⁵³⁰ and 127^{531, 532}). Reaction (127) is not, however, without



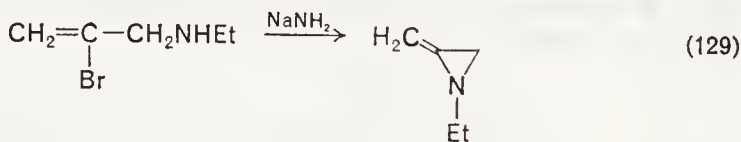
complications^{533, 534}. Trapping of allenes can be done *in situ* by conjugated diene reagents such as 1,3-diphenylisobenzofurane (86)^{531, 532}, as shown in reaction (127).



Sodamide converts vinyl halides into acetylenes⁵¹⁷ (reaction 128).



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

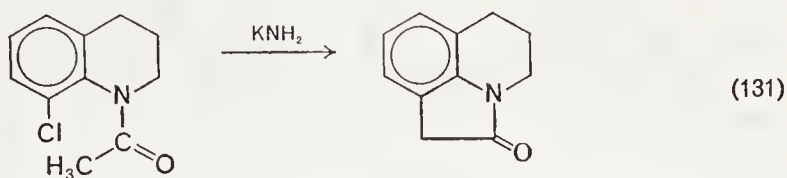


4. Aryl halides

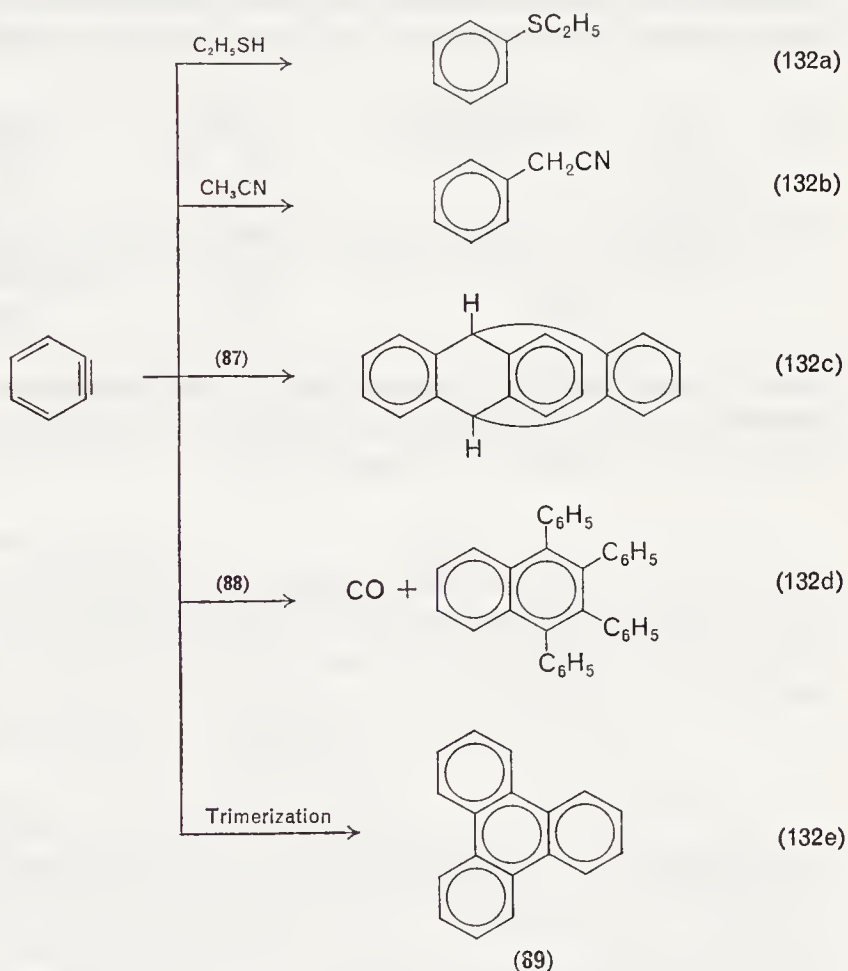
These compounds require specially drastic conditions to eliminate hydrogen halide and produce an aryne, e.g. reaction (130)^{536, 537}. The



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



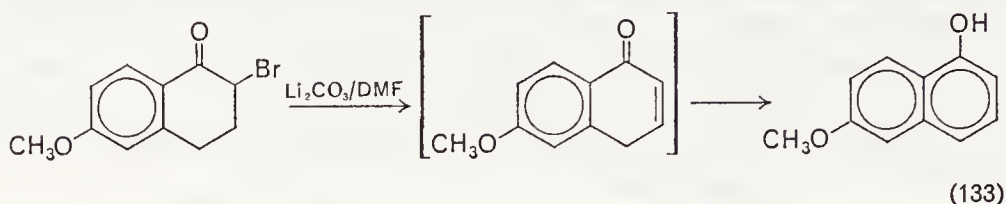
mercaptans, acetonitrile^{536, 537}, or dienic systems, e.g. anthracene (87)⁵³⁹, tetraphenylcyclopentadienone (88)⁵⁴⁰, with itself forming triphenylene (89)⁵⁴¹, as shown in reactions (132a-e).



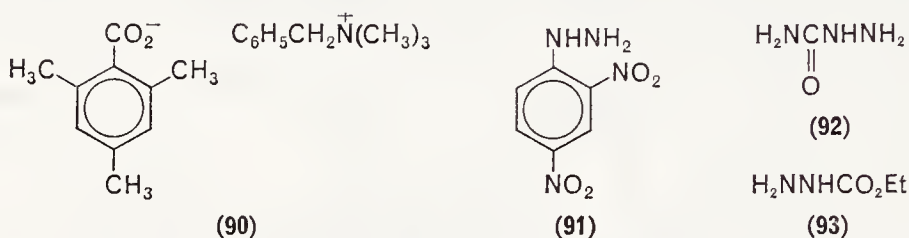
5. α -Halocarbonyl compounds

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

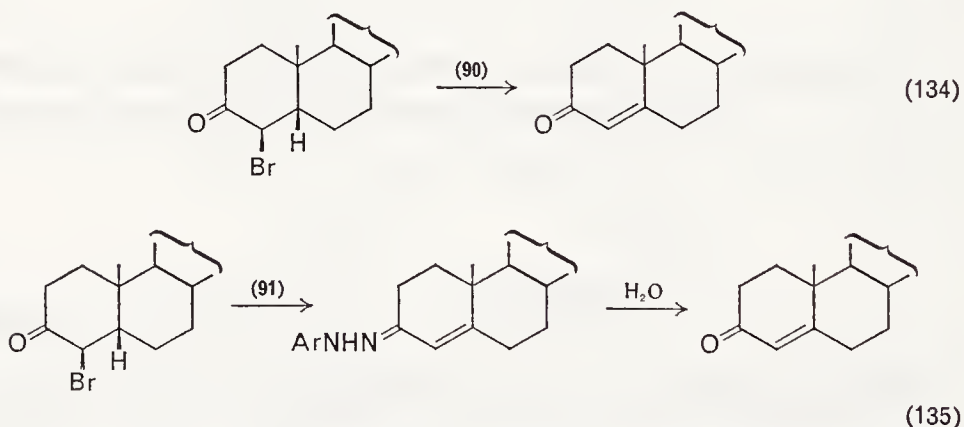
purpose are ethanolic silver nitrate⁵⁴², weak bases like sodium bicarbonate^{543, 544}, lithium carbonate (reaction 133⁵⁴⁵, see also reaction 201), or



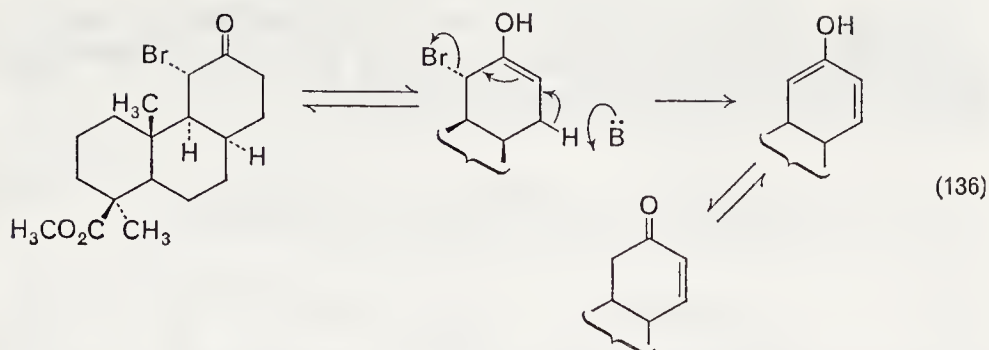
calcium carbonate⁵⁴⁶ and salts such as lithium bromide⁵⁴⁷, tetraethylammonium chloride⁵⁴⁸ or benzyltrimethylammonium mesitoate (**90**) (reaction 134⁵⁴⁹). Reagent **90** effected the elimination from a *cis* conformation under mild conditions, while the former weak bases usually



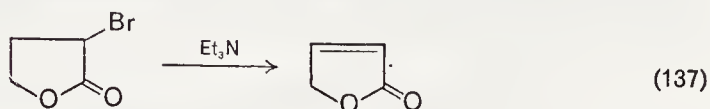
require a *trans*-diaxial conformation. Other similar reagents are hydrazine derivatives such as 2,4-dinitrophenylhydrazine (**91**), semicarbazide (**92**) and ethyl carbazate (**93**)⁵⁵⁰⁻⁵⁵³ (reaction 135).



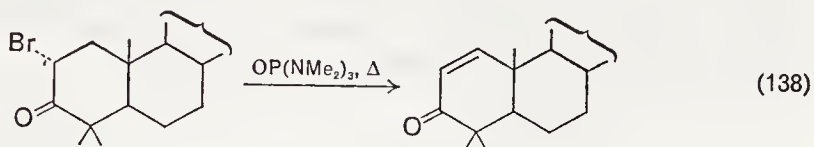
The eliminations performed in aprotic solvents may take a 1,4-pathway if no neighbouring *trans*-axial hydrogen is present. This may be confusing when the halogen substitution site is to be assigned (reaction 136)⁵⁵⁴.



Amines are also capable of dehydrohalogenating α -haloketones and α -haloesters, e.g. tri-*n*-butylamine⁵⁵⁵ and triethylamine (reaction 137)⁵⁵⁶.



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

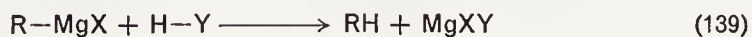


D. Reduction

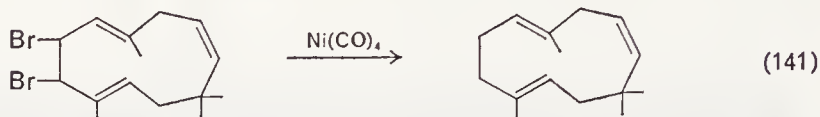
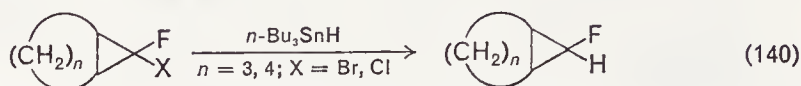
Two main types of derivatives can be obtained from reductive treatment, namely compounds where a hydrogen atom takes the place of the halogen and compounds where an unsaturation is formed in place of two monovalent oxidizing leaving groups, of which at least one is halogen. Polarographic reductions are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

I. Substitution of halogen by hydrogen

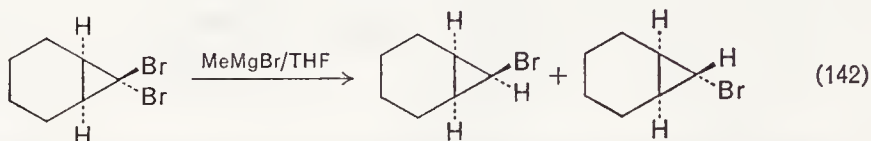
a. Alkyl halides. These can be reduced by magnesium in the presence of isopropanol⁵⁵⁸. Very stable halides can be reduced by this method, however, fluoro compounds are less reactive. This is in fact a particular case of the general reduction of Grignard reagents with active hydrogen compounds (reaction 139).



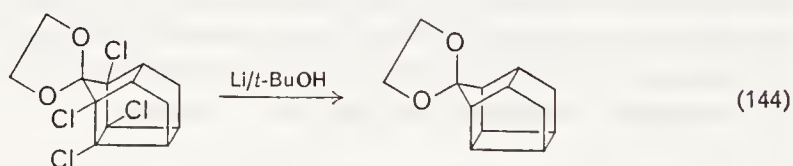
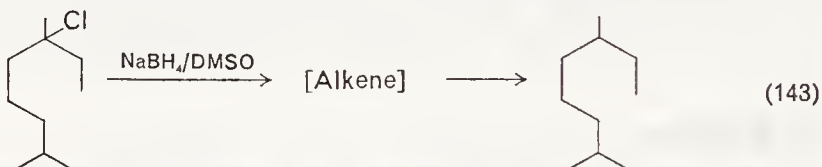
Tri-*n*-butyltin hydride (reaction 140⁵⁵⁹, see also reactions 155 and 171) and nickel tetracarbonyl (reaction 141⁵⁶⁰, see also reaction 159) reduce halides without touching the skeleton structure.



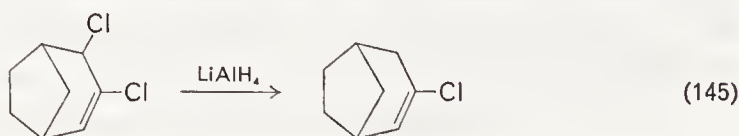
Methylmagnesium bromide is capable of effecting non-stereospecific monodehalogenations in *gem*-dihalocyclopropanes (reaction 142⁵⁶¹).



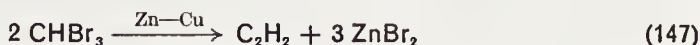
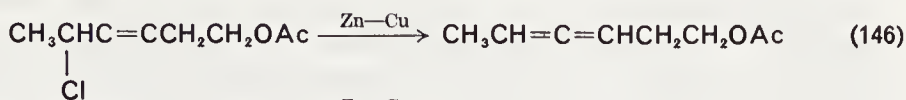
Sodium borohydride in dimethyl sulphoxide reduces alkyl halides. Optically active *t*-alkyl halides produce a racemic compound, probably as shown in reaction (143)⁵⁶². Lithium in *t*-butyl alcohol reduces alkyl halides leaving the skeleton intact (reaction 144)⁵⁶³.



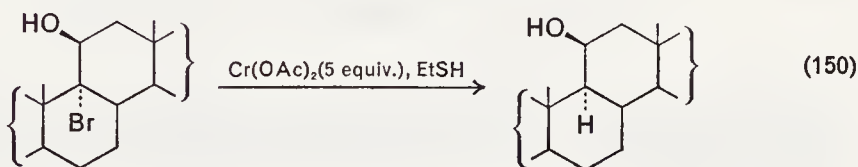
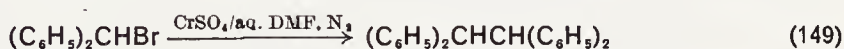
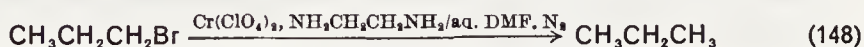
Alkyl halides can be reduced without touching less reactive halogens by means of lithium aluminium hydride (reaction 145)¹. With the same reagents α -bromohydrins yield the alcohol⁵⁶⁴.



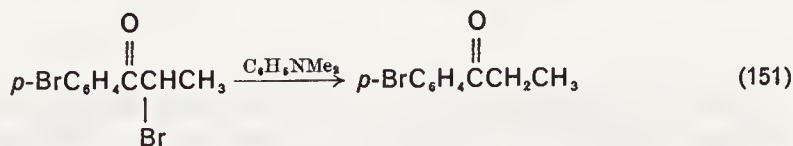
Propargyl halides undergo a reduction with zinc-copper couple which is accompanied by rearrangement to allenes (reaction 146)⁵⁶⁵. Bromoform yields acetylene on heating with zinc-copper couple (reaction 147)¹². Carbon tetrachloride and tetrabromide give the same reactions but are less sensitive¹².



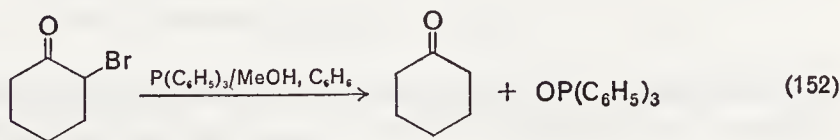
Chromium(II) salts are capable of reducing alkyl halides in high yields⁵⁶⁶, e.g. reaction (148). The course of the reaction may lead to dimerization (reaction 149). Bromohydrins usually undergo other types of reduction, as will be shown in section IV. D. 2. a; however, in the presence of a hydrogen donor such as a mercaptan, the hydroxyl group is left intact (reaction 150)^{525, 567}.



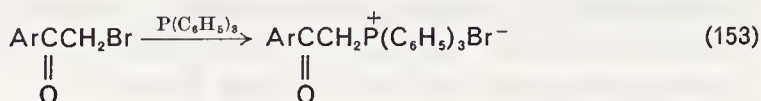
b. *α-Halo ketones and α-halo acids*. These undergo many reactions which are impossible with ordinary alkyl halides. *α*-Bromo and *α,α*-dibromo ketones are reduced by dimethylaniline (reaction 151)⁵⁶⁸.



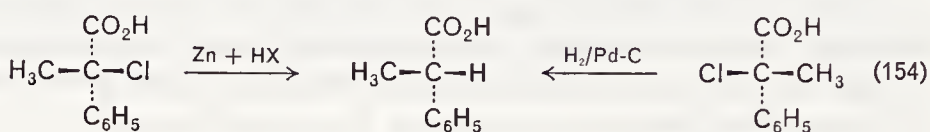
Triphenylphosphine reduces secondary and tertiary *α*-haloketones (reaction 152)⁵⁶⁹. On the other hand, phenacyl halides yield quaternary



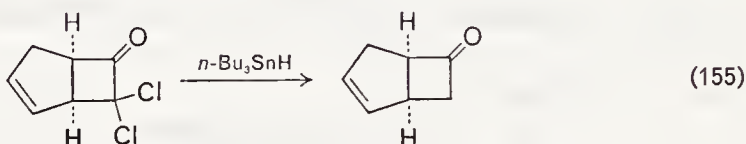
phosphonium salts (reaction 153)⁵⁷⁰.



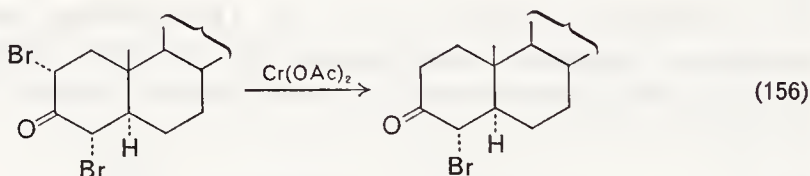
Catalytic hydrogenation of α -haloketones has to be carried out in the presence of a base such as triethylamine, in order to avoid catalyst poisoning⁵⁷¹. Catalytic reduction of α -chloro- α -phenylpropionic acid in the presence of palladium is carried out with inversion of configuration while reduction with nascent hydrogen preserves the configuration (reaction



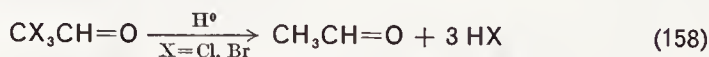
154)⁵⁷². Tri-*n*-butyltin hydride effects dehalogenations without touching the skeleton structure (reaction 155)⁵⁷³.



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

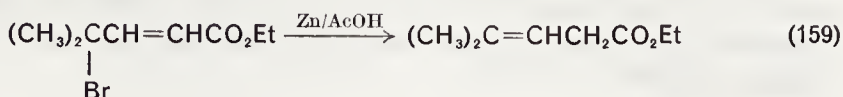


Nascent hydrogen produced by zinc in acid solution or formaldehyde sodium sulfoxylate (reaction 157) can lead to α -halocarbonyl reduction^{12, 575}. This has been used for specific detection of chloral and bromal¹²,

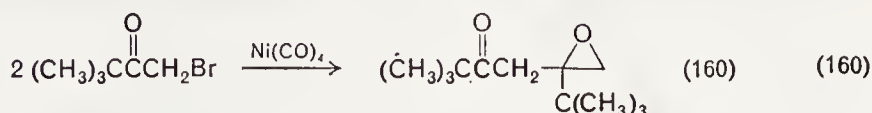


in which reduction (158) is followed by the Rimini test for aldehydes. γ -Bromo- α,β -unsaturated carbonyl compounds (ketones and esters) are

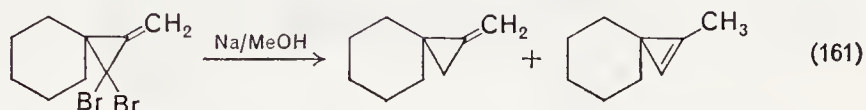
reduced and rearranged simultaneously to the corresponding β,γ -unsaturated compound, with zinc in protonic solvents (reaction 159)^{576, 577}.



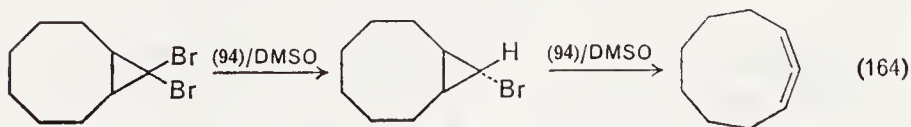
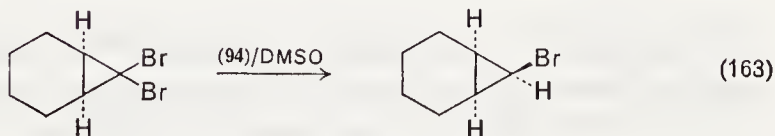
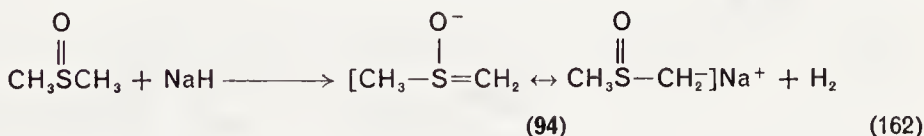
Nickel tetracarbonyl effects reductive dimerization of α -bromoketones (reaction 160)^{578, 579}, to yield β -epoxyketones.



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.

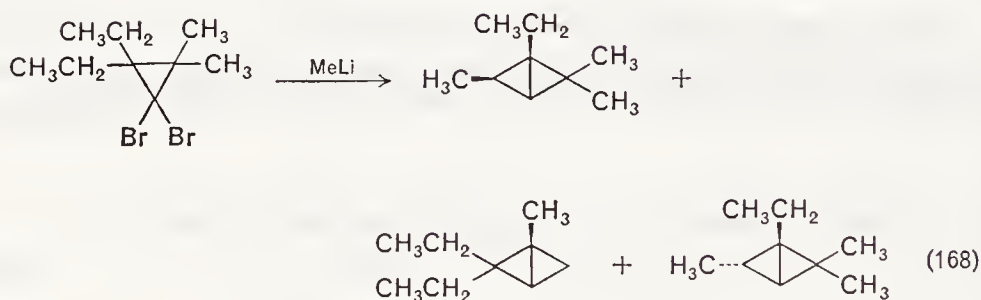
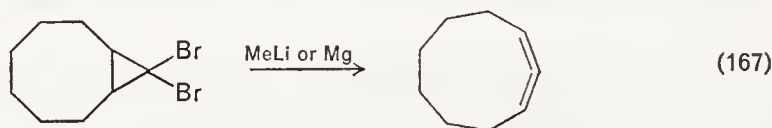
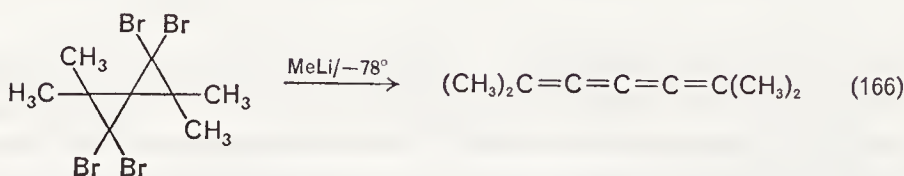
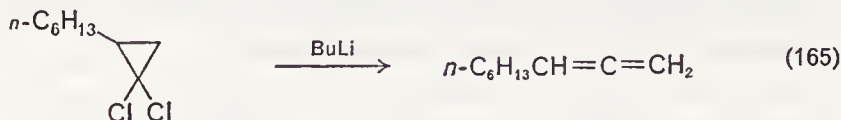


Sodium methylsulphinylmethide (**94**) is obtained *in situ* on dissolving sodium hydride in dimethyl sulphoxide (reaction 162). This reagent can reduce *gem*-dihalocyclopropanes stepwise (reactions 163 and 164). If

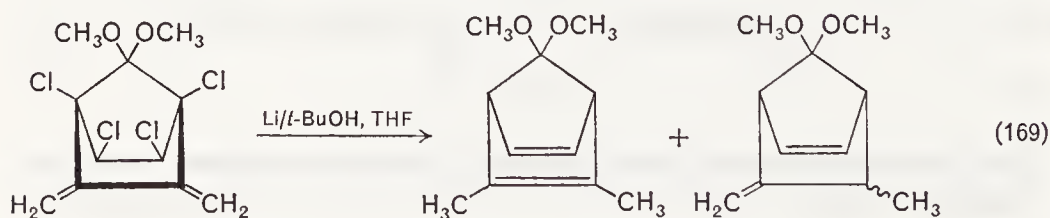


steric conditions allow, excess reagent brings about allene formation (reaction 164)⁴⁴⁹.

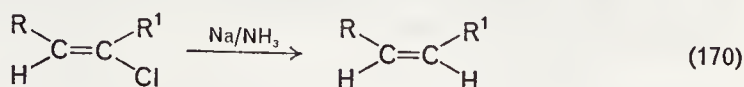
Alkyl lithium reagents convert *gem*-dihalocyclopropanes directly into allenes (reactions 165 and 166). In the case of bicyclo[*n*.1.0] compounds good results are obtained for $n \geq 6$ (reaction 167)⁴⁴⁹. Tetraalkyl-*gem*-dibromocyclopropanes yield with methyllithium bicyclo[1.1.0]butanes (reaction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



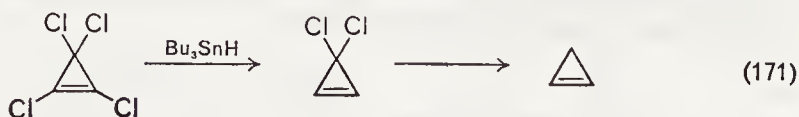
d. Vinyl halides. Both lithium⁵⁸¹ and sodium⁵⁸² in *t*-butyl alcohol are capable of reducing vinyl halides without disrupting the skeleton; however, some overhydrogenation and double-bond migration (reaction 169)⁵⁸³



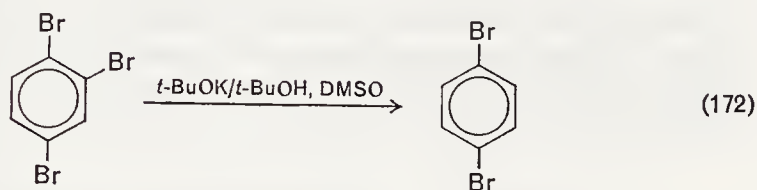
may occur. The *cis* or *trans* configuration of vinyl halides is preserved on reducing with sodium in liquid ammonia (reaction 170)⁵⁸⁴.



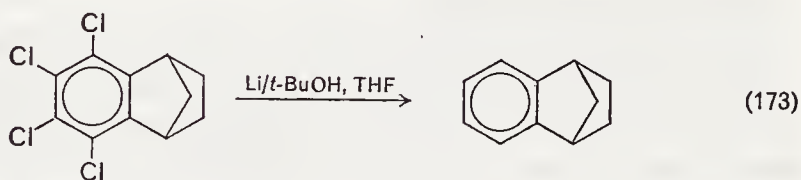
Tributyltin hydride also leaves the skeleton untouched (reaction 171)^{559, 585}.



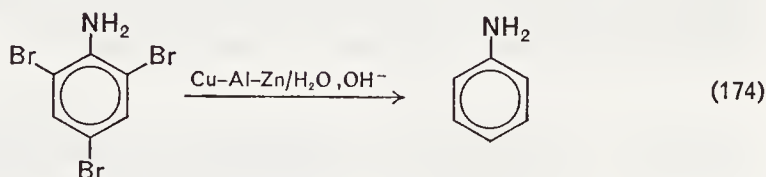
e. Aryl halides. Monodebromination or monodeiodination of *vic*-dihalides is performed by potassium *t*-butoxide (reaction 172)⁵⁸⁶.



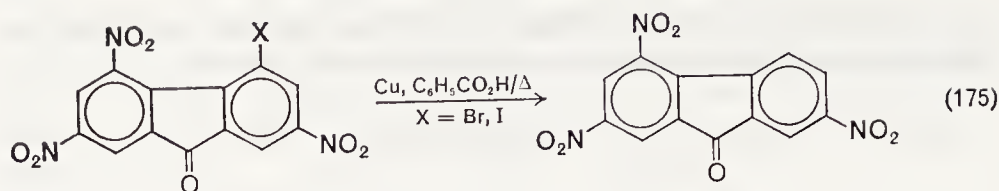
Lithium in *t*-butyl alcohol is capable of dehalogenating polyhaloaromatic compounds (reaction 173)⁵⁸⁷.



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

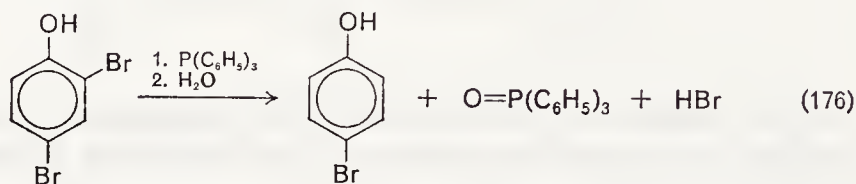


Aromatic nitro compounds are dehalogenated by copper powder in the presence of molten benzoic acid (reaction 175)⁵⁸⁹ and by hydrazine in the presence of Raney nickel⁵⁹⁰. Magnesium in isopropanol is very effective in

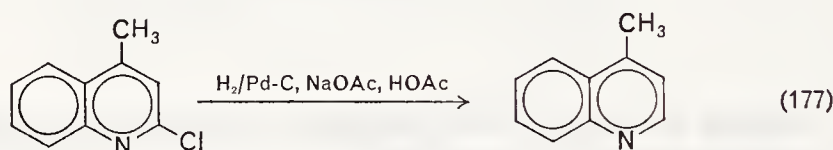


dehalogenations⁵⁵⁸ (see also section IV. D. 1. a), but fluorobenzene is inert towards this reagent.

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

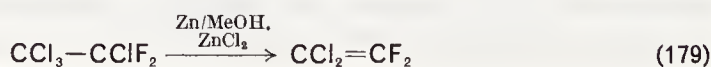
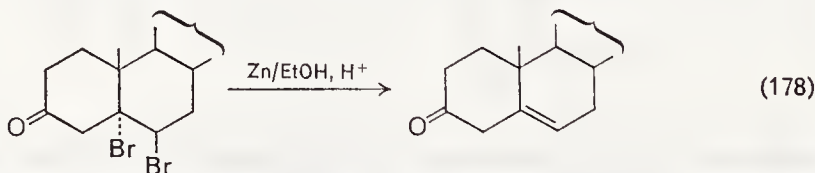


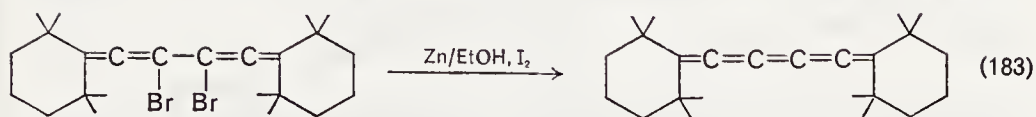
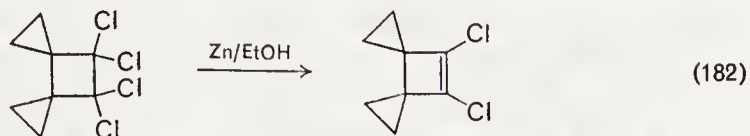
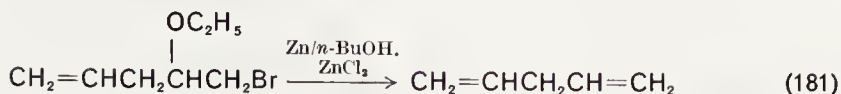
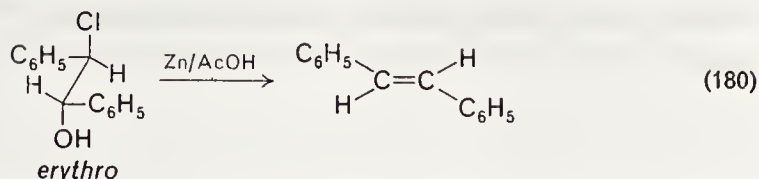
Reaction (52) affords a reduction method for certain heterocyclic halides. Catalytic hydrogenation in the presence of a base can also be applied for these compounds (reaction 177)⁵⁹².



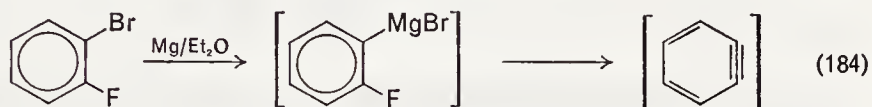
2. Reductive eliminations

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 known⁵⁹⁶. These reductions have been widely applied in the steroid field⁵⁹⁷. 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 conducive to free radical formation (reaction 183)⁵⁹⁹.



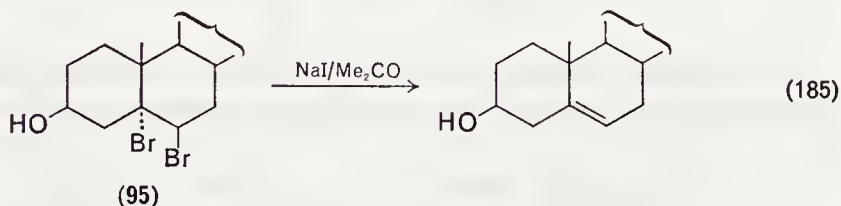


Magnesium can cause dehalogenation in many types of *vic*-dihalides via Grignard intermediates. When the substrate is aromatic (reaction 184)⁵³⁹

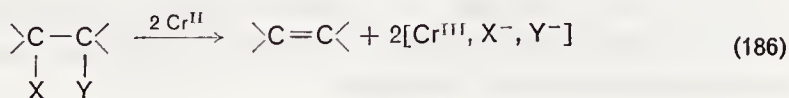


the resulting benzyne can be further trapped as shown in reactions (132a-e). Lithium reacts similarly to magnesium with aromatic dihalides⁵⁴¹.

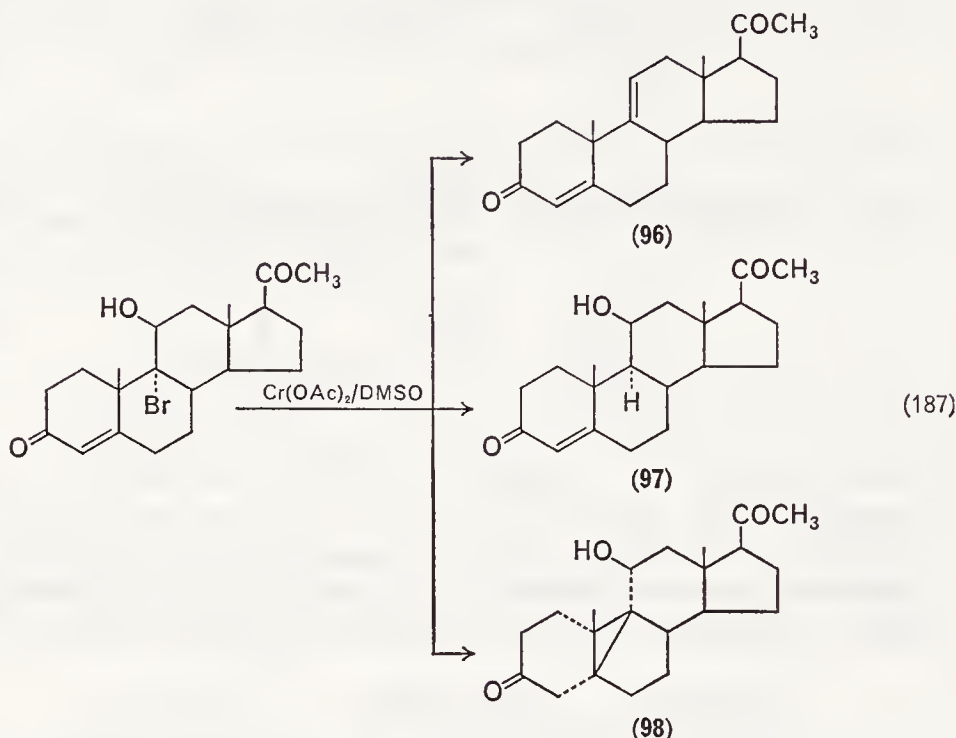
(ii) Reducing salts such as magnesium iodide⁶⁰⁰ and sodium iodide (reaction 185)^{601, 602} also yield olefinic products. Only the *trans*-diaxial form of a steroid, (95), reacts⁶⁰³.



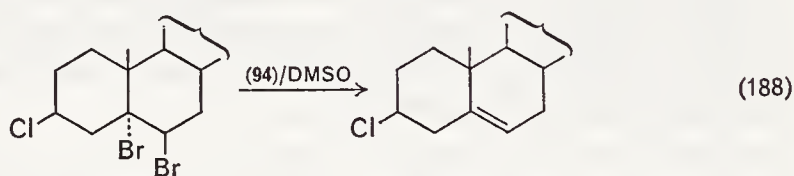
Chromium(II) salts are also useful reducing agents, both for *vic*-dihalides and bromohydrins (reaction 186)⁶⁰⁴. Reaction (187) shows that besides the



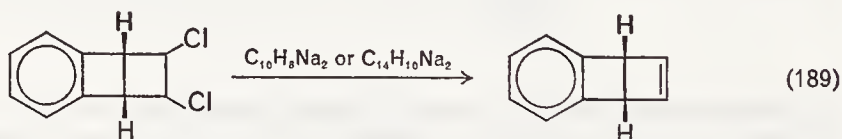
normal route leading to **96**, bromine replacement⁶⁰⁵ yielding **97** (cf. reaction 150) and rearrangement to **98**^{605, 606} also take place.



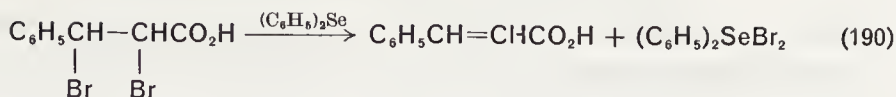
Sodium methylsulphinylmethide (**94**) is capable of dehalogenating *vic*-dibromides without touching other isolated alkyl halides (reaction 188⁶⁰⁷, see also reactions 162–164).



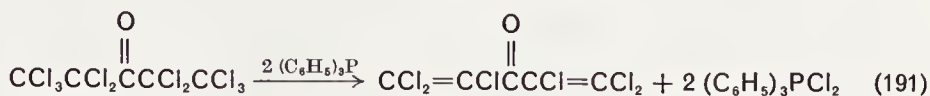
(iii) Disodium phenanthrene and disodium naphthalene are useful in debrominating *vic*-dihalobenzocyclobutanes (reaction 189)^{608, 609}.



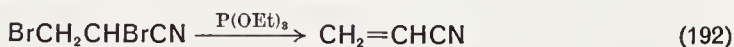
(iv) Diphenyl selenide and diphenyl telluride can be used to dehalogenate *vic*-dibromides (reaction 190)⁶¹⁰. The dibromo reagent obtained can be regenerated with bisulphite.



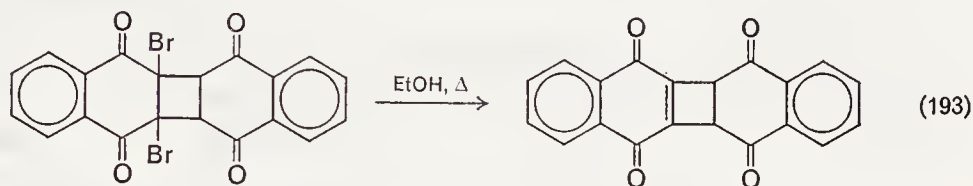
(v) Triphenylphosphine acts in a way similar to reaction (190) to yield olefins with many classes of *vic*-dihalides⁶¹¹⁻⁶¹³ (e.g. reaction 191).



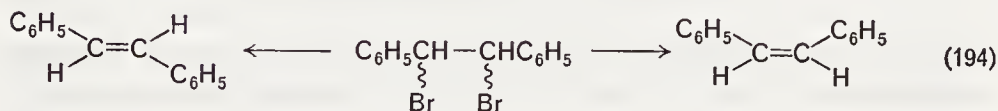
Triethyl phosphite⁶¹⁴ and triisopropyl phosphite⁶¹⁵ also dehalogenate alkylene *vic*-dihalides (reaction 192). The condition for this reaction is the presence of electronegative substituents attached to the Hal—C—C—Hal central structure⁶¹⁴.



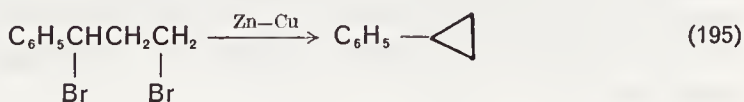
(vi) *vic*-Dihalides are debrominated on heating in ethanol solvent (reaction 193)⁶¹⁶. A faster reduction is attained in the presence of bases⁶¹⁷.



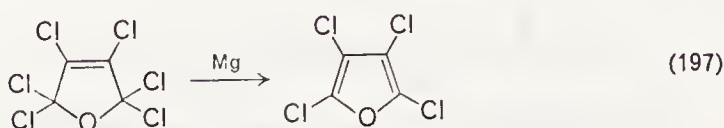
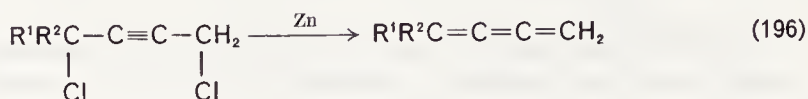
The stereoselectivity of various reducing agents mentioned above has been studied in the debromination of stilbene dibromides (reaction 194)⁶¹⁸.



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

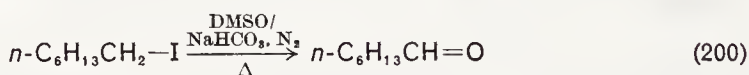
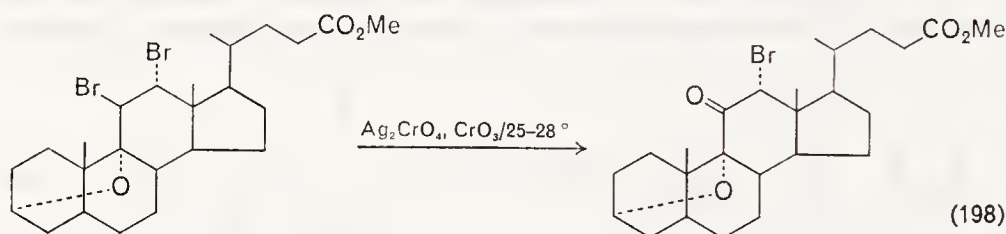


leads to cumulenes (reaction 196)⁶²⁰, and of 1,4-dichloro-2-alkenes to 1,3-butadienes (reaction 197)⁶²¹.

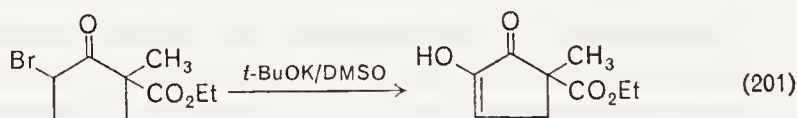


E. Oxidation

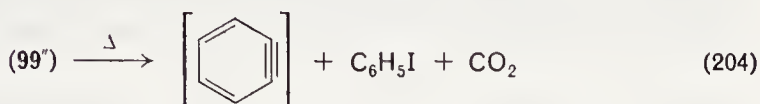
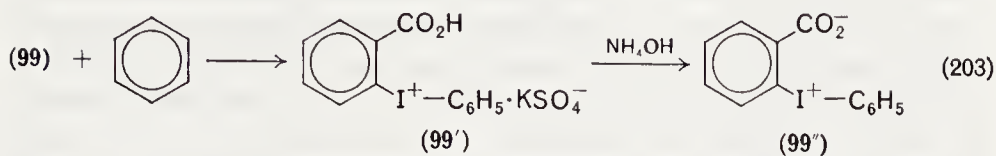
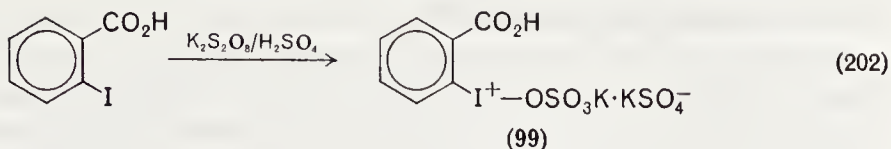
Only a few oxidative processes seem to have potential analytical value in organic halide analysis. Silver chromate oxidizes β -bromoethers to α -alkoxyketones (reaction 198)⁶²². Dimethyl sulphoxide oxidizes *sec*-alkyl bromides to ketones (reaction 199)⁶²³, and primary alkyl halides to



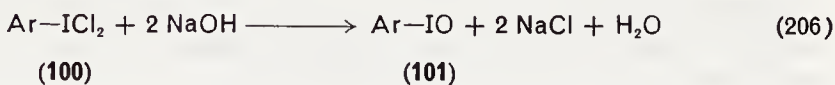
aldehydes (reaction 200)⁶²⁴. Silver salts catalyse these oxidations. Dimethyl sulphoxide oxidizes cyclic α -bromoketones as shown in reaction (201)⁴²⁷.



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.



Conversion to iodoso compounds (101) by reactions (205–206) has been proposed for identification of aromatic iodo compounds⁶²⁶. The process involves the intermediate formation of aryl iodochlorides (iodoarene dichlorides, 100).



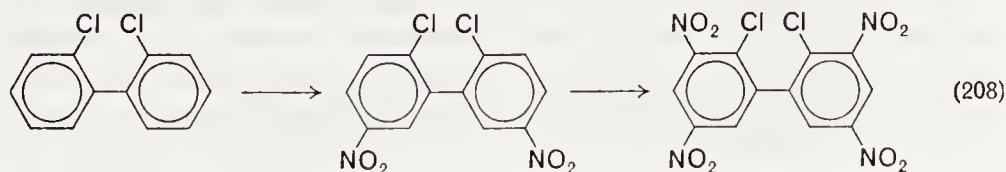
F. Miscellaneous Reactions

I. 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°.

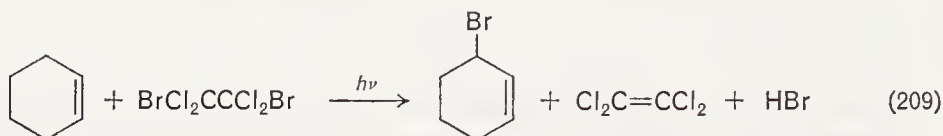


Nitration affords useful derivatives for identification purposes (reaction 208)^{11, 14, 19}.



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 halogen¹⁹² 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 sulphur⁶²⁸. Polychlorinated compounds containing a few bromine atoms and no hydrogen are brominating agents under photolytic conditions⁶²⁹. 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.



Polyhalogenated aromatic compounds yield a colour reaction on treatment with pyridine and aqueous alkali (the Fujiwara reaction⁶³¹). Various modifications have been proposed both for submicro scale detection¹² 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 $\text{p}K_{\text{a}}$ values of most organic acids or amines, and the difference defined according to equation (210)

$$\Delta\text{p}K_{\text{a}} = \text{p}K_{\text{a}} - \text{p}K_{\text{a,ref}} \quad (210)$$

(where $\text{p}K_{\text{a,ref}}$ 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 $\Delta\text{p}K_{\text{a}}$ increases with the degree of substitution in the order $\text{H} < \text{I} < \text{Br} \sim \text{Cl} < \text{F}$, 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

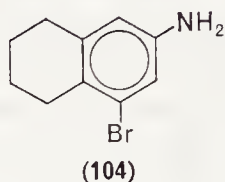
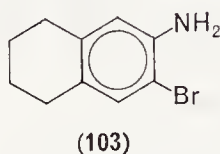
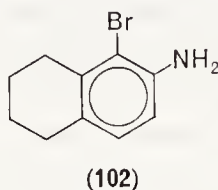
No.	Reference compound	$pK_{a,ref}$	Number of ω halogen atoms	ΔpK_a^b			
				F	Cl	Br	I
1	CH ₃ CO ₂ H	4.76	1	-2.19	-1.89	-1.87	-1.59
2			2	-3.52	-3.47		
3			3	-4.63	-4.11		
4	CH ₃ CH ₂ CO ₂ H	4.88	1		-0.85	-0.88	-0.79
5			3	-1.86			
6	CH ₃ CH ₂ CH ₂ CO ₂ H	4.82	1		-0.30	-0.23	-0.18
7			3	-0.66			
8	CH ₃ CH ₂ CH ₂ CH ₂ CO ₂ H	4.86	1		-0.16	-0.14	-0.09
9	$ \begin{array}{c} \text{CH}_3 \quad \text{H} \\ \diagdown \quad \diagup \\ \text{C} = \text{C} \\ \diagup \quad \diagdown \\ \text{H} \quad \text{CO}_2\text{H} \end{array} $	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 compounds⁶³⁴

Substituent	ΔpK_a^a		
	<i>ortho</i>	<i>meta</i>	<i>para</i>
<i>A. Substitution in benzoic acid (pK_a 4.20)</i>			
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	
<i>B. Substitution in phenol (pK_a 9.95)</i>			
F	-1.14	-0.67	0.0
Cl	-1.47	-0.93	-0.57
Br	-1.53	-0.84	-0.61
I		-0.78	
<i>C. Substitution in anilinium salts (pK_a 4.58)</i>			
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-acetylamino-tetralin 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}.

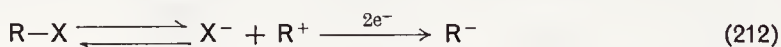


B. Polarography

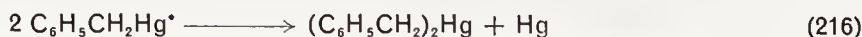
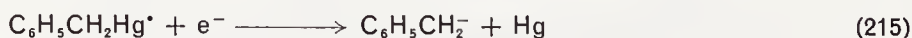
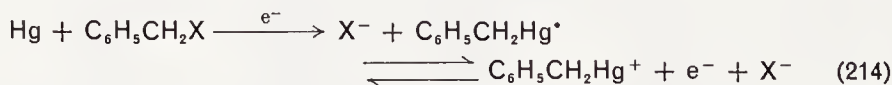
I. General considerations

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.

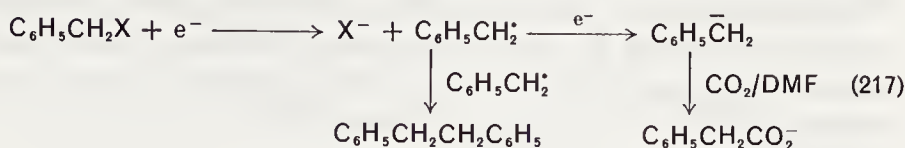
Three limiting mechanisms have been proposed resembling S_N2 , S_N1 and free-radical chain reactions^{638, 639} (reactions 211, 212 and 213, respectively). The nature of the cathode is also important in determining the mechanism, thus, for example, simple alkyl bromides and iodides undergo one-electron reduction at a stationary lead electrode⁶⁴⁰, while at mercury electrodes the reductions are usually two-electron processes (see below).



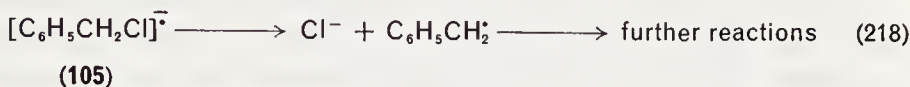
The most satisfactory mechanism seems to be a free radical one that incorporates some S_N -like features. Reactions (214–216) show the reduction of benzyl halides to toluene with concurrent formation of dibenzyl-mercury⁶⁴¹. Benzyl chloride also yields bibenzyl from coupling of free



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



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,



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 potentials⁶⁴².

Allyl and propargyl halides (but not benzhydryl bromide⁶⁴⁶) 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 appeared⁶⁵¹.

2. Alkyl halides

The ease of reduction of alkyl halides parallels the relative leaving-group ability of the anion in S_N2 reactions, namely $\text{I} > \text{Br} > \text{Cl}$. 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 retention⁶⁵⁴.

Cyclopentyl bromide is easily reduced but not cyclohexyl bromide. Even more difficult to reduce are cyclopropyl, cyclobutyl and neopentyl (**106**) bromides⁶⁵³. 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.

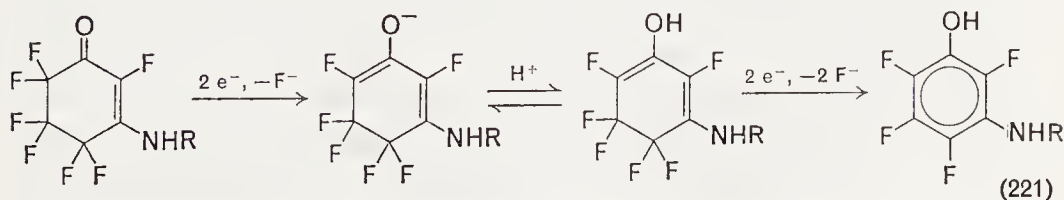
3. *gem*-Polyhalides

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

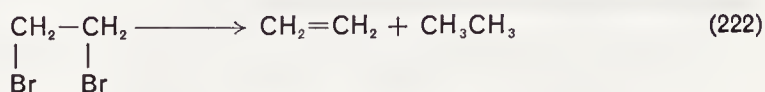
Compound	Remarks	Reference
Carbon tetrachloride	Two two-electron waves. The $E_{\frac{1}{2}}$ of the second one is that of chloroform	661
Carbon tetrabromide	Analogous to carbon tetrachloride	661
Benzotrifluoride	Several electrons consumed. Nature of products not established	662
Trichloroacetic acid	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(<i>p</i> -chlorophenyl) ethane (115)	Two-electron reduction to DDD (116)	675
	$(p\text{-ClC}_6\text{H}_4)_2\text{CClCl}_3$ (115) $(p\text{-ClC}_6\text{H}_4)_2\text{C}=\text{CCl}_2$ (116)	

The trifluoromethyl group does not ordinarily undergo reduction unless it is attached to a benzene ring, preferably substituted with electronegative groups⁶⁶². Geminal difluoromethyl groups undergo reduction as shown in reaction (221) for polyfluorocyclohexenones⁶⁶⁸.



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.

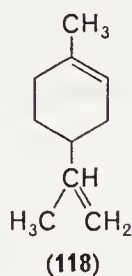
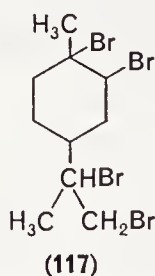


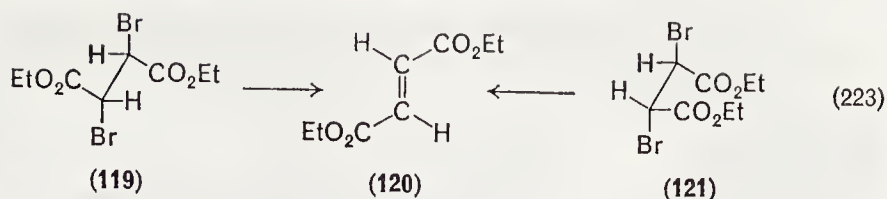
An axial halogen is more easily reduced in cyclohexane systems⁶⁷¹. Among the isomers of hexachlorocyclohexane the most difficult one to reduce is the so-called β -isomer of benzene hexachloride, because of its all-equatorial conformation (79)⁶⁷², while an isomer containing a pair of geminal chlorine atoms is more readily reduced⁶⁷¹.

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.

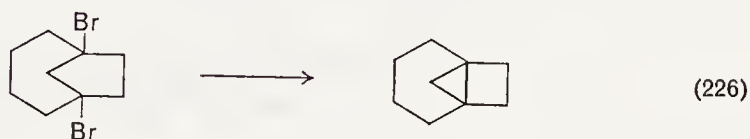
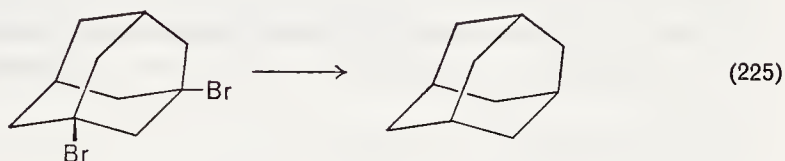
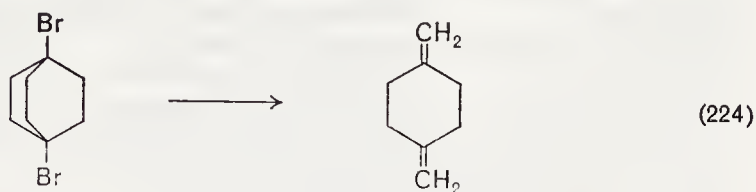
TABLE 23. Polarographic reduction of some *vic*-dihalides

Compound	Remarks	Reference
Various hexachloro-cyclohexanes	Six-electron reduction to benzene	671-673
Limonene tetrabromide (117)	Four-electron reduction to limonene (118)	674
Diethyl <i>meso</i> -2,3-dibromo-succinate (119)	Two-electron reduction to diethyl fumarate (120)	676
Diethyl <i>dl</i> -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





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.



5. Aromatic halides

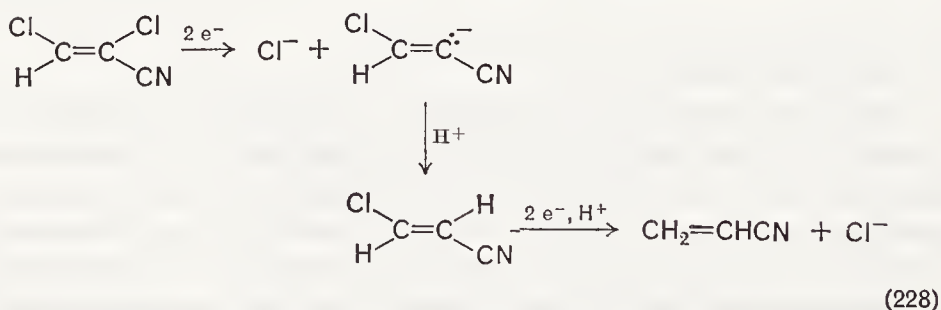
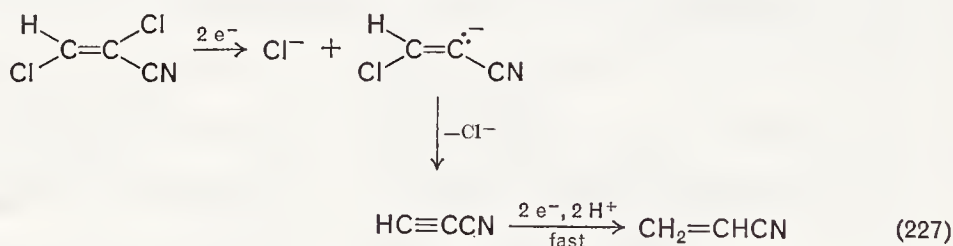
These compounds are more difficult to reduce than alkyl halides. The process is a two-electron reduction in which halide is expelled and a hydrogen atom takes its place. Polyhalogenated aromatic compounds undergo stepwise reduction⁶⁸⁰. Studies of several halonitrobenzenes in non-aqueous solvents show 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
<i>m</i> -Chloronitrobenzene	No halide loss	681
<i>p</i> -Fluoronitrobenzene	No halide loss	681
<i>m</i> -Dibromobenzene	Two two-electron waves corresponding to a stepwise reduction to benzene	686
<i>o</i> -Dibromobenzene	One four-electron reduction	686
Iodobenzenes	One-electron reduction, rate-determining	687, 688
<i>o</i> -Bromochlorobenzene	Benzyne formation	686
Iodobenzoic acids	pH-dependent reduction	689
Iodoanilines	pH-dependent reduction	689
<i>p</i> -Cl-, <i>m</i> -Br- and <i>p</i> -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

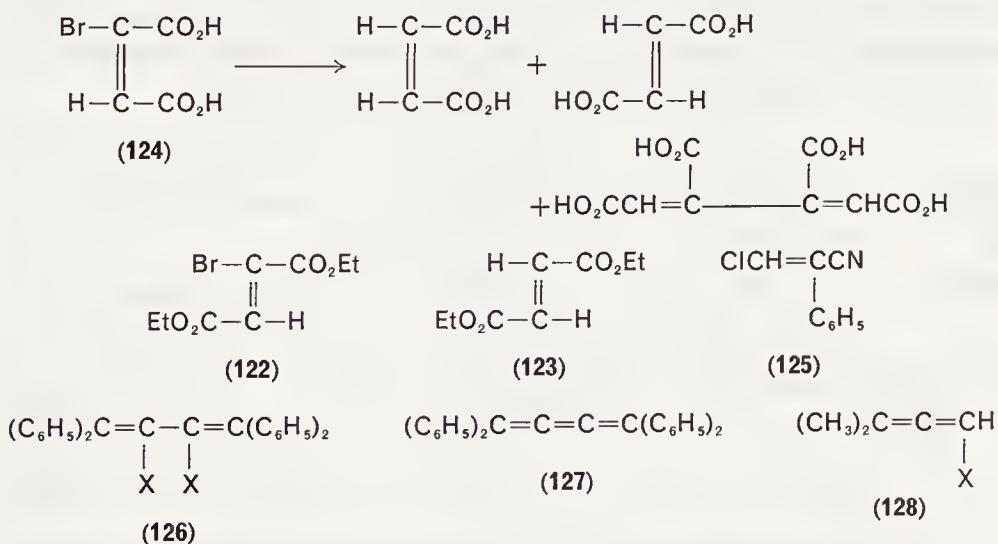


two-step halide reduction (reaction 228)⁶⁹¹. Some examples are summarized in Table 25.

TABLE 25. Polarographic reduction of some vinyl halides

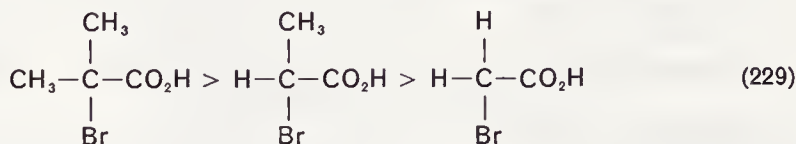
Compound	Remarks	Reference
Diethyl bromofumarate (122)	Two-electron reduction to diethyl fumarate (123)	692
Bromomaleic acid (124) ^a		692
Dihalo ethylenes	Two-electron reduction to an ethylene	693, 694
3-Chloro-2-phenylacrylonitrile (125)	Two two-electron steps reduction to 2-phenylpropionitrile	695
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:

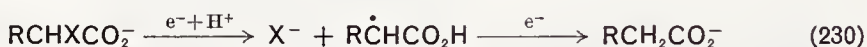


7. α -Halo acids

The ease of reduction of three α -bromo acids was found to be as shown in relation (229)^{700, 701}.



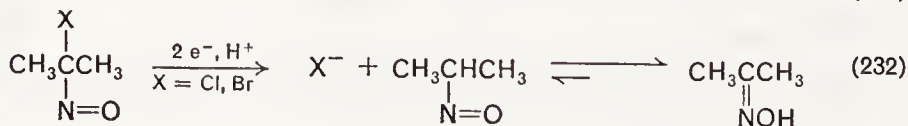
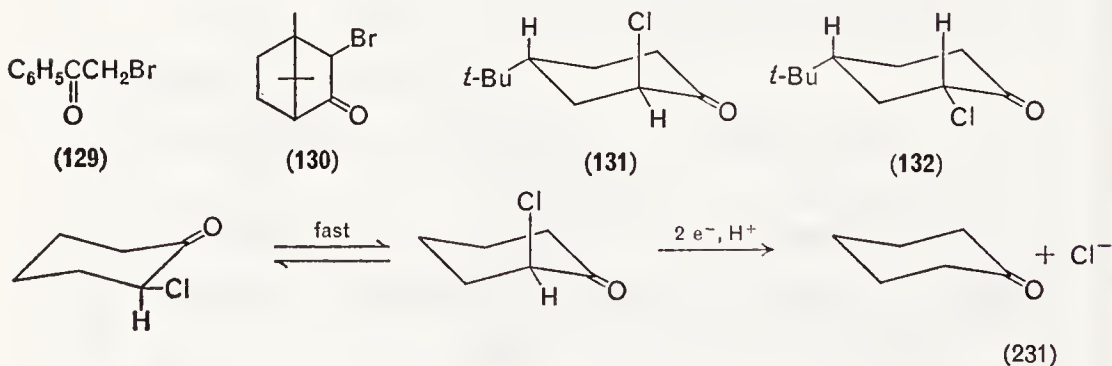
The $E_{\frac{1}{2}}$ value for organic halides is generally pH independent^{702, 703}. However, compounds containing groups affected by pH near the halogen, such as α -bromoalkanoic acids⁷⁰⁴, iodoacetic acid, iodobenzoic acids⁷⁰⁵ and iodoanilines⁶⁸⁹, show complications. At low pH values the protonated 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 $\text{p}K_a$ 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).



The reduction of optically active 2-phenyl-2-chloropropionic acid yielded an optically active product of inverted configuration⁷⁰⁶.

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 displacements⁶⁴⁹. Some examples of reductions of these compounds are summarized in Table 26.



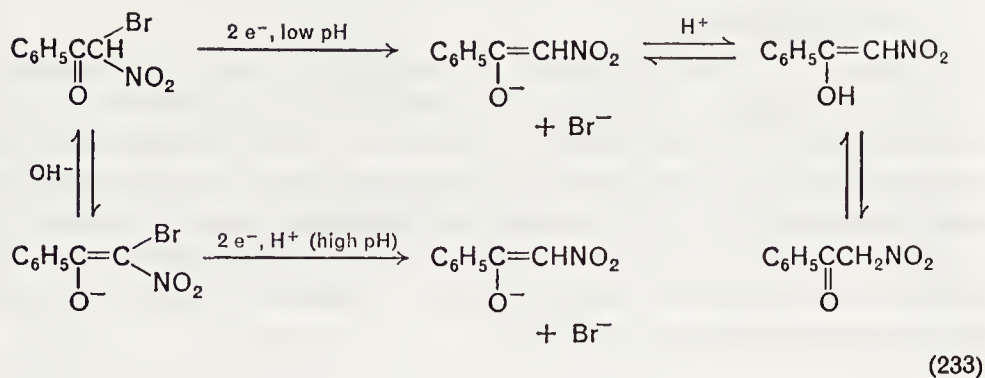
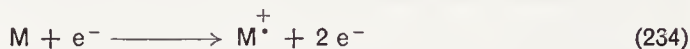


TABLE 26. Polarographic reduction of some activated organic halides

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	710
	(see Table 22) into which pentabromoacetone is hydrolysed	
<i>trans</i> -4- <i>t</i> -Butyl-2-chlorocyclohexanone (131)	Two-electron reduction to the ketone. Reduction easier than that of 132 with E_1 equal to that of 2-chlorocyclohexanone (reaction 231)	711
<i>cis</i> -4- <i>t</i> -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

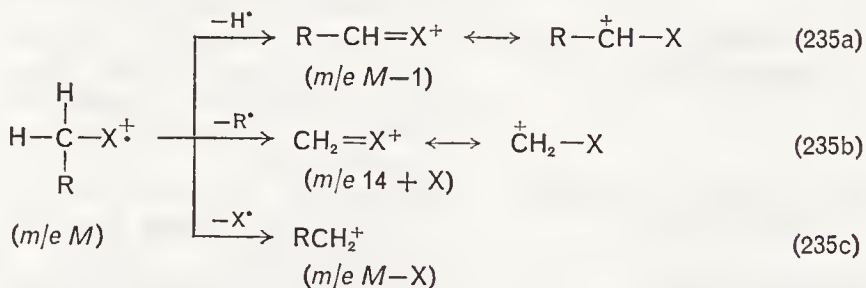
In section II. E the application of mass spectrometry to elementary analysis of halogen compounds was considered. In the following section some features of the degradation patterns of organic molecules will be correlated with their structure. The *molecular peak* is the most abundant peak corresponding 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%.



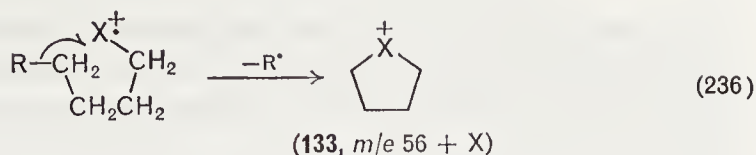
I. Alkyl halides

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: $R-I < \dots < R-F$ ⁷¹⁵. The abundance of the X^+ ion decreasing in the order $I^+ > Br^+ > Cl^+ > F^+$, is in accord with the electron affinity of these elements⁷¹⁶. When R increases the molecular ion $[R-X]^+$ tends to disappear⁷¹⁷.

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 halogen⁷¹⁷⁻⁷¹⁹.

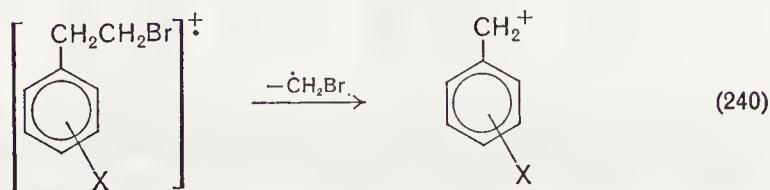
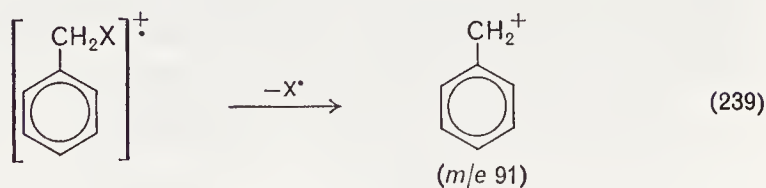
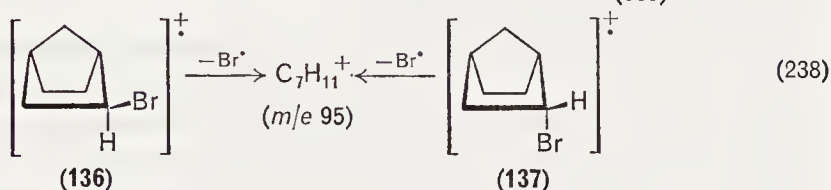
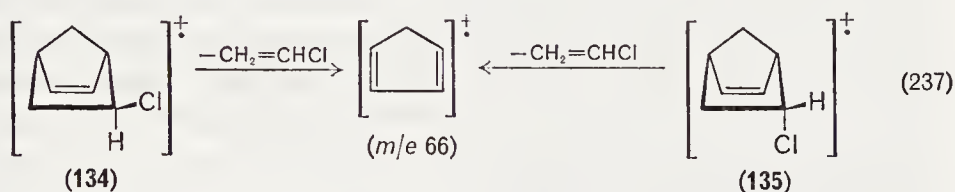


In n -alkyl chlorides and bromides (but not iodides) where the alkyl is sufficiently large (n -hexyl and upwards) one of the most prominent peaks (sometimes the base peak) corresponds to ion **133** arising as shown in reaction (236)^{717, 719}. Branching at the α -site drastically reduces the intensity of this peak and increases that of the $M-HX$ peak⁷¹⁸.



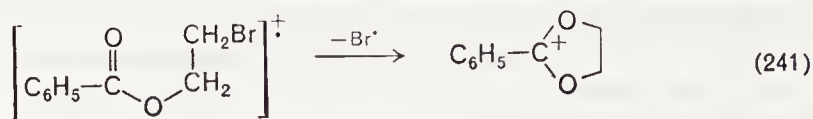
Among the lower secondary alkyl chlorides the tendency to lose Cl^+ is nearly equal to that of losing HCl , while in similar tertiary alkyl chlorides the tendency to lose Cl^+ is prevalent. The general tendency in alkyl fluorides and chlorides is to lose hydrogen halide. This need not be, however, a 1,2-elimination⁷²⁰. The ions obtained from such eliminations show the homologous series of fractionations, similar to that of the corresponding alkanes⁷¹⁹.

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.



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.



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 process⁷²³. 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 elimination⁷²⁷, and variously substituted chlorobenzenes undergo carbon scrambling before Cl^+ loss⁷²⁸.

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 structure⁷²⁹, 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 $\text{C}_3\text{Br}_2\text{F}_3^+$ (m/e 232, 234, 236) appears in the spectrum of $\text{BrF}_2\text{CCF}=\text{CF}(\text{CF}_2)\text{Br}$; 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 $\dot{\text{C}}\text{F}_3$ or $\dot{\text{C}}\text{HF}_2$ ⁷³¹.



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 molecules⁷³². The $M-CF_3$ peak is also important in compounds containing the CF_3 group⁷³². 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 reviewed⁷³³.

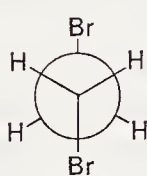
As with paraffins, in the case of fluorocarbons the series of ions of formula C_nF_{2n+1} is such that each of these ions is the most abundant among those containing n carbon atoms. The only exception is the $M-CF_3$ peak, of formula C_nF_{2n-1} . A common impurity accompanying perfluorocompounds is 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 spectrometers⁷³⁴.

The mass spectra of polychlorinated ferrocenes have been discussed¹²².

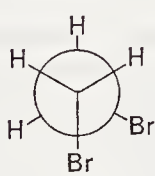
D. Dipole Moments

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 structure⁷³⁵. 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.

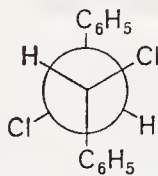
The dipole moment of 1,2-dibromoethane ($\sim 1D$)⁷³⁶ is indicative that this compound does not exist exclusively in the *anti* conformation (138) or in a state of free rotation. This, together with additional spectroscopic evidence, was proof of the existence of the *gauche* (139) conformation³.



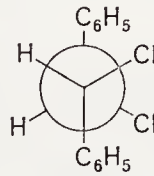
(138)



(139)



(140)



(141)

The most stable conformations of the two diastereoisomers 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 respectively⁷³⁷.

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, 0.75D⁷³⁵.

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 considered⁷³⁵. Correlations between dipole moments and properties of the OH groups were observed in halogenated phenols⁷⁴⁰. The conformations of 4-halocyclohexanones were studied in parallel by dipole moment measurements and n.m.r. spectroscopy⁷⁴¹.

E. Ultraviolet Spectra

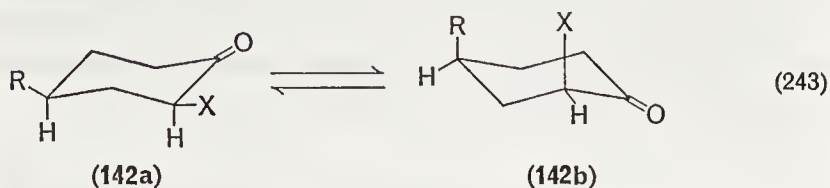
Introduction of an α -substituent in a cyclohexanone system causes a wavelength shift in the 280 nm absorption band of cyclohexanone, as shown in Table 27. By this method it was found that the equilibrium of

TABLE 27. Effects of α -substituents on the 280 nm absorption band of cyclohexanone^{742, 743}

α -Substituent	$\Delta\lambda_{\max}(\text{nm})$	
	Axial	Equatorial
F ⁷⁴⁴	~ 16	~ 0
Cl	22	- 7
Br	28	- 5
OH	17	- 12
O ₂ CCH ₃	10	- 5

α -halocyclohexanone was displaced to the axial halogen conformation (**142b**, R = H) but the equatorial halogen conformation (**142a**, R = CH₃)

was preferred if a methyl group *cis* to the halogen was introduced in position 4 (reaction 243)⁷⁴².



F. Optical Properties of Asymmetric Compounds

I. 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 substituents⁷⁴⁵

Substituent	Atomic refraction ^a	Substituent	Atomic refraction ^a
I	13.954	CO ₂ H	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 ₆ H ₅	3.379		

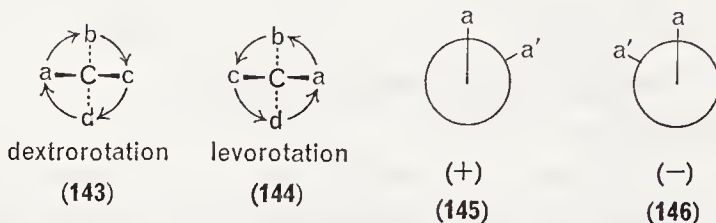
^a The values for polyatomic groups are given as measured at their point of attachment. The refractions of a group as a whole are given in parentheses.

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.

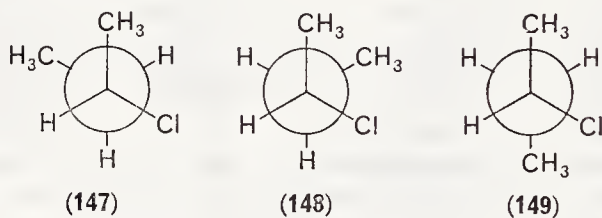
Brewster developed a series of useful rules for correlating the absolute configuration of a compound with its optical rotation. A molecule with

* 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 $[\alpha]_D \times \text{molecular weight}$ according to certain authors or $[\alpha]_D \times \text{molecular weight}/100$ according to others⁷⁴⁵. 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 cases⁷⁴⁶.



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 compound⁷⁴⁷. Thus, for example⁷⁴⁸, 2-chlorobutane can be in three conformations (**147–149**), of



which **148**, with a methyl staggered between methyl and chlorine, should

$$\Delta[M] = \pm 160 \sqrt{R_a R_{a'}} \quad (244)$$

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 $[M] = \frac{1}{2}(170 - 60^\circ) = 55^\circ$ is supported by the experimental value of 36° .

$$[M] = 160(\sqrt{R_{\text{Me}} R_{\text{H}}} - \sqrt{R_{\text{H}} R_{\text{Cl}}} + \sqrt{R_{\text{Cl}} R_{\text{H}}} - R_{\text{H}} + \sqrt{R_{\text{H}} R_{\text{Me}}} - R_{\text{Me}}) = -60 \quad (245)$$

$$[M] = 160(\sqrt{R_{\text{Me}} R_{\text{H}}} - \sqrt{R_{\text{H}} R_{\text{Cl}}} + \sqrt{R_{\text{Cl}} R_{\text{Me}}} - \sqrt{R_{\text{Me}} R_{\text{H}}} + R_{\text{H}} - \sqrt{R_{\text{H}} R_{\text{Me}}}) = 170 \quad (246)$$

The same principles can be applied to compounds with more than four atoms in a straight chain, to saturated cyclic compounds⁷⁴⁹ and to endocyclic unsaturated compounds⁷⁵⁰.

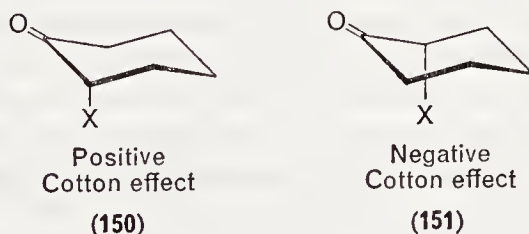
The optical rotation of a compound at the sodium D line is only one point of the dispersion curve, and it may be situated in a long-wave tail of rotation sign opposite to that of the peak rotations. In such cases Brewster's rules fail. For example⁷⁵¹, of the three isomers of α -(iodophenoxy)propionic 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 compound⁷⁵².

$$[M]_D = a \sum R_D + b \quad (247)$$

2. Optical rotatory dispersion

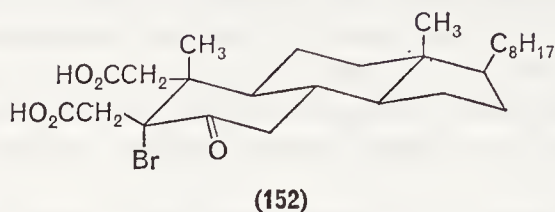
The shifts shown in Table 27 for the u.v. absorption peaks of cyclohexanones have a similar counterpart for the peaks and troughs of o.r.d. curves⁷⁵³. The amplitude of the peak is nearly doubled for an α -axial substituent and the sign of the Cotton effect can be inverted by introducing an α -halo group. 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 elsewhere⁴.



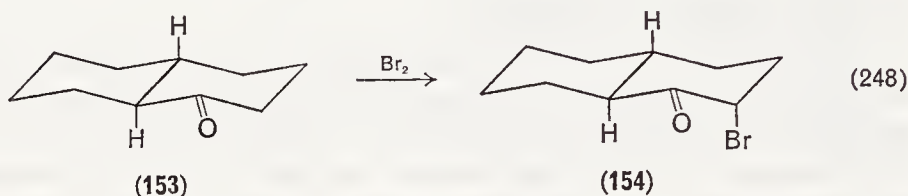
Various applications of the α -haloketone rules have been made:

- (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 axial⁷⁵⁶.
- (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 example⁷⁵⁶, 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.



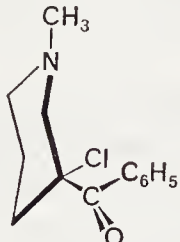
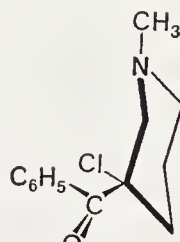
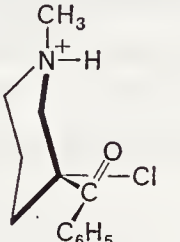
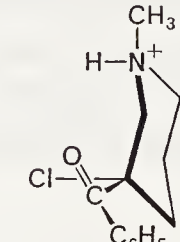
(iii) If both location and conformation of the halogen are known the absolute configuration of the haloketone and ketone may be deduced. For example^{756, 757}, *trans*-decalone (**153**) yields 2-bromo-*trans*-decalone (**154**) with a strong positive Cotton effect, thus showing that the absolute configuration of **153** and **154** are as depicted in reaction (248) and not their enantiomorphs.

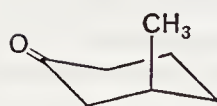


The structure involving the keto group need not be a rigid one if further information or assumptions are introduced. Thus, for example⁷⁵⁸, if it is assumed that the electron-rich centres N and O of an amino and a keto group in the same molecule will repel each other while the N⁺ of an ammonium group 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** \rightleftharpoons **156**). The product has one of two possible configurations, each of which may have two stable conformations, as depicted by the pairs **157** \rightleftharpoons **158** (*trans*) and **159** \rightleftharpoons **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-bromocyclohexanone⁷⁶⁰.

TABLE 29. Cotton effects for the two enantiomorphs of 3-benzoyl-3-chloro-1-methylpiperidine⁷⁵⁸

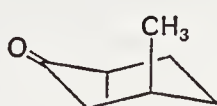
Solvent	N—O interaction	Conformations and sign of Cotton effect	
Octane	Repulsion		
		Negative (cf. 151)	Positive (cf. 150)
Aqueous acid	Attraction		
		Positive (cf. 150)	Negative (cf. 151)



(155)



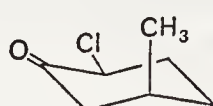
(156)



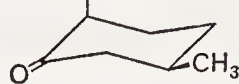
(157)



(158)

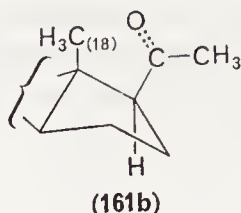
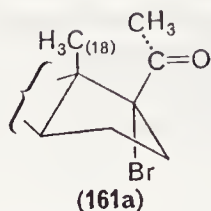


(159)



(160)

Also open-chain ketones can sometimes assume a preferred conformation. Thus for example⁷⁵³, in 17 α -bromo-3 β -acetoxy-5 α -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**.



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 ₃ X	(a) $\nu(\text{C}-\text{X})$ and force constant of H—X stretching	763
	(b) $\nu(\text{C}-\text{X})$ and C—X distance	763
	(c) $\nu^2(\text{C}-\text{X})$ and electronegativity of X	764
2 X—Hal _n	(d) See items 4(b) and 6(a)	
	(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) $\nu(\text{CH}_2=$, wagging) and various σ substituent constants	766
	(b) $\nu(\text{CH}_2=$, wagging) and $\nu(\text{CH}$, out of plane) of XC \equiv CH compounds	767
4 HC \equiv CX ^c	(a) See item 3(b)	
	(b) $\nu(\text{C}\equiv\text{C})$ and C—X force constant in CH ₃ —X	768
5 N \equiv C—C ₆ H ₄ —X	(a) C \equiv N stretching intensity and X Hammett σ constants	769, 770
6 N \equiv C—X ^c	(a) $\nu(\text{C}\equiv\text{N})$ and C—X force constant in CH ₃ —X	768
7 HO—C ₆ H ₄ —X	(a) $\nu(\text{OH})$ and X Hammett σ constants	771-776
	(b) $\nu(\text{OH})$ 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 ₂ C—C ₆ H ₄ —X	(a) $\nu(\text{OH}, \text{non-associated})$ in non-aqueous solvents and pK_a	777, 778
9 HO ₂ C—R _X	(a) $\nu(\text{OH}, \text{non-associated})$ in non-aqueous solvents and pK_a	778, 779
10 XCH ₂ CH ₂ Y; X, Y = Br, Cl, F	(a) $\nu(\text{C—X})$ and dielectric constant of solvent	780
11 XCH ₂ CH ₂ CN	(a) $\nu(\text{C—X})$ and dielectric constant of solvent	780
12 X ₂ C=CX ₂ ; X = F, Cl, Br, I	(a) $\nu(\text{CX}_2, \text{bending})$ and changes in electronic and geometric structure of the molecule	781
13 H ₂ C=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.

1. 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⁻¹²⁹. The C₂F₅ group presents bands at 1325–1365 and 730–745 cm⁻¹²⁹. Halogenated aromatic compounds present characteristic substitution patterns in the 1100 cm⁻¹ region⁷⁸². Two rotamers of 4-halo-1-butenes were recognized from the analysis of C-halogen stretching frequencies⁷⁸³.

2. Alkyl halides

The C—H stretching frequencies are raised by fluoro substituents²⁹, e.g. for $R_F\text{CHF}_2$ $\nu(\text{C—H})$ 3000 cm^{-1} (R_F is a perfluoroalkyl group). The symmetrical deformation frequencies of $\text{CH}_3\text{—X}$ 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 ($1370\text{--}1380\text{ cm}^{-1}$)⁷⁶³.

3. Vinylic halides

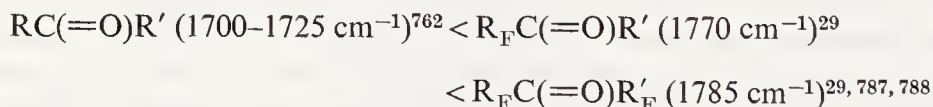
Table 31 shows the stretching frequencies of the ethylenic double bond variously substituted with halogens. For all series of analogous compounds the frequencies are in the order $\text{F} > \text{Cl} > \text{Br} > \text{I}$, usually with F much higher than H and Cl approximately the same as H. The $\text{C}=\text{C}$ twisting frequencies do not vary with the halogen but halogenated ethylenes differ from non-halogenated ones (Table 31). The $\text{CH}_2=$, wagging, on the contrary, shows no effect of halogen, except for fluorine (Table 31).

Perfluorination has a strong influence on the $\text{C}=\text{C}$ 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 $\text{C}=\text{O}$ 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 $\text{C}=\text{O}$ 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 $\text{C}=\text{O}$ stretching frequency, e.g.,



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

X	$\text{CH}_2=\text{CHX}$			$\text{CH}_2=\text{CX}_2$		$\text{CF}_2=\text{CHX}$		$\text{CF}_2=\text{CFX}$		$\text{CF}_2=\text{CX}_2$	
	Stretching	Twisting	Wagging	Stretching	Stretching	Stretching	Stretching	Stretching	Stretching	Stretching	Stretching
F	1650	925	863	1728	1788	1872 ^b	1872 ^b	1792	1747	1872 ^b	1872 ^b
Cl	1610	938	894	1620	1750	1742	1788	1788	1718	1788	1718
Br	1605	936	898	1593	1742	1788	1788	1788	1718	1788	1718
I	1593	943	905								
H	1623 ^b			1623 ^b	1728	1788	1788	1788	1728	1788	1728
CH_3	1647	983	908								

^a Stretching frequencies are those of $\text{C}=\text{C}$, $\nu(\text{C}=\text{C})$ and $\nu(\text{C}-\text{Hal})$ 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}

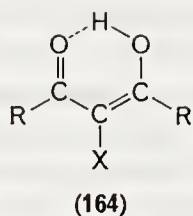
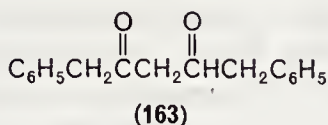
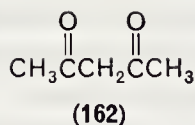
Structure ^a	Perhydrogenated	Perfluorinated
	1623 ^b	1872 ^b
	1640-1645	1800
	1635-1675	1735
	1640-1660	1750
	1685	1789
	1686	1754
	1685	1740

^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 other⁷⁶³.

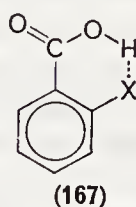
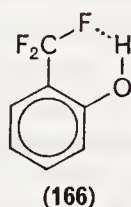
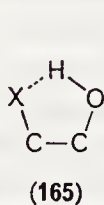
α -Halogenation of aldehydes raises the C=O stretching frequencies but no double bands appear due to rotational isomers⁷⁸⁹, as was the case with α -haloketones. This may be due to free rotation in α -haloaldehydes which



disappears in α -haloketones or α -haloacyl halides (e.g. $\text{CF}_3\text{C}(=\text{O})\text{F}$)⁷⁹⁰. Evidence for rotational isomerism in dihaloacetaldehydes was found from i.r. and Raman spectra⁷⁹¹ and from n.m.r. spectra⁷⁹².

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 isooctane⁷⁹⁶. 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 recognized⁷⁹⁷. Perfluoroalkyl carbinols ($\text{R}_\text{F}\text{CH}_2\text{OH}$) show the O—H stretching band at frequencies as low as 3300 cm^{-1} ²⁹. See also Table 30.



6. Halogenated carboxylic acids and derivatives

a. Free carboxyl groups. Under ordinary resolution, halogenated carboxylic acids show only one $\text{C}=\text{O}$ 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 $\text{C}=\text{O}$ 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 observed⁸⁰¹. 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 $\text{X}-\text{CO}_2^-$ are ordered as shown in relations (249) and (250) respectively.

$$\left. \begin{aligned} t\text{-Bu (1551 cm}^{-1}\text{)} &< \text{Et} < \text{Me (1583 cm}^{-1}\text{)} = \text{CH}_2\text{I} < \text{CH}_2\text{Br} < \text{CH}_2\text{Cl} \\ &= \text{CH}_2\text{CN} < \text{CHBr}_2 < \text{CH}_2\text{F} < \text{CHCl}_2 \\ &< \text{CBr}_3 \text{ (1659 cm}^{-1}\text{)} < \text{CCl}_3 < \text{CF}_3 \text{ (1689 cm}^{-1}\text{)} \end{aligned} \right\} \quad (249)$$

$$\left. \begin{aligned} \text{CBr}_3 \text{ (1338, 1355 cm}^{-1}\text{)} &< \text{CCl}_3 < \text{CHBr}_2 < \text{CH}_2\text{CN} < \text{CH}_2\text{I} < \text{CHCl}_2 \\ &< \text{CH}_2\text{Br} < \text{CH}_2\text{Cl} < \text{Me (1413 cm}^{-1}\text{)} < \text{Et} \\ &< \text{CF}_3 \sim \text{CH}_2\text{F (1448 cm}^{-1}\text{)} \end{aligned} \right\} \quad (250)$$

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 solutions⁷⁶³.

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 thioesters ($\text{XCH}_2\text{C(=O)SR}$ or $\text{X}_2\text{CHC(=O)SR}$) has the highest C=O stretching frequencies⁸⁰⁶.

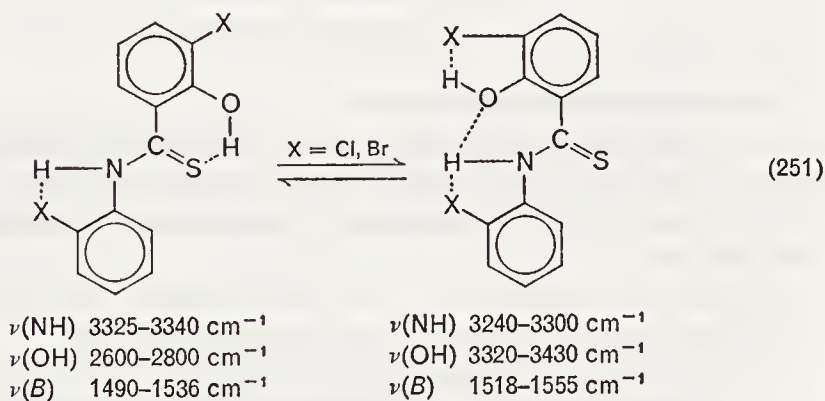
d. Acyl halides. α -Halogenation has the same effect in acyl chlorides as in ketones on the C=O stretching frequencies. The high frequency band moves to lower frequencies with increasing α -halogenation⁷⁸⁹. Mono- and dihaloacetyl chlorides were found to be in two rotational states in the vapour and liquid phases^{807,808}. Further details on the i.r.

spectra of these compounds are treated elsewhere in the *Functional Groups* series⁸⁰⁹.

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 enhanced⁸¹¹⁻⁸¹³. There is probably competition between intramolecular hydrogen bonding and the intermolecular type common in amides⁸¹⁴.

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.



7. Halogenated acetylenes and cyanogen halides

The C \equiv C and C \equiv N stretching frequencies in compounds X—C \equiv CH and X—C \equiv 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 CH₂-halogen groups is only slight (Table 33). See also Table 30.

TABLE 33. Stretching frequencies (cm^{-1}) of acetylenes and nitriles of formula $\text{X}-\text{C}\equiv\text{CH}$ and $\text{X}-\text{C}\equiv\text{N}^a$

X	$\equiv\text{C}-\text{H}$	$\text{C}\equiv\text{C}$	$\text{C}\equiv\text{N}$
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 $\text{N}=\text{O}$ 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}.

$$\text{C} \sim \text{N} < \text{OR} < \text{Cl} < \text{F} \quad (252)$$

$$\text{N} \sim \text{OR} < \text{Cl} < \text{F} < \text{C} \quad (253)$$

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 examples⁸²⁶ have appeared.

I. 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
$\text{CH}_3\text{—X}$	4.25	3.05	2.70	2.15
$\text{C—CH}_2\text{—X}$	4.50	3.45	3.40	3.15
$\begin{array}{c} \text{C} \\ \diagdown \\ \text{CH—X} \end{array}$	4.80	4.05	4.10	4.25
$\begin{array}{c} \text{C} \\ \diagdown \\ \text{CH}_3\text{—C—X} \end{array}$	1.55	1.55	1.80	1.75
$\text{C—CH}_2\text{—C—X}$	1.85	1.80	1.85	1.80
$\begin{array}{c} \text{C} \\ \diagdown \\ \text{CH—C—X} \\ \diagup \\ \text{C} \end{array}$	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 $\text{X—CH}_2\text{—Y}$ 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 $\text{X—CH}_2\text{—Y}$ ^{27, 827}

Substituent	Z	Substituent	Z
—C=C	1.32	—CF_2	1.21
$\text{—C}\equiv\text{C}$	1.44	—CF_3	1.14
—CH_3	0.47	—Br	2.33
$\text{—C}_6\text{H}_5$	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
$\text{CH}_2=\text{CHCH}_2\text{Cl}$	4.08	4.08
$\text{CH}_2=\text{CHCH}_2\text{Br}$	3.88	3.93
$\text{CH}_2=\text{CHCH}_2\text{I}$	3.37	3.87
$\text{CH}_3\text{CH}_2\text{Cl}$	3.23	3.57
$\text{CH}_3\text{CH}_2\text{Br}$	3.03	3.43
$\text{CH}_3\text{CF}_2\text{CH}_2\text{Cl}$	3.97	3.63

^a From data in Table 35, according to equation (254).^b In chloroform solution, from reference 826.

$$\delta(\text{CH}_2) = 0.23 + Z_X + Z_Y \quad (254)$$

Many interesting applications of the chemical shifts and coupling constants to the study of conformations 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

$$\delta(\text{olefinic H}) = 5.28 + Z_{\text{gem}} + Z_{\text{cis}} + Z_{\text{trans}} \quad (255)$$

TABLE 37. Shielding constants (p.p.m.) for ethylene substituents, for the estimation of chemical shifts of ethylenic protons⁸³³

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 ₂ Cl	0.72	0.12	0.07
—CH ₂ Br	0.72	0.12	0.07
—CH ₂ I	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
$\begin{array}{c} \text{H}^{\text{A}} \quad \text{CH}_2\text{Br} \\ \diagdown \quad / \\ \text{C}=\text{C} \\ / \quad \diagdown \\ \text{H}^{\text{B}} \quad \text{Br} \end{array}$	$\left\{ \begin{array}{l} \text{A} \\ \text{B} \end{array} \right.$	5.95 5.75	6.02 ^c 5.62 ^c
$\begin{array}{c} \text{H}^{\text{A}} \quad \text{CH}_2\text{Cl} \\ \diagdown \quad / \\ \text{C}=\text{C} \\ / \quad \diagdown \\ \text{H}^{\text{B}} \quad \text{Cl} \end{array}$	$\left\{ \begin{array}{l} \text{A} \\ \text{B} \end{array} \right.$	5.43 5.54	5.42 5.59
$\begin{array}{c} \text{H}^{\text{A}} \quad \text{CH}_3 \\ \diagdown \quad / \\ \text{C}=\text{C} \\ / \quad \diagdown \\ \text{H}^{\text{B}} \quad \text{Br} \end{array}$	$\left\{ \begin{array}{l} \text{A} \\ \text{B} \end{array} \right.$	5.57 5.39	5.52 ^c 5.33 ^c
$\begin{array}{c} \text{H}^{\text{A}} \quad \text{CH}_2\text{Br} \\ \diagdown \quad / \\ \text{C}=\text{C} \\ / \quad \diagdown \\ \text{H}^{\text{B}} \quad \text{H}^{\text{C}} \end{array}$	$\left\{ \begin{array}{l} \text{A} \\ \text{B} \\ \text{C} \end{array} \right.$	5.40 5.35 6.00	~ 5.32 ~ 5.12 ~ 6.05
$\begin{array}{c} \text{H}^{\text{A}} \quad \text{CH}_2\text{I} \\ \diagdown \quad / \\ \text{C}=\text{C} \\ / \quad \diagdown \\ \text{H}^{\text{B}} \quad \text{H}^{\text{C}} \end{array}$	$\left\{ \begin{array}{l} \text{A} \\ \text{B} \\ \text{C} \end{array} \right.$	5.26 5.21 5.95	5.15 5.05 5.93
$\begin{array}{c} \text{H}_3\text{C} \quad \text{Cl} \\ \diagdown \quad / \\ \text{C}=\text{C} \\ / \quad \diagdown \\ \text{H}_3\text{C} \quad \text{H}^{\text{A}} \end{array}$	A	5.73	5.77
$\begin{array}{c} \text{ClH}_2\text{C} \quad \text{H}^{\text{A}} \\ \diagdown \quad / \\ \text{C}=\text{C} \\ / \quad \diagdown \\ \text{H}^{\text{A}} \quad \text{CH}_2\text{Cl} \end{array}$	A	6.12	5.93
$\begin{array}{c} \text{H}^{\text{A}} \quad \text{Br} \\ \diagdown \quad / \\ \text{C}=\text{C} \\ / \quad \diagdown \\ \text{H}_5\text{C}_6 \quad \text{H}^{\text{B}} \end{array}$	$\left\{ \begin{array}{l} \text{A} \\ \text{B} \end{array} \right.$	7.03 6.69	7.10 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 series⁸³⁴. 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 particular⁸³⁵⁻⁸³⁸.

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 spectrum⁸²². 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.

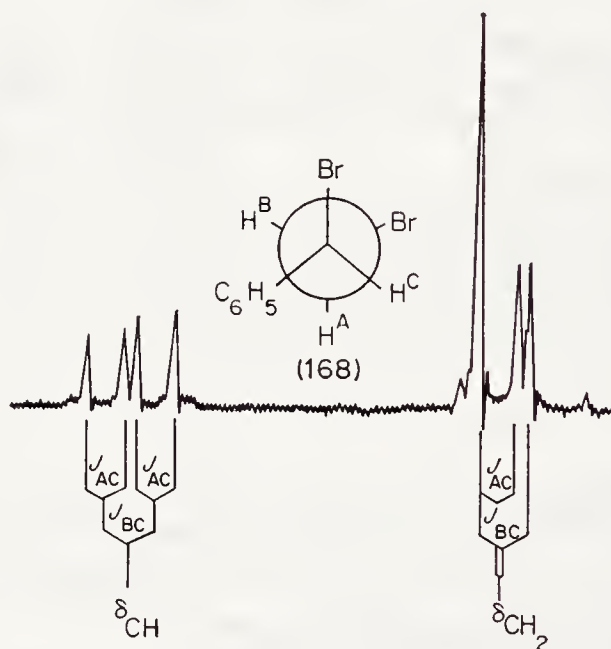
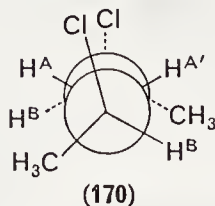
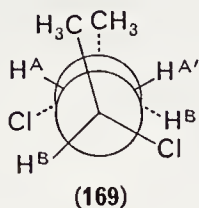


FIGURE 12. Splitting of the aliphatic proton signal of α,β -dibromoethylbenzene. Spectrum determined in chloroform-*d* solution with tetramethylsilane as internal reference⁸²⁶. Reproduced by permission of Varian Associates.

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 chapter⁸³⁹, 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-dichloropentane⁸⁴⁰⁻⁸⁴³, 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



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

$$J_{AB} = x_1 J_t + x_2 J_g \quad (256)$$

$$J_{AB'} = x_1 J_g + x_2 J_t \quad (257)$$

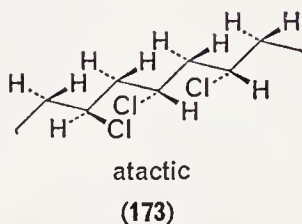
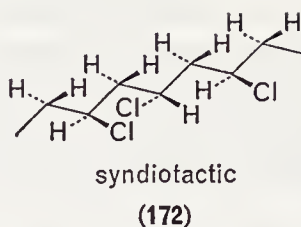
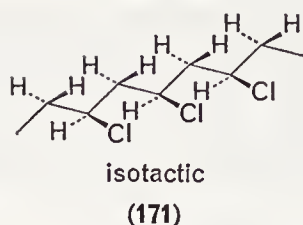
$$J_{AB} - J_{AB'} = (x_2 - x_1)(J_g - J_t) \quad (258)$$

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-perfluoropentane⁸⁴⁴, 2,4-dibromopentane⁸⁴² and other non-halogen substituted pentanes⁸²².

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



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* methylenes⁸⁴⁵ (the triplets arise from splitting by two adjacent CClH protons). Characteristic bands are also shown for the CClH protons, at δ 4.29 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 studied⁸⁴⁴.

3. ¹³C magnetic resonance

Chemical shifts of ¹³C 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 ¹³C causes deshielding, but iodine or more than one bromine on the same atom cause shielding, e.g. methyl iodide-¹³C is more shielded than methane-¹³C⁸⁴⁸. The ¹³C magnetic resonance spectra of

chlorinated ethanes and ethylenes has been studied⁸⁴⁹ and stereochemical assignments similar to those of section V. H. 2. a have been made, based on ^{13}C magnetic resonance spectra⁸⁵⁰.

Of more immediate application are the satellite spectra arising from ^{13}C - ^1H coupling, as they are superimposed on the ordinary proton spectra. Satellite spectra are closely related to the s character of the $\text{C}-\text{H}$ 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 bond⁸⁵¹ (see, however, reference 852). For compounds of

$$\rho_{\text{CH}} = 0.20J_{\text{CH}} \quad (259)$$

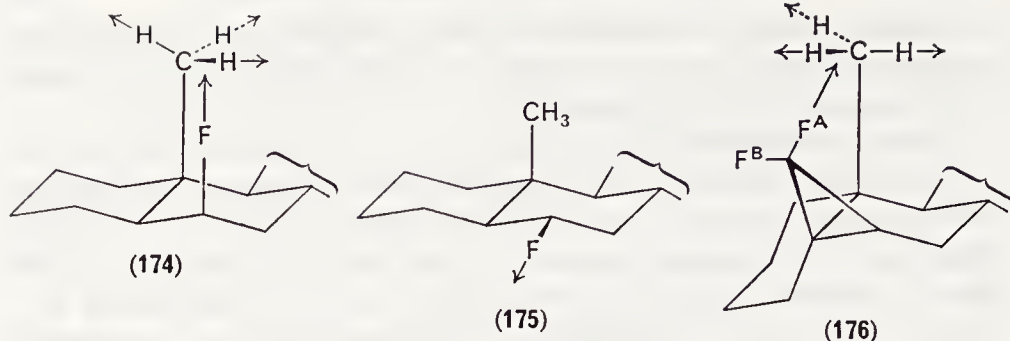
general formula CHXYZ the value of J_{CH} is an additive function of the substituents⁸⁵³. The sign of $J_{^{13}\text{C}^1\text{H}}$ is positive⁸⁵⁴ and that of $J_{^{13}\text{C}^{19}\text{F}}$ is negative and its value is about 250 Hz⁸⁵⁵. Bilinear correlations between J_{CH} and $\delta(^{13}\text{C})$ or $\delta(^1\text{H})$ have been observed for methane derivatives CH_3-X , with the halides forming a separate class⁸⁵².

4. ^1H - ^{19}F spin-spin coupling

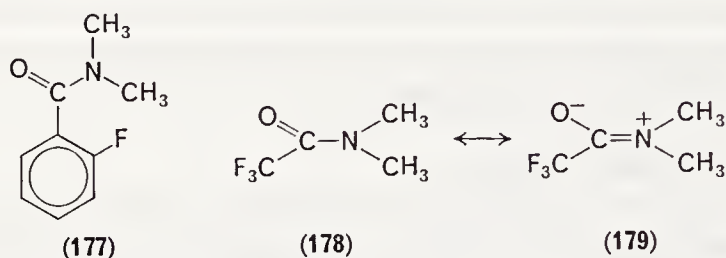
Coupling between protons and fluorine nuclei can be observed in the ordinary proton spectra and are very useful in structural elucidation. Geminal couplings are of the order of 45–55 Hz but they may increase up to 75 Hz in compounds with the CHF_2Z structure with electronegative Z groups⁸⁵⁶. Vicinal couplings tend to follow a Karplus behaviour similar to that of ordinary ^1H - ^1H couplings, but substituents may cause large variations in the J_{HF} values^{785, 831, 856–858}. $\text{H}-\text{F}$ 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 $\text{H}-\text{F}$ couplings are established if the vector anchored on C and directed along the $\text{C}-\text{F}$ bond intersects the vector anchored on C and directed along the pertinent $\text{C}-\text{H}$ 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 $\text{C}_{(19)}\text{H}_3$, as these protons fulfil the rule on freely rotating around the $\text{C}_{(10)}-\text{C}_{(19)}$ 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 $\text{C}_{(19)}\text{H}_3$ splitting is observed, due to the coupling with F^{A} while F^{B} cannot afford such coupling⁸⁵⁹. Studies on the long range couplings of $\text{F}-\text{F}$ and $\text{F}-\text{H}$ are now in progress^{863, 864}.

N,N -Dimethyl- o -fluorobenzamide (**177**) shows $\text{H}-\text{F}$ coupling with one of the methyl groups, as these are non-equivalent, due to restricted



rotation around the amidic C—N bond⁸⁶⁵. *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 prevalent⁸⁶⁶.



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. ¹⁹F 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 CCl₃F both as reference and solvent, and it is designated as Φ^* after extrapolation to infinite dilution. For fluorocarbons and their halogen derivatives equation (260) holds⁸²³.

$$\delta = \Phi^* - 76.5 \quad (260)$$

The δ values of organic fluoro compounds vary in the range of -150 to $+150$ p.p.m. with respect to CF₃CO₂H. The lower fields, from 100 to 150 p.p.m. correspond to fluorine-containing groups such as $-\text{C}(=\text{O})\text{F}$, $-\text{C}(=\text{S})\text{F}$ and $-\text{SO}_2\text{F}$. 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 CF₃—I to 69 p.p.m. for CF₃—F. In perfluoroisopropyl

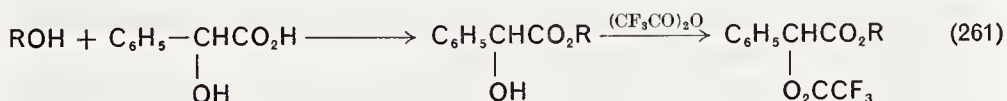
halides, on the other hand, the deshielding of the secondary fluorine atom follows a reversed order, with Φ^* 131.2 p.p.m. for $>\text{CF}-\text{F}$ to 148.6 p.p.m. for $>\text{CF}-\text{I}$. At the same time the chemical shifts of the trifluoromethyl groups in these compounds follow the opposite order, from Φ^* 75.7 p.p.m. for the 2-iodo derivative up to 82.8 p.p.m. for perfluoropropane⁸²³.

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 compounds⁸⁶⁷. The chemical shifts and coupling constants of some perfluorovinyl compounds have been studied⁸⁶⁸.

^{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 perfluorocyclohexane⁸⁶⁹. 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 coupling⁸⁷⁰. This statement has been criticized, however^{871, 872}. The sign of the through-space F-F couplings has been determined in various compounds⁸⁷³.

^{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 ^1H spectra. Such studies have been reported for fluoroethanes⁸⁷⁴ 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 performed⁸⁷⁵. 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 diastereoisomer appeared always at a field lower than that of the D,L diastereoisomer, by 1.5-2.5 Hz⁸⁷⁶.



1. Nuclear Quadrupole Resonance

Of the 'organic' elements listed in Table 6, those with nuclear spin $I \geq 1$ 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

$$\nu = \frac{e^2Qq}{2h} \left(1 + \frac{\eta^2}{3} \right)^{\frac{1}{2}} \quad (262)$$

$$\nu_1 = \frac{3e^2Qq}{10h} \left(1 - \frac{11}{54}\eta^2 \right) \quad (263)$$

$$\nu_2 = \frac{3e^2Qq}{20h} \left(1 + \frac{5}{54}\eta^2 \right) \quad (264)$$

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 ₂ Cl	$\nu(\text{RCH}_2^{35}\text{Cl}) - \nu(\text{Et}^{35}\text{Cl})$ vs Taft's σ^* constants (see next entry)	878
R ¹ R ² R ³ CCl	$\nu = 32.5 + 1.019(\sigma_1^* + \sigma_2^* + \sigma_3^*) \pm 0.35$	879
Organic chlorides and bromides	$(\nu/\nu_0)_{\text{Br}}$ vs $(\nu/\nu_0)_{\text{Cl}}$	878
	$\frac{\nu(\text{RBr}) - \nu(\text{MeBr})}{\nu(\text{MeBr})}$ vs $\frac{\nu(\text{RCl}) - \nu(\text{MeCl})}{\nu(\text{MeCl})}$	
Organic chlorides and iodides	$(\nu/\nu_0)_{\text{I}}$ vs $(\nu/\nu_0)_{\text{Cl}}$	878
	$\frac{\nu(\text{RI}) - \nu(\text{MeI})}{\nu(\text{MeI})}$ vs $\frac{\nu(\text{RCl}) - \nu(\text{MeCl})}{\nu(\text{MeCl})}$	
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	$\nu(\text{Ar}^{35}\text{Cl}) = 36.826 + 1.024\sigma$	887
Substituted bromobenzenes	$\nu(\text{Ar}^{81}\text{Br}) = 227.19 + 8.18\sigma$ $\nu(\text{Ar}^{81}\text{Br}) = 226.932 + 7.693\sigma \pm 2.98$	888, 889
Substituted iodobenzenes	$\nu(\text{Ar}^{127}\text{I}) = 267.0 + 1.424\sigma$ ν and η values vs double-bond character of C— ¹²⁷ I	889
	ν vs half-wave potentials in polarographic reduction	885
C ₆ H _{6-n} Cl _n ($n = 1, \dots, 6$) ^b	(ν/ν_0) vs n	890
	$(\nu/\nu_0) = (\nu/\nu_0)_{\text{C}_6\text{H}_5\text{Cl}} + 1.30n_o + 0.45n_m + 0.25n_p$	891
RSiCl ₃	$\nu = 18.919 + 0.457\sigma^* \pm 0.099$	878
R ¹ R ² R ³ SiCl	$\nu = 16.649 + 0.399(\sigma_1^* + \sigma_2^* + \sigma_3^*) \pm 0.128$	878
R ¹ R ² R ³ GeCl	$\nu = 17.420 + 0.937(\sigma_1^* + \sigma_2^* + \sigma_3^*)$	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.

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CHAPTER 4

Mass spectrometry and the carbon-halogen bond

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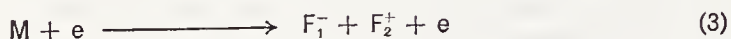
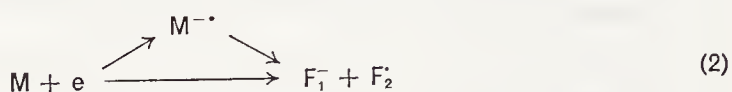
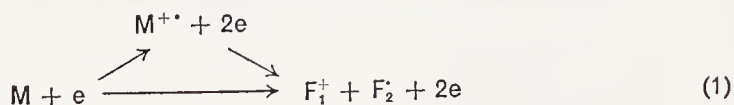
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INTRODUCTION

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. $[F_1]^{+\bullet}$ or $[F_1]^{-\bullet}$ and non-radical neutral fragments in processes (1) and (2).



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 theory⁴ gives equation (4) for the rate $[k(E)]$ of such a fragmentation. In this ν is a

$$k(E) = \nu(1 - E_0/E)^{N-1} \quad (4)$$

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 reduced⁵ or modified⁶.

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 $k(E) > 10^5 \text{ s}^{-1}$. 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 flight⁷. Extending McLafferty's approach⁷ 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

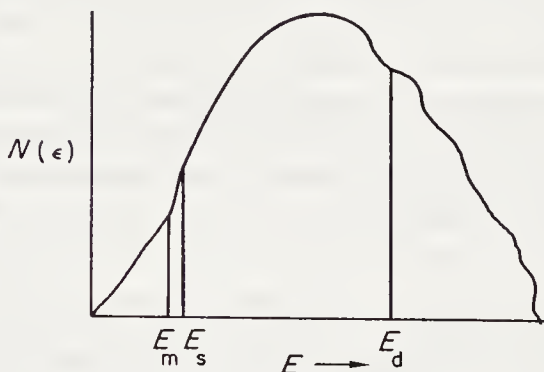


FIGURE 1. Arbitrary graph of $N(\epsilon)\nu(\epsilon)$.

curve bounded by $E < E_d$. The metastable ions can often be used to identify some of the precursors⁸ 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 ions⁹. 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 determined¹⁴. 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

$$I(M) = \Delta H_f[M^{+\cdot}] - \Delta H_f(M) \quad (6)$$

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 shift⁷. 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 shift⁷. 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 monohaloalkanes¹⁶ and the monohalo-aromatics¹⁷,

unless otherwise specified, the m/e values versus intensity data have been taken from the work of McLafferty. For the polyhaloalkanes the data of McCarthy¹⁸ have been used, supplemented where necessary by data from compilations which give the eight¹⁹ or ten²⁰ 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 coworkers²¹ 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 ± 0.05 eV (eV = electron volts) and appearance potentials to ± 0.2 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 Sinke²².

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 mono-haloalkanes and the corresponding alkanes are given in Table 1.

By examination of the photoionization curves of alkyl bromides and alkyl iodides Hashmall and Heilbronner²³ and Cocksey and coworkers²⁴, 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)^a

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 Heilbronner²³ (Y = Br), Cocksey and coworkers²⁴ (Y = I) and Watanabe and coworkers²⁵ (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 eV²⁶.

^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 coworkers²⁴ imply that the lone-pair ionization potential is the lowest, but Krauss and coworkers²⁶ 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 fluorides²⁴ and found that they can be represented by equation (7) where $\chi_{(R-X)}$ depends only on the

$$I(R-X) = I(M-X) + \chi_{(R-X)} |\mu_R| \quad (7)$$

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 data²³⁻²⁵ 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.

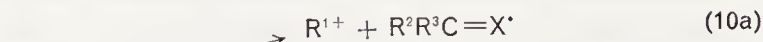
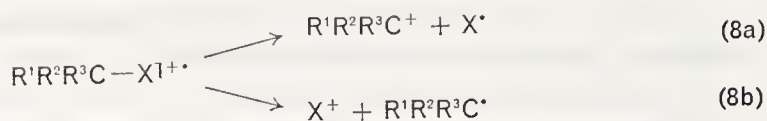
^d For CF_4 this is the spectroscopic value, reference 30.

^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



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 ($\text{R}^1\text{R}^2\text{R}^3\text{C}-\text{X}$)

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 ≠ 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			
	R				R			
	Me	Et	Pr	Bu	Me	Et	Pr	Bu
(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 ≠ 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 values³² are too low to fit direct cleavage according to equation (5) and have been interpreted by Baldwin and coworkers³² 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 correct³³ (see section III. B).

^c Calculated (see section III. B).

^d Calculated assuming 1,3-elimination; see section III. B.

^e E_s values.

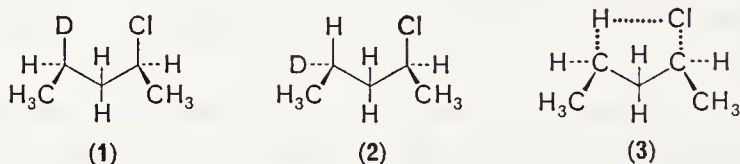
^f For process (8b) in the methyl halides the E_s values are X = Cl, 5.3, Br, 4.2 and I, 3.8 eV³⁴.

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 potential³² and, as shown by Baldwin and coworkers in a similar case³², 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 $[M-X]^+$ ions before subsequent fragmentation³⁵. This suggests but does not require isomerization before or during the formation of these ions.

In the case of process (9), Duffield and coworkers³⁶ 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 eV³⁷. In the case of *n*-propyl chloride $\Delta H_f[C_3H_6]^+$ 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 $\Delta H_f[\text{C}_4\text{H}_6]^+$ 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/mole³⁸ 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 ($\Delta H_f = 214$ kcal/mole) but are in good agreement with the value for the cyclic cation ($\Delta H_f = 225$ kcal/mole). The ΔH_f values for the ethylcyclopropyl and methylcyclobutyl cations are not available for comparison.

The work of Green and coworkers³³ 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



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 suggestion³⁶ 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 coworkers³³. 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 $[M-HX]^{+*}$ 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 coworkers³³ 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-elimination³⁹. 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 source²¹.

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 $[M-H]^+$ 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 $[M-H]^+$ ion in methyl fluoride nor in the $[M-Me]^+$ 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) ^e	(10b) ^c	(10a) ^e	(10b) ^c	(10a) ^e	(10b) ^c	(10a) ^e	(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 coworkers⁷ 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 low³². 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)
<i>n</i> -Pr	3	4	40	16	3	19	40	1	26	38	5
<i>i</i> -Pr	14	42	2	0.5	16	20	44	2.5	17	37	6
<i>n</i> -Bu	0.2	1	38	12	0.4	7	26	0.5	18	33	2
<i>s</i> -Bu	0.1	20	23	1.5	16	0.1	40	1.5	16	41	2
<i>i</i> -Bu	0.2	1.5	3	3.6	4	3	33	2	15	38	2
<i>t</i> -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^1 's).

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 $[M-Br]^+$

ion in the case of *t*-butyl bromide and the threshold voltage for photo-ionization to occur²³ 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) ($[M-C_2H_5]^+$, $[M-Me]^+$, 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 mono-haloalkanes, 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 ^e	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.

^c See Tables 4 and 5.

^e Calculated.

^b Reference 42.

^d Reference 18.

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 $(\text{M-Cl})/(\text{M-F})$ is 6, but E_s is 2.4 eV⁴³. In all these compounds the $[\text{M-X}]^+$ and $[\text{M-Y}]^+$ 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 $[\text{M-HX}]^{+\bullet}$ ions are gradually replaced by $[\text{M-XY}]^{+\bullet}$ ions ($\text{Y} = \text{X}$ 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 $A[\text{M-F}]^+$ and $A[\text{CF}_3^+]$ than that recorded (1.75–1.3 eV)^{44,45} would be expected. With the exception of $(\text{CHCl}_2)_2$ and CHCl_2CH_3 the same ratio in the

TABLE 8. Some intensity data for the perfluorochloroethanes^a

Compound:	C_2F_6	$\text{CF}_2\text{ClCF}_3^{b,c}$	$(\text{CF}_2\text{Cl})_2$	$\text{CCl}_2\text{FCF}_3^c$	$\text{CF}_3\text{CCl}_3^c$
(8a)/(10)	2.2	33.0	1.8	1.3	1.0
$\frac{(\text{CF}_n\text{Cl}_{3-n})^d}{(\text{CF}_m\text{Cl}_{3-m})}$		26.6		2.2	7.0 ^e
Compound:	$\text{CCl}_2\text{FCF}_2\text{Cl}^c$	$(\text{CCl}_2\text{F})_2$	$\text{CCl}_3\text{CF}_2\text{Cl}$	C_2Cl_6	
(8a)/(10)	2.0	2.0	1.1	0.7	
$\frac{(\text{CF}_n\text{Cl}_{3-n})^d}{(\text{CF}_m\text{Cl}_{3-m})}$	3.0		5.5		

^a For $(\text{CCl}_2\text{F})_2$ 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 available¹⁸.

^c Data from reference 18.

^d $n < m$.

^e For values of $A[\text{CF}_3^+] - A[\text{CCl}_3^+]$ 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_s (eV) data for the polychloroethanes

Compound	(8a)/(10)	(8a) (M-Cl)	(10)	$(CH_mCl_{3-m})/(CH_nCl_{3-n})^b$	ΔE_s^f
C ₂ Cl ₆	0.7	32	44	—	—
C ₂ Cl ₅ H	0.8	36	46	0.3	0.6 ^g
(CHCl ₂) ₂	0.1	8	68	—	—
CCl ₃ CH ₂ Cl	1.3	38	29	0.1	0.6 ^d
CHCl ₂ CH ₂ Cl	1.0	29	29	0.08	0.0 ^d
CCl ₃ CH ₃	4.0	52	13	0.2	1.0 ^d
(CH ₂ Cl) ₂	0.5	7	14	—	—
CHCl ₂ CH ₃	6.9	48	7	0.3	0.6
C ₂ H ₅ Cl ^c	1.6	16	10	0.05	0.6 ^d (1.7) ^e

^a In all cases except (CH₂Cl)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_s calculated from data in reference 46.

^e Obs., reference 47.

^f $\Delta E_s = A[CH_nCl_{3-n}^+] - A[CH_mCl_{3-m}^+]$.

^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-Cl]⁺ ion in the 1,1-isomer is replaced by the [M-HCl]⁺ ion (intensity 35).

In the monohaloalkanes the more intense of the ions formed by processes (10a) and (10b) when R¹ 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 $A[CH_3^+] - A[CF_3^+] = 1.1$ eV and $(CF_3)/(CH_3) = 9$. In the perfluorochloroethanes no experimental appearance potential data are available but, depending on the value chosen⁴⁶ for $\Delta H_f[CF_3]^+$, $A[CF_3^+] - A[CCl_3^+]$ lies between 0.3 and 1.3 eV, for CF₃CCl₃. 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 $[\text{CH}_2\text{Cl}]^+$ and $[\text{CHCl}_2]^+$ are not very reliable⁴⁶. 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 $E_s[\text{M-Br}]^+$ 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 effect⁷ 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		$\text{CF}_2\text{XCF}_2\text{Y}$	CFCIXCFClY	$\text{CH}_2\text{ClCH}_2\text{X}$
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 $[\text{CXYZ}']^+$ in which a substituent from one of the carbons (see equation 11) has interchanged with one on

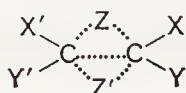


the other carbon atom is also noticeable¹⁸. Thus in 1,1-dichlorotetrafluoroethane the intensity of the ion CF_2Cl ($\text{Z}' = \text{Cl}$) is 16 and in general this rearrangement seems most marked in those molecules containing fluorine and/or chlorine and less than three hydrogens. These reactions presumably 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

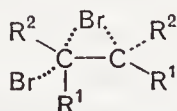
cleavage reaction, there will be a certain portion of the molecular ions in which the rate constant for the rearrangement will be faster than for cleavage and the rearranged molecular ions will then have enough energy to fragment.

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 Stone⁴⁸ do not necessarily invalidate the preceding argument. Steele and Stone found in the case of 1,1,1-trifluoroethane⁴⁸ that $A[\text{CF}_3^+] = 13.9$ eV, $A[\text{CH}_3^+] = 15.0$ eV, but $A[\text{CH}_2\text{F}^+] = 15.9$ eV. In the case of trifluoromethylethane⁴⁸ $A[\text{C}_2\text{H}_5^+] = 12.8$ eV and $A[\text{CH}_3^+] = 14.8$ eV whereas for the rearrangement ions $[\text{CF}_2\text{H}]^+$ and $[\text{CH}_2\text{F}]^+$ the appearance potentials are 15.9 and 15.7 eV respectively. Calculation of $\Delta H_f[\text{CF}_3]^+$ 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 ion⁴⁶. This indicates that the ion is formed with excess energy. This could be either due to a competitive shift⁷ (see Introduction) caused by the rearrangement reaction or due* to the fact that the $[\text{CF}_3]^+$ ion is planar whereas in the paraffin the fluorines of the CF_3 radical are not. Similarly $\Delta H_f[\text{CH}_3]^+$ is high in this case but this could be caused by a competitive shift⁷ (see Introduction) due to the easier formation (lower E_s) of the $[\text{CF}_3]^+$ 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 Pechine⁴⁹ to explain his



observations in some vicinal dibromoalkanes. Thus in the case of racemic (*r*) and *meso* (*m*) 2,3-dibromobutanes Pechine found that⁴⁹ $(M)_m/(M)_r$ 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 ΔH_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 $(M-Br)_m/(M-Br)_r$ and $(M-Br)_m + (M-HBr_2)_m / (M-Br)_r + (M-HBr_2)_r$ increase with decreasing electron voltage which is consistent with his proposal⁹. In these and the cyclic compounds discussed below the presence of metastables shows that the $[M-HBr_2]^+$ ion is formed from the $[M-Br]^+$ 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 $[M-Br]^+$ 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 $[M-HBr_2]^+$ 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 $[M-Cl]^+$ ion observed for the 1,1-compound is replaced by an $[M-HCl]^+$ ion. Now this cannot be explained by anchimeric assistance and the mass spectra of the 1,2-dichlorocyclopentanes and hexanes⁵⁰ show no evidence for the occurrence of anchimeric assistance. Any slight differences in the cyclohexane spectra have been attributed to neutral molecule enthalpy differences⁵¹. 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 nucleus³³. (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 $[M-Cl]^+$ 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 $[M-HCl]^{+\bullet}$ 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 compilations¹⁸⁻²⁰. The molecular ion of methane has an intensity of 47.

the calculated appearance potential for the $[M-X]^+$ ion is below the probable electron impact ionization potential. In the case of the tetrafluoride the observed appearance potential for the $[M-F]^+$ ion is about 0.3 eV above the apparent spectroscopic ionization potential³¹; the latter are, however, often a little lower than the electron impact ionization potentials. Walter and coworkers suggest⁵², from examination of the $[M-F]^+$ ionization efficiency curve, that this ion is formed by direct dissociation. In the trihalo compounds $A[CF_3^+] = 14.7$ eV⁴³ and is the same as the lowest ionization process detected in the photoionization experiments²⁸. A similar situation exists for $A[CCl_3^+]$ in the case of chloroform⁴¹ and for $A[CBr_3^+]$ (calculated) in the case of bromoform.

In the dihalo compounds $A[CHF_2^+]$ is essentially the same⁴⁶ as the ionization potential (see Table 2). In the dichloro and dibromo compounds $E_s(M-X)$ is 0.9 and 0.7 eV respectively⁵³. 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	$n = 4$	$n = 3$	$n = 2(1,1-)$	$n = 2(cis)$	$n = 2(trans)$	$n = 1$
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 coworkers⁵⁶ have determined the vertical ionization potentials of CF_2CHCl (10.00 eV), CF_2CFCI (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 $[M-F]^+$ and $[M-H]^+$ ions in the fluoroethylenes have been investigated in detail by

Lifshitz and Long^{54, 57} and by Jennings⁵⁸. The E_s values for these and other haloethylenes are given in Table 13.

TABLE 13. E_s values (eV) for the $[M-X]^+$ and $[M-H]^+$ 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:	<i>cis</i> -(CHCl) ₂	<i>trans</i> -(CHCl) ₂	<i>cis</i> -(CHBr) ₂	<i>trans</i> -(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 $[M-Br]^+$ ion is observed in the spectra of CF_2CClBr , CF_2CBr_2 , $CFCICFBr$, $CClBrCCl_2$ 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 energy⁵⁸, presumably generated due to the low bonding radius of fluorine not allowing complete hydrogen-fluorine bond formation in the transition state³³. The possibility of the rest being due to a kinetic shift⁷ has been ruled out in the case of monofluoroethylene by

Jennings⁵⁸. The explanation could lie in a competitive shift⁷ 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 $E_s[\text{M-HCl}]^{+\bullet}$ 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 intensities⁵⁸, suggests the same situation in these compounds*.

Direct cleavage of the carbon-carbon bond to give ions of the type $[\text{CXY}]^{+\bullet}$ often occurs. Thus the ion $[\text{CF}_2]^{+\bullet}$ comes from all the poly-fluoroethylene molecular ions as shown by the presence of metastable ions⁵⁸, although its intensity is very small in some cases. In the tetrafluoro compound it comes also from the $[\text{M-F}]^+$ ion and in the trifluoro compound from the rearrangement ion $[\text{CHF}_2]^+$. The latter ion and its counterpart $[\text{CX}]^+$ come not only from the molecular ion but other ions as well in the case of the fluoroethylenes⁵⁸. 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 $E_s[\text{CH}_2\text{F}]^+$ is 0.3 eV higher than $E_s[\text{M-F}]^+$ and the former ion is observed. However, the calculated E_s for the $[\text{CHF}_2]^+$ ion in this compound is 0.8 eV higher than for the $[\text{M-F}]^+$ 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 $[\text{CH}_2\text{Cl}]^+$ 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 Jennings's comments that the spectra of these molecules and the metastables are very similar to the 1,1-compound⁵⁸. 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 issue⁵⁹. 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 carbons⁶⁰. 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 ₂ X)	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 coworkers¹² 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 eV⁶¹ compared with the value given in Table 4. Thus it does not seem necessary to invoke anchimeric assistance in this case. Tomer and coworkers¹² have also examined the spectra of some ring-substituted 5-bromo-2-phenyl-2-pentenenes 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 $[M-CH_2Br]^+$ ion. This can be taken as indication, but is not proof (see Introduction), of the fact that rearrangement occurs in the formation of the $[M-Br]^+$ ion. Finally, where observed, the loss of C_4H_8 from the $[M-Br]^+$ ion must involve a rearrangement, requiring complete hydrogen scrambling¹² 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) $E_s[M-X]^+$ is the same for both isomers ($X = Cl$, 1.9 eV⁶²; $X = Br$, 0.95 eV¹²). Thus any anchimeric assistance cannot amount to more than a few kcal/mole. For $X = Br$ in both isomers the intensity of the $[M-Br]^+$ ion increases relative to that of the other primary fragmentation, the retro-Diels-Alder reaction⁵⁹, on decreasing the electron voltage. The measured appearance potentials for these reactions are the same within experimental error. Tomer and coworkers¹² conclude on the basis of the E_s values that anchimeric assistance occurs here in both isomers but the fact that the $(M-Br)/(\text{retro-Diels-Alder ion})$ 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 $[M-Br]^+$ are no lower than in the alkyl bromides (Table 4). It could be argued, following a suggestion of Cooks and coworkers⁶³, 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 $A([M-Br]^+)$ 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-cyclohexene⁶⁴, this reaction of the molecular ions should have a very high frequency factor. That the $[M-Br]^+$ 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 $[M-Cl]^+$ 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 coworkers⁶⁵. 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 Pesco⁶⁶ 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 analogues is observed.

Shapiro and Jenkins¹³ 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 $[M-Br]^+$ ion was larger in this compound than in the case of 3-phenylpropyl bromide¹⁷. In all the compounds studied¹³ it was found that the intensity of the $[M-Br]^+$ ion relative to the other primary fragment ion $[M-CH_2Br]^+$ 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 $E_s[M-Br]^+$ and $E_s[M-CH_2Br]^+$ values in Tables 4 and 5, that $E_s[M-CH_2Br]^+ > E_s[M-Br]^+$. This is also in keeping with the results for 4-bromo-1-butene and 5-bromo-1-pentene discussed above. Further, Grützmacher⁶¹ has shown that $E_s[M-Br]^+$ 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 $E_s[M-Br]^+$ 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 $[M-Br]^+$ ion is almost independent of it (Table 16). This

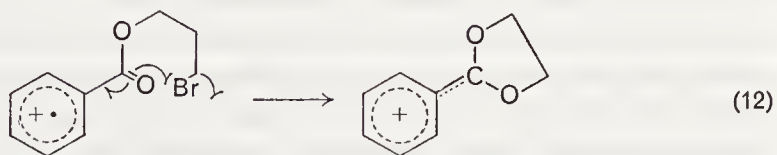
TABLE 16. Ionization potentials of and $A([M-Br]^+)$ for some ring-substituted 2-phenylethyl bromides

Substituent	<i>p</i> -NO ₂	<i>p</i> -Cl	<i>m</i> -Cl	H	<i>p</i> -MeO	<i>m</i> -MeO	<i>p</i> -NH ₂
I(M) (eV)	9.6	8.8	9.1	9.0	8.2	8.5	7.8
A([M-Br] ⁺) (eV)	10.3	10.1	10.3	10.1	10.1	9.9	10.1

he interprets as showing that in the $[M-Br]^+$ 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 coworkers⁶³ 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.

Grützmacher⁶¹ 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 Grützmacher⁶¹ and Nibbering and de Boer⁶⁷ that the hydrogens in the $[M-Br]^+$ ion are completely randomized before expulsion of acetylene does not tell us whether this occurs before or after the formation of the $[M-Br]^+$ ion. Although the metastable intensity for the $[M-Br]^+$ ion is always larger than that for the $[M-CH_2Br]^+$ ion this is also not conclusive evidence for phenyl participation. Grützmacher rationalizes the original observation of the relatively low intensity of the $[M-Br]^+$ ion in the 3-phenylpropyl bromide by pointing out that, unlike the case of the 2-phenylethyl compound, cleavage of the $[M-Br]^+$ 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 $[M-C_2H_4]^+$ ion⁶⁸ shows phenyl participation in this case and generally (see section VI. D) five-membered ring ion formation⁷⁰ 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 Tomer¹¹ have shown that in the case of β -bromoethyl benzoate the $[M-Br]^+$ ion probably has a cyclic structure. Labelling the carbonyl group with ^{18}O and measuring the metastable intensity for the



transition $[M-Br]^+$ 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

oxygen atoms have become equivalent, which is most easily explained by the formation of the $[M-Br]^+$ 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 detected⁷¹. 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 halotoluenes⁷⁰.

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 $[M-Y]^+$ 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 eV⁷⁰ 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 observed¹⁷.

Brown⁷⁴ 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 remarked⁷⁴ 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 Williams⁷⁰ have studied all the halotoluenes except the fluoro compounds and determined E_s values for the $[M-X]^+$ 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 authors⁷⁰ 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 $p\text{-RC}_6\text{H}_4\text{Y}$

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 ($R = \text{Me}$)* and methyl ($R = \text{Et}$)*. This is based on the figures for $E_s[\text{M-H}]^+$ in toluene† (ca. 1.5 eV) and for $E_s[\text{M-Me}]^+$ 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 Williams⁷⁰ is too high, essentially due to a kinetic shift effect⁷ due to the low frequency

* There is a marked increase in the intensity of the $[\text{M-H}]^+$ ions in the chloro and fluoro toluenes and the $[\text{M-CH}_3]^+$ 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 shift⁷ 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 Williams⁷⁰.

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 Lossing⁷⁵ 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 Lossing⁷⁵, determined by photoionization, that ΔH_f is the same for the tropylium and benzyl cation. Lossing⁷⁵ 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 coworkers⁷⁶ 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 coworkers⁷⁷ 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 formed⁷⁷. The ionization potentials of the substituted benzyl radicals have been determined or estimated⁷⁸ and thus the validity or otherwise of equation (13) can be determined. For $X = F$ and $R = Me$ or F the observed difference in

$$A([M-X]^+)_m - A([M-X]^+)_p = I(RC_6H_4CH_2^\bullet)_m - I(RC_6H_4CH_2^\bullet)_p \quad (13)$$

appearance potentials was zero, within experimental error, whereas the difference in the ionization potentials of the corresponding radicals was 0.2 ± 0.06 and 0.4 ± 0.16 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 1.15 ± 0.1 eV is in good agreement with the estimated difference in ionization potentials of 1.00 ± 0.1 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 scrambled⁶⁷. However, the ^{13}C results⁷⁹ 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

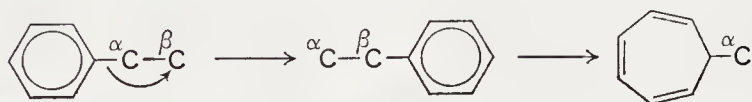
TABLE 21. Partial analysis of the ^{13}C labelling results for $\alpha^{13}C_1$, $\beta^{13}C_1$ and $\alpha, \beta^{13}C_2$ 1-phenylethyl bromide

Ion formulae	C_6H_5		C_6H_6		C_6H_7		
	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 $[C_6H_6]^{2+}$ 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 $\alpha^{13}\text{C}_1$, $\beta^{13}\text{C}_1$ and $\alpha,\beta^{13}\text{C}_2$ 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 $[\text{C}_6\text{H}_5]^+$ ion but there is no trace of this ion nor its $^{13}\text{C}_1$ 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 $[\text{C}_6\text{H}_6]^{+\bullet}$ ion but the observation of 100% label retention in the case of the $\alpha^{13}\text{C}_1$ compound rules out direct loss of the side-chain carbons in its formation. The observation of approximately two-thirds label retention only in the $\beta^{13}\text{C}_1$ 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 $\beta^{13}\text{C}_1$ compound if the carbon atoms are completely randomized in the seven-membered ring, i.e. the $(\alpha)\text{C}-(\beta)\text{C}$ bond being broken.



The labelling results for the $[\text{C}_6\text{H}_5]^+$ 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 $[\text{C}_6\text{H}_6]^{+\bullet}$ ion. The percentage loss of label in the $\alpha^{13}\text{C}_1$ and $\beta^{13}\text{C}_1$ compounds gives values of 27 and 33% respectively for the direct cleavage reaction. On this combination of mechanisms the loss of label in the $\alpha,\beta^{13}\text{C}_2$ 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 $[\text{M}-\text{Br}]^+$ 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 $[\text{C}_6\text{H}_6]^+ \cdot$ ions. In the case of the $[\text{C}_6\text{H}_5]^+$ ions partial involvement of this mechanism would require equal or greater retention of the label in the $\beta^{13}\text{C}_1$ compound than in the $\alpha^{13}\text{C}_1$ compound, assuming the other mechanism was direct cleavage or expansion to a C-8 ring. In the case of the $[\text{C}_6\text{H}_7]^+$ 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 $(\alpha)\text{C}-(\beta)\text{C}$ 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 $\alpha,\beta^{13}\text{C}_2$ 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 $[\text{M-X}]^+$ 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

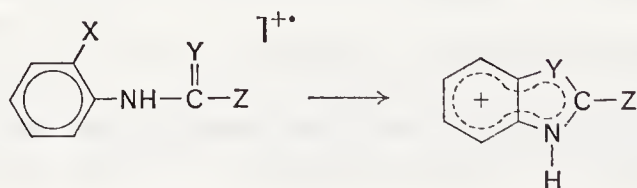
TABLE 22. $E_s[\text{M-X}]^+$ in compounds of the type $o\text{-XC}_6\text{H}_4\text{NHC(Y)Z}$

Compound	X = F	X = Cl	X = Br	X = I
Acetanilide ($\text{Y} = \text{O}, \text{Z} = \text{CH}_3$) ^a	^b	0.85	0.85	0.85
Halophenylurea ($\text{Y} = \text{O}, \text{Z} = \text{HN}_2$)	^b	0.90	0.90	0.85
Thioacetanilide ($\text{Y} = \text{S}, \text{Z} = \text{CH}_3$)	1.20	0.60	0.45	0.40
Halophenylthiourea ($\text{Y} = \text{S}, \text{Z} = \text{NH}_2$)	1.40	0.45	0.30	0.20

^a These values agree with those determined by Benezra and Bursey⁸¹ except for $\text{X} = \text{I}$ 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 guanidines⁸² and in other aromatic compounds⁸³. The formation of a six-membered ring ion in the case of *o*-chlorobenzylthiourea⁶⁹ has also been demonstrated and the absence of any difference between the spectra of *o*- and *p*-chlorobenzylamines⁸⁴ 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

$$A[R^{1-}] = E(R^1 - R^2) - E_a[R^{1-}] + E_x \quad (14)$$

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

$$E_a[R^{1-}] = \Delta H_f(R^1) - \Delta H_f(R^{1-}) \quad (15)$$

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 eV⁸⁵. As pointed out by Blaunstein and Christophorou⁸⁶, 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 $A[Cl^-] = 0.038$ eV and similar results have been found for other halomethanes not containing fluorine⁸⁵. For compounds of the type $C_nH_{2n+1}Br$ ⁸⁷ for $n = 1, 10$ $A[Br^-] = 0.0$ and when $2 \leq n \leq 6$ 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 molecules⁴⁵.

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 moiety⁸⁹. 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 ($E_a[CF_3^-] = 1.8$). This has also been confirmed in the case of trifluorochloromethane and dichlorodifluoromethane⁸⁶ where $A[F^-] = 3.8$ 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-trifluoroethane⁸⁸ and carbon tetrafluoride⁸⁹ and for the formation of $[CF_3]^-$ from perfluoroethane⁸⁸. 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 coworkers⁹¹ 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 Carter⁹² 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 pentafluorobenzene⁹¹. 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 $A[X^-] = 0.00$ eV⁹³. 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 Coulson⁹⁴.

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 book¹⁴. 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

$$A[F_1^-] = \Delta H_f(F^-) + \Delta H_f(F_2)^+ - \Delta H_f(M) + E_x \quad (16)$$

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 ₂ H ₅		R = <i>n</i> -Pr		R = <i>i</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_g 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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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 $\text{C}-\text{H}\cdots\text{O}$ or $\text{C}-\text{H}\cdots\text{N}$ 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 points¹. 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)		
	<i>ortho</i> -	<i>meta</i> -	<i>para</i> -	<i>ortho</i> -	<i>meta</i> -	<i>para</i> -
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 Friend² that hydrogen-bonding has a profound effect upon the viscosities of certain groups of compounds. Following up this point, Kendall³ 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

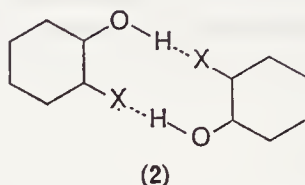
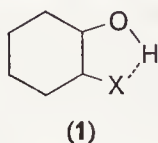
		Temperature (°C)				
		20	25	40	50	80
Chlorophenols	<i>ortho</i> -	4.20	4.11	—	2.015	—
	<i>meta</i> -	16.7	11.55	—	—	—
	<i>para</i> -	23.0	—	—	4.99	—
Bromoanilines	<i>ortho</i> -	—	—	3.19	—	—
	<i>meta</i> -	6.81	—	3.70	—	1.70
	<i>para</i> -	—	—	—	—	1.81
Xylenes	<i>ortho</i> -	0.810	—	0.627	—	—
	<i>meta</i> -	0.620	—	0.497	—	—
	<i>para</i> -	0.648	—	0.513	—	—
Cresols	<i>ortho</i> -	—	—	4.49	—	—
	<i>meta</i> -	20.8	—	6.18	—	—
	<i>para</i> -	—	—	7.00	—	—
Toluidines	<i>ortho</i> -	4.39	—	—	—	—
	<i>meta</i> -	3.81	—	—	—	—
	<i>para</i> -	—	—	—	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.



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 Liddel⁴ 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. Pauling⁵ 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 Bauer⁶ 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 Hendricks⁷ 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 $\text{Cl} < \text{Br} < \text{I}$, 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 $\text{H} \cdots \text{X}$ 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 Jones⁸ 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 Deming⁹.

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 Davies¹⁰. 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, Davies¹¹ 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 calculated 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 Badger¹² found that over the temperature range of about 450–540K the enthalpy of the *trans* form exceeded that of the *cis* form by 3.9 ± 0.7 kcal/mole. The free energy change accompanying the interconversion of the two forms was 2.8 ± 0.5 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, Rossmly, Luttkie and Mecke¹³ 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

	<i>o</i> -Chloro-		<i>o</i> -Bromo-		<i>o</i> -Iodo-	
	Frequency difference (cm ⁻¹)	Intensity ratio	Frequency difference (cm ⁻¹)	Intensity ratio	Frequency difference (cm ⁻¹)	Intensity ratio
<i>Vapour</i>						
Fundamental	83 (174°C)	70 : 1	93 (174°C)	—	115	16 : 1 (125°C) 19 : 1 (200°C)
<i>Solution</i>						
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.

Rossmly, Luttke and Mecke pointed out that, when these results are taken into account, calculations based on simple electrostatic interaction¹¹ 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 Baker¹⁴, 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	<i>cis</i> : <i>trans</i> Ratio
	<i>trans</i>	<i>cis</i>		
<i>o</i> -Fluorophenol	—	3584	—	—
<i>o</i> -Chlorophenol	3600	3582	18	56 : 1
<i>o</i> -Bromophenol	3598	3524	74	38 : 1
<i>o</i> -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 Rossmly 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 Rule¹⁵ 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 Kaeding¹⁶. 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

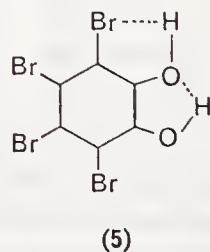
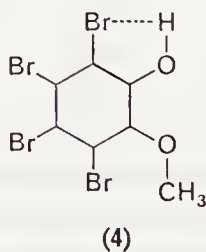
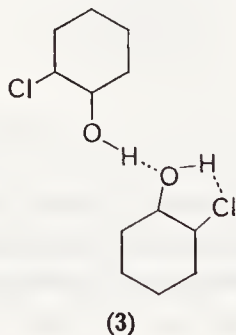
Substituent			Frequency when bonded to		Intensity ratio bonded to 2- : bonded to 6-
2-	4-	6-	2-	6-	
F	I	I	3568	3504	1.96
F	Br	Br	3574	3522	0.72
F	Cl	Cl	3580	3541	0.66
Cl	Cl	I	3535	3502	3.25
Cl	Cl	Br	3535	3515	1.6
Br	Br	I	3515	3496	2.2

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 $\text{Cl} < \text{Br} < \text{I}$. As this interaction was postulated to occur between the $\text{O}-\text{H}$ 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 Fishman¹⁷ 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 $\text{O}-\text{H}$ and $\text{O}-\text{D}$ 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 Mollet¹⁸ of a maximum at 6620 cm^{-1} in the first overtone spectrum of *o*-chlorophenol was attributed by Pauling¹⁹ to the formation of double molecules of the type shown in 3. These would be stabilized by the energy of the strong intermolecular $\text{O}-\text{H}\cdots\text{O}$ 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 $\text{O}-\text{H}\cdots\text{Cl}$ bond, with resultant decrease in the hydroxyl group stretching frequency.



Similarly, a broad peak in the first overtone of the hydroxyl stretching band of tetrabromoguiacol (**4**) was found⁷ 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, Pauling¹⁹ inferred that under the particular steric conditions prevailing in this compound the proton attachment of the $\text{O}-\text{H}\cdots\text{Br}$ bond seems to be greater than that of the $\text{O}-\text{H}\cdots\text{O}$ bond. He also inferred that the two equal peaks reported⁷ 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 Curran²⁰ 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 $\text{C}-\text{O}$ 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 $\text{H}\cdots\text{Br}$ hydrogen bonds are more easily broken than $\text{H}\cdots\text{Cl}$ or $\text{H}\cdots\text{F}$ bonds. They were therefore forced to conclude that the strengths of the intramolecular bonds followed the order $\text{F} > \text{Cl} > \text{Br}$, 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	<i>o</i> -Fluoro-	<i>o</i> -Chloro-	<i>o</i> -Bromo-	<i>o</i> -Iodo-
μ_{calc} $\left\{ \begin{array}{l} \textit{cis} \\ \textit{trans} \\ \text{free rotn.} \end{array} \right.$	—	0.42 ^b	0.44 ^b	0.43 ^b	0.43 ^b
	—	2.79 ^b	2.89 ^b	2.87 ^b	2.72 ^b
	—	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	
μ_{benzene}	1.53 ^a	1.32 ^b	1.33 ^c	1.39 ^b	1.54 ^b
$\mu_{\text{cyclohexane}}$	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 Walker²² 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 Shoolery²³, 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
<i>o</i> -Cresol	3.1	-5.15	16
<i>p</i> -Chlorophenol	3.3	-5.6	20
<i>m</i> -Chlorophenol	3.1	-5.6	22
<i>o</i> -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 Reeves²⁴ 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 <i>trans</i> : <i>cis</i>	ΔH (kcal/mole)
<i>o</i> -Chlorophenol	1 : 56	2.356
<i>o</i> -Bromophenol	1 : 38	2.141
<i>o</i> -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 $\text{H} \cdots \text{F}$ distance.

In a very different method of attacking the problem by proton magnetic resonance, Krakova and Reeves²⁵ 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. Fischer²⁶ 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 chromatography²⁷, 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 Jenkins²⁸ 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 Brown²⁹ 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 coworkers³⁰ have utilized the circumstance that the hydroxyl group stretching frequency of brominated phenols, which is at 2.84μ (3520 cm^{-1}) as against 2.7μ (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

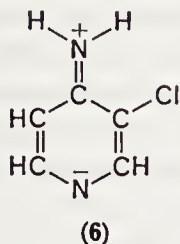
The evidence of boiling point and viscosity determinations appears to suggest that, after *o*-halophenols, the most likely compounds in which

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 Krueger³¹ 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 equations³² 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 NH₂ · · · 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'Grady³³ 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 Williams³⁴ 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 Singleton³⁵ 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



to persist in aqueous solution, the pK_a values of these compounds were interpreted by McDaniel and Brown³⁶ 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 1939²⁸ 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 Brown²⁹ 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 Wilkowski³⁷ 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 $\text{O}-\text{H}\cdots\text{X}$ 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 coworkers³⁸, 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, Jenkins³⁹ showed that the *o*-halobenzoic acids conformed to his law²⁸, as discussed under *o*-halophenols, removing the necessity of invoking intramolecular chelation to explain acid strength. Here McDaniel and Brown²⁹ 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 observed⁴⁰ 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 Badger¹². 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 $10,460\text{ cm}^{-1}$, 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 $10,460\text{ cm}^{-1}$. 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 $\text{O} > \text{Cl} > \text{Br}$ 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 $10,326\text{ cm}^{-1}$ band as in propylene chlorohydrin corresponds to the interaction of the hydroxyl group hydrogen atom with one chlorine atom, whilst the $10,243\text{ cm}^{-1}$ 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 $2.0 \pm 0.5\text{ kcal/mole}$ 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 Ypsilanti⁴¹ to the conclusion that molecules of the type $\text{CH}_2\text{X}-\text{CH}_2\text{Y}$ 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 coworkers⁴², 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 0.95 ± 0.02 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 Shulgin⁴³ 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 Bastien⁴⁴ as a result of electron-diffraction measurements. He found a peak corresponding to an inter-atomic distance of 3.17 \AA , 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 $2.61\text{--}3\text{ }\mu$, Davies¹¹ found chloral hydrate and bromal hydrate

to have hydroxyl bands at 2.82 and $2.81\ \mu$ (about 3546 and 3559 cm^{-1}), respectively, while the latter gave indications of a subsidiary maximum at $2.76\ \mu$ (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 $7.5\text{--}8.5\ \mu$ and $12\text{--}15\ \mu$. 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 question¹³.

The fact that the effects of the formation of intramolecular hydrogen bonds go further than to the atoms concerned was also shown by Nickson⁴⁵. 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 $25\text{--}48\text{ cm}^{-1}$ and that of the carbon-oxygen frequency is increased by $13\text{--}25\text{ cm}^{-1}$. 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 $\text{I} > \text{Br} > \text{Cl}$ 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 Marvel⁴⁶ 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 Ginsberg⁴⁷ on the suggestion that anomalies arise through the existence of weak $C-H \cdots F$ 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 $C-H \cdots F$ 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 $C-H \cdots O$ bonds of strengths greater than those of the $C-H \cdots F$ 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 $O-H \cdots F$ 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 $\text{O}-\text{H}\cdots\text{X}$ 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 $\text{O}-\text{H}\cdots\text{X}$ 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 Wertyporoch⁴⁸ on the conductivities of solutions of aluminium tribromide in

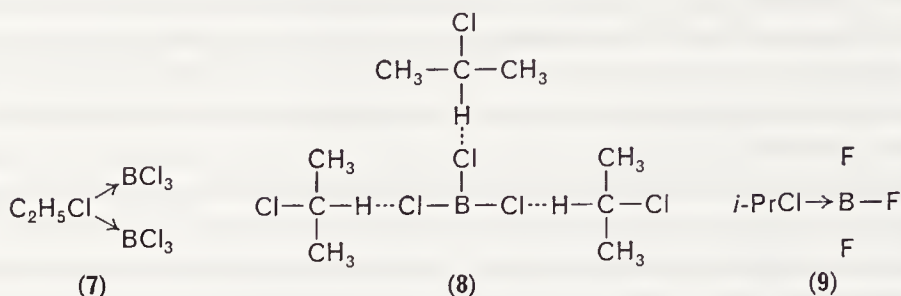
ethyl bromide and the effect of subsequent addition of benzene, Wohl and Wertyporoch⁴⁹ came to the conclusion that the first stage in the Friedel-Crafts reaction was association of the aluminium and alkyl halides to give a product which was converted gradually into a strongly conducting compound on the 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 Heyne⁵⁰ 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 observation⁵¹ that boron trifluoride catalysed the condensation of benzene with cyclohexyl fluoride but not with the bromide, whilst Brown and coworkers⁵² 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 $-100^{\circ}C$ to $-150^{\circ}C$: 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 $(i-PrCl)_3BCl_3$ and to these most improbable looking products they assigned the even more improbable looking formulae 7 and 8. Subsequent cryoscopic

studies⁵⁵, however, have indicated the existence of the more probable 1 : 1 addition complexes, which may be formulated as in 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 fluorides⁵⁶. 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 Brown⁵².

Whilst studying the alkylation of toluene with alkyl chlorides in the presence of boron trifluoride, Nakane, Kurihara and Matsubori⁵⁵ 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: $\text{Me}_3\text{CCl}-\text{BF}_3 > \text{MeF}-\text{BF}_3 > \text{Me}_2\text{CHCl}-\text{BF}_3 > \text{MeCl}-\text{BF}_3$, 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 $400\text{--}4000\text{ cm}^{-1}$, it was found⁵⁷ 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 Hemmings⁵⁸ 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 $\text{RX}-\text{BY}_3$. 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 Williams⁵⁹ 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 $\overset{+}{\text{C}}-\bar{\text{Cl}}$ 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 $\text{F}-\text{H}\cdots\text{F}$, and that it is quite arbitrary where a line should be drawn separating the two phenomena.

Earp and Glasstone⁶⁰ 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 Sutton⁶¹ on the grounds of the misapplication of the law of mass action.

Partington and Middleton⁶² 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, Granier⁶³ 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 coworkers⁶⁴ 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 indicate⁶⁵ 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 slight⁶⁶.

Sharpe and Walker⁶⁷ 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 reported⁶⁸ 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.

Later⁶⁹ 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 coworkers⁷⁰ 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 Glasstone⁶⁰ used dielectric polarization methods to study the interaction of chloroform and pentachloroethane with ethers, acetone and quinoline. Similarly in a series of papers⁷¹, 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 fluoroform⁴⁷, with the formation of $C-H\cdots F$ bonds. Even more surprising is the suggestion that the fluorine atoms in benzo-trifluoride 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 bonds⁴⁷.

In recent years other and more sophisticated methods of studying these properties have been used. For instance, Gent and Martin⁷² 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 elsewhere⁷³.

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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 Properties¹

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 ($RCOOH$)¹

R =	CH ₃	CH ₂ F	CH ₂ Cl	CH ₂ Br	CH ₂ I	
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—CH ₃	CH—CH ₃	CH ₂ —CH ₂	CH ₂ —CH ₂		
	Cl	Br	Cl	Br		
pK_a	2.88	2.97 (18°C)	3.99	3.99 (18°C)		

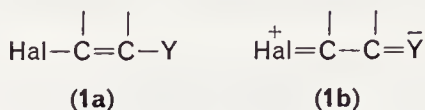
of the bond strength between the 'central atom' and the other substituents. This would cause decreasing carbon hydrogen bond lengths and increasing ¹³C coupling constants with halogen substitution. Although the differences are sometimes small and the experimental errors, at least in some cases⁵, fairly large the data reported in Table 3 show the expected trends^{5, 6, 7}.

TABLE 3. Carbon hydrogen bond distances (C—H) and ¹³C 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**.



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 $\text{F} > \text{Cl} > \text{Br} > \text{I}$, 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 water⁸

	Benzoic acids			Phenols			Anilines		
	<i>o</i> -	<i>m</i> -	<i>p</i> -	<i>o</i> -	<i>m</i> -	<i>p</i> -	<i>o</i> -	<i>m</i> -	<i>p</i> -
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*-orbitals⁹. 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 Halogens¹⁰

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
$\sigma \begin{cases} m \\ p \end{cases}$	0.337 0.062	0.373 0.227	0.391 0.232	0.352 0.18	0.42 ^a 0.53 ^a	From ionization of benzoic acids ¹¹
$\sigma^n \begin{cases} m \\ p \end{cases}$	0.337 0.056	0.373 0.238	0.391 0.265	0.352 0.299	— —	Based on acidity of <i>m</i> -substituted benzoic acids. Values for <i>para</i> substituents evaluated through the Hammett equation by using an average ρ value ¹²
$\sigma^o \begin{cases} m \\ p \end{cases}$	0.35 0.17	0.37 0.27	0.38 0.26	0.35 0.27	— —	From ionization of ArCH ₂ COOH ¹³
$\sigma^+ \begin{cases} m \\ p \end{cases}$	0.352 -0.073	0.399 0.114	0.405 0.150	0.359 0.135	— ^b	From solvolysis of <i>t</i> -cumyl chlorides ¹⁴
σ_I	0.52	0.47	0.45	0.38	0.33 ^a	From ionization of XCH ₂ COOH ¹⁵
$\sigma_R^o \begin{cases} m \\ p \end{cases}$	-0.17 -0.35	-0.10 -0.20	-0.07 -0.19	-0.03 -0.11	— —	Resonance polar effects ($\sigma^o - \sigma_I$).

^a Taken from reference 16.

^b Values of σ_p^- ranging from 0.6 to 0.7 have been reported¹⁷⁻¹⁹.

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.

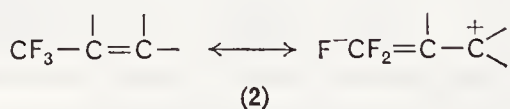
The σ_p parameters begin to give a clearer indication of how much the inductive effect of fluorine may be overweighted by the resonance effect. The σ_p of fluorine is very near to zero: a *para*-fluorine behaves almost like hydrogen. The different magnitude of resonance effects of the various halogens 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^o values ($\sigma_R^o = \sigma^o - \sigma_I$). 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.

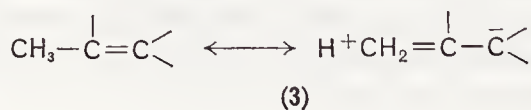
Because of the large resonance effect of fluorine the statement found in many organic chemistry textbooks, 'halogens are deactivating, *ortho-para*-directing substituents in electrophilic aromatic substitution' is, in the case of fluorine, not correct since fluorine is often in fact an *activating* substituent.

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.

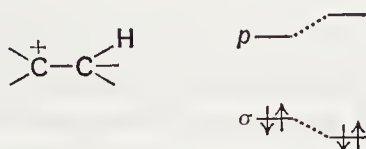


The hyperconjugation of CF_3 is formally the counterpart of the methyl hyperconjugation:



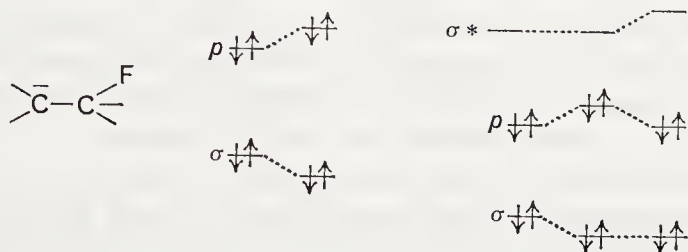
However, there are fundamental differences between the two 'hyperconjugative mechanisms' which make the hydrogen hyperconjugation more feasible than that of fluorine.

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.

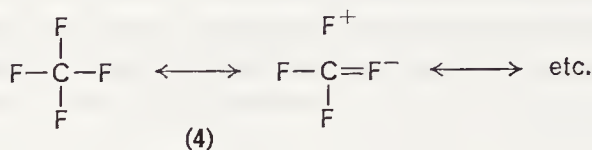
obtained if interaction with the σ^* orbital is taken into consideration. However, it is difficult to assess how effective this interaction may be.

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 methanes⁶

X	CH ₃ —X	CH ₂ X ₂	CHX ₃	CX ₄
F	1.391	1.358	1.332	1.323
	1.385		1.326	
Cl	1.784	1.772	1.767	1.766
	1.781		1.761	
Br	1.939	1.930		

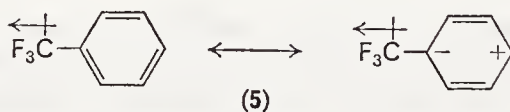
character of the C—F bond (see 4). This is not fully satisfactory since for one fluorine doubly bonded, there is another not bonded (i.e. one bond is



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 1.14 ± 0.05 , taken by Exner²⁰ as typical when only inductive effects are operative, and 1.75–1.84 or even larger ratios (up to ~ 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.



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 Effects²¹

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 bonds²², complexes with

Lewis acids²³, dialkyl halonium salts²⁴, and also by the formation of cyclic halonium ions²⁵ 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 properties²² 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)	$-\Delta S^0$ (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).

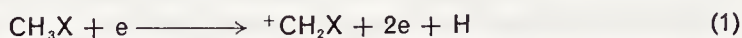
Although the different nature of the bond in the two cases may be sufficient to explain the change in the series, it seems probable that other factors, such as the size of the halogens and their polarizability, cooperate in making the iodine a much better bridging atom than fluorine.

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:



The difference between the appearance potentials relative to CH_4 and $\text{X}-\text{CH}_3$ (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.

$$\text{S.E.} = -(\text{A}_{\text{CH}_3\text{X}} - \text{A}_{\text{CH}_4}) \quad (2)$$

TABLE 9. Stabilization energy (S.E.), relative to CH_3^+ , of substituted methyl cations²⁷

Cation	S.E. (kcal/mole)
CH_3CH_2^+	37 ± 3
$\text{F}-\text{CH}_2^+$	27 ± 3
$\text{Cl}-\text{CH}_2^+$	30 ± 4
$\text{Br}-\text{CH}_2^+$	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 $\text{Br} > \text{Cl} > \text{F}$, 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 documented²⁸. For instance, the gas-phase acidities of some alcohols are²⁹ in the order $t\text{-Bu} > i\text{-Pr} > \text{Et} > \text{Me}$, 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 ions³⁰ indicates that although the energy gain is not quite as large as that obtained upon

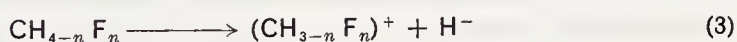
introduction of the first fluorine, a second fluorine atom increases the stability of a methyl carbonium ion. The calculated total energies of the carbonium ions (in atomic units, a.u.) are reported in Table 10 together with their heat of formation.

TABLE 10. *Ab initio* calculations of total energies of fluoro-carbonium ions and their heat of formation³⁰

	<i>E</i> (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 ₂ CH ⁺	-233.7933	—	+144	—

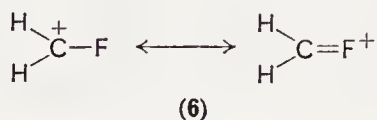
The decrease in ΔE by difluoro substitution compared to monofluoro substitution of 0.0218 a.u. (or 13.7 kcal/mole) is in good agreement with the corresponding decrease in the experimental heat of formation change of 11 kcal/mole.

The discrepancy between the results of Baird and Datta³⁰ and of Taft and coworkers²⁷ has been attributed³⁰ to neglect of the effect of substituents on the neutral molecule. In fact Taft and coworkers²⁷ compared the energy changes in the hydride abstraction reaction (equation 3) which



may not reflect the energy properties of the ion. As a matter of fact the *ab initio* calculations by Baird and Datta³⁰ 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 calculation³⁰ the C—F bond length in CH₂F⁺ was evaluated as 1.26 Å: this is very short for a linkage of this type (the average value in neutral fluoroethylenes and fluorobenzenes is³¹ 1.33 Å) which is indicative of relatively strong dative π -bonding from F to C:



Recent calculations on fluoroethyl cations³² 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 $\text{RH} \rightarrow \text{R}^+ + \text{H}^-$, taking this reaction with ethane as standard, gives relative energies for the production of $\text{CH}_3\text{CH}^+\text{F}$ (−29.5 kcal/mole) and of $\text{CH}_2\text{F}-\text{CH}_2^+$ (+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 Taft²⁷.

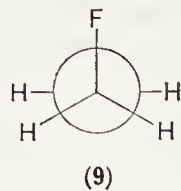
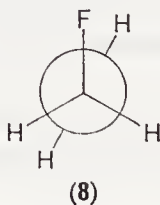
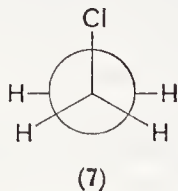
Calculations of barriers to internal rotations in ethyl cations are quite interesting (see Table 11). The data show that the effect of the substituent

TABLE 11. Calculated barriers to rotation in carbonium ions $\text{XCH}_2-\text{C}^+\text{H}_2$

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

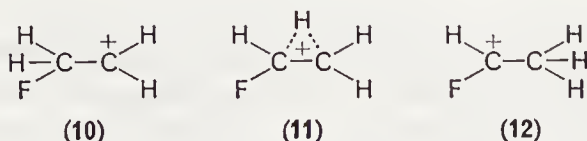
on rotational barriers is quite important. Rotation is hindered even in the unsubstituted propyl cation which is in contrast to what was calculated for substituted propanes, where the barrier is independent from the substituent³⁵.

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).



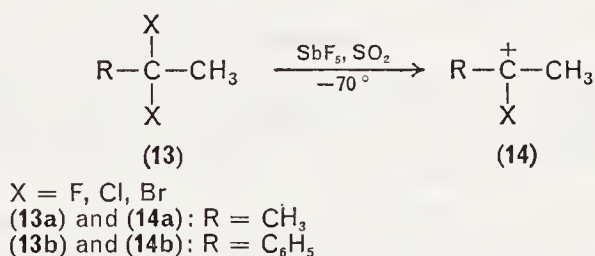
The staggered conformation, however, is the preferred one for the 1-fluoroethyl cation where a very low barrier to rotation was computed (0.62 kcal/mole)³². Dissection of the total energies into attractive and repulsive terms indicates that the barrier to rotation is dominantly attractive in the fluoro cation and dominantly repulsive in the chloro cation.

It has also been calculated³⁶ 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



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 ethylene³⁷.

Other information on the relative stabilities and geometries of halocarbonium ions comes from n.m.r. studies. Olah and Comisarow³⁸ observed that by treating dimethyl or methylphenyl dihalomethanes with SbF_5 in SO_2 at -70° the corresponding halocarbonium ions are formed.



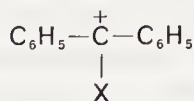
The proton resonances in **14** (see Table 12) are considerably deshielded from those of precursors **13** and the deshielding depends on the halogen

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 $J_{\text{CH}_3-\text{F}}$ (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.

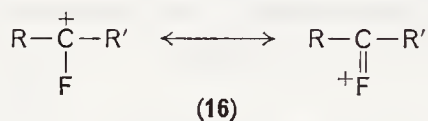


(15)

$$X = F, Cl$$

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



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 ₆ H ₅	C ₆ H ₅	-11.26	-100.87
C ₆ H 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 $^+\text{CF}_2$ groups for **18** are reported in Table 14 together with CF_3 resonances of benzotrifluorides **17**.

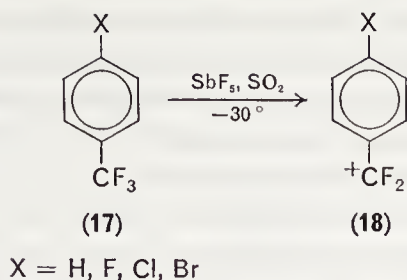


TABLE 14. Chemical shifts of substituted benzotrifluoride ($p\text{-XC}_6\text{H}_4\text{CF}_3$, **17**) and the corresponding aryldifluorocarbonium ions (**18**)

X	$\phi(\text{CF}_3)$	$\phi'(\text{CF}_2^+)$	$\Delta (= \phi' - \phi)$
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: $\text{X} = \text{F} < \text{Cl} \simeq \text{Br} < \text{H}$. 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 $p\text{-F}$ group does, in fact, stabilize the resulting carbonium ion^{39,40}, (see Table 15), since the pK_{R^+} of



triphenylcarbonium ion (-6.44)⁴¹ is slightly increased to -6 for the tris-(p -fluorophenyl)carbonium ion^{39,40}. The m -fluoro substitution is destabilizing³⁹. The tris-(p -chlorophenyl)carbonium ion on the contrary is less stable than the triphenyl carbonium ion⁴². This is at variance with

TABLE 15. pK_{R^+} values for phenyl-carbonium ions

	pK_{R^+}	Reference
$(m\text{-FC}_6\text{H}_4)_3\text{C}^+$	-10.71	39
$(p\text{-FC}_6\text{H}_4)_3\text{C}^+$	-5.96	39
	-6.05	40
$(\text{C}_6\text{H}_5)_3\text{C}^+$	-6.44	41
$(p\text{-ClC}_6\text{H}_4)_3\text{C}^+$	-7.74	42

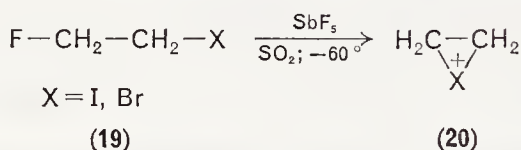
what is found for deshielding of CF_2^+ resonance in *para*-substituted phenyl difluorocarbonium ions. It once again emphasizes the point^{10,43} that the resonance effect of substituents (quantified generally as σ^+ or σ^- constants) changes with the electronic requirement of the reaction centre which 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 hypothesis³². However, kinetic and stereochemical studies suggest that a β -halogen substituent may stabilize a carbonium ion by bridging and forming a cyclohalonium ion:



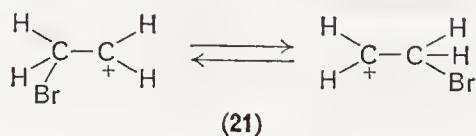
The relative stabilities of bridged ions compared to the corresponding open ions seem to vary with the halogen, whose bridging ability follows the series $\text{I} > \text{Br} > \text{Cl} > \text{F}$, and with the ability of the α -groups to disperse the positive charge. Direct evidence of bridged ions has been presented by Olah and coworkers⁴⁴⁻⁴⁶.

Treatment of 1-fluoro-2-iodo (**19**, $\text{X} = \text{I}$) or 1-fluoro-2-bromo ethane (**19**, $\text{X} = \text{Br}$) with antimony pentafluoride in sulphur dioxide at -60° results in the formation of the corresponding ethylene iodonium (**20**,



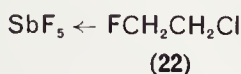
$\text{X} = \text{I}$) or bromonium (**20**, $\text{X} = \text{Br}$) ions⁴⁶. This conclusion was based on (i) a sharp singlet in the ^1H n.m.r. spectrum, indicating loss of fluoride and production of equivalent methylene groups; (ii) downfield shifts of the methylene protons; (iii) isolation of 1-methoxy-2-halo-ethane on solvolysis of **20** in methanol.

More recently⁴⁷ the ^{13}C shift of the ethylene bromonium ion has been measured in $\text{SbF}_5\text{-SO}_2$ solution: the value obtained (120.8 p.p.m. from $^{13}\text{CS}_2$) 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



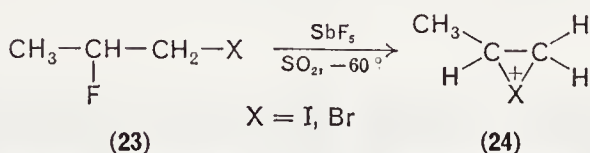
reasonable agreement with the predicted chemical shift of 125 p.p.m. for a cyclic ethylene bromonium ion (**20**, X = Br)⁴⁷.

1-Chloro-2-fluoroethane does not give in SbF₅—SO₂ 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



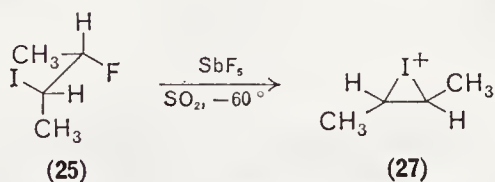
unknown substance and of protonated acetaldehyde in nearly equal amounts. Protonated acetaldehyde is also formed on treating with SbF₅—SO₂ 1,1-dichloro and 1,1-dibromoethane⁴⁶.

Similarly, 2-fluoro-1-iodo (**23**, X = I) and 2-fluoro-1-bromopropane (**23**, X = Br) form stable cations in SO₂—SbF₅ at -60°, whereas 1,2-dichloropropane gives polymerization⁴⁶.

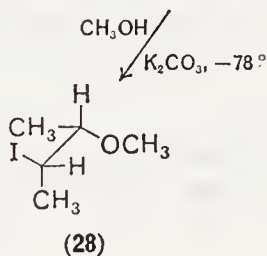


Since primary or secondary alkylcarbonium ions are not stable in these conditions and it is apparent that alkylcarbonium ions bearing a β-halogen atom should be even less stable, the formation of the cations is in itself evidence for the cyclic nature of propylene iodonium and bromonium ions (**24**, 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

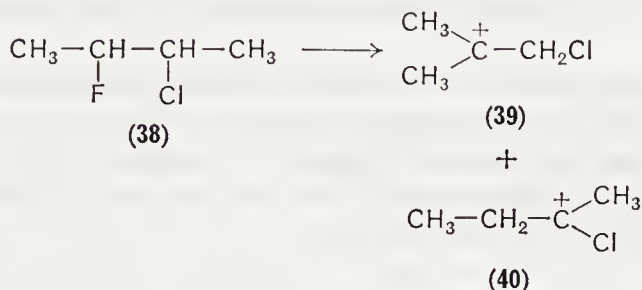


(5)



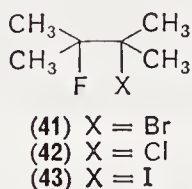
It was not stated whether equilibration occurs during ionization or after the formation of the bridged ion. Warming **33** and **34** at -40° for 5 min causes 1,2-methyl shift to give the 1,1-dimethylethylene bromonium ion (**37**).

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 rearrangement⁴⁶.

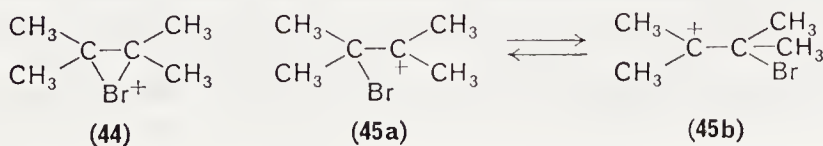


The results reported above for halobutanes may be explained assuming that the iodonium ions (**27** and **29**) are stable. The bromonium ions (**33** and **34**) are in equilibrium with the corresponding open ion, although cyclic structures are favoured; whereas the chloronium ion is, possibly, only an intermediate along the path leading to the rearrangement products **39** and **40**.

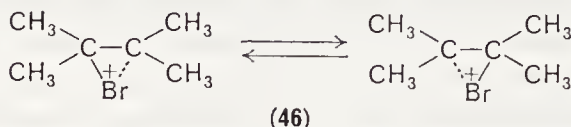
By treating 2-fluoro-3-bromo-2,3-dimethylbutane (**41**) with SbF_5 in SO_2 , the corresponding bromocation is obtained. ^1H n.m.r. spectrum shows that the methyl groups are all equivalent. However, the ^{13}C chemical shift of the tetramethylethylene bromonium ion is $+55.2$ (from $^{13}\text{CS}_2$)⁴⁷,



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 oxide⁴⁷. An open equilibrating ion is expected to give a shift of about -10 p.p.m. The observed chemical shift was explained by

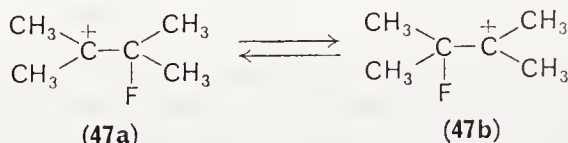


assuming that the ion exists as a 1 : 1 mixture of **44** and **45** or that the ion is present in a rapidly equilibrating pair of partially bridged ions.



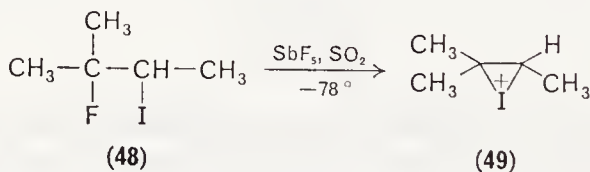
It is interesting to observe how the increased stability of the open carbonium ion (passing from a secondary to a tertiary) favours the open structure.

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.

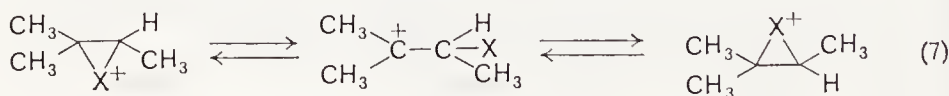


The bridged fluoronium ion may, in principle, take part in the equilibrium, but it may also be a representation of the transition state of the transformation of **47a** into **47b**.

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.

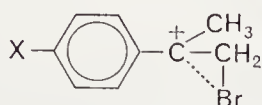


The corresponding chloro and bromo derivatives show only one resonance absorption for the geminal methyls. Either they are made equivalent by a fast equilibration (equation 7) or they happen to have the same chemical shift. In this case also a ^{13}C study would be desirable.

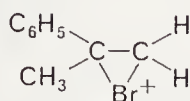


Another example of the importance of the inherent stability of the open structure in affecting the balance between open and bridged structures is given below.

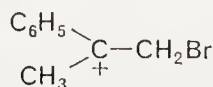
It has been shown⁴⁸ that the β -bromocumyl cation (**49a**) cannot have a symmetrical bridged structure (**49b**), since the methylene protons are equivalent and the ^{13}C shift (**49a**; $\text{X} = \text{H} = -37.9$, $p\text{-CH}_3 = -28.0$, $p\text{-CF}_3 = -44.4$ p.p.m. from $^{13}\text{CS}_2$) 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)

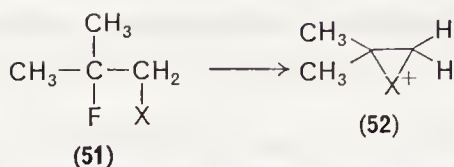
Moreover, in the series **49a** from $\text{X} = p\text{-CH}_3$ to $\text{X} = p\text{-CF}_3$ the bridging becomes most important for the $p\text{-CF}_3$ derivative for which stabilization from the phenyl ring is least. However, equilibration between an open (**50**) and bridged ions (**49a** or **49b**) could probably also explain the reported ^{13}C shift⁴⁸.

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**, $\text{X} = \text{Br}$, I). In the case of the chlorine derivative the cation is certainly open (**53**). Finally, the corresponding fluoro cation, obtained by another route (**54** \rightarrow **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 obtained⁴⁵ by following the fate of 1-halogeno-2-methyl-2-methoxypropanes (**57**) when treated with $\text{FSO}_3\text{H-SbF}_5$ in SO_2 at -60° .

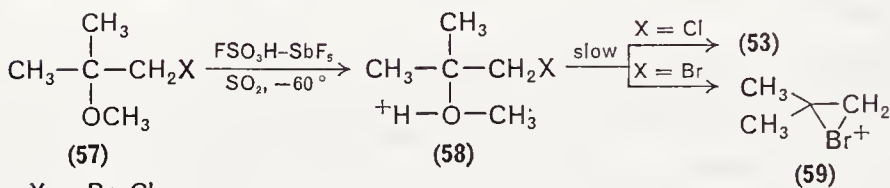
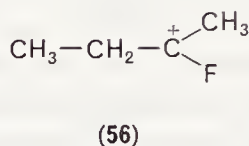
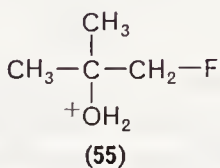
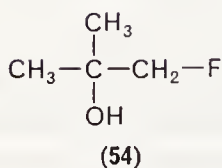
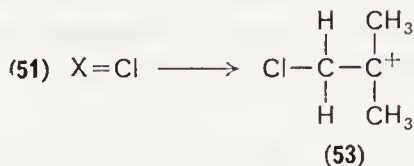
For **57**, $\text{X} = \text{Cl}$, the protonated ether (**58**) slowly undergoes loss of methanol to give the open cation (**53**); for **57**, $\text{X} = \text{Br}$ the loss of methanol is faster and the cyclic ion **59** is formed. Finally in the case of the iodo compound (**57**, $\text{X} = \text{I}$) 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

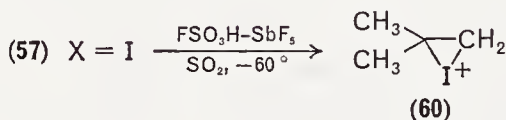


(51)

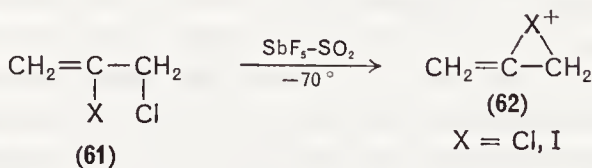
X = Br, I



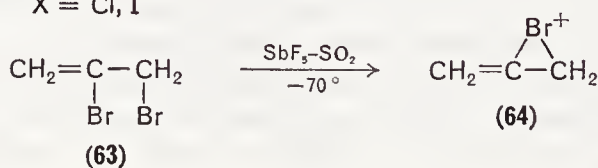
X = Br, Cl



further example is offered by the observation⁴⁹ 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.



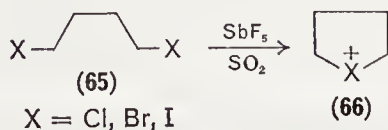
X = Cl, I



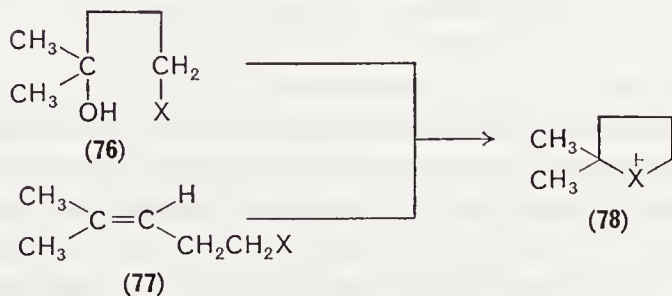
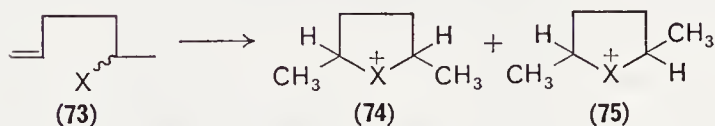
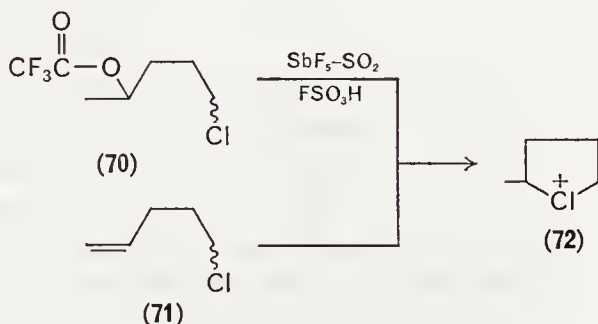
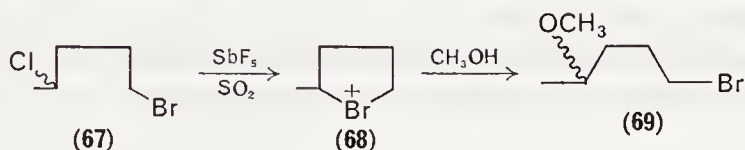
(63)

When the halogens are further removed from the cationic centre, they may still give cyclic ions, particularly when medium size rings are formed.

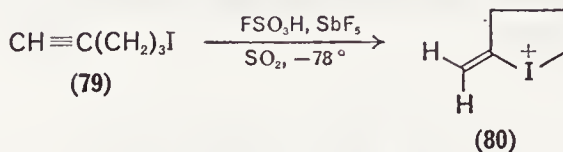
By the action of SbF_5 in SO_2 on 1,4-dichloro-, 1,4-dibromo- and 1,4-diiodo-butan-2-ones (65) the corresponding tetramethylene halonium ions (66) were obtained^{50, 51}.



Also in this case⁵⁰, reaction of 1,4-difluorobutane gives only unidentifiable species, with no absorption interpretable as arising from the tetramethylene-fluoronium ion. 2-Methyl⁵⁰, 2,2-dimethyl⁵¹ and 2,5-dimethyl-⁵⁰tetramethylene-halonium ($\text{X} = \text{Cl, Br, I}$) 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.



Reaction of 5-chloro and 5-fluoro-1-pentyne in the same solutions gave uninterpretable spectra⁵¹.

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 $\text{SbF}_5\text{--FSO}_3\text{H}$ ⁵² or HF--SbF_5 ^{53,54} solutions. Since the properties of arenonium ions have been recently reviewed⁵⁵ 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).

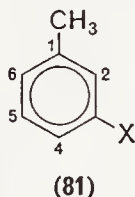


TABLE 16. Percentage of protonation occurring at the various positions of 3-halotoluenes (81)⁵⁴

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 systems⁵⁵. 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.

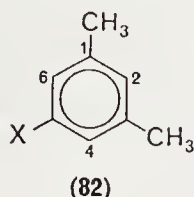


TABLE 17. Percentage of protonation occurring at the various positions of 5-halo-*m*-xylenes (82)⁵³

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.

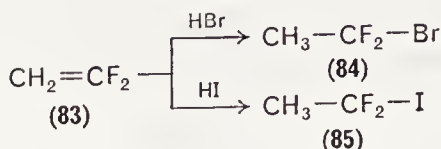
B. Effects on Reactivity

I. 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 ion⁵⁶. It is expected, in the light of the above discussion, that proton addition to haloolefins would give the α -halogeno carbonium ion.

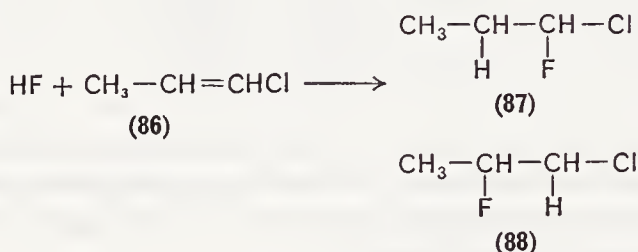
Between 1928 and 1940, Kharasch and coworkers⁵⁷ conducted a long series of comparative experiments on the mechanism of the addition reactions of HCl, HBr and HI on $\text{CH}_2=\text{CHCl}$. They concluded that the additions of HCl and HI, although at somewhat different rates, occur by similar mechanisms 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-isomer⁵⁸. Similarly, ionic addition of HBr and HI to 1,1-difluoroethylene gives 1,1,1-trihaloethane⁵⁹.



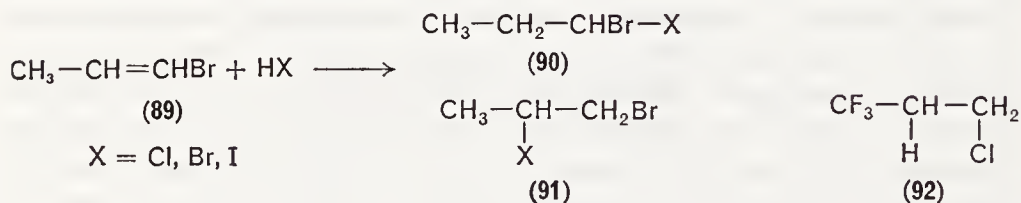
The 1-chloro-2,2-difluorethylene adds HI to give as the only product 1-chloro-2-iodo-2,2-difluoroethane: qualitatively, the reaction occurs at a rate much slower than addition to 83. HF addition to haloalkenes follows the same general features, giving products derived from proton addition to the carbon bearing less halogens^{60, 61}.

It is interesting to compare the addition of hydrogen halides to 1-halo-propenes. The HF addition to 1-chloropropene (86)⁶¹ gives a mixture of 87 and 88.



The yield of 88 is about twice that of 87. Similarly⁵⁷, 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 HCl⁶² gives as the only product the compound 92.



It is evident that the strong electron-withdrawing effect of the CF₃ 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 suggests⁵⁹⁻⁶¹ that halogen substitution decreases the reactivity of a carbon-carbon double bond towards electrophiles. For instance, perfluorobut-2-ene is unreactive towards hydrogen halide additions⁵⁹. On the other hand, the

gas-phase addition of HI to vinyl chloride was estimated⁶³ to be faster than to ethylene although ten times slower than to propene.

More recently Peterson and Bopp⁶⁴ 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 $\text{F} > \text{H} > \text{Cl} > \text{Br}$, 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 predicted⁶⁶ 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 ($\text{C}_6\text{H}_5\text{—CR}^1\text{R}^2\text{—X}$) 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 solvent⁷⁰, 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 $\text{C}_6\text{H}_5\text{CHBr}_2$ increases the solvolysis rate 263-fold whereas the replacement of α -hydrogen by chlorine in $\text{C}_6\text{H}_5\text{CHBrCl}$ 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 systems⁷¹, 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 $\text{Et}_2\text{O}/\text{EtOH}$ (1 : 1) at 0°⁷¹

Substrate	$k \times 10^6$ (s^{-1})
$\text{CH}_3\text{—O—CH}_2\text{—Cl}$	1210
$\text{CH}_3\text{—O—CHCl}_2$	30
$\text{CH}_3\text{—O—CCl}_3$	0.46

This behaviour was explained⁷¹ 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.

$$\text{CH}_3\text{---O---CHX}_2 \xrightarrow[-60^\circ]{\text{SbF}_5\text{---SO}_2} \begin{array}{c} \text{CH}_3 \\ \text{O}^+\text{---} \\ \parallel \\ \text{X---C---H} \end{array} + \begin{array}{c} \text{CH}_3 \\ \text{O}^+\text{---} \\ \parallel \\ \text{H---C---X} \end{array}$$

(94)

(a) X = F	70%	30%
(b) X = Cl	80%	20%

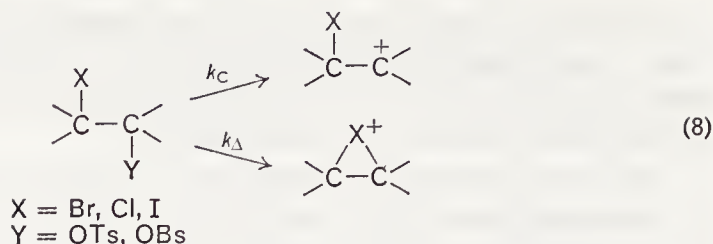
(95) (96)

The solvolysis of 2-X-cyclohexyl aryl sulphonates in CH_3COOH was studied by Winstein, Grunwald and coworkers⁷⁵ and the effect of β -halogens discussed in a series of classical papers on neighbouring-group participation.

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}	$k_{\text{C}}/k_{\text{H}}$
Cl	0.94×10^{-4}	—	0.94×10^{-4}
Br	7.12×10^{-2}	383	1.87×10^{-4}
I	1120	1.7×10^6	6.7×10^{-4}

The ratios $k_{\text{C}}/k_{\text{H}}$ show that halogeno substitution decreases the rates of unassisted reactions following the series $\text{Cl} > \text{Br} > \text{I}$ as expected from their



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 Streitwieser⁷⁶. 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

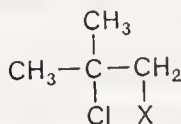
TABLE 22. Acetolysis of 2-substituted cyclohexylbrosylates at 75°

Substituent (X)	k_X/k_H	$k_{\text{obs}}/k_{\text{calc}}$
<i>cis</i> -2-Cl	1.27×10^{-4}	—
<i>cis</i> -2-Br	1.24×10^{-4}	—
<i>trans</i> -2-Cl	4.80×10^{-4}	—
<i>trans</i> -2-Br	0.101	450
<i>trans</i> -2-I	1170.0 ^a	1,500,000

^a 2-Iodocyclohexyltosylates at 23.6°C.

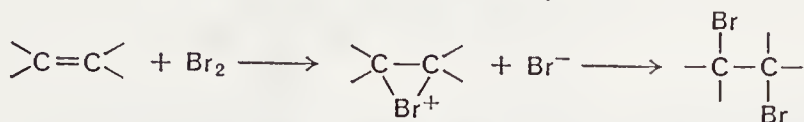
for the anchimeric effect of *trans*-2-Br and *trans*-2-I groups are somewhat different in absolute magnitude from those reported by Winstein and Grunwald⁷⁵ but the trend is very much the same, indicating that the iodine is more effective than bromine as a neighbouring group.

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-fold⁷⁶.



4. β -Halogenocarbenium ions via halogen addition

To explain the fact⁷⁷ that bromination of maleic and fumaric acid occurs in a stereospecific *anti* fashion, Roberts and Kimball⁷⁸ 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 coworkers⁷⁹⁻⁸² 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	% <i>anti</i> addition
$\begin{array}{c} \text{H} \quad \text{H} \\ \diagdown \quad \diagup \\ \text{C}=\text{C} \\ \diagup \quad \diagdown \\ \text{Ph} \quad \text{Me} \end{array}$	73
$\begin{array}{c} \text{H} \quad \text{Me} \\ \diagdown \quad \diagup \\ \text{C}=\text{C} \\ \diagup \quad \diagdown \\ \text{Ph} \quad \text{H} \end{array}$	83
$\begin{array}{c} \text{Me} \quad \text{Me} \\ \diagdown \quad \diagup \\ \text{C}=\text{C} \\ \diagup \quad \diagdown \\ \text{Ph} \quad \text{H} \end{array}$	68
$\begin{array}{c} \text{Me} \quad \text{H} \\ \diagdown \quad \diagup \\ \text{C}=\text{C} \\ \diagup \quad \diagdown \\ \text{Ph} \quad \text{Me} \end{array}$	63
$\begin{array}{c} \text{H} \quad \text{H} \\ \diagdown \quad \diagup \\ \text{C}=\text{C} \\ \diagup \quad \diagdown \\ \text{Me} \quad \text{Me} \end{array}$	100
$\begin{array}{c} \text{H} \quad \text{Me} \\ \diagdown \quad \diagup \\ \text{C}=\text{C} \\ \diagup \quad \diagdown \\ \text{Me} \quad \text{H} \end{array}$	100

stereochemistry of bromine addition to *cis* (97) and *trans* (98) 1-phenylpropene was found⁸¹ to depend on the solvent (see Table 24).

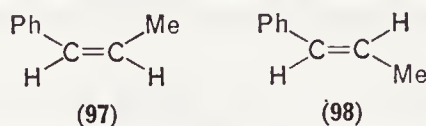


TABLE 24. Solvent dependence of stereochemistry of bromine addition to *cis* (97) and *trans* (98) 1-phenylpropene⁸¹

Solvent	% <i>anti</i> addition to		Dielectric constant
	97	98	
CH ₃ COOH	73	83	6.2
HCCl ₂ —CHCl ₂	66	85	8.2
CH ₂ Cl ₂	70	87	9.1
(CH ₃ CO) ₂ O	49	83	21.0
C ₆ H ₅ NO ₂	45	82	35.0
CCl ₄ ^a	83	88	2.2
CDCl ₃ ^a	78	84	4.8
CH ₂ Cl ₂ ^a	74	—	9.1

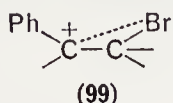
^a From reference 83.

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* stilbenes⁸⁴.

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 Kimball⁷⁸, 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.

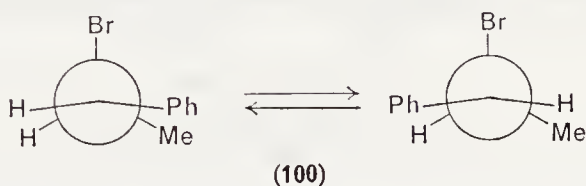
The above results are consistent with an unsymmetrical bridged intermediate (99) in which there is a weak interaction between the carbonium

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



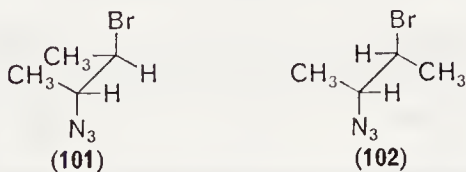
easily overcome, particularly in the more polar solvents where open-charged species such as benzylic carbonium ions can be more effectively stabilized.

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.



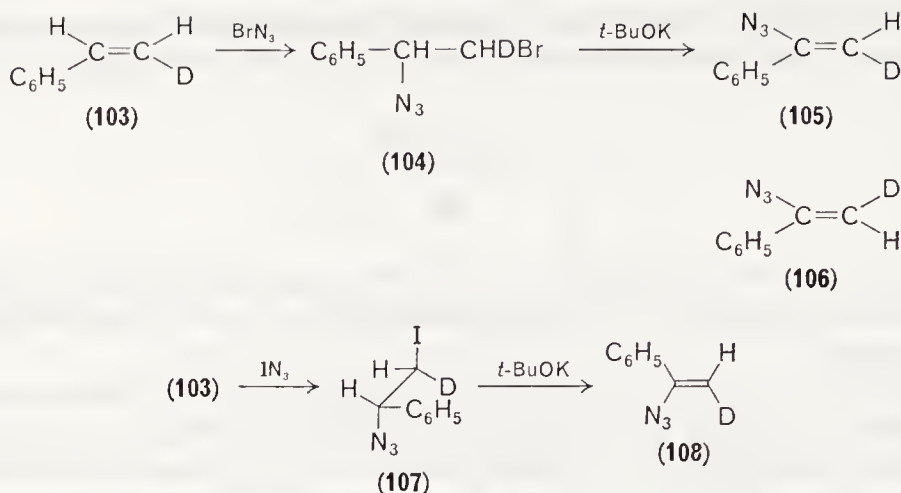
Kinetic evidence for an unsymmetrical charge distribution at the transition state for bromine additions to styrene systems has also been reported⁸².

Substantially similar results were reported by Hassner and coworkers⁸⁵ 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

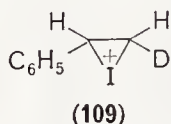


potassium-*t*-butoxide in ether, affords a 1 : 1 mixture of *cis*- and *trans*-deuterated vinyl azides (**105** and **106**). This implies the formation of an open, or partially bridged, β -bromo cation.

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% yield⁸⁵.

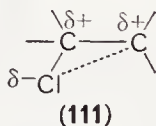
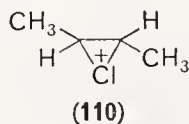


These results suggest the formation of a cyclic iodonium intermediate (109), which does not equilibrate readily to an open carbonium ion, as



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 acid⁸⁸ 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 Mare⁸⁹ (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.

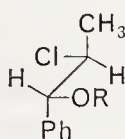


The addition of chlorine to 1-phenylpropene occurs in a different way (see Table 25)⁸⁸. The products obtained are those expected for carbonium ion reactions as shown by the formation of solvent-incorporated adducts (112 and 113) in CH_3OH and CH_3COOH . The lack of stereospecificity indicates an open, rather than a bridged, ion intermediate.

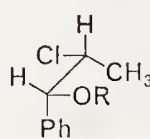
Moreover, the dichloride formed in largest quantity is usually the *syn* addition product. Preferential *syn* collapse is not unreasonable if ion pairs

TABLE 25. Stereochemistry of chlorine addition to *cis* (97) and *trans* (98) -1-phenylpropene⁸⁸

Solvent	% <i>anti</i> addition to	
	98	97
CCl ₄	46	31
CH ₂ Cl ₂	66	26
AcOH	41 ^a	25 ^b
CH ₃ OH	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 = COCH₃
(b) R = CH₃

(113)

(a) R = COCH₃
(b) R = CH₃

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 collapse⁹⁰.

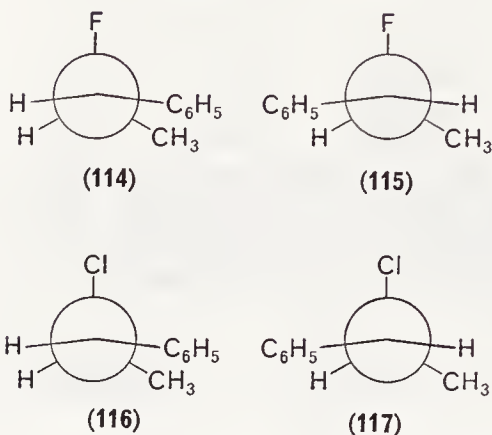
Addition of fluorine to *cis*- and *trans*-1-phenylpropene has been carried out in polar and non-polar solvents to give a mixture of *erythro* and *threo* 1,2-difluoro-1-phenyl propane⁹¹. The stereochemical results are collected in Table 26.

TABLE 26. Product composition in the fluorination of *cis*- (97) and *trans*- (98) 1-phenylpropene⁹¹

Solvent	T (°C)	98		97	
		<i>erythro</i>	<i>threo</i>	<i>erythro</i>	<i>threo</i>
CCl ₃ F	-78	31	69	78	22
	-126	27	73	—	—
CCl ₂ F ₂	-145	29	71	79	21
CH ₃ OH ^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.



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)	% <i>anti</i> addition to		Reference
			97	98	
IN ₃ ^a	CH ₂ Cl ₂ —CH ₃ NO ₂	RT ^b	100	—	85
Br ₂	CCl ₄	2–5	83	88	83
	C ₆ H ₅ NO ₂	RT ^b	45	82	81
Cl ₂	CCl ₄	0	31	46	88
F ₂	CCl ₃ F	–78	22	31	91

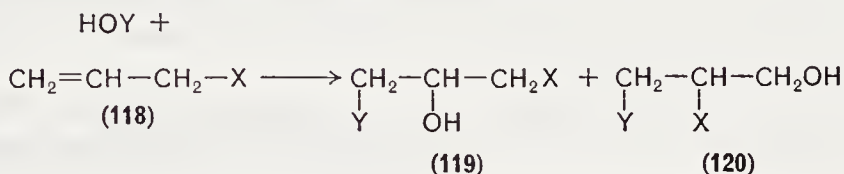
^a The addition was run on β -deuteriostyrene.

^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 process⁷⁹ 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 formed⁹²⁻⁹⁴.

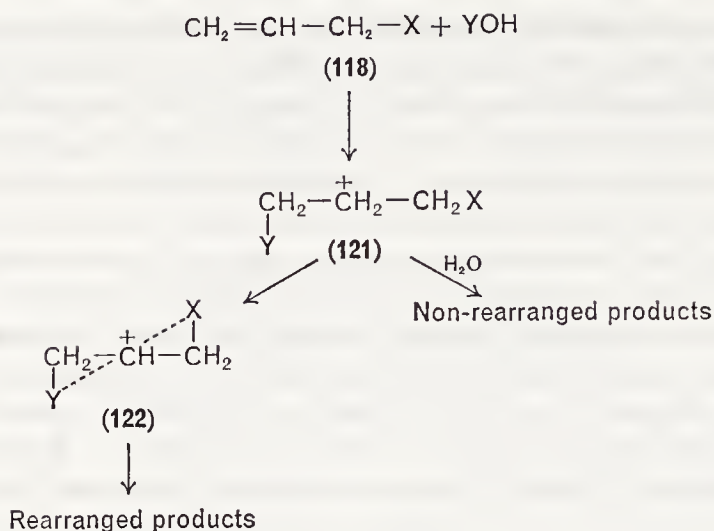


The amount of rearrangement is a function of X and Y as can be seen from Table 28.

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		

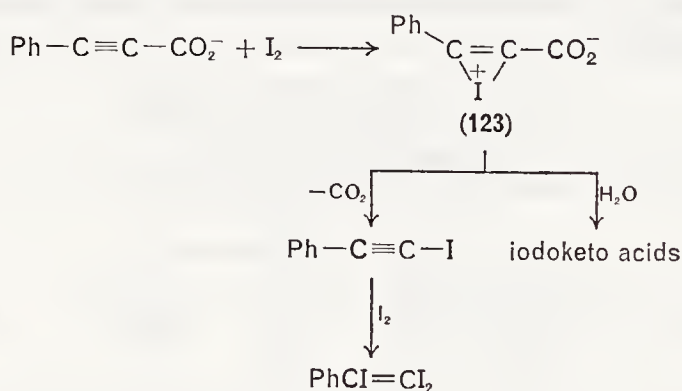
The results have been explained (see the following scheme) by intervention of bridged structures such as **122**. The importance of **122** will increase with the ability of X to bridge, that is in the order $\text{I} > \text{Br} > \text{Cl}$. Moreover, a decrease in yield of rearranged product is expected if Y is able to compete with X in forming bridged structures.



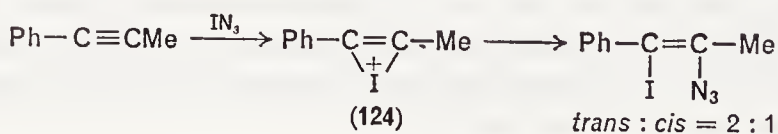
5. β -Halogenovinyl cations

The influence of halogen substituents on vinylic carbonium ions⁹⁵ 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 Berliner⁹⁶ suggested that one of the mechanisms of addition of I_2 to phenylpropionic acid involves the formation of a cyclic iodonium ion (123).



Similarly, Hassner and coworkers⁹⁷ 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 arylacetylenes⁹⁸: the stereochemical data are collected in Table 29.

TABLE 29. Stereochemistry of bromine addition to acetylenes in CH_3COOH

Acetylene	% <i>trans</i> -dibromo ^a
$\text{Ph}-\text{C}\equiv\text{CH}$	42
$p\text{-CH}_3\text{C}_6\text{H}_4-\text{C}\equiv\text{CH}$	69 ^b
$\text{Et}-\text{C}\equiv\text{C}-\text{Et}$	100
$n\text{-Bu}-\text{C}\equiv\text{C}-\text{H}$	100

^a Based on dibromo adducts.

^b Solvent-incorporated products (14%) and 1-bromophenyl acetylene (25%) also formed.

Very recently⁹⁹ 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.

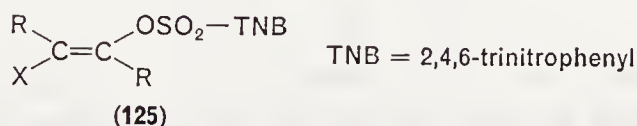


TABLE 30. Relative rates of solvolysis of vinyl sulphonates **125** in nitromethane-methanol at 25°⁹⁹

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).

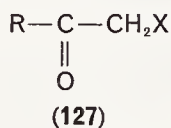
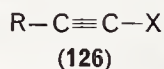
^b In nitromethane : methanol (9 : 1).

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 obtained⁹⁹ 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 = 8–9000⁹⁹. 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.

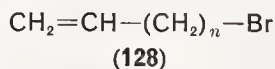
Acid-catalysed additions to halogenoacetylenes should form halogeno-vinyl cations. Apparently, these reactions have not been studied in detail¹⁰¹. Some data are available for acid-catalysed addition of water to phenyl and alkyl haloacetylenes (**126**). For $X = Br, Cl, I$ and $R = C_6H_5$ or alkyl the only product observed is **127**.



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

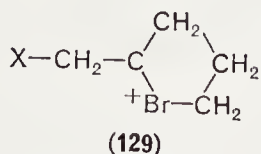
The influence of a halogen substituent in a position farther away than β has been studied¹⁰² in bromination (in methanol) and iodination (in water) of **128**. By using an attenuation plot ($n = 1-4$) it was shown that for



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-

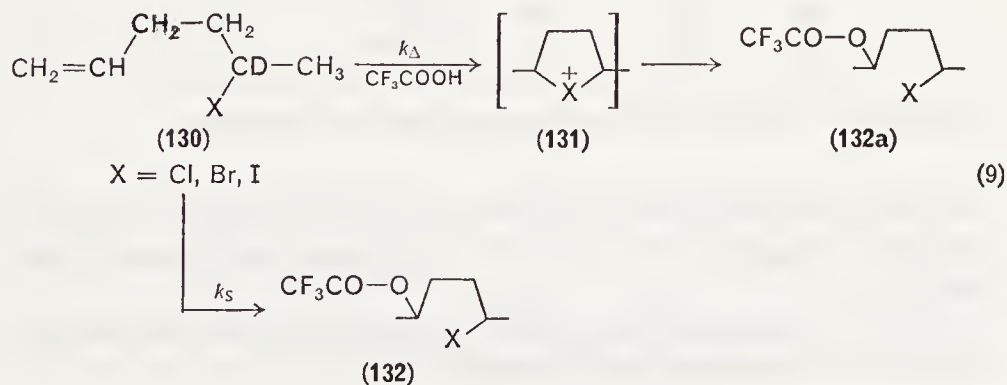


ever, Peterson and coworkers¹⁰³ observed participation via five- and six-membered rings, in the addition of trifluoroacetic acid to olefins, in the order $\text{Cl} \sim \text{Br} \sim \text{I} \sim \text{OR}$. First evidence was given by the observation¹⁰⁴ that the rates of trifluoroacetic acid addition 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).

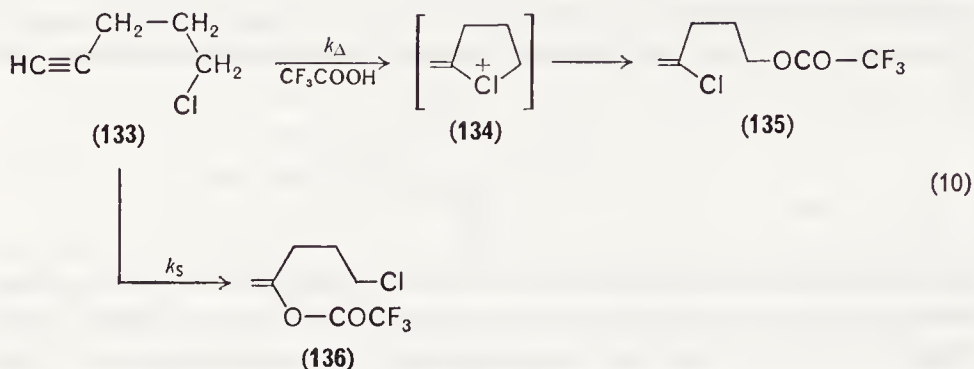
TABLE 31. Relative rates of addition of trifluoroacetic acid to 5-X-1-hexenes (**130**)¹⁰⁴

X	$k_{\text{H}}/k_{\text{X}}$
H	1.0
Cl	4.13
Br	33.35
I	3.50
CH_3COO	32.6

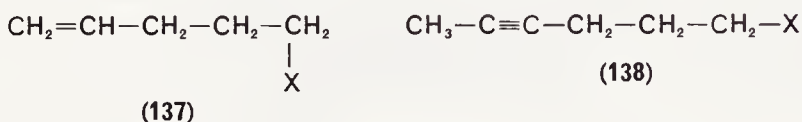
The hypothesis was further substantiated by direct observation of ions **131** by ^1H n.m.r. spectra (see section II. A) and by experiments on **130** labelled with deuterium on the carbon bearing the halogen ($\text{X} = \text{Cl}$) which gives 60% of unrearranged and 40% of halogen-shifted products (see equation 9).



A similar 1,4-chlorine shift was observed in the trifluoroacetic acid addition to 5-chloro-1-pentyne (see equation 10).



Among other systems, the trifluoroacetic acid addition to 5-halogenopentenes (137) and 6-halogeno-2-hexynes (138) have also been studied.



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.

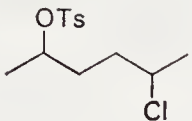
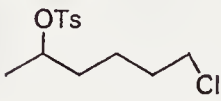
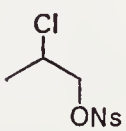
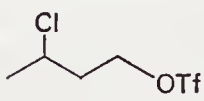
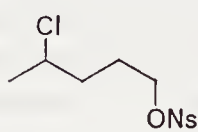
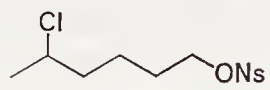
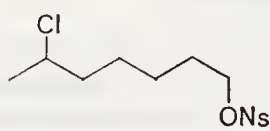
The effect of chlorine on the solvolysis of several nosylates and tosylates was studied in more detail (see Table 34)¹⁰⁶.

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.

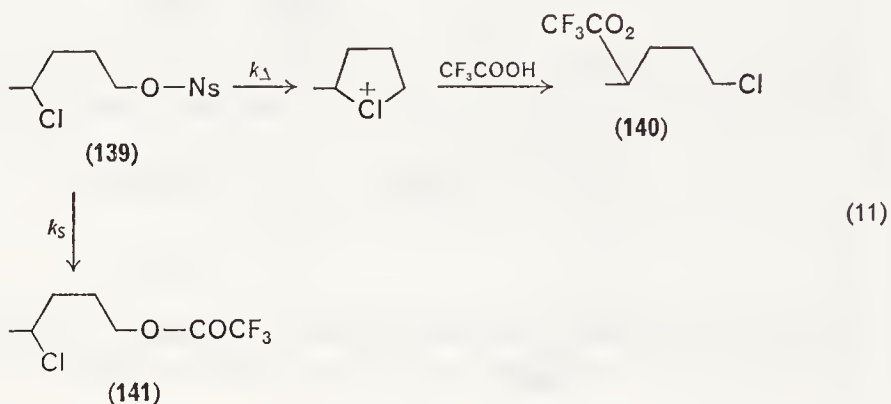
TABLE 34. Chlorine participation in trifluoroacetolysis¹⁰⁶

Compound ^a	k_{Δ}/k_s
	<i>erythro</i> 99 <i>threo</i> 65
	33
	2000
	< 7.1
	760
	7.1
	0.20

^a OTs = $p\text{-CH}_3\text{C}_6\text{H}_4\text{SO}_2\text{O}$; ONs = $p\text{-NO}_2\text{C}_6\text{H}_4\text{SO}_2\text{O}$; 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 trifluoroacetylsolysis of 4-chloro-1-pentyl nosylate (**139**)¹⁰⁶.

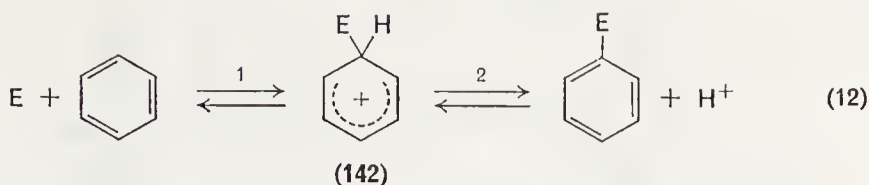
It would be interesting to know whether fluorine could be a 1,4-participating substituent. Earlier data on trifluoroacetic acid addition to alkenes and alkynes suggested a weak participation. Recently, however, it was shown that 4-fluorobutyl *p*-nitrobenzene sulphonate solvolyses without rate enhancement¹⁰⁶ and 4-fluoro-4,4-dideutero butyl trifluoromethane sulphonate without fluorine shift¹⁰⁷. Further work appears necessary to resolve these contradictory results.



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).



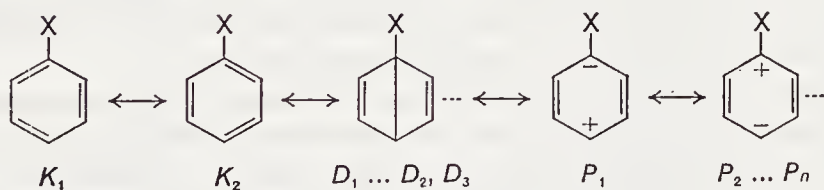
For many, but not all, cases the first step is rate-determining. When the substituent effects are examined, the formation of the Wheland intermediate (142) is taken as the stage in which the substituent has the greatest effect. This assumption usually does not lead to great errors even in the cases where 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.

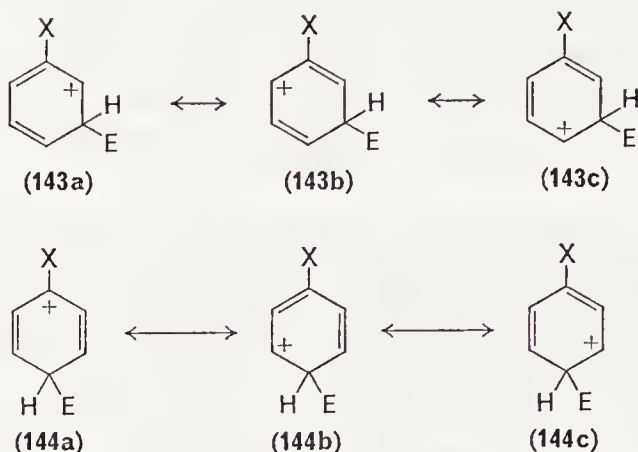
Moreover, it must be remembered that the former situation is associated with low energy of activation and hence low selectivity, contrary to the situation of the latter case.

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.

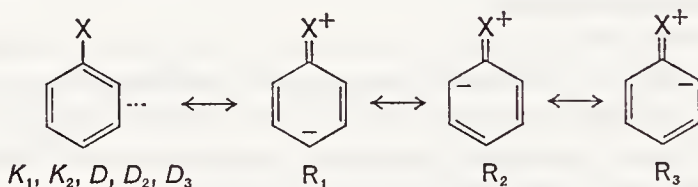


Investigation of the Wheland intermediate derived from *meta* and *para* (or *ortho*) attack of an electrophile would lead to similar conclusions, since the former (143) appears to be less destabilized than the latter (144).



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 $R_1 \dots R_3$ to the resonant system.



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.

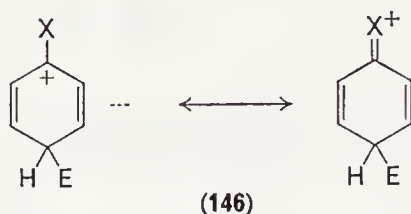
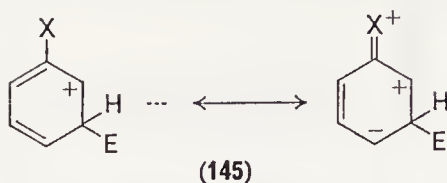
On the other hand, it must be expected that, if the transition state resembles the reagent and hence the substituent affects the reactivity in much the same way as it affects the initial state, the contribution of the inductive effect should be relatively more important than in the case in which the 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 ₃ CO ₃ H	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 ₃ COO) ₂ Hg	23.2	1	2.98	0.36	0.27	—	117
Detritiation	CF ₃ COOH/H ₂ SO ₄ /H ₂ O	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 ₂ SO 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 CF₃COOH/H₂O/HClO₄; in the same conditions the *f_p*F is 1.7.



The data show that the series $F > Cl > Br \sim I$ 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 σ_{p-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)

	<i>ortho</i> (%)	<i>meta</i> (%)	<i>para</i> (%)
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 group¹²⁵. In the case of halogen substitution, however, the inductive effect may be counterbalanced by the lone-pair repulsion⁵, 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 ₂ F	CDBr ₂ F	CDCl ₂ F
$k \times 10^2$ (s ⁻¹)	60.1	57.9	0.47	5.07	2.07	0.00893

	Substrate			
	CDBr ₂ Cl	CDCl ₂ Br	CDCl ₂ I	CDBrClF
$k \times 10^2$ (s ⁻¹)	14.3	2.9	2.75	0.21

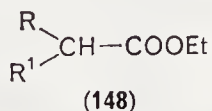
of the substrate increases, showing the presence of saturation effects. However, the fluorine is found to increase by a factor of 10⁶ the acidity of polyhalogenomethanes with respect to hydrogen¹²⁸ (see Table 39).

TABLE 39. Rates of hydrogen exchange in various polyhalogenomethanes in CH₃OD at 35°¹²⁸

	Substrate			
	CBr ₂ H ₂	CBr ₂ FH	Cl ₂ H ₂	Cl ₂ FH
k (M ⁻¹ s ⁻¹)	3.1×10^{-6}	0.67 ^a	18×10^{-6}	1.4 ^a

^a Estimated.

By comparison of the data in Table 39 with the results¹²⁸ on hydrogen exchange in ethyl acetate derivatives **148** (see Table 40) it is possible to show the importance of the lone-pair repulsion effect.



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 10³. 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 $\text{CH}_3\text{O}^-/\text{CH}_3\text{OD}$ at 35° ¹²⁸

R	R ¹	k ($\text{M}^{-1} \text{s}^{-1}$)
H	H	1.26×10^{-3}
H	Et	1.29×10^{-4}
H	F	2.28×10^{-3}
F	F	7.55×10^{-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 barrier¹²⁹ 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}.

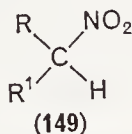
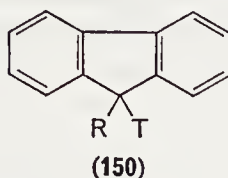


TABLE 41. pK_a Values of halogenonitroalkanes (149) in water at 25° ^{131, 132}

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 reported¹³³ for the 9-tritio-9-fluorofluorene (**150**, $R = F$).



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 ₂ H ₅	CH ₂ -C ₆ H ₅	CH ₂ OCH ₃	CF ₃
$(k/k_0)_{\text{exch}}$	1	0.26	0.18	0.72	12.9	2×10^4

	R		
	Br	Cl	F
$(k/k_0)_{\text{exch}}$	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-CF₃ derivative. The CF₃ and F groups have almost the same inductive effect but the rates of exchange are very different with the CF₃ 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.

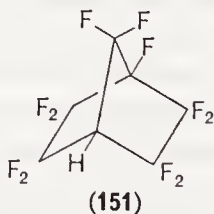
To explain these results Streitwieser and Mares suggested that the 9-fluoro-fluorenyl anion is planar whereas the α, α' -difluorobenzyl anion is pyramidal. For the benzal fluoride the increased conjugation of a planar benzyl anion is counteracted by the corresponding increase in repulsions between fluorine 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 fluoride¹³³.

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 $\text{CH}_3\text{O}/\text{CH}_3\text{OD}$ of some polyfluoroalkanes^{135, 136}

Relative rates	
$\text{CF}_3\text{—H}$	1
$\text{CF}_3(\text{CF}_2)_6\text{—H}$	6
$(\text{CF}_3)_2\text{CF—H}$	2×10^5
$(\text{CF}_3)_3\text{CH}$	10^9
151	5×10^9

The substitution of CF_3 for F in trifluoromethane causes a 10^9 increase in rates of hydrogen exchange¹³⁵. This was taken as evidence¹³⁵ of carbanion stabilization through bond–no-bond resonance¹³⁷. 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

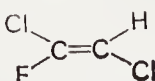
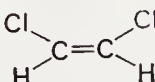
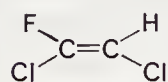
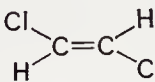


showed (see Table 42) a rate of exchange of the same order of magnitude as $(\text{CF}_3)_3\text{CH}$ ¹³⁶. This is further evidence that the CF_3 effect on rates of exchange is that normally expected from its electron-withdrawing power,

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 coworkers¹³⁹ reported the rates of base-catalysed hydrogen-deuterium exchange of several di- and trihalogenoethylenes in $\text{CH}_3\text{ONa}-\text{CH}_3\text{OD}$ solutions. Pertinent data are collected in Table 44.

TABLE 44. Rates of hydrogen exchange of halogenoethylenes in $\text{CH}_3\text{O}^-/\text{CH}_3\text{OD}$ 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	$\text{CCl}_2=\text{CHBr}$	68	7	$\text{CF}_2=\text{CHCl}$	9.8 ^a
3	$\text{CCl}_2=\text{CHCl}$	24.1	8	$\text{CF}_2=\text{CHF}$	0.05
4	$\text{CCl}_2=\text{CHF}$	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 $\text{Br} > \text{Cl} > \text{F}$ 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 coworkers¹⁴⁰ 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, CF₃, OCH₃, 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 Mares¹⁴¹ measured the rates of deuterium exchange in the lithium cyclohexylamide-cyclohexylamine system with fluorobenzene. They found partial rate factors of 6.3×10^5 , 1.1×10^2 and 1.1×10 for the *ortho*, *meta* and *para* positions, respectively. These factors are to be compared with the above data of Roberts¹⁴⁰ which were transformed to partial rate factors by Shatenshtein¹⁴²: *ortho* = 10^6 , *meta* = 10^3 , *para* = 10^2 . Roberts' data¹⁴⁰ for *meta* and *para* positions were not as accurate as Streitwieser's¹⁴¹, due to the slowness of the exchange in liquid ammonia.

Shatenshtein¹⁴² 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 Mares¹⁴¹ 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 group¹⁴³ 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

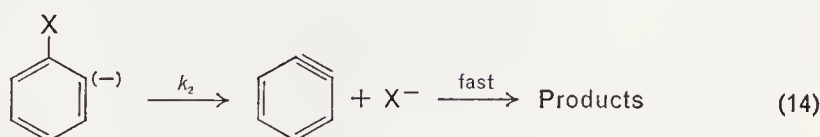
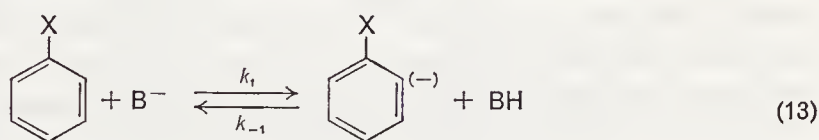
X	Y = H	Y = <i>m</i> -OCH ₃	Y = <i>p</i> -OCH ₃
F	8.75	3.6	15
Cl	1	2	1
Br	1.25	2	1.4
I	1 ^a	1 ^b	1 ^c

^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 Sauer¹⁴⁴ for reactions of aryl halides with phenyl lithium and lithium piperidide in ether. They found that the reactions follow the scheme:



The rate of benzyne formation, as evaluated by halide ion titration, can be derived from the expression:

$$\frac{d[\text{X}^-]}{dt} = \frac{k_1 k_2 [\text{ArX}] [\text{B}^-]}{k_2 + k_{-1} [\text{BH}]} \quad (15)$$

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 $k_{-1}[\text{BH}]$ term cannot be neglected and the rate of halide ion production will depend on the ability of halogen as leaving group ($\text{I} > \text{Br} > \text{Cl} > \text{F}$) as well as on the effect of halogen on hydrogen abstraction ($\text{F} > \text{Br} > \text{Cl} > \text{I}$). By varying the nature and the amount of BH almost any reactivity scale can be obtained. An example is given in Table 47.

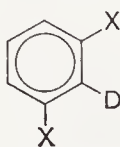
TABLE 47. Relative rates of the reactions of halogenobenzenes ($\text{C}_6\text{H}_5\text{—X}$) with $\text{C}_6\text{H}_5\text{—Li}$ (A), and lithium piperidide (B and C) in ether at 20° ¹⁴⁴

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 $\text{Br} : \text{I} : \text{Cl} = 20 : 8 : 1$ and $13.5 : 5 : 1$ for halogenobenzenes¹⁴⁵ and 3-halogenotoluenes¹⁴⁶, respectively. In both cases the fluorine derivative remained unchanged.

Further substitution of halogenobenzenes with electron-withdrawing groups increases, as expected, the reactivity towards strong bases¹⁴⁷. Hine and Langford¹⁴⁸ measured the rates of hydrogen exchange of 1-deutero-2,6-dihalobenzenes in the $\text{CH}_3\text{O}^-/\text{CH}_3\text{OH}$ system. Their data are shown in Table 48. Replacement of chlorine by fluorine enhances the



(152)

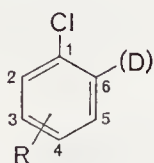
TABLE 48. Rates of hydrogen exchange of halobenzenes **152** in $\text{CH}_3\text{O}^-/\text{CH}_3\text{OH}$ at 100° ¹⁴⁸

X	Y	$k \times 10^6$ ($\text{l mole}^{-1} \text{s}^{-1}$)
F	F	978
F	Cl	151
Cl	Cl	20.2

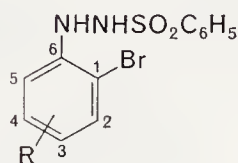
rate by a factor of about 7. This effect appears to be additive. Moreover, no halide ion was found, showing that proton capture by the aryl anion is, in this case, faster than halide ion loss from it.

Two methods have been developed to estimate the relative rates of proton capture and halide ion loss. Roberts and coworkers¹⁴⁹ 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. Hoffman¹⁵⁰ 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 coworkers¹⁴⁹, 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.



(153)



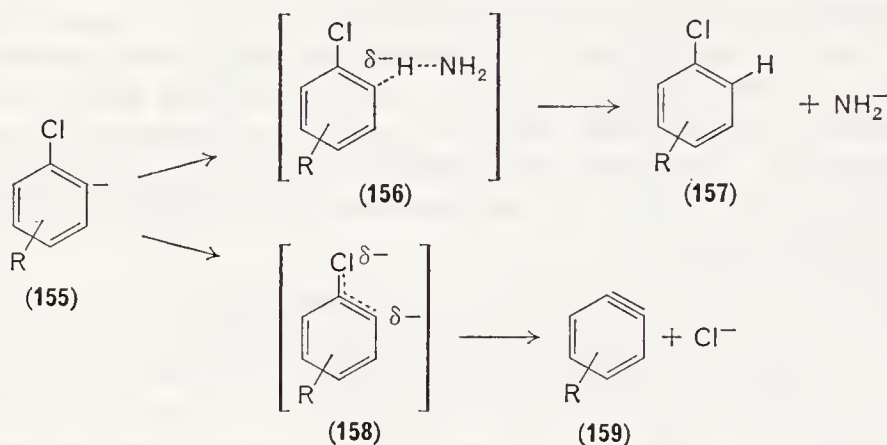
(154)

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 $\text{CH}_3\text{ONa}/\text{CH}_3\text{OH}$ 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, CF₃) 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 Zirngibl¹⁵³ and used to explain the small steric effects found in the addition of nucleophiles to 1,2-naphthalene.

The effects of CH₃ and OCH₃ substituent are more difficult to explain. They should destabilize phenyl anions^{140, 147} and, possibly, increase the energy level of the aryne-forming transition state¹⁵¹.

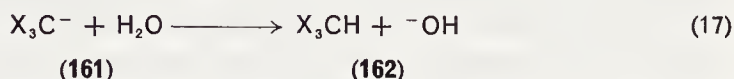
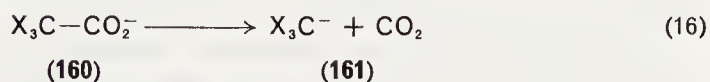
Similar behaviour was found in the reaction of substituted 1-(*o*-bromophenyl)-2-sulphonhydrazides (**154**) with 2M CH₃ONa in CH₃OH at 61°¹⁵². Also in this reaction, which involves decomposition of **154** to aryl anions, the ratio k_{-1}/k_2 , evaluated following Hoffmann¹⁵⁰ is increased both by electron-attracting 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

I. 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



decarboxylation rates of **160** follow the order¹⁵⁴⁻¹⁵⁷: $\text{X}_3 = \text{Br}_3 > \text{Br}_2\text{Cl} > \text{Cl}_3 > \text{BrClF} \gg \text{F}_3$ (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,

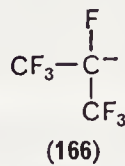
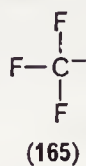
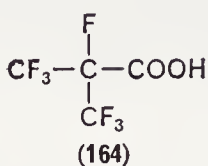
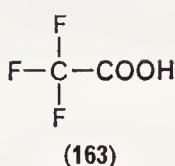
TABLE 50. Rates of decarboxylation of trihaloacetate ions (CX_3-COO^-) at 70° in water

X_3	$k\text{s}^{-1}$	Reference
I_3	Very fast	155, 158
Br_3	6.5×10^{-4}	155
Br_2Cl	3.0×10^{-4}	156
Cl_3	1.7×10^{-5}	154
BrClF	1.0×10^{-6}	156
F_3^a	2.8×10^{-11}	157

^a In ethylene glycol, extrapolated from data at higher temperatures; in the same solvent the rate of decarboxylation for trichloroacetate ion is $2.48 \times 10^{-6} \text{ s}^{-1}$ 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 anion¹²⁶.

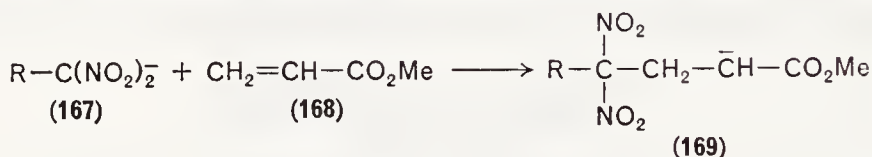
It is interesting to compare the behaviour of trifluoroacetic **163** and perfluoroisobutyric acid **164**. The former is very stable in water and



measurable rates of decarboxylation are attained only at high temperature: at 170° in ethylene glycol the rate of decomposition is $k = 2.98 \times 10^{-5} \text{ s}^{-1}$ ¹⁵⁷. The latter¹⁵⁹ is completely decomposed after 45 min in basic aqueous solution at 100° ($k_{\text{dec}} > 10^{-3} \text{ s}^{-1}$).

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 acrylate¹⁶⁰.



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 substitution¹⁶⁰. 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 $30^\circ 160$.

R	H ₂ O		50% Dioxan		
	$k \times 10^4$ (1 mole ⁻¹ s ⁻¹)	ΔH^* (kcal/mole)	ΔS^* (cal mole ⁻¹ deg ⁻¹)	$k \times 10^4$ (1 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
C ₆ H 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-dihaloethanes (**170**) in alkaline methanol undergo H/D exchange at a rate faster than fluoride ion elimination^{161, 162}. Data are collected in Table 52.

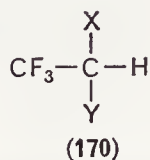


TABLE 52. Rates of hydrogen exchange (k_{exch} at 20°) and dehydrofluorination (k_{el} at 55°) of 1,1,1-trifluoro-2,2-dihaloethanes (**170**) in alkaline methanol^{161, 162}

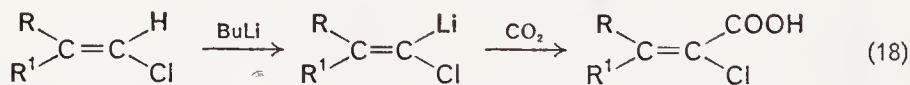
X	Y	$k_{\text{exch}} \times 10^3$ ^a (l mole ⁻¹ s ⁻¹)	$k_{\text{el}} \times 10^6$ (l mole ⁻¹ s ⁻¹)
Cl	Cl	10.2	1.5
Br	Br	74.0	5.5
Br	Cl	22.0	2.9
I	I	29.0	51.0

^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 8.9×10^{-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 E1cB mechanism in reaction of saturated halogenoalkanes¹⁶⁴.

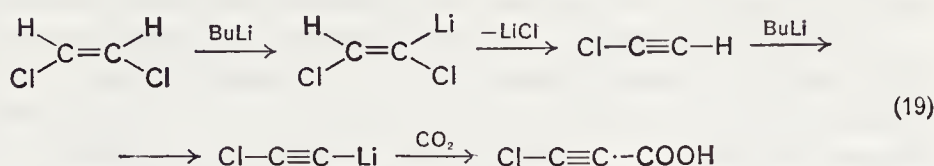
2. Vinyl anions

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.



$\text{R} = \text{R}' = \text{H}, \text{Cl}$ or aryl; $\text{R} = \text{H}, \text{R}' = \text{Cl}$; $\text{R} = \text{Cl}, \text{R}' = \text{H}$

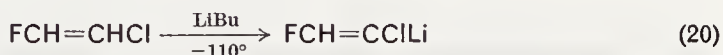
The only exception was the reaction with *cis*-dichloroethylene where chloropropiolic acid was formed.



From the yields of the carboxylic acids the following stability scale was set up¹⁶⁶:

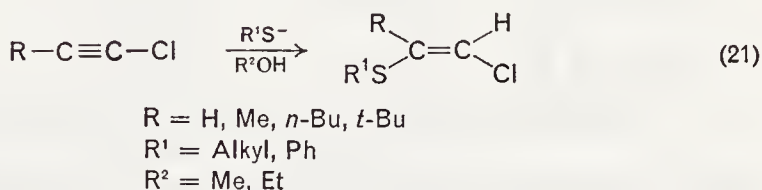


It is interesting that 1-chloro-2-fluoroethylene (*cis* or *trans*) metalates on the chlorine-bearing carbon¹⁰¹:

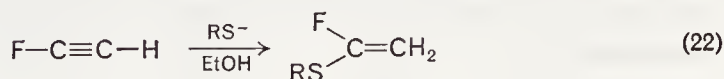


this is in agreement with the rates of hydrogen exchange of halogenoethylenes (see section III. A) and with the general finding that α -fluorine does not favour carbanions.

Other examples are provided by the nucleophilic additions to halogenoacetylenes¹⁰¹. The base-catalysed addition of thiols and alcohols to chloro- and chloroalkyl-acetylenes occurs directiospecific β to the halogen^{101, 167-172}:



On the contrary, the addition of the thiophenolate anion to fluoroacetylene¹⁷³ occurs with opposite orientation:

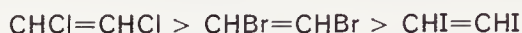


This is another manifestation of the destabilizing effect of fluorine on α -carbanions by lone pair-lone pair repulsion.

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 paths¹⁷⁴⁻¹⁷⁶. 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-dihaloethylenes¹⁷⁷. These ethylenes, in fact, undergo elimination at a slower rate than H/D exchange. The rates of exchange in alkaline D₂O are similar for *cis*-dibromo- and dichloro-ethylene, whereas the *trans* derivatives follow the series:



Moreover, the isotope effect found for elimination in the *cis*-dibromo compound at 35.2°C is 1.03, a very low value¹⁷⁸, 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

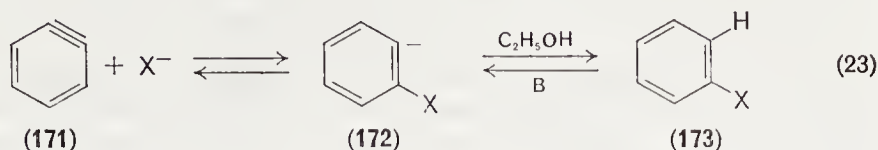
	k (1 mole ⁻¹ s ⁻¹)	E_a (kcal/mole)	ΔS^* (cal mole ⁻¹ deg ⁻¹)
$C_2H_2Cl_2$ { <i>cis</i>	1.4×10^{-5}	35.1	+22
{ <i>trans</i>	4.2×10^{-9}	29.0	-12
$C_2H_2Br_2$ { <i>cis</i>	1.8×10^{-2}	28.1	+16
{ <i>trans</i>	3.3×10^{-8}	33.4	+5
$C_2H_2I_2$ { <i>cis</i>	1.6	24.7	+14
{ <i>trans</i>	1.2×10^{-5}	35.8	+24

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/mole¹⁷⁸. This value was confirmed by theoretical calculations¹⁷⁹.

3. Aryl anions

Several examples of benzyne formation through *o*-halogenoaryl anions are available and since they have been collected in a recent book¹⁸⁰ they will not be discussed here.

Ortho-halogenoaryl anions are obtained via addition of halide ions to dehydrobenzene in tetrahydrofuran or ethanol:



This is the reverse of the formation of dehydrobenzene from aryl halides and demonstrates the reversibility of the processes¹⁸¹.

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 are¹⁵⁰ I : Br : Cl = 100 : 40 : <2. This made it possible to calculate the ratios of the equilibrium constants in the reaction **171** \rightleftharpoons **172**. The results obtained were about 3.2 for the ratio $K_{\text{I}}/K_{\text{Br}}$ and about 2.5 for the ratio $K_{\text{Br}}/K_{\text{Cl}}$.

Orientation in the addition of nucleophiles to substituted benzyne may be influenced by several factors¹⁸⁰, 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.

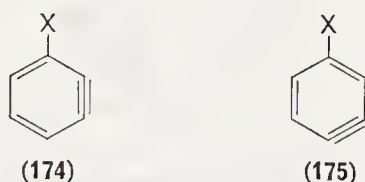


TABLE 54. *Meta/ortho* isomer ratio in nucleophilic additions to 3-substituted benzyne **174**

X	Reacting system ^a			
	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 KNH₂/NH₃ = potassium amide in liquid ammonia at boiling point ($\sim -33^\circ$); LiPip/Pip = lithium piperidide in the presence of piperidine in ethyl ether at room temperature ($\sim 20^\circ$).

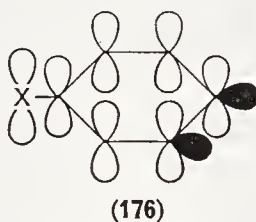
^b No numerical value is reported; NaNH₂ in liquid ammonia at reflux.

TABLE 55. *Para/meta* isomer ratio in nucleophilic addition to 4-substituted benzyne **175**

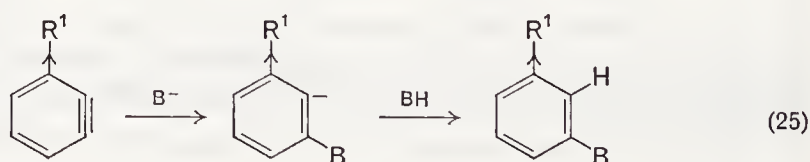
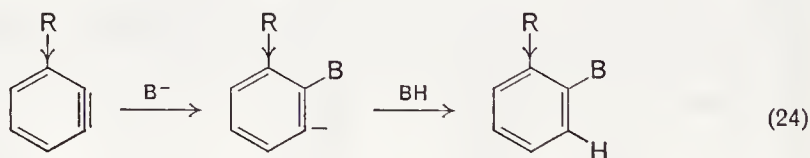
X	Reacting system ^a			
	KNH ₂ /NH ₃	Reference	LiPip/Pip	Reference
F	4.0 ± 0.2	182	1.95	184
Cl	4.2	151	—	—
Br	—	—	1.4	185
I	—	—	(1.55) ^b	186
CH ₃	0.67	182	0.83 ± 0.05	187

^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.



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 R¹ are electron-donating and electron-attracting, respectively.



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 benzyne 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 hypothesis¹⁸⁰.

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 ion¹⁸⁹. 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 methanol¹⁸⁹

CH ₃ ONa (M)	0	0.2	0.4	0.8	1.9
<i>p/m</i>	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-chlorobenzyne¹⁸⁸. The ratio of rates of methoxide and methanol attack was evaluated as 157 and 70 for the *meta* and *para* positions, respectively¹⁸⁹.

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 methoxide¹⁹⁰. 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.

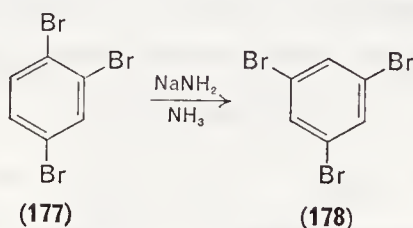
In dimethyl sulfoxide (DMSO) solution the nucleophilicity of the halide ions is increased¹⁹² and the *p/m* ratio, as expected, decreased.

TABLE 57. *Para/meta* isomer ratios as a function of the solvent in the addition of LiCl and LiBr to 4-chlorobenzene (**175**, X = Cl)¹⁹¹

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

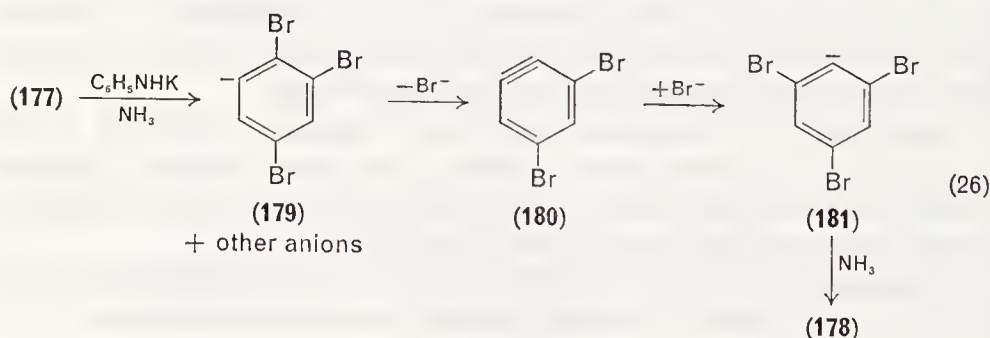
The discovery that electron-attracting groups enhance the rate of proton capture versus that of halide ion expulsion in *o*-halogenophenyl anions^{151, 152}, is of particular importance to understanding the behaviour of trihalogenobenzenes in strongly basic media.

It was observed by Wotiz and Huba¹⁸³ 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**).



This reaction was subsequently reinvestigated by Bunnett's group¹⁹³⁻¹⁹⁵, who also observed similar isomerizations in several other polyhalogenobenzenes.

It was found¹⁹³ 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).



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 ₂ O	KNH ₂	120	71.4	28.6
177	NH ₃ —Et ₂ O	PhNHK	120	41	59
177	NH ₃ —Et ₂ O	PhNHK	480	41	59
178	NH ₃ —Et ₂ O	PhNHK	480	0	100
178 + 182 ^c	NH ₃ —Et ₂ O	PhNHK	147	24	76
177	DMF	<i>t</i> -BuOK	0.45	49.4	50.6
177	DMF	<i>t</i> -BuOK	5400	48.6	51.4
178	DMF	<i>t</i> -BuOK	76.0	0	100
178 + 182 ^c	DMF	<i>t</i> -BuOK	1.67	49.1	50.9
177	HMPA	<i>t</i> -BuOK	2.67	59.7	40.3
177	HMPA	<i>t</i> -BuOK	1500	63.9	36.1
178	HMPA	<i>t</i> -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.

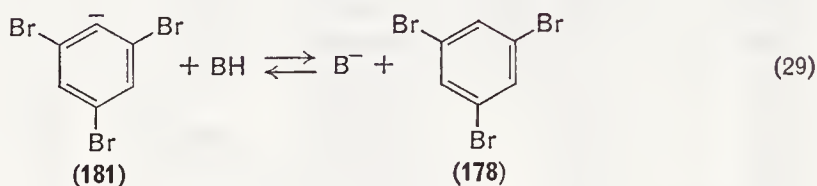
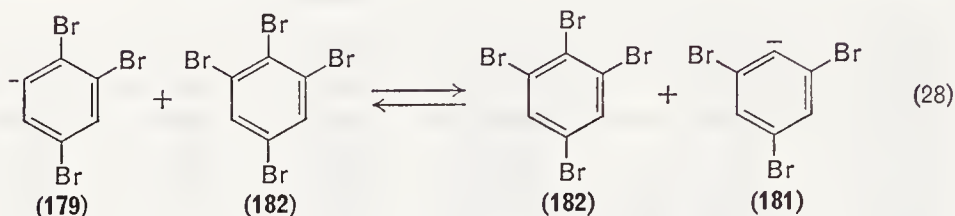
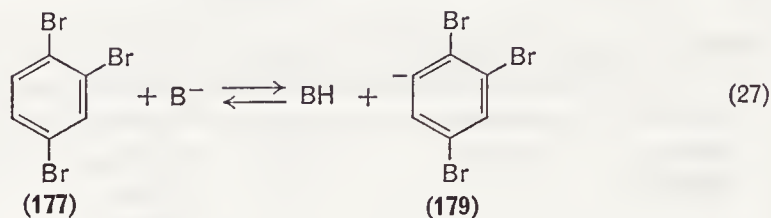
^b NH₃—Et₂O stands for a 50 : 50 mixture of the two solvents; DMF is dimethylformamide, and HMPA is hexamethylphosphoramide.

^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.

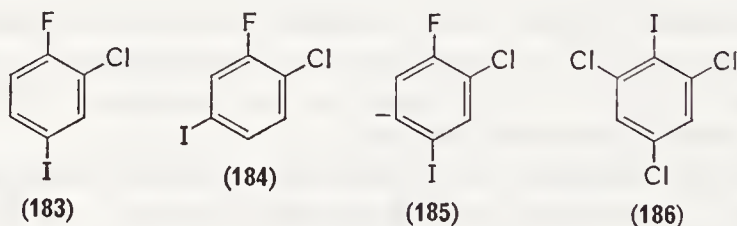
Bunnett and Scorrano¹⁹⁴ investigated the **177** ⇌ **178** isomerization in more detail. It was found that the isomerization of 1,2,4- into 1,3,5-tribromobenzene is actually an equilibrium reaction. However the establishment of the equilibrium seems to require catalysis by 1,2,4,5-tetrabromobenzene (**182**) 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 example¹⁹⁴ 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**).

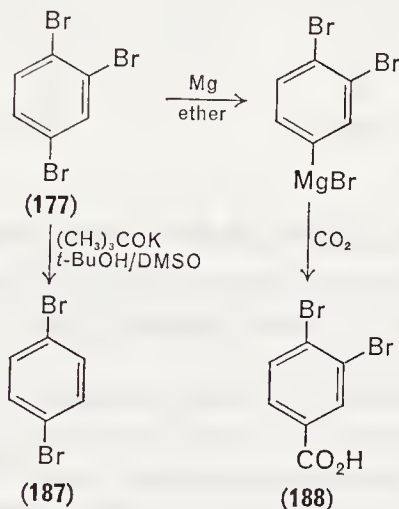


It was found that conversion was possible only via reaction of aryl anion **185** with an iodine donor as 1-iodo-2,4,6-trichlorobenzene (**186**). No isomerization was observed in absence of catalyst **186** ruling out a conceivable 1,2-iodine shift¹⁹⁴.

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 HMPA at ca. 25° ¹⁹⁴. It is interesting that the recovered 1,2,4-tribromobenzene also appears to have undergone reaction. McLennan and Bunnett¹⁹⁵ studied the reaction of 1,2,4-tribromobenzene-1-⁸²Br under the same reaction conditions leading to the **177** \rightleftharpoons **178** equilibration.

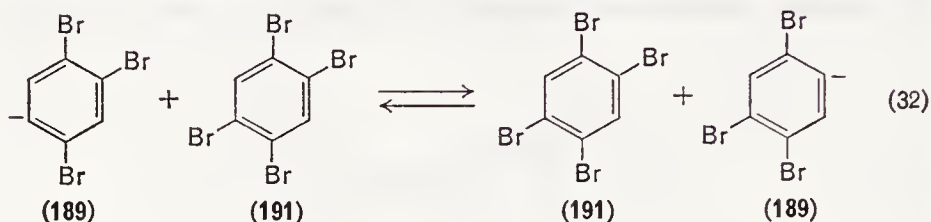
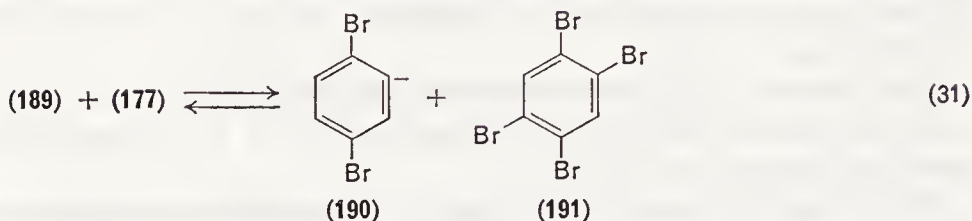
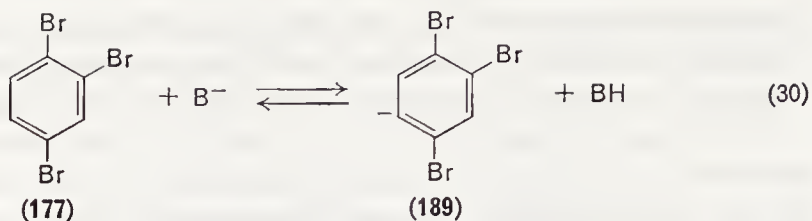
The recovered 1,2,4-tribromobenzene was degraded according to the following scheme. The reaction leading from **177** to **187** was studied in detail by Bunnett and Victor¹⁹⁶.

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 halogenothiophenes¹⁹⁷, halogenoisothiazoles¹⁹⁸ and halogenoimidazoles¹⁹⁹.



IV. EFFECTS ON RADICALS

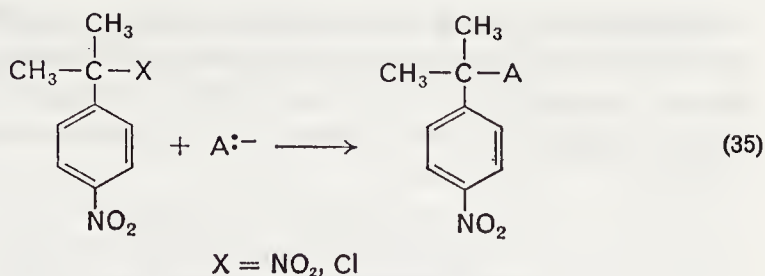
In the previous sections the effects of halogens were considered mainly from the point of view of polar interactions with positive and negative centres.

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).

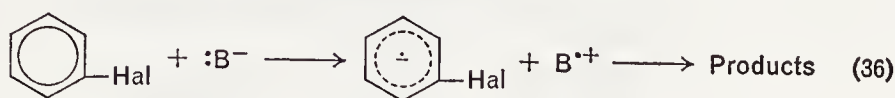


However, much evidence indicates that polar effects do play a role in radical reactions. On the other hand, the classical sharp separation between homolytic and heterolytic processes is under critical revision and numerous well-documented cases of formally nucleophilic reactions which in fact occur via electron transfer to give radical ion intermediates are now in the literature.

Kornblum and coworkers²⁰⁰, for example, reported that substitutions such as equation (35) occur via radical anions.



Recently Bunnett and Kim²⁰¹ reported that unactivated halogenobenzene may react with strong nucleophiles following the scheme (36). The other conceivable electron transfer processes (37), (38), (39) have not,



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 large²⁰², 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 interactions²⁸.

The data of Taft²⁷ 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.

$$\text{S.E.} = D[\text{CH}_3 - \text{H}] - D[\text{X} - \text{CH}_2 - \text{H}] \quad (40)$$

The stabilization energies (S.E.) of the halogenomethyl radicals (relative to CH_3^{\bullet}) were obtained by the relationship (40) taking for $D[\text{CH}_3 - \text{H}]$ the revised value²⁰³ of 104 kcal/mole (see Table 59).

Halogens have much less stabilization effect on radicals than on the corresponding cations²⁷. 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	$D[\text{R—H}]$ (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 phase²⁸.

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 compounds²⁰³.

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 ₂ H 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 -orbital²⁰⁴.

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 plane²⁰⁵⁻²⁰⁷. Halogen substitution seems to modify this geometry. Fessenden and Schuler²⁰⁸ 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 gauss²⁰⁹.

From data in the literature²¹⁰ it was estimated²⁰⁸ that in CF_3^\bullet the electron is in an orbital having 21% s -character ($\widehat{FCF} = 111.1^\circ$; 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 ($\theta = 12.7^\circ$). The CH_2F^\bullet is near planar ($\theta < 5^\circ$).

Thus the CF_3^\bullet radical almost maintains tetrahedral geometry ($\theta = 19.5^\circ$, 25% s -character).







Similar results have been obtained from theoretical calculations²¹¹ 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 radicals²¹¹

CH ₃	H $\hat{\text{C}}$ H	119.7		
CH ₂ F	H $\hat{\text{C}}$ H	121	H $\hat{\text{C}}$ F	114
CHF ₂	F $\hat{\text{C}}$ F	109	F $\hat{\text{C}}$ H	116
CF ₃	F $\hat{\text{C}}$ F	112		

In Table 62 a selection of data obtained by different calculation methods are reported²¹²⁻²¹⁴. 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
$\cdot\text{CHFCl}$	0.7	CNDO/2	212
$\cdot\text{CH}_2\text{F}$	0.6	LCAO-MO-	213
$\cdot\text{CF}_3$	27.4	SCF	213
$\cdot\text{CH}_3$	-4.9 ^a	SCF-MO (MINDO)	214

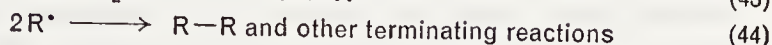
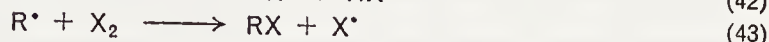
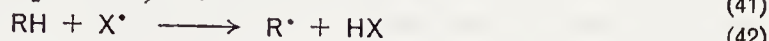
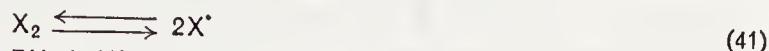
^a Energy difference between the less stable pyramidal and the more stable planar structure.

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}.

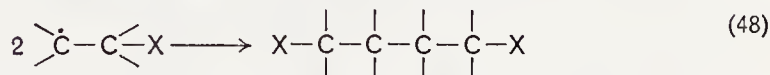
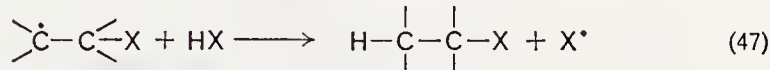
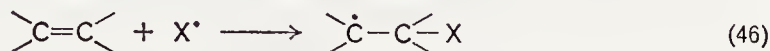
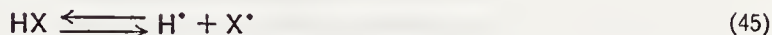
B. Effects on Reactivity

Homolytic reactions, when chain processes, may be generally formulated as shown in Schemes A (equations 41–44) and B (equations 45–48).

SCHEME A:



SCHEME B:



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 substitution²¹⁸

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^\bullet) from ethane²¹⁸

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 $F > Cl > Br \gg I$. 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.

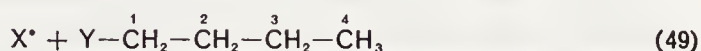
TABLE 66. Selectivity of different radicals at 300 K ²¹⁸

X^\bullet	$-CH_3$	$\begin{array}{c} \diagup \\ CH_2 \\ \diagdown \end{array}$	$\begin{array}{c} \diagup \\ -CH \\ \diagdown \end{array}$
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 state¹⁹⁰.

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 chlorination²¹⁹ and bromination²²⁰ of substituted toluenes whose reaction rates are correlated by the Hammett relationship with ρ values of -0.76 and -1.05 , respectively.

Polar effects were invoked to explain the directing effect of halogens in the halogenation of halogenoalkanes²¹⁸. Some data for the gas-phase reactions:



where $X, Y = \text{Hal}, \text{CF}_3$ 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

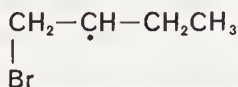
TABLE 67. Relative reactivity at the various carbon atoms in the gas-phase halogenation (X) of n -butyl derivatives ($Y-\text{C}_4\text{H}_9$ - n , reaction 49)^{221, 222}

X^{\bullet}	Y	1	2	3	4	$T(^{\circ}\text{C})$
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 , $\text{F} > \text{Cl}$.

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 alkene²²¹. However, the very important



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 $\text{F} < \text{Cl} < \text{Br}$, 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:

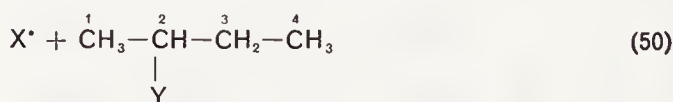


The more the transition state resembles the radical intermediate, the more important will be the conjugative stabilization (e.g. in bromination). In the less selective reaction (fluorination) the more important factor will be the inductive effect of the substituent which deactivates to the attack of the electrophilic radical.

In the chlorination reaction the slight deactivation at the α -position follows the order $\text{Br} > \text{Cl} \simeq \text{F}$ 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 ($\text{p}K_a$ of fluoroacetic and 3,3,3-trifluoropropionic acid 2.58 and 3.07, respectively)⁴, but it strongly deactivates even the bromination at α -carbon²²².

Table 68 collects data²²³ on the gas-phase reaction (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

X	Y = F			Y = Cl	
	F ^a	Cl ^b	Br ^c	F ^a	Cl ^b
<i>erythro</i> (%)	60.2	59.4	64.3	66.6	71.4
<i>threo</i> (%)	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 reactions²²⁴, 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 phase²²⁵.

More recently Tedder and coworkers²²⁶ 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 CCl₄ 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:

$$(\text{gas}) \ k_s/k_p = (2.2 \pm 0.6) \exp(214 \pm 127 \text{ cal/RT})$$

$$(\text{liquid}) \ k_s/k_p = (0.8 \pm 0.2) \exp(597 \pm 20 \text{ cal/RT})$$

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 atom²²⁶.

In certain solvents the selectivity may become greater than in the gas phase, as shown by Russell²²⁷ for the chlorination of hydrocarbons in aliphatic and aromatic solvents and in CS₂, and by Walling and Mayahi²²⁸ 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 ₆ H ₆	11M in CS ₂	13M in CS ₂
<i>s/p</i>	3.6	2.69	5.1	6.6	8.0

However, when *n*-butyl chloride was chlorinated the results collected in Table 71 were obtained²²⁸.

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 ₆ H ₆	0.114	0.443	0.317
7.5M in C ₆ H ₆	0.120	0.444	0.267

Ashton and Tedder²²⁹ 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 CS₂ 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 additions²³⁰

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 latter²³¹.

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- $\text{C}_3\text{H}_7^\bullet$ ^a	Br^\bullet ^b	CF_3^\bullet ^b
$\text{CH}_2=\text{CH}_2$	1	1	1	1
$\text{CH}_2=\text{CHF}$	0.53	0.69	0.014	0.16, 0.24 ^c
$\text{CH}_2=\text{CHCl}$	5.7	1.7	0.301	0.61
$\text{CH}_2=\text{CHBr}$	7.6	3.4	0.676	0.79
$\text{CH}_2=\text{CF}_2$	0.65	0.48	0.012	0.088
$\text{CF}_2=\text{CF}_2$	10.1	—	—	0.15
$\text{CH}_2=\text{CHCH}_3$	—	—	—	1.5 ^c

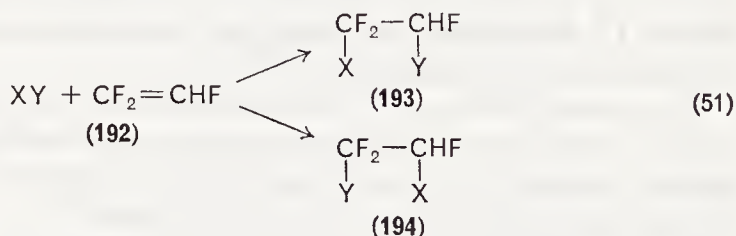
^a At 65°C, from reference 232.^b At 40°C, from reference 233.^c At 200°C, from reference 234.

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 $\text{Br} > \text{Cl} > \text{F}$, 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).



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

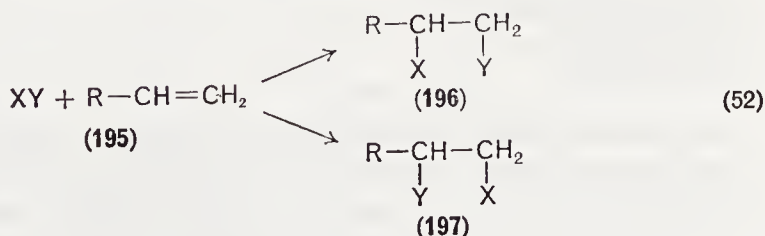
TABLE 74. Addition of XY to $\text{CF}_2=\text{CHF}$ (192) (see equation 51)

XY	Radical (X^\bullet)	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
		5	95	Peroxide initiated	236
SF_5Cl	Cl^\bullet	27	73	Photochemical	236
		2	98	Photochemical	237
$(\text{CF}_3)_2\text{PH}$	$(\text{CF}_3)_2\text{P}^\bullet$	15	85	Photochemical	238
H_3P	$\text{H}_2\text{P}^\bullet$	52	48	Photochemical	237
$(\text{CH}_3)_2\text{PH}$	$(\text{CH}_3)_2\text{P}^\bullet$	23	77	Photochemical	239
CCl_3Br	CCl_3^\bullet	20	80	Photochemical	240
$\text{C}_3\text{F}_7\text{I}$	$\text{C}_3\text{F}_7^\bullet$	88	12	Photochemical	241
$\text{CH}_3\text{N}=\text{NCH}_3$ + CH_3I	CH_3^\bullet				

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).



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	$\sim 80^c$	$\sim 20^c$	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	
$\text{CF}_2=\text{CH}_2$	—	100	245	—	100	59
$\text{CF}_2=\text{CHF}$	11	89 ^a	234	—	—	—
	26	74 ^b	235	42	58	235
	32	68 ^c	234	—	—	—
$\text{CF}_2=\text{CHCl}$	90	10	246	100	—	246
$\text{CF}_2=\text{CHCF}_3$	40	60	247	72	28	247
$\text{CF}_2=\text{CFCl}$	100	—	248	100	—	249
$\text{CF}_2=\text{CFCF}_3$	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.

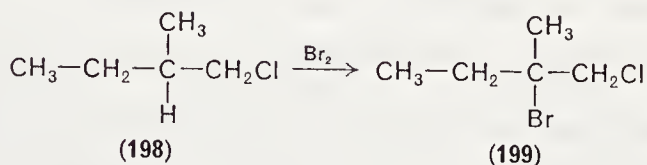
The results reported in Table 76 as well as those in the previous tables of this section show that there are many factors which co-operate in determining the rates and orientation of the homolytic addition to carbon-carbon double bonds. The relative stabilities of the radicals to be formed always play 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}.

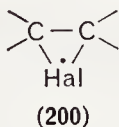
3. Stereochemistry

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 works²⁵³ reported that chlorination of (+)-1-chloro-2-methylbutane (**198**) in the pure liquid yielded inactive 1,2-dichloro-2-methylbutane, it was more recently found²⁵⁴ that the photobromination of the same compound (**198**; $\alpha = +1.38$) gives optically active 2-bromo-1-chloro-2-methylbutane (**199**; $\alpha = -1.45$).



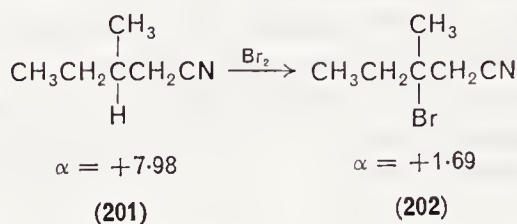
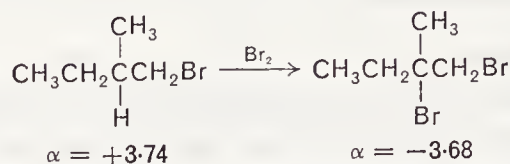
Similar results²⁵⁴ were obtained in the photobromination of (+)-1-bromo-2-methylbutane ($\alpha = +4.89$) which gives (−)-1,2-dibromo-2-methylbutane ($\alpha = -2.86$). The bromination with *t*-butyl hypobromite of the same substrates gave similar results although with lower optical yields ($\alpha = -1.8/-2.0$), 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.



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. studies²⁵⁵ 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.

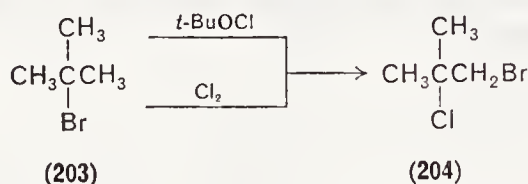
The intervention of bridged species in these reactions has been questioned by Haag and Heiba²⁵⁶. They confirmed the results of Skell and

coworkers²⁵⁴ 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



would act by bridging, and the changes in optical rotation are similar, some other explanation for the stereospecificity must be sought. The authors²⁵⁶ 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.

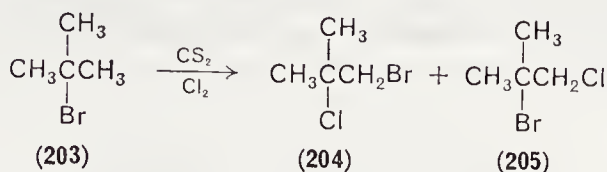
However, there is other evidence which may suggest that halogens act as bridging atoms at a radical centre. The chlorination of *t*-butyl bromide (203) with *t*-butyl hypochlorite at -78° and the photoreaction with chlorine at 24° gives only 1-bromo-2-chloro-2-methylpropane (204)²⁵⁷.



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.

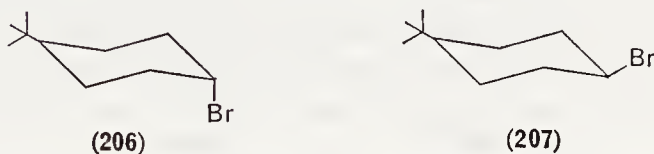
The formation of 1-bromo-2-chloro-2-methylpropane requires the $2 \rightarrow 1$ bromine shift and may be explained by bromine bridging across the two carbons. The classical controversy, whether the bridged structure is representative of the transition state of the shift or of an intermediate

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-methylpropane²⁵⁸.



The authors²⁵⁸ 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 bromocyclopentane²⁵⁹. Moreover, the greater reactivity of *cis*-4-bromo-*t*-butylcyclohexane (206) in respect to the *trans*-isomer (207) ($k_{\text{cis}}/k_{\text{trans}} > 15$)²⁶⁰ may suggest an anchimeric effect of the



axial bromine. Similarly Thaler²⁵⁹ 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 $\text{C}_{(3)}$ 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-bromobutane²⁵⁹ 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°²⁵⁹

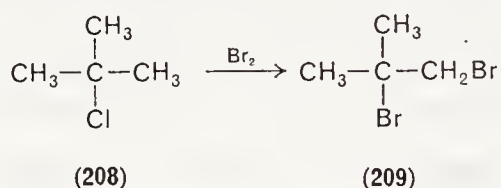
Y	1	2	3	4
Cl	—	1.00	0.0858	—
Br	—	1.00	5.13	—

^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 obtained²⁵⁷ 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.



The intervention of the elimination-addition mechanisms has been recently stressed^{261, 262}. Ashton, Tedder and Walton²⁶² 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 claimed²⁵⁹ 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 olefins²⁶³. The addition to 1-bromo-²⁶⁴ and 1-chloro-cyclohexene²⁶⁵ gives more than 99% of the *cis*-1,2-dihalogeno-cyclohexane. Similar preference for *anti* addition²⁶⁶ was also found in other cyclic 1-bromoalkenes (see Table 79), although in the small rings, possibly

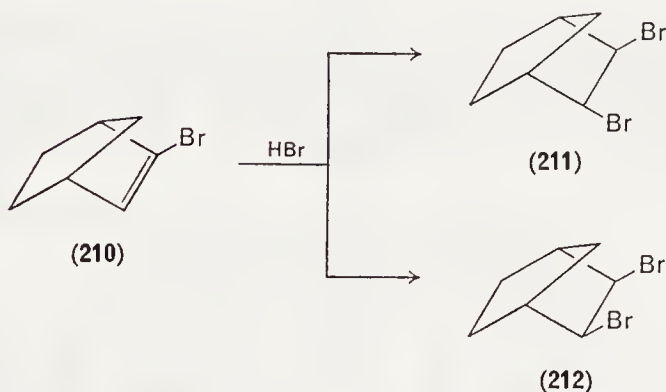
TABLE 79. Percentage of *anti* adducts in the hydrobromic acid addition to 1-bromocycloalkenes²⁶⁶

1-Bromocyclobutene	79
1-Bromocyclopentene	94
1-Bromocyclohexene ^a	99
1-Bromocycloheptene	91

^a From reference 264.

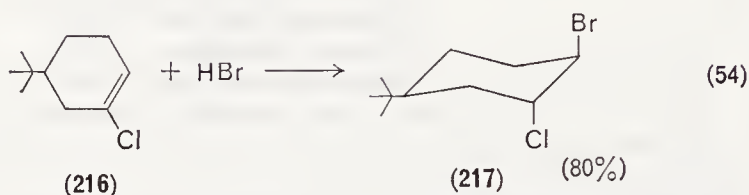
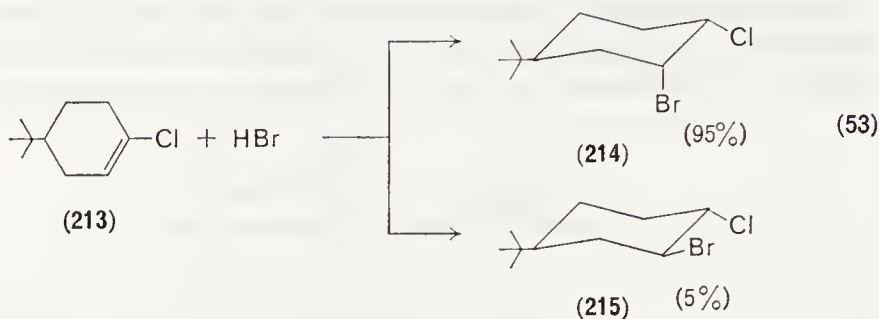
because of *cis* repulsion of the halogens, substantial amounts of products derived from *syn* addition are formed.

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 important²⁶⁷.

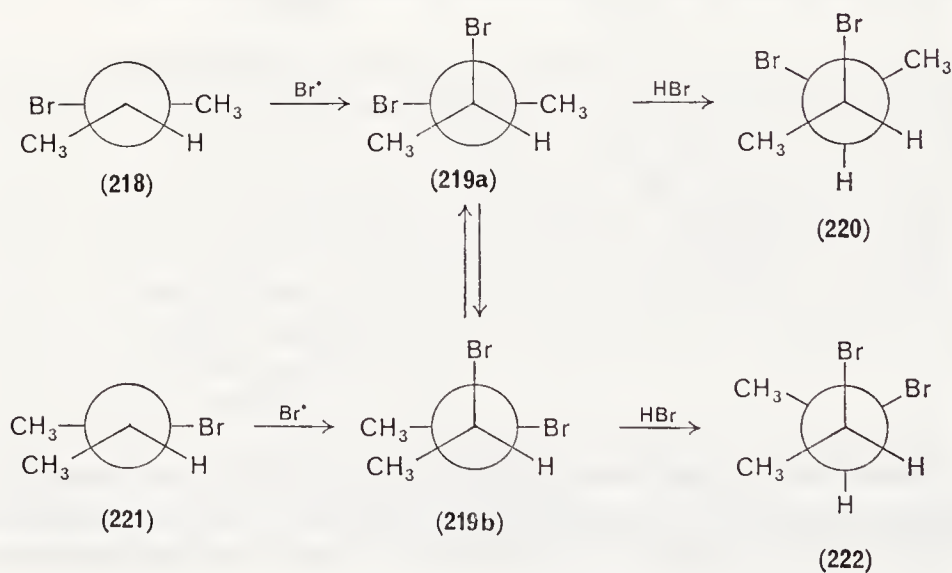


The addition of hydrobromic acid to 1-chloro²⁶⁸ (**213**) and 2-chloro²⁶⁹ (**216**)-4-*t*-butylcyclohexene, which gives the products reported in equations (53) and (54) may again be explained on the basis of the requirement for

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.



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 formed²⁷⁰ 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 $80^\circ C$ 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 substituents²⁷². 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	<i>ortho</i>	<i>meta</i>	<i>para</i>	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 radical²⁷¹.

TABLE 82. Relative rates of arylation with substituted phenyl radicals ($\text{XC}_6\text{H}_4^\bullet$) at 80° ²⁷¹

X	Relative rates ($\text{C}_6\text{H}_6 = 1$)		
	$\text{O}_2\text{NC}_6\text{H}_5$	ClC_6H_5	BrC_6H_5
<i>p</i> -NO ₂	0.94	1.17	1.5
<i>p</i> -Cl	1.5	1.02	—
<i>p</i> -Br	1.8	—	—
<i>p</i> -OCH ₃	2.9	1.6	—
H	4.0	1.5	1.7
<i>p</i> -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 ($\text{C}_6\text{H}_6 = 1$) for reactions of substituted benzenes ($\text{C}_6\text{H}_5\text{X}$) 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			Reference
	<i>ortho</i>	<i>meta</i>	<i>para</i>	<i>ortho</i>	<i>meta</i>	<i>para</i>	<i>ortho</i>	<i>meta</i>	<i>para</i>	
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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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 stoichiometry 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.

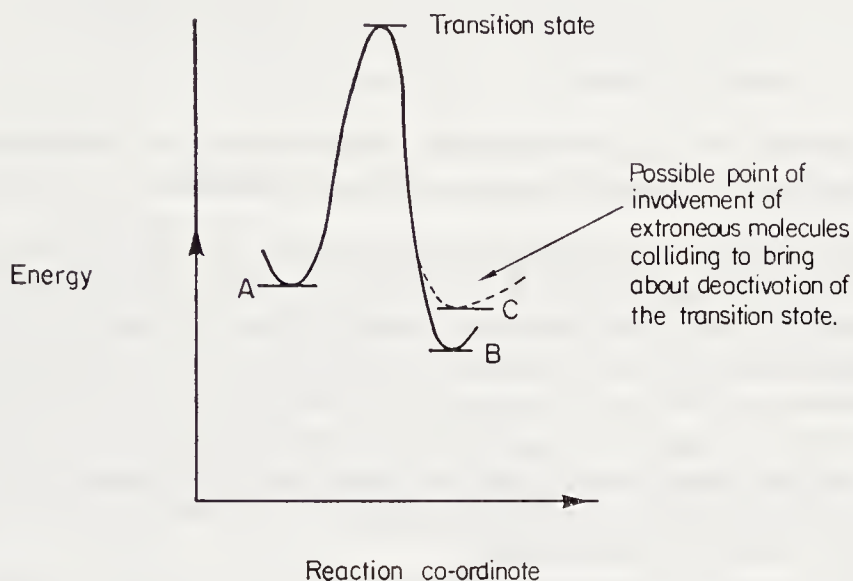


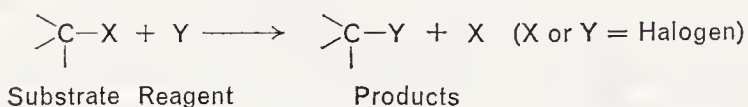
FIGURE 1.

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, $\begin{array}{c} >C-X \\ | \end{array}$, 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 following²:

(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 $F \geq Cl, Br, I$.

(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 stoichiometric 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 stoichiometry.

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 stoichiometry (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 stoichiometry is represented



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 , $S_N2(\text{C}^+)$, $S_N2(\text{Ar})$. 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

I. 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.



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 anion³.



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

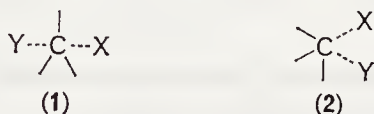
TABLE 1. Relative reactivities ($\text{RCl} = 1$) of aliphatic halides in bimolecular nucleophilic displacements with sodium ethoxide in ethanol

	X: F	Cl	Br	I
$n\text{-C}_4\text{H}_9\text{X}$ at 50°	0.004	—	29	—
$\text{C}_2\text{H}_5\text{X}$ 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 summarized⁴. The comparison given in Table 1 is illustrative and is derived from data summarized elsewhere⁵. 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,

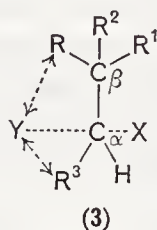


has rather precise geometric requirements. The geometry **1** is favoured over geometry **2** by such a large energy-difference that even when the entering and leaving groups initially have opposite charge, so that electrostatic interaction would favour the latter, it is the former that is experimentally 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 example⁶, 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; Gillespie⁹ 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, R¹ in 3) can be just as effective in hindering replacement as are similar groups in the α -position (e.g. R³ in 3). The most spectacular illustration of this comes from the extraordinary unreactivity of neopentyl halides (e.g. Me₃CCH₂Br)¹⁰; this was shown to be associated with the

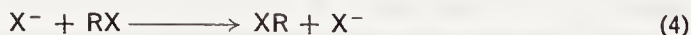


*S*_N2 mechanism by Dostrovsky, Hughes and Ingold¹¹, and can be illustrated by the rate and energy sequences in Table 2.

TABLE 2. Relative rates and Arrhenius activation energies for bimolecular substitutions of primary alkyl bromides, RBr, with ethoxide ions in ethanol

	R: Me	Et	<i>n</i> -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
<i>E</i> _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



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
$\Delta E_A (E_A^R - E_A^{Et};$ 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 $R = \text{Me}$, $\log_{10}B$ (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 coworkers¹³ 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 Parker¹⁷ have re-examined one of the unsymmetrical exchange reactions ($\text{RBr} + \text{Cl}^-$) 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 calculated¹⁸.

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 $^{12}\text{C} : ^{14}\text{C}$ isotope effect is ca. 1.12 at 25°; but for the reaction of methyl iodide with cyanide ions¹⁹, values of $k_2(^{12}\text{CN}^-) : k_2(^{13}\text{CN}^-)$ around 1.01 have been obtained. Such relatively small values arise because of opposing, partially cancelling, components in the frequency changes¹⁸.

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, $^{35}\text{Cl} : ^{37}\text{Cl}$ isotope effects of ca. 1.006–1.007 were obtained²⁰, 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.

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 Holness¹⁴, and subsequently abandoned¹⁵, should be revived for this case, though probably not for most others¹⁶.

Related results for nucleophiles reacting with *n*-butyl chloride and with some substituted benzyl chlorides²¹ 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: $T^\circ\text{C}:$	$p\text{-MeOC}_6\text{H}_4\text{CH}_2\text{Cl}$ 20°	$\text{C}_6\text{H}_5\text{CH}_2\text{Cl}$ 20°	$p\text{-O}_2\text{NC}_6\text{H}_4\text{CH}_2\text{Cl}$ 20°	$\text{C}_4\text{H}_9\text{Cl}$ 40°
Nucleophile, PhS^- ; 10^4k_2 $k_2(^{35}\text{Cl}) : k_2(^{37}\text{Cl})$	820 1.0098	130 1.0095	760 1.0092	2.3 1.0084
Nucleophile, PhO^- ; 10^4k_2 $k_2(^{35}\text{Cl}) : k_2(^{37}\text{Cl})$	— —	— —	0.080 1.0079	— —
Nucleophile, $n\text{-C}_4\text{H}_9\text{S}^-$; 10^4k_2 $k_2(^{35}\text{Cl}) : k_2(^{37}\text{Cl})$	— —	— —	1000 1.0087	3.1 1.0081
Nucleophile, CH_3O^- ; 10^4k_2 $k_2(^{35}\text{Cl}) : k_2(^{37}\text{Cl})$	— —	0.12 1.0080	0.20 1.0076	0.01 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 report²², 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	$T^\circ\text{C}$	$k_2(^{12}\text{C}) : k_2(^{14}\text{C})$	Reference
$p\text{-MeC}_6\text{H}_4\text{CH}_2\text{Cl}$	CN^-	80% Dioxan	40	1.09	18
$p\text{-ClC}_6\text{H}_4\text{CH}_2\text{Cl}$	CN^-	80% Dioxan	40	1.11	18
$\text{C}_6\text{H}_5\text{CH}_2\text{Cl}$	CN^-	80% Dioxan	40	1.10	18
$\text{C}_6\text{H}_5\text{CH}_2\text{Br}$	OMe^-	MeOH	0	1.10 ^a	23
$\text{C}_6\text{H}_5\text{CH}(\text{Me})\text{Br}$	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 $k_2(^{12}\text{C}) : k_2(^{13}\text{C})$ and has been corrected appropriately¹⁸.

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 Nathan²⁸ 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	$10^4 k_2$
2,4-Dinitrobenzyl	ca. 33
<i>p</i> -Nitrobenzyl	8.2
Benzyl	4.3
<i>p</i> - <i>t</i> -Butylbenzyl	6.8
<i>p</i> -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 results²⁹ 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.

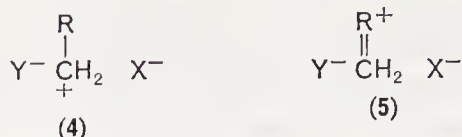
Substrate	Nucleophile (M)	$10^5 k_2$ 0°C (1 mole ⁻¹ s ⁻¹)	E_A (kcal mole ⁻¹)	$\log_{10} B$ (B in 1 mole ⁻¹ s ⁻¹)
CH ₃ Cl	LiCl (0.028)	0.16	20.2	10.4
PhCH ₂ Cl	LiCl (0.028)	0.16	18.3	8.9
CBr ₄	LiBr (0.024)	Very small	—	—
CH ₂ Br ₂	LiBr (0.024)	0.23	20.9	10.7
CH ₃ Br	LiBr (0.024)	1120	15.8	10.7
PhCH ₂ Br	LiBr (0.024)	1120	—	—
Ph ₂ CHBr	LiBr (0.024)	3.3	17.2	9.2

Comparison of the increment in activation energy, (BrCH₂Br—CH₃Br, $\Delta E_A = 5.1$ kcal mole⁻¹: Table 6) with the corresponding value for the methyl substituent (MeCH₂Br—CH₃Br, $\Delta E_A = 1.7$ 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 substituent³⁰.

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 given³¹; methoxymethyl chloride is more reactive than methyl chloride with ethoxide ions in ethanol at 0° by a factor of about 10⁵.

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.



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 Parker³², who

TABLE 8. Rates of bimolecular (S_N2) reactions of some alkyl bromides, RBr, with chloride ions

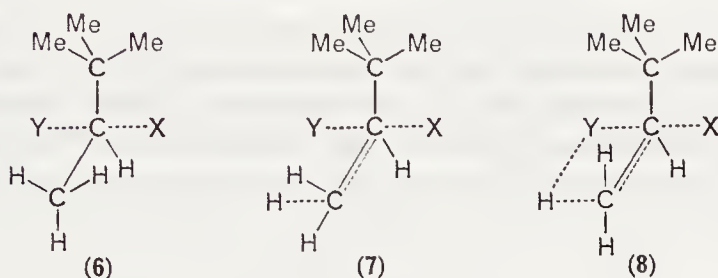
R	Solvent	T °C	log ₁₀ k ₂
MeCH ₂	Dimethylformamide	100	0.95
<i>t</i> -BuCH ₂	Dimethylformamide	100	-3.26
MeCH(Me)	Acetone	100	-1.0
<i>t</i> -BuCH(Me)	Acetone	100	-3.4

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 bromide¹², 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 $t\text{-BuCH(Me)Br}$ 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 $t\text{-BuCH(Me)Br}$ 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 coworkers¹², but more like the so-called $E2C$ transition state. As applied to Cook and Parker's particular example, the representations under consideration are 6 (S_N2), 7 ($E2C$ -like) and 8 (intermediate between 7 and the transition state for an $E2$ elimination, though considered to be leading to substitution).

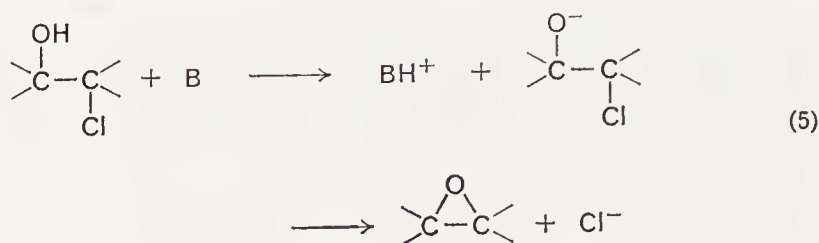


The hyperconjugative structure 7 must bring one hydrogen atom of the methyl group into such great proximity to the entering group Y that the steric repulsion between them would, on the usual assumptions concerning non-bonding interactions, be prohibitive. Structure 7, therefore, provides no rationale 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).

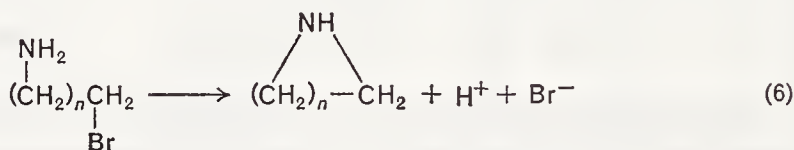
2. Intramolecular ('internal') processes

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 involved³³.



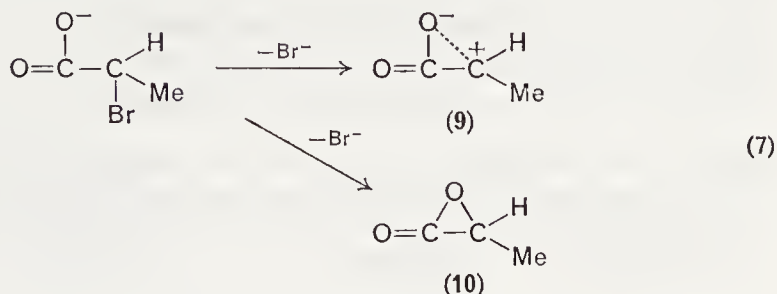
Chlorohydrins with the reactive substituents more distant from each other react similarly, providing that the stereochemistry allows them to come within effective bonding distance and to give an S_N2 -like transition state. Similar considerations apply to the ring-closures of bromo-amines according to equation (6). The ease of formation of these products as it



relates to ring-size was reviewed by Bennett³⁴. 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 halogen³⁵, where the sequence is S_N2 , followed by S_N2 , giving overall retention of configuration by way of two formal inversions.

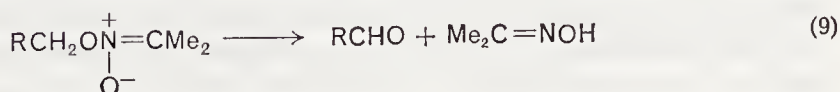
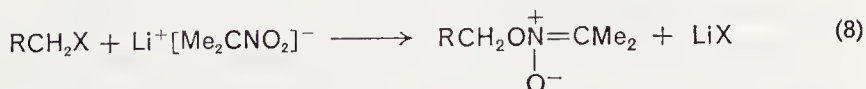


The question of whether the reaction actually gives an α -lactone (**10**), and so differs from the other cases only because α -lactones undergo subsequent reactions different from those of their β -, γ - and δ -analogues, has been discussed by other workers: Winstein, Grunwald and coworkers³⁶ concluded that no firm distinction could be made between the intermediacy of **9** and **10** on the basis of the existing evidence.

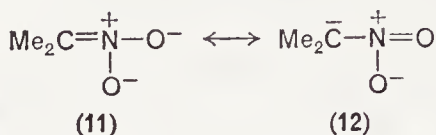
The writers consider that most rigid schemes of classification, if pressed too far, introduce unhelpful semantic difficulties; the intramolecular reactions clearly have analogies both with S_N2 and with unimolecular processes, and we shall return in a later section to the kinetics and stereochemistry associated with the formation of unstable intermediates of displacement such as **9** or **10**.

3. Bimolecular radical-ion processes

These reactions have recently been reviewed³⁷. 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 coworkers³⁸



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



cases become dominant, especially for the reactions involving attack on *p*- and *o*-nitrobenzyl chlorides. In the example of equation (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

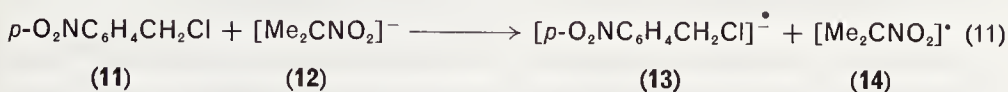
TABLE 9. Rates and products in the reaction of some nitrobenzyl halides with the lithium salt of 2-nitropropane in dimethylformamide at 0°C

Halide	Second-order rate-coefficients (k_2 , l mole ⁻¹ s ⁻¹)		
	$k_2(\text{total})$	$k_2(\text{carbon})$	$k_2(\text{oxygen})$
<i>p</i> -O ₂ NC ₆ H ₄ CH ₂ Cl	0.023	0.02	0.002
<i>p</i> -O ₂ NC ₆ H ₄ CH ₂ Br	0.34	0.068	0.27
<i>p</i> -O ₂ NC ₆ H ₄ CH ₂ I	1.9	0.15	1.8
<i>m</i> -O ₂ NC ₆ H ₄ CH ₂ Cl	0.0013	—	0.0013
<i>m</i> -O ₂ NC ₆ H ₄ CH ₂ Br	0.28	—	0.28
<i>m</i> -O ₂ NC ₆ H ₄ CH ₂ I	1.4	—	1.4

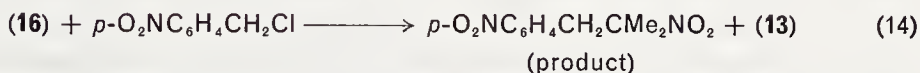
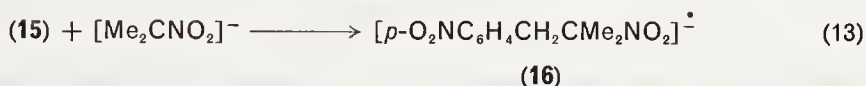
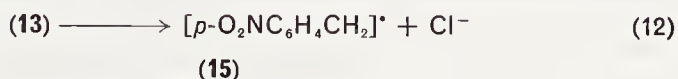
sequence of reactivity, I > Br > Cl, and the spread through the series, is that observed for other S_N2 reactions both for *m*- and for *p*-nitrobenzyl halides. The much smaller spread for the C-alkylation of the *p*-nitrobenzyl halides, and the consequent change in product-ratio with change from iodide 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, therefore³⁸, that carbon-alkylation in this system is effected through the intermediacy of a radical anion. Later work³⁹ showed that a chain-process was involved, so we can amplify the mechanism as in equations (11)–(15).

Chain-initiating process:



Chain-propagating processes:



Chain-terminating process:



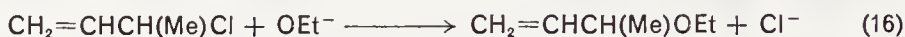
In still later work⁴⁰ it was shown that the C-alkylation of some β -keto-esters by nitrophenyl-substituted alkyl halides (particularly tertiary halides, such as *p*-nitrocumyl chloride) can also involve chain-reactions with radical-anions as intermediates; these could often, but not always, be inhibited 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 processes⁴¹.

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

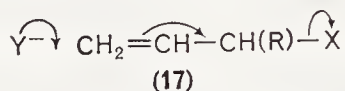
in organic compounds⁴². Some measurements of relative reactivities of organic halides with radical-anions have been made^{43, 44}; the reactions are bimolecular in dioxan as solvent, and alkyl chlorides seem to react more rapidly than the corresponding bromides or iodides, thus reinforcing Kornblum's 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).



It was first proposed independently by Hughes⁴⁵ and by Winstein⁴⁶ that the analogous bimolecular mechanism giving rearrangement could exist. The process can be formulated as in 17. The simplest form that could be



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 us⁴⁷ 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 report¹⁸ that the reaction of diethylamine with 3-chlorobut-1-ene (equation 17) gives substantial isotope effects. Values obtained were:

$$\begin{aligned} k_2(^{12}\text{C}_1) : k_2(^{14}\text{C}_1) &= 1.057; & k_2(^{12}\text{C}_2) : k_2(^{14}\text{C}_2) &= 1.074 \\ k_2(^{12}\text{C}_3) : k_2(^{14}\text{C}_3) &= 1.079; & k_2(^{35}\text{Cl}) : k_2(^{37}\text{Cl}) &= 1.011 \end{aligned}$$

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.



Secondly, an important comparison has been made between allylic chlorides and allylic bromides reacting with and without rearrangement by bimolecular mechanisms⁴⁸. 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.

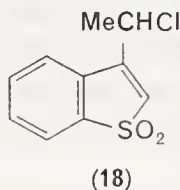
TABLE 10. Rates (k_2) and activation parameters for exchange and rearrangement of 1- and 3-methylallyl halides in acetone (bromides) or acetonitrile (chlorides)

Compound	Halide	Mechanism	$10^6 k_2$ at 25°C (l mole ⁻¹ s ⁻¹)	ΔH^\ddagger (kcal mole ⁻¹)	ΔS^\ddagger (e.u.)
$\text{CH}_2=\text{CHCH}(\text{Me})\text{Br}$	Br^-	S_N2	879	15.9	-19.1
$\text{CH}_2=\text{CHCH}(\text{Me})\text{Br}$	Br^-	S_N2'	14.9	18.8	-17.7
$\text{BrCH}_2\text{CH}=\text{CHMe}$	Br^-	S_N2	141,000	14.1	-15.0
$\text{BrCH}_2\text{CH}=\text{CHMe}$	Br^-	S_N2'	5	ca. 18	ca. -19
$\text{CH}_2=\text{CHCH}(\text{Me})\text{Cl}$	Cl^-	S_N2	2.87	20.8	-13.9
$\text{CH}_2=\text{CHCH}(\text{Me})\text{Cl}$	Cl^-	S_N2'	0.0133	24.2	-13.4
$\text{ClCH}_2\text{CH}=\text{CHMe}$	Cl^-	S_N2	315	18.8	-11.6
$\text{ClCH}_2\text{CH}=\text{CHMe}$	Cl^-	S_N2'	0.0053	24.3	-14.9

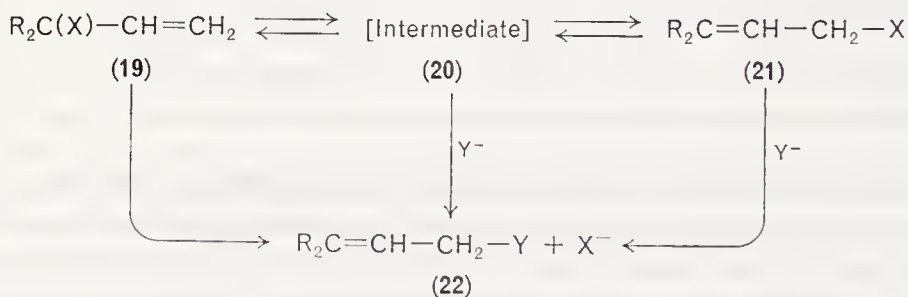
The use of isotopic tracers in such an investigation has the advantage that exchange does not change the starting material chemically, so that both S_N2 and S_N2' processes can be investigated under the same conditions, even if the first is much more rapid than the second. The pattern of results for 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

$\text{CH}_2=\text{CHCHCl}_2$ and $\text{CH}_2=\text{CHCH}(t\text{-Bu})\text{Cl}$ referred to in the review mentioned above⁴⁷.

Thirdly, Bordwell and coworkers⁴⁹ 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.



These workers have expressed reservations concerning the mechanistic classification of most of those 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 us⁴⁷, as also by others⁵⁰. One path which Bordwell considers⁵¹ 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 $\text{R}_2\text{C}(\text{X})-\text{CH}=\text{CH}_2$

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 criticized⁵², and the writers consider that, Bordwell's view to the contrary notwithstanding, the path $19 \rightleftharpoons 21 \rightarrow 22$ has in fact been made quite improbable for a number of important representative

examples. The route $19 \rightleftharpoons 20 \rightarrow 22$, 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 cited⁴⁷. Attention on one of these may be focused by reference to the inclusion by Bordwell and coworkers⁴⁹ 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:



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 $19 \rightleftharpoons 20 \rightarrow 22$ (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.

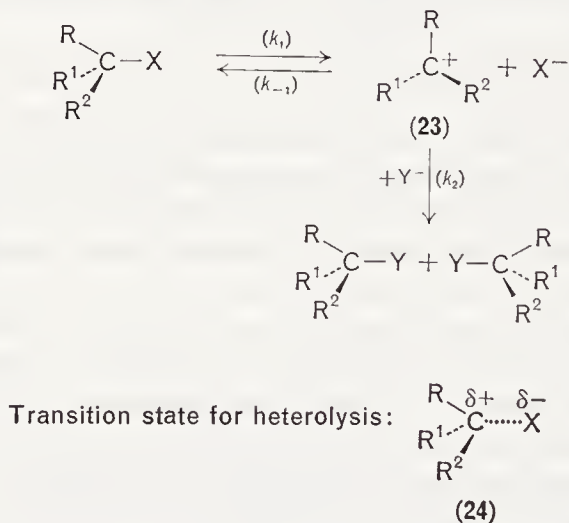
There have in fact been rather few mechanistic investigations of the reactions of allylic fluorides. A number of preparative examples of bimolecular displacements with rearrangement have been recorded for highly substituted fluorocompounds, as has been discussed elsewhere⁴⁷.

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 Patel⁵⁴ 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).



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

$$d[\text{products}]/dt = k_1[RR'R^2CX] \quad (20)$$

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.

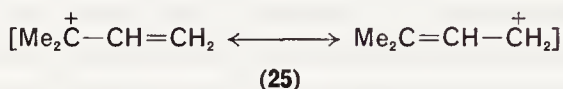
The most satisfactory experimental criterion for such a reaction is achieved when it is possible to show that with two nucleophiles of widely different nucleophilic power (e.g. a hydroxylic solvent and the derived lyate ion) the reaction proceeds at the same rate. This gives clear evidence that the nucleophile 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 behaviour⁵⁷.



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 group⁴⁵. 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 terms⁵⁸. It is not, however, the only possible interpretation. Doering and Zeiss⁵⁹ proposed an alternative in terms of discrete intermediates, the formation of which follows the original rate-determining ionization. Streitwieser⁶⁰ 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

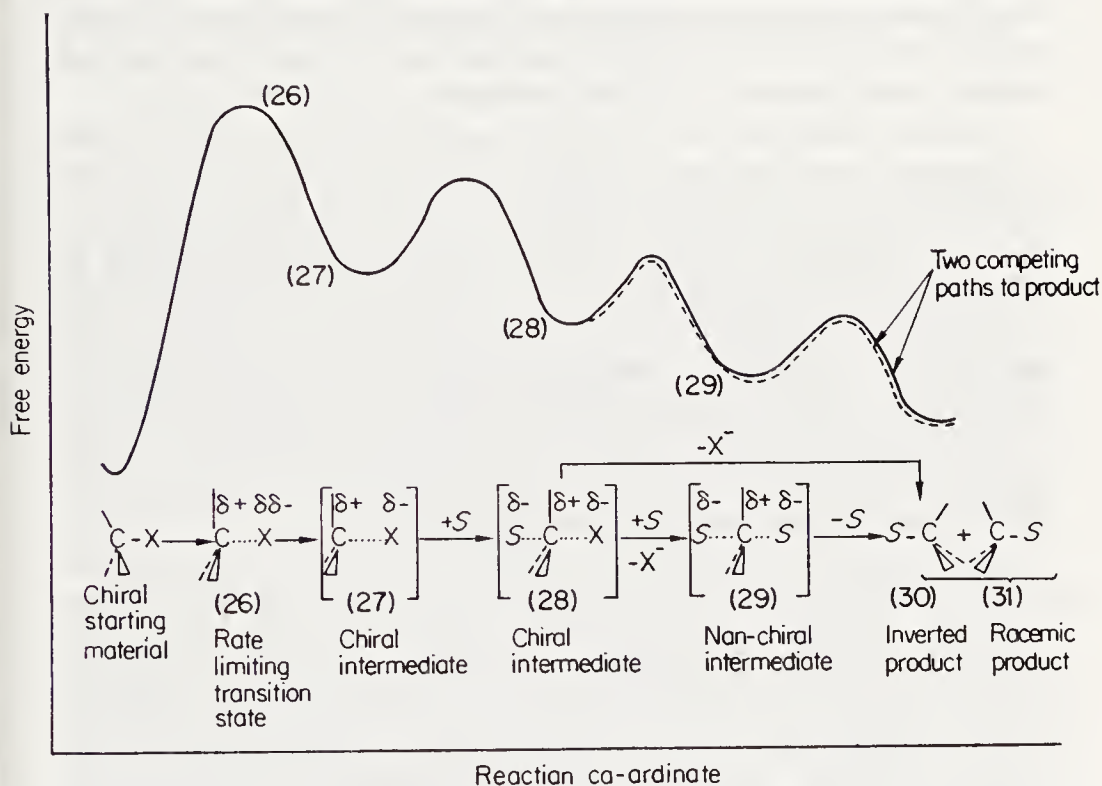


FIGURE 2

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 $C\cdots X$ 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.

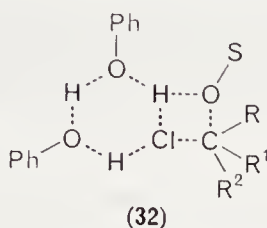
(iii) A very rapid conversion, still needing some energy of activation, of **27** to a new, still chiral, intermediate, **28**, in which the solvent is now partly bonded to the reaction centre.

(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 halides⁶¹ and of 1-phenylethyl halides⁶² 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 Taylor⁶³, was put on a firm footing by Okamoto and coworkers⁶⁴. 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 interpretation⁶⁴ 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 group⁶⁵.

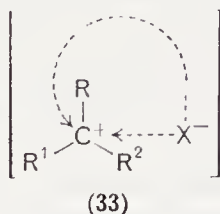


Further new information is sometimes revealed if the overall rate of reaction can be followed by more than one technique. In particular, there have been a number of studies in which it has been shown that the rate-coefficient for a solvolysis followed by titrimetric measurement of the production of the 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 acetone⁶⁶ and of 1-phenylethyl chloride in aqueous acetone and other solvents^{67, 68}.

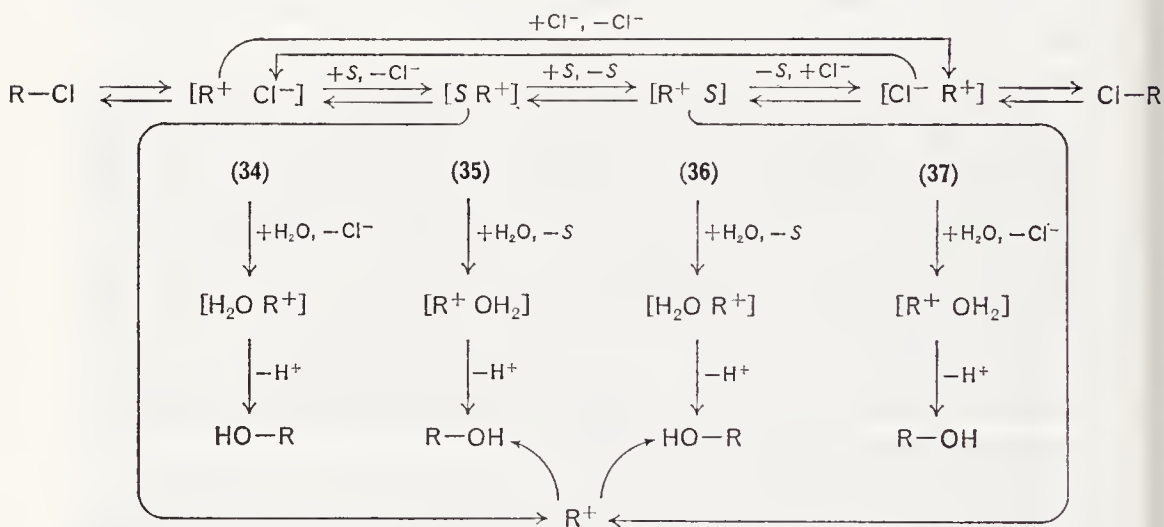
This observation implies that the starting material has in part racemized or undergone some other change before solvolysis is complete. This could happen in a number of ways, a trivial one of which would involve bimolecular exchange between the developing halide ion and the unchanged organic halide. 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 suggested⁶⁷ that all of the results that



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 proposal⁵⁹, 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 publication⁶⁷, 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 \rightleftharpoons **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.

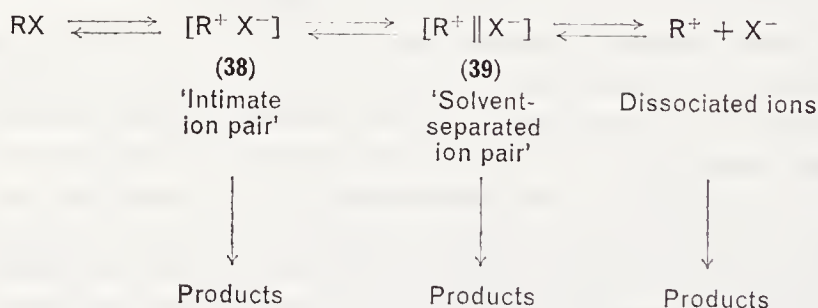
(iv) If the bulk of the product is derived from **34**, then solvolysis will proceed with overall inversion of configuration.

(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 coworkers⁷² 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. LiClO₄) the rate increases approximately linearly with salt concentration. Some organic halides, however, of which cholesteryl chloride is an example⁷³, 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 10⁻³M. Two theories have been proposed for interpretation of the results. The first is that indicated in Scheme 4 and advocated by Winstein and coworkers⁷².

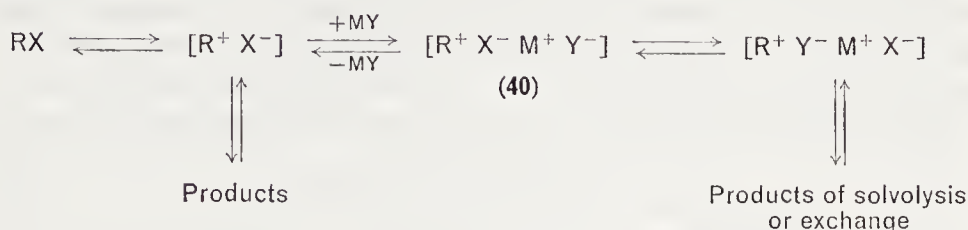


SCHEME 4. 'Two ion pairs' interpretation of solvolyses in acetic acid.

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.



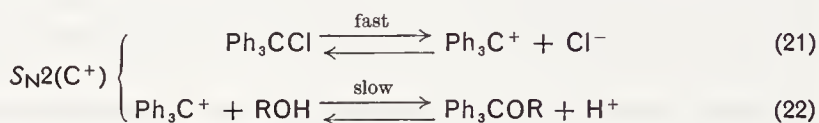
SCHEME 5. Ion-quadruplet formulation of solvolyses in acetic acid in the presence of an added electrolyte, MY.

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 coworkers⁷⁴, 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.

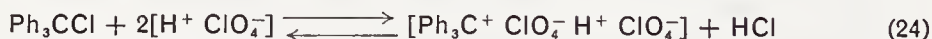
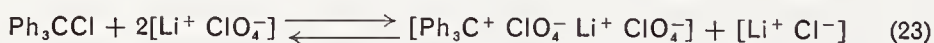
6. The $S_N2(C^+)$ mechanism

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 nitromethane⁷⁸ (equations 21, 22). This mechanism can be categorized as $S_N2(C^+)$ on the convention that the whole process (equations 21, 22) is a



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 Buchholz⁷⁹ 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



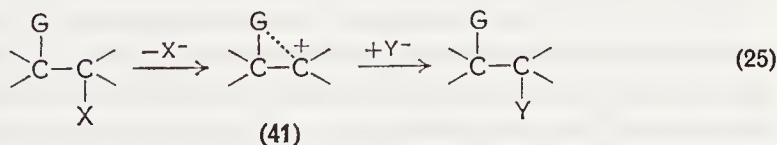
results focus further attention on the importance of ionic aggregates in determining the course and rate of such a reaction.

Leffek⁸⁰ 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 $\text{S}_{\text{N}}2$ 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).



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, $G-CH_2CH_2-X$

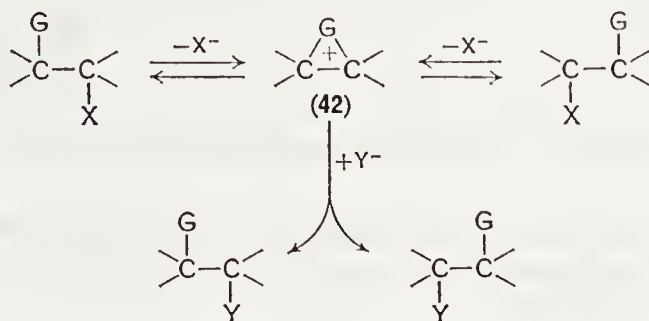
G in GCH_2CH_2X :	$HOCH_2CH_2S$	I	NH_2	O^-	Br	OH	Cl
L_0 (kcal mole ⁻¹ , 25°C)	13	8.7	8.0	6.0	4.5	1.3	0.0

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).

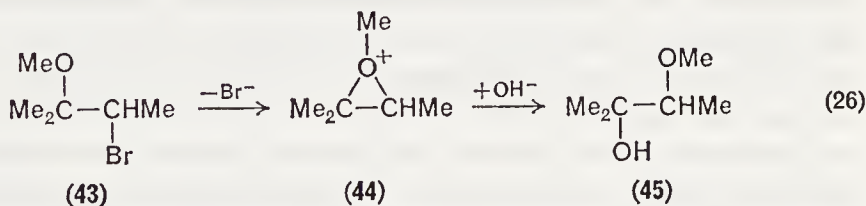
We now need to consider the situation in which the participation by the neighbouring group G gives an intermediate which, though reactive enough

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.

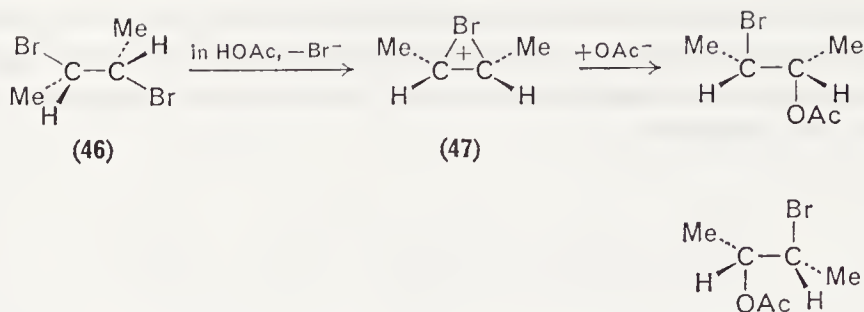


SCHEME 6. Some chemical and stereochemical consequences of heterolysis assisted by neighbouring-group participation.

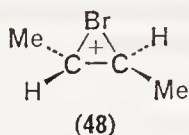
Two methods have been used for establishing this type of behaviour. The first is applicable when the two carbon atoms to which G is attached in the intermediate **42** have different substituents attached to them. Then, if reaction is followed from the appropriate starting material, the existence of 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.



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

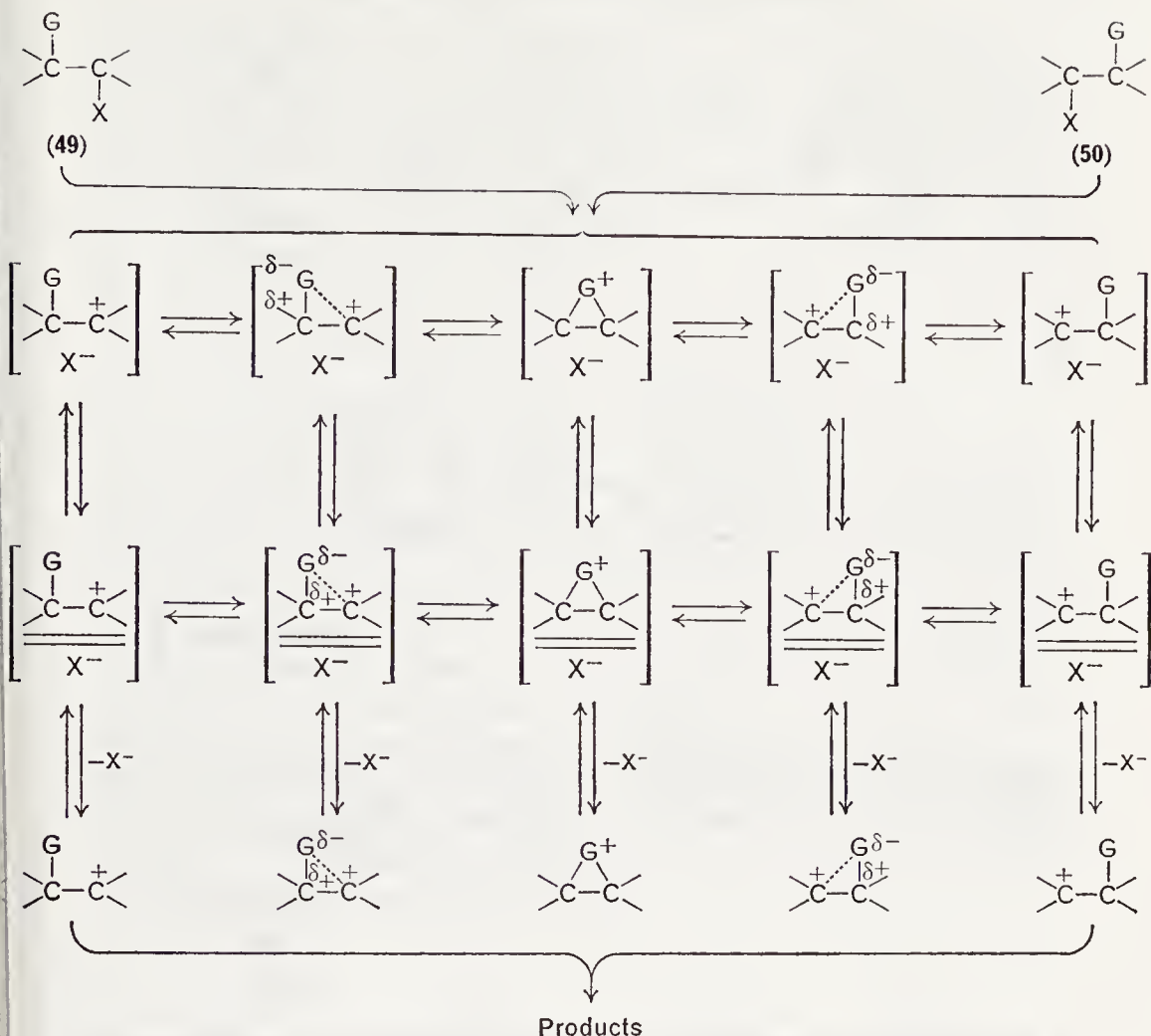
SCHEME 7. Acetolysis of a *threo*-2,3-dibromobutane.

starting material, on the other hand, gives the chiral intermediate (48), and so gives replacement with retention of optical activity despite the accompanying migration.



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.

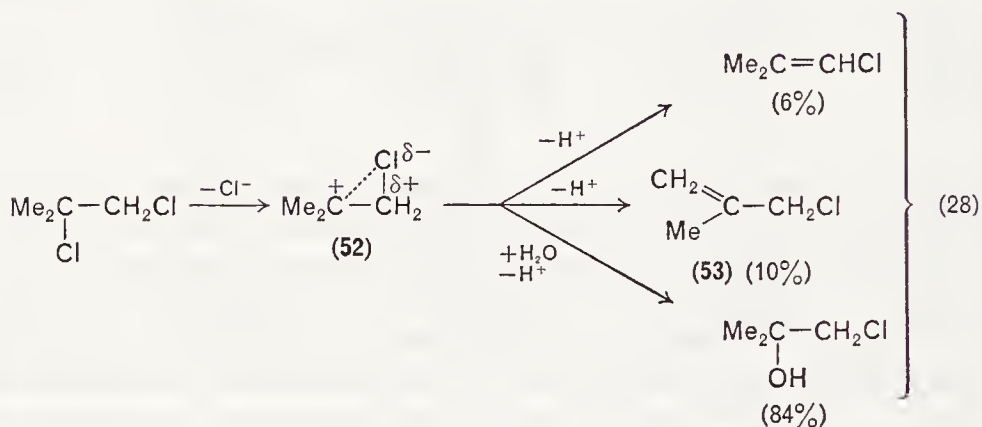
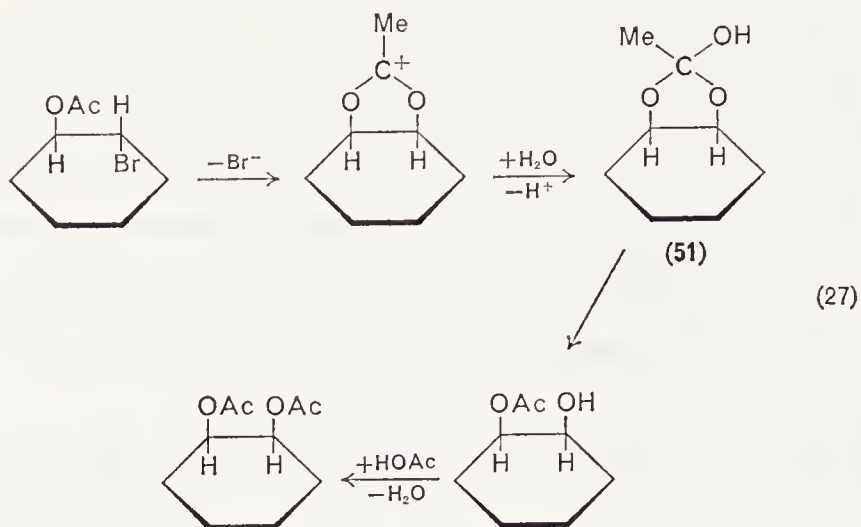
These considerations do not exhaust the ramifications of substitutions controlled by neighbouring-group participation. With certain complex neighbouring groups, the chemistry of the intermediate written for generality as **41** is such that its further reactions may not necessarily involve either of 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.

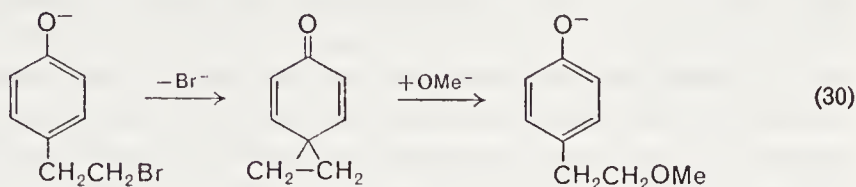
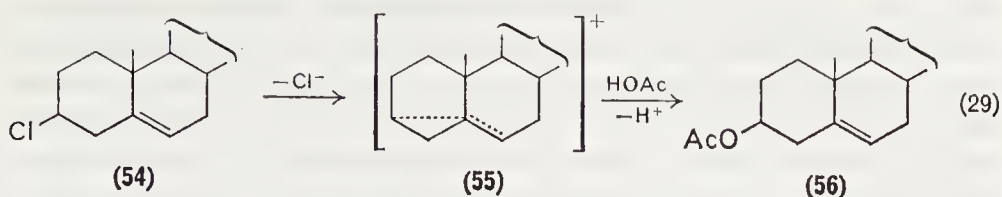
Neighbouring-group interaction can also modify the course of other reactions accompanying nucleophilic substitution. Thus the proportion of the isomeric products of elimination formed in the hydrolysis of 1,2-dichloro-2-methylpropane⁸⁵ is probably modified in favour of 53 through the neighbouring-group interaction indicated in 52 (sequence 28).



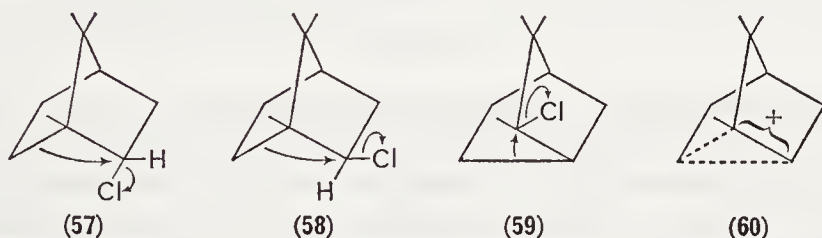
8. Unimolecular processes with participation by neighbouring carbon or hydrogen

Interaction between a neighbouring group and a carbonium ionic centre is not confined to groups bearing a lone pair of electrons. Shoppee⁸⁶ 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 Winstein⁸⁷ have exemplified this by examination of a case in which the intermediate is sufficiently stable to be isolated (equation 30).



The possibility that saturated groups might similarly participate in replacement reactions was first indicated by Nevell, de Salas and Wilson⁸⁸; 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 chloride⁸⁹. 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.

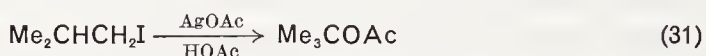


The most direct interpretation of these results is that the electron movements shown in 57 have to be consecutive, for steric reasons; so this solvolysis is non-accelerated, though it gives rearranged products. The movements shown in 58, on the other hand, can be concerted, so that an accelerated rearrangement 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.

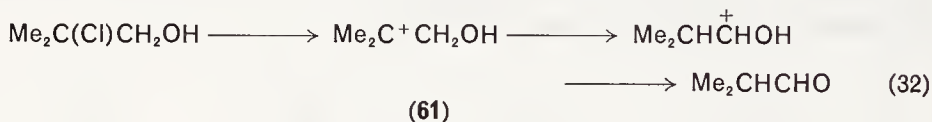
The type of intermediate concerned in such reactions has been termed 'non-classical', 'synartetic' and 'anchimeric' by different groups of workers.

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



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**



probably occurred intra-, rather than intermolecularly, since it had been shown that the analogous cation $\text{Me}_2\text{C}^+\text{CH}_2\text{OMe}$ could undergo intramolecular hydrogen-shift⁹². It may be noted that the related cation $\text{Me}_2\text{C}^+\text{CH}_2\text{Cl}$ gives only a very small proportion of rearrangement to isobutyraldehyde under analogous conditions⁸⁵. Recently it has been shown⁹³ 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 systems⁹⁴.

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

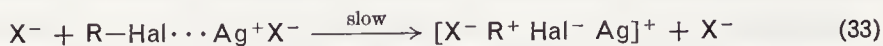
solvolysis of halides in hydroxylic solvents, catalysis by acids has been established for alkyl fluorides, but not for chlorides, bromides or iodides. It would seem^{4, 95, 96} that primary and secondary alkyl fluorides, when undergoing solvolysis in solvents such as aqueous ethanol, use a bimolecular 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 $\text{H}_2\text{O} \cdots \text{R} \cdots \text{F} \cdots \text{H} \cdots \text{F}$, 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 $[\text{R} \cdots \text{F} \cdots \text{H}]^+$, 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 solvents⁹⁷. In these solvents, it seems that the hydrogen chloride molecule can act as a general acid in catalysing the exchange reaction.

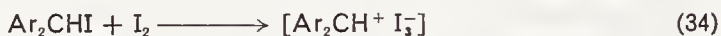
Catalysis by salts of metals appears normally to be S_N1 -like, with transition states of the form $[\text{R} \cdots \text{Hal} \cdots \text{M}]^+$. The most cogent argument supporting the availability of transition states of this form derives from the nature of the products; both heterogeneous silver-catalysed 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 adduced¹⁰⁰. 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 substrates¹⁰¹. 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.



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

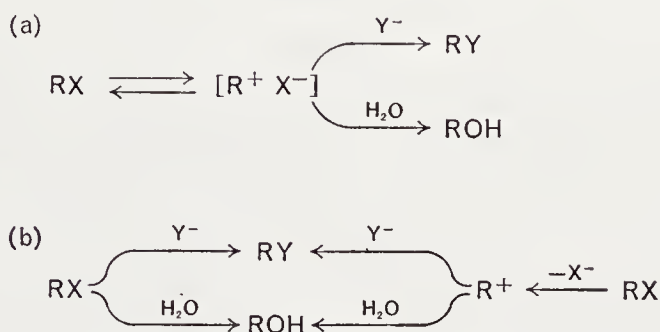


the kinetic measurements, the intermediates and transition states must have the nature of ion pairs rather than of free ions; kinetic evidence for the participation of more than one iodine molecule was obtained also.

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 review⁶⁰. 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 group¹⁰³ 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, Snee 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 Halford¹⁰⁵ used such a relationship as evidence that any solvolysis of an alkyl halide is bimolecular. Kohnstam and coworkers¹⁰⁶ have analysed Snee 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



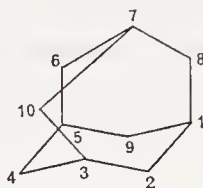
SCHEME 9. Alternative simplified reaction pathways in the 'border-line' area of solvolytic displacements.

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 reactions¹⁸. Similar

deductions have been made¹⁰⁷ from the relative rates of displacement in charged and uncharged systems such as $\text{BrCH}_2\text{CO}_2\text{H}$ and $\text{BrCH}_2\text{CO}_2^-$.

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 coworkers¹⁰⁸. 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 ($10^9 k_1 \text{ s}^{-1}$) for solvolyses of 1-adamantyl bromide, *t*-butyl bromide and *t*-butyl chloride at 25°C

Solvent	<i>t</i> -Butyl chloride ¹⁰⁹	<i>t</i> -Butyl bromide ¹⁰⁹	1-Adamantyl bromide ¹⁰⁸
40% EtOH	1.29×10^6	—	1.21×10^5
HCO ₂ H	1.1×10^6	—	8.25×10^4
60% EtOH	1.27×10^5	3.76×10^6	7.19×10^3
90% EtOH	1.73×10^3	7.14×10^4	2.47×10
CH ₃ CO ₂ H	2.13×10^2	—	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 employed¹¹⁰ 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, ΔC^\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-YC₆H₄CH₂Cl in aqueous acetone at 50°C

Y:	NO ₂	H	Me	<i>p</i> -MeOC ₆ H 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 chlorides¹¹¹.

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

I. 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)^{11,12}. This reaction would proceed to an



unfavourable equilibrium but for the precipitation of the insoluble potassium salt. The reaction was used by Conant and coworkers^{11,13} 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^{11,14}. For a single substrate in hydroxylic solvents, the

established¹¹⁵ 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 found¹². 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 pair¹¹⁶. Treatments of this kind have been used for reactions in ethanol¹¹⁶ and in acetone¹¹⁷. 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 inappropriate¹¹⁸. 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, Parker¹¹⁹ 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 ₂ NCHO	MeNHCHO	Me ₂ NCHO	Me ₂ CO
Relative rate:	1	12	45	1.2×10^6	1.6×10^6

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 catalysts¹²¹ such as SbCl₃

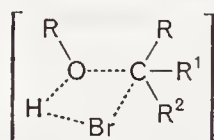
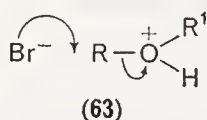
suggests the intervention also of mechanisms involving electrophilic catalysis, but mechanistic work on these reactions is lacking.

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



bromide have been examined in a number of solvents, acetyl bromide being added to combine with the alcoholic product¹²². The rate was found to be proportional to the concentration of diethyl ether and to $[\text{HBr}]^2$ in toluene and some other solvents, to $[\text{HBr}]^{\frac{3}{2}}$ in chloroform and to $[\text{HBr}]$ 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.



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-equilibrium¹²³. 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 mechanism¹²⁴. 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 solvent¹²⁶. 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 alcohols¹²⁴. The rate-sequences $\text{Me} > \text{Et}$, and $t\text{-Bu} > i\text{-Pr} > n\text{-Pr}$, 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 observed¹²⁹. Arcus¹³⁰ 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.

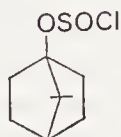
3. Replacement of hydroxyl by halogen by the use of thionyl chloride and related reagents

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



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 implicated¹³¹. 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 chloride¹³². Retention of configuration in the formation of cholesteryl chloride from cholesterol⁸⁶ 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 system¹³³.

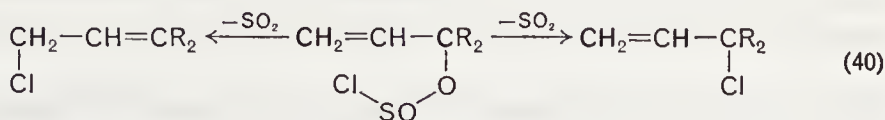
In all of these studies, it is clear that the rate of decomposition of the chlorosulphite responds to electron-release to the reaction centre. Chloride ions catalyse the decomposition of the chlorosulphite and promote reaction by the S_N2 mechanism, with characteristic inversion of configuration¹³⁴. 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 route¹³⁵.

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 stoichiometry of typical reactions can be represented as in equations (38) and (39). General experience would suggest (reference 7, p. 535 ff.) that



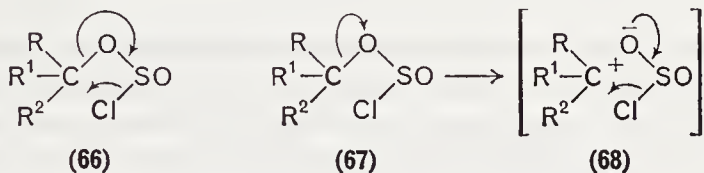
retention of configuration is less often encountered with halides of phosphorus than with thionyl chloride, though retention resulting from neighbouring-group interaction is known⁸⁶. Where retention of configuration is found in the absence of any such special structural influence, it has often been assumed 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 solvent¹³¹. 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 path⁵⁷. 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



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



fundamental point at issue, formulated for the decomposition of a chloro-sulphite, 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 solvent¹³⁷. Here an intramolecular concerted process may be implicated; whereas the corresponding rearrangement of cinnamyl thiocyanate ($\text{PhCH}=\text{CHCH}_2\text{SCN}$) is slower,



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

I. The bimolecular mechanism: general considerations and the possible existence of the synchronous mechanism

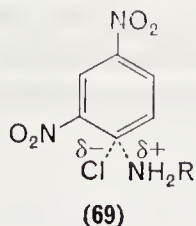
Aryl and vinyl halides are commonly considered to be rather inert to nucleophilic replacement and in this respect contrast sharply with the alkyl halides, most of which are relatively reactive. In order to realize bimolecular substitution of halogen at unsaturated carbon, some facilitating feature must be present. This may be structural; thus $p\text{-O}_2\text{NC}_6\text{H}_4\text{Hal}$ is much more reactive than $\text{C}_6\text{H}_5\text{Hal}$; $\text{N}\equiv\text{CCR}=\text{CR}^1\text{Hal}$ than $\text{HCR}=\text{CR}^1\text{Hal}$; and $\text{O}=\text{CRHal}$ than $\text{H}_2\text{C}=\text{CRHal}$. 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.

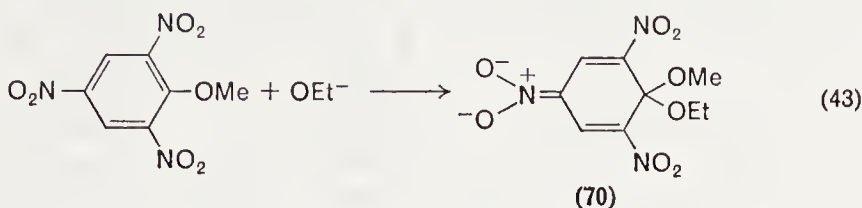
Direct replacement of one nucleophile by another in a bimolecular reaction analogous to the S_N2 process is conceptually perhaps as simple a process as could be envisaged for these reactions at unsaturated centres. It has been known for very many years¹³⁸ that second-order kinetics characterize such reactions as that shown in equation (42). It was natural,



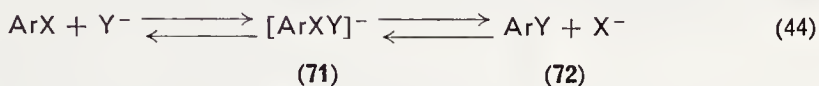
therefore, at an early stage in the discussion of the mechanisms of these and related reactions, for some authors^{139,140} to favour strongly the simple hypothesis that the transition state is that of a direct displacement, with forming and breaking bonds both incomplete, as is illustrated in 69 for 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



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



formation of the complex **71** or its breakdown could in principle be rate-determining.



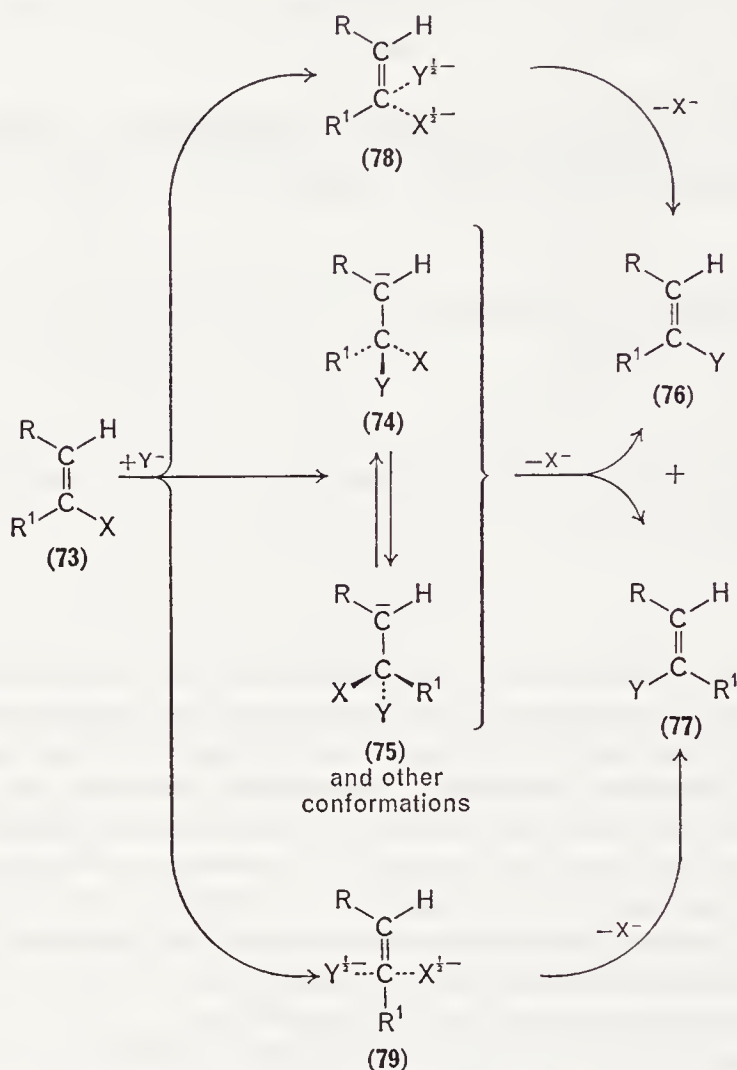
A number of important and comprehensive reviews and books^{143,145-148} are available to document the evidence that the stepwise mechanism, which has often been labelled $S_N2(\text{Ar})$ to distinguish it from the synchronous S_N2 process, is important for nucleophilic replacements at aromatic centres 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 entered¹⁴⁹ 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's⁷ terminology: 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 statements¹⁵⁰ 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 -chloro-crotonate system (Scheme 10: $R = \text{EtOCO}$, $R^1 = \text{Me}$), 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 Rappoport¹⁵⁵, 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 $S_N2(\text{Ar})$ 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 aromatic¹⁴⁵⁻¹⁴⁸ and with vinylic¹⁵⁵ 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 $\text{F} < \text{Cl} < \text{Br} < \text{I}$ (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 compilation¹⁴⁸, exemplifies this.

Similar ratios have been noted for the picryl halides reacting with hydroxide ions: in their reactions with water¹⁵⁶ the $\text{F} : \text{Cl}$ 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 $\text{C}-\text{F}$ 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

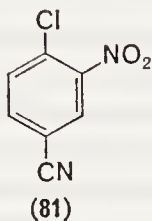
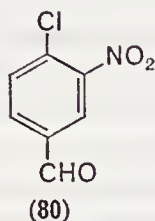
X in RX:	F	Cl	Br	I
R = C ₆ H ₅ at 200°C	1960	1	—	—
R = 4-O ₂ NC ₆ H ₄ at 50°C	312	1	0.85	0.36
R = 2-O ₂ NC ₆ H ₄ at 50°C	722	1	0.70	0.33
R = 2,4-(O ₂ N) ₂ C ₆ H ₃ at 0°C	890	1	0.69	0.15

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.

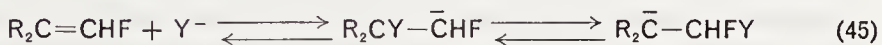
b. The identification of stable complexes. Meisenheimer's beautiful experiments¹⁴¹ which established the existence of complexes between nitro-substituted aromatic compounds and anions, and showed that these complexes could be decomposed to give products of replacement, have been followed by very wide documentation of their formation, and a recent review¹⁵⁷ summarizes some aspects of their chemistry which seem particularly important at this time. Both anionic¹⁴¹ 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 coworkers¹⁶⁰, by Bunnett and his group¹⁶¹, by Bourns and his group¹⁶² and by Illuminati and coworkers¹⁶³. 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 case¹⁶⁴. 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.



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



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 source¹⁶², but none for the reactions of halides as far as we know, although one study of vinylic compounds has been made¹⁶⁷. 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 [1-²H]-piperidine with 4-chloro-3-nitrobenzotrifluoride¹⁵⁹, 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 solvents¹⁶⁷. Results are given in Table 15. Comparison

TABLE 15. Solvent medium isotope effects in some typical nucleophilic substitutions and comparison with elimination

Substrate	Reagent	$T^{\circ}\text{C}$	$\frac{k_2(\text{EtOD})}{k_2(\text{EtOH})}$
1-Chloro-2,4-dinitrobenzene	OEt ⁻	25	1.84
1-Chloro-2,4-dinitrobenzene	Pyridine	90	1.30
1-Chloro-2,2-di(<i>p</i> -nitrophenyl)-ethylene	OEt ⁻	25	1.83
<i>n</i> -Butyl chloride (S_N2)	OEt ⁻	70	1.34
<i>n</i> -Butyl chloride (<i>E2</i>)	OEt ⁻	70	1.71

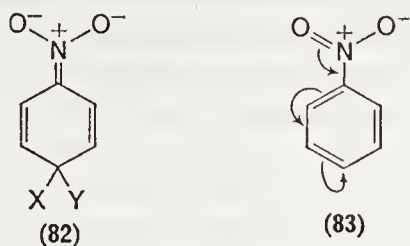
being restricted to nucleophilic substitutions by ethoxide ions, it seems that attack on unsaturated centres is subject to a larger solvent medium isotope effect than is attack on a saturated centre. Further study is needed to clarify whether this generalization is of wide utility.

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 Monack¹⁶⁸, 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, $\text{Me} > t\text{-Bu} > \text{H}$, thus giving a reactivity-sequence affected by *para*-substituents (R) in the order $\text{R} = \text{H} > t\text{-Bu} > \text{Me}$. 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 Berliner¹⁷⁰.

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



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 reaction¹⁷³. 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 substitution¹⁷⁴.

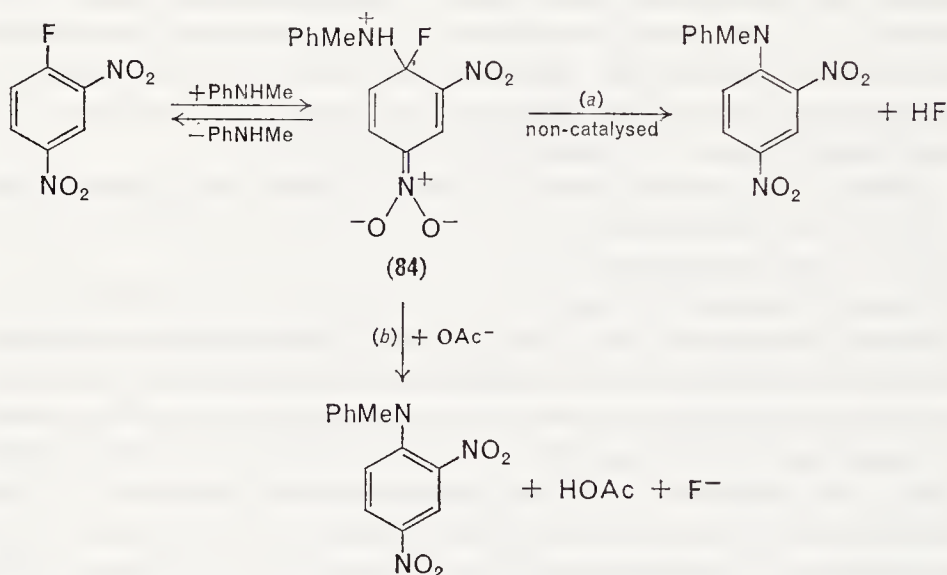
Thirdly, it should be noted that both secondary and primary steric effects can be significant in determining the rate and orientation of nucleophilic aromatic substitution¹⁴⁹.

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 $\text{C}_5\text{H}_{10}\text{NH}$, by factors in the range 2–30, it accelerates by a factor of nearly 2 the reaction with the benzenethiolate ion¹⁷⁵.

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 Nudelman¹⁷⁶ 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.

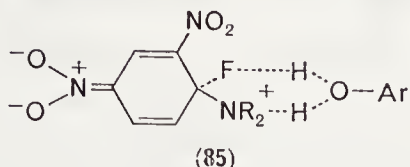
f. Examples in which the second (heterolysis) stage of the reaction can become rate-determining. For aromatic halides, therefore, it would seem that the situation in which the decomposition of the intermediate **71** (equation 44) becomes rate-determining is difficult to realize. Illustrations have been found, however, in the reactions of some amines with 2,4-dinitrofluorobenzene. Thus Bunnett and Randall¹⁶¹ 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 Garst¹⁶¹, 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

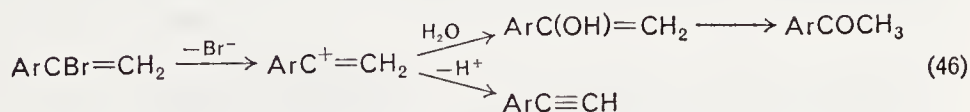
understood¹⁴⁶. In particular, it is not clear whether the stage of proton-loss from the intermediate **84** or the stage involving loss of fluoride is rate-determining. From the effects of phenols and of bifunctional catalysts such as 2-pyridone, Pietra and Vitali¹⁷⁷ have proposed a cyclic transition 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}.



The corresponding situation in vinylic systems has been discussed very recently by Rappoport and Ta-Shma³⁸² with reference to the reactions of 1,1-dicyano-2-*p*-dimethylaminophenyl-2-halogenoethylenes, $p\text{-Me}_2\text{NC}_6\text{H}_4\text{C}(\text{X})=\text{C}(\text{CN})_2$ ($\text{X} = \text{F}, \text{Cl}$), with aromatic amines in various solvents. Variations in the kinetic form depending on the substrate, the halogen and the medium were noted, and the $\text{F} : \text{Cl}$ 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.

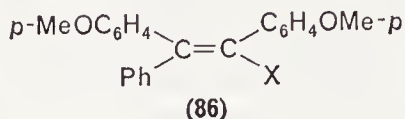
3. The unimolecular mechanism

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 coworkers¹⁷⁸ 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

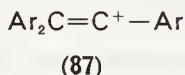


polar solvent, as is expected for the situation where charge becomes well developed in the transition state, and electron-releasing groups very powerfully increased the rate of reaction. The unimolecular mechanism of solvolysis, with the first stage of sequence (46) rate-determining, was proposed to account for these results, and it has been generally accepted¹⁵⁵.

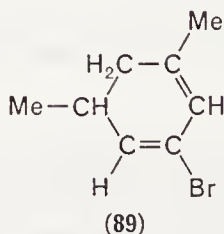
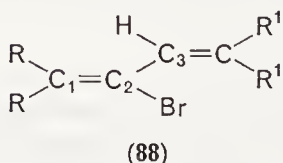
More recent evidence relating to this mechanism has come from study of the effect of change in the leaving group. Rappoport and Gal¹⁷⁹ have shown for the reactions of trianisylvinyl halides in 80% ethanol at 120°C, the rate ratio $k_{\text{Br}}:k_{\text{Cl}} = 58$, a result which supports reaction by the unimolecular mechanism. Further details concerning the intermediate stages have been given by Rappoport and Apeloig¹⁸⁰. The 1,2-dianisyl-2-phenylvinyl halides (**86**; X = Cl, Br) and their geometric isomers on



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,

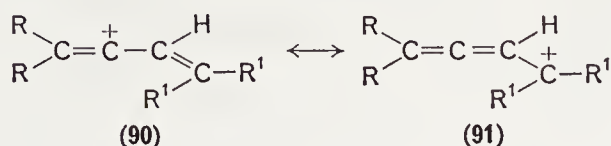


which throws light on the geometry not only of the product-forming intermediate but also of the transition state, has been revealed by the work of Grob and coworkers¹⁸¹. They have examined the solvolyses of substituted butadienes (e.g. $\text{CH}_2=\text{CBr}-\text{CMe}=\text{CHMe}$ and more highly C-methylated 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 $\text{C}_1-\text{C}_2-\text{C}_3$ system, as is possible in the reactions of substituted butadienes but not in those of the cyclic system of **89**. This



geometry allows contribution of structure **91** to the resonance hybrid structure of the cation ($\text{90} \leftrightarrow \text{91}$). 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.



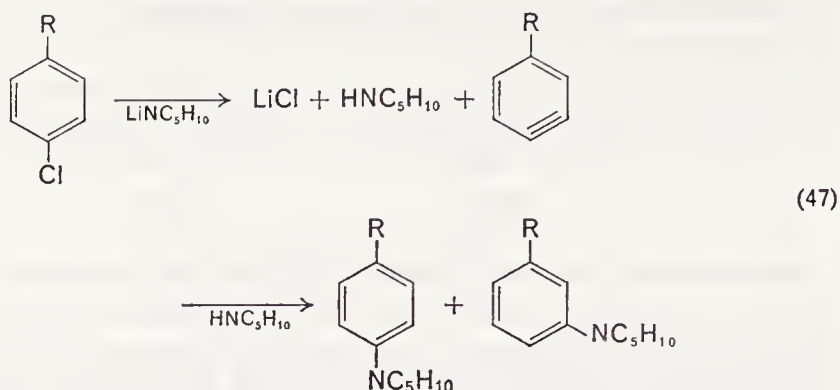
Bergman and coworkers¹⁸² have investigated the properties of systems in which a cyclopropyl group is attached to an olefinic centre with special reference to the solvolyses of the *cis*- and *trans*-isomers of 1-cyclopropyl-1 iodoprop-1-ene in acetic acid. Each isomer gives substantially the same mixture 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 trifluoromethanesulphonates¹⁸³. Further cases are known¹⁸⁴ 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 Hanack¹⁸⁵, 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

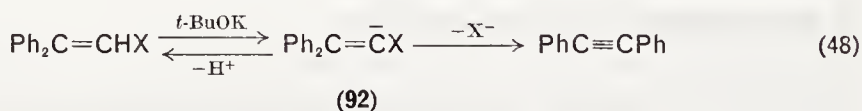
Competing with the mechanisms already discussed, particularly for reactions in sufficiently basic media, are those processes in which elimination to give a more highly unsaturated compound is followed by addition to regenerate the original degree of formal unsaturation. Such reactions are not very commonly 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 benzyne 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



substituent provides one criterion for reaction by this mechanism. Substituent effects in these additions have been discussed by various groups¹⁸⁷⁻¹⁸⁹.

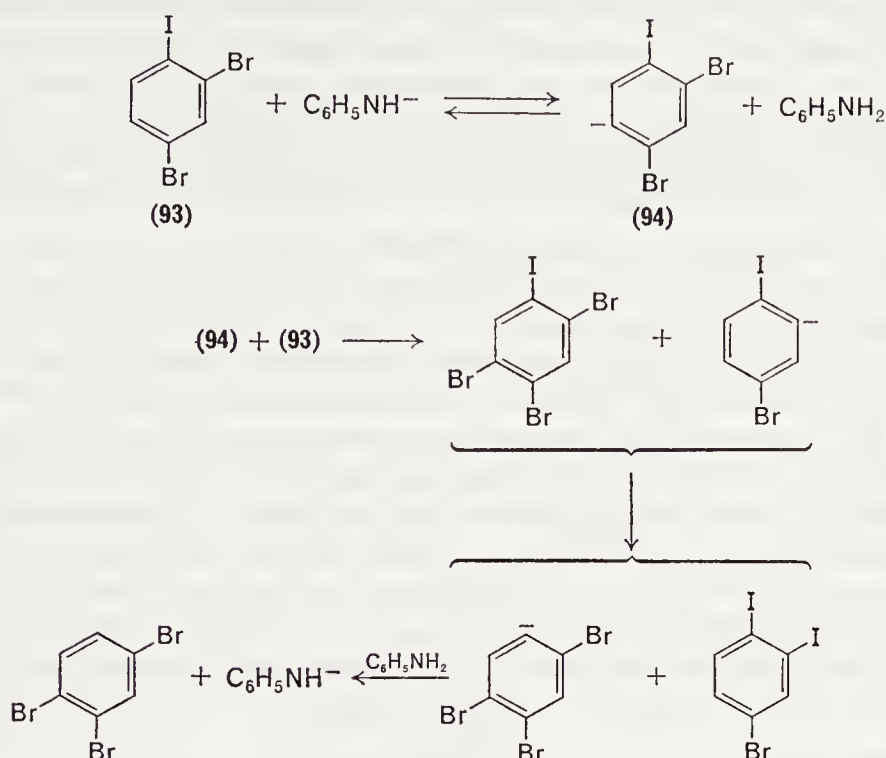
An equally comprehensive account of the availability of the elimination-addition route in replacements at vinylic centres has been given by Rappoport¹⁵⁵ and discussions of the availability of the competing possibilities will be found in a number of the papers already cited^{153, 154, 185}. In certain 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 $\text{Br} > \text{I} > \text{Cl}$, was observed¹⁹⁰ 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 mechanism¹⁵⁵.



5. Replacements and rearrangements involving nucleophilic attack on halogen

Some polyhalogenobenzenes have been shown by Bunnett and co-workers¹⁹¹⁻¹⁹³ to undergo base-catalysed isomerization and disproportionation by yet another mechanism which involves nucleophilic attack by a suitably substituted phenylanion 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.

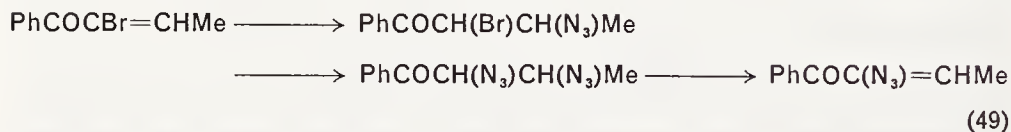
6. Replacements and rearrangements involving addition-elimination sequences

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 writers¹⁵⁵.

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 Rappoport¹⁵⁵, 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 Smith¹⁹⁴. 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 $\text{Ph}_2\bar{\text{C}}-\text{CH}(\text{OEt})\text{F}$, or of the adduct $\text{Ph}_2\text{CH}-\text{CH}(\text{OEt})\text{F}$. In reviewing the ionic reactions of fluoro-olefins, Chambers and Mobbs¹⁹⁵ 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 fluoride¹⁹⁸. 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 characterized¹⁹⁹ by ^1H n.m.r. spectroscopy of the reacting mixture.



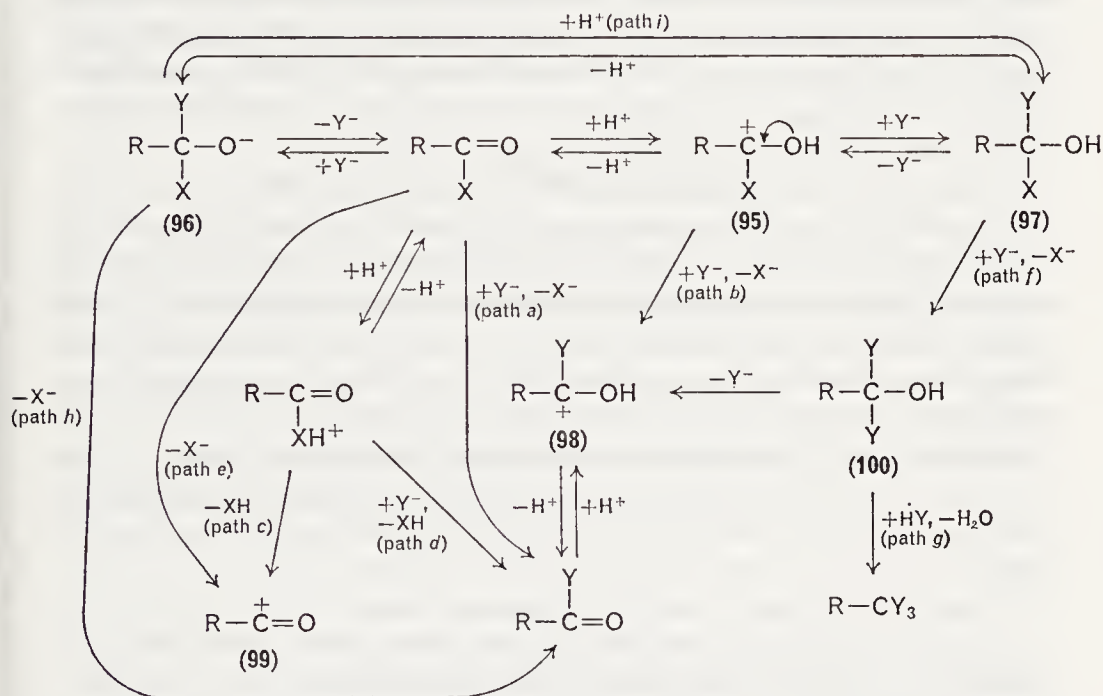
The direct conversion of the unsaturated bromide to the corresponding azide was considered also to contribute to the reaction. It should be remembered in any such case that again this type of evidence alone is not necessarily compelling or conclusive, since the supposed intermediate may merely represent 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 >C=O bond towards the formal structure $\text{>C}^+-\text{O}^-$.

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.

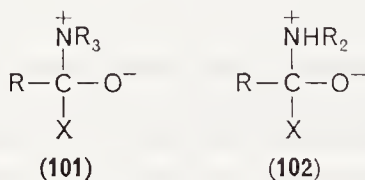
expect that bimolecular nucleophilic replacement (path *a*) would be more rapid than with saturated halides²⁰², both because of the polarization indicated and because the attacked carbon atom must be less congested. Attachment of an electrophile (a proton or a Lewis acid) to the oxygen atom, as in **95**, 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. $\text{MeO}-\text{CH}_2\text{Cl}$) is known²⁰³ 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 centre²⁰³, 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



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 Capon²⁰⁴.

examples have been given²⁰⁵ 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 coworkers²⁰⁶ 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:



This reaction of benzoyl chloride may well be an example of the S_N2 mechanism. Bunton and Lewis²⁰⁷ 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 iodide²⁰⁸ can be interpreted similarly. Here the relative reactivities were as shown in Table 16.

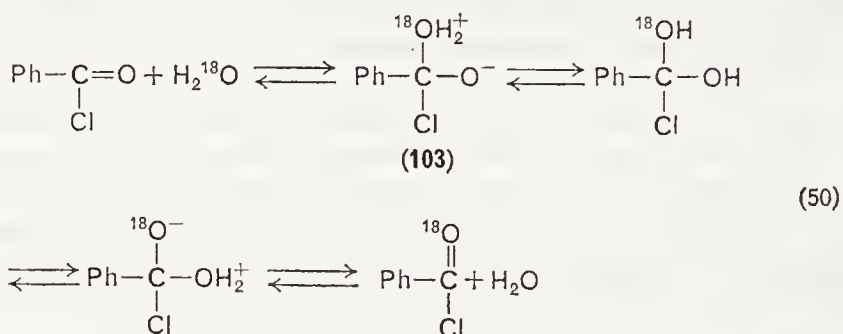
TABLE 16. Relative reactivities of benzoyl halides with morpholine in cyclohexane at 25°C

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 Jones²⁰⁸, 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.

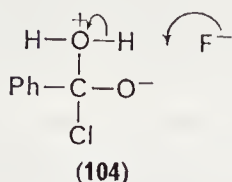
Study of reactions of this kind in solvents containing water, whether with or without other nucleophiles, indicates several trends of mechanistic significance. First, the 'element effect', as manifested by the relative ease of displacement of fluoride and chloride, becomes less. Thus acetyl fluoride in water hydrolyses less rapidly than acetyl chloride by a factor²⁰⁹ 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 ¹⁸O-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% acetonitrile²¹⁰, but, in the hydrolyses of benzoyl chloride and various derivatives in mixtures of dioxan and water²¹¹, exchange of ¹⁸O 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



leading to hydrolysis. Acid-catalysis could facilitate the proton-transfers within this sequence by further protonation of the tetrahedral intermediate.

It has been noted also²⁰⁹ 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, $k_2^{\text{ArND}_2} : k_2^{\text{ArNH}_2} = 1.17$, in the second-order reaction of benzoyl chloride with aniline in benzene as solvent²¹².



Fry¹⁸ has recently discussed a study of chlorine isotope effects in the hydrolyses of *p*-substituted benzoyl chlorides, *p*-RC₆H₄COCl, in 50% acetone. With R = MeO, Me, H, Cl and O₂N, the values of $k(^{35}\text{Cl}) : k(^{37}\text{Cl})$ were 1.0089, 1.0085, 1.0082, 1.0067 and 1.0051 respectively; the accuracy was assessed in each case as ± 0.0004 . 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 notes¹⁸ 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 work²¹⁰ 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 Bender²⁰⁰ and Satchell²¹⁶ 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 stoichiometric concentration of H^+ rather than on the acidity function, h_0 , as has been noted for a number of acyl fluorides²¹⁶, 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 reviews²¹⁹ of these reactions, and we do not treat them specifically in this article.

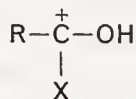
d. Reactions through adducts (paths f, i). Evidence that displacements of halogen can be forced through routes involving addition is mostly preparative in character. Many years ago, Hübner and Müller²²⁰ showed that acetyl chloride reacts with phosphorus pentachloride to give first trichloroacetyl chloride and then hexachloroethane (sequence 51). Exactly



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.



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

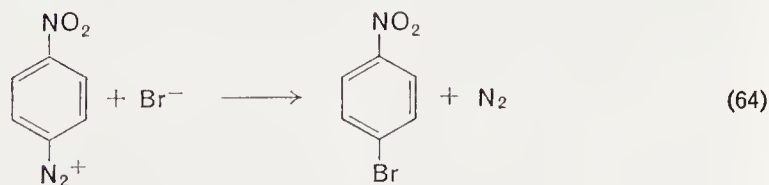
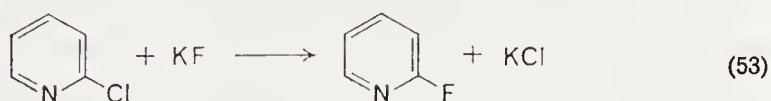
way of the anionic intermediate **96**, which has a natural route (path *h*) directly to the product, but by protonation gives **97** (path *i*). It is by no means impossible that the chlorohydroxycarbonium ion is sometimes involved, perhaps through the sequence via **96**, **97** leading to **95**, 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

I. Second-order processes

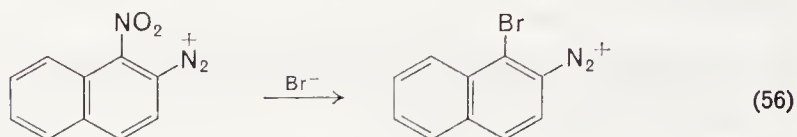
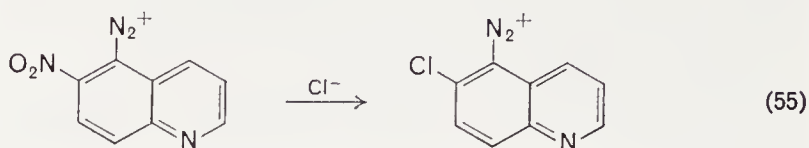
Although there are some well-known preparative methods for nucleophilic introduction of halogen at unsaturated centres, there have been few mechanistic studies, and most of these apply to replacement in aromatic systems. In principle, introduction of nucleophilic halogen should be possible by most of 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 coworkers²²³ (equation 54).



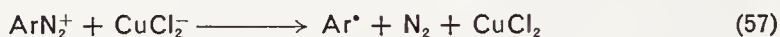
The latter reaction probably has a number of preparative counterparts²²⁴, and situations exist in which the diazonium substituent acts as an activating

group, promoting replacements of other substituents by a nucleophilic process (equations 55, 56)^{143, 225, 226}.



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 products²²⁷. The radical-producing process is believed to be that shown in equation (57). Uncatalysed replace-



ments in aqueous solution are, however, thought to be heterolytic and a recent review is given by Chapman²²⁸. 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 products²³¹. 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 conclusions²³² have recently been modified²³³; 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 appears²³⁴ 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 reaction²³⁵ 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, however²³⁶, 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



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 experiments²³⁸, 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 Tolgyesi²³⁹ 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.

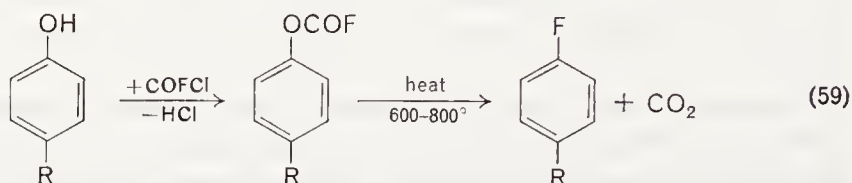
TABLE 17. Products of decomposition of diazonium salts suspended in fluorobenzene

Diazonium salt	<i>T</i> (°C)	Time (h)	Main product	Fluorobiphenyls (% of biphenyl fraction)		
				<i>o</i>	<i>m</i>	<i>p</i>
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 Suschitzky²⁴⁰.

3. S_Ni reactions

Fluorides can be prepared also from alcohols or thiols by a reaction path (sequence 59) which has been considered²⁴¹ 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.



III. ELECTROPHILIC REPLACEMENTS

A. Electrophilic Replacement by Halogen at Unsaturated Centres

I. 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



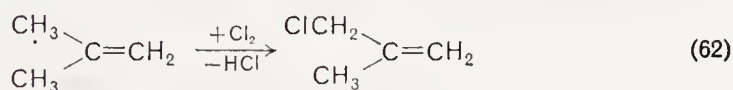
For the case of an aromatic hydrocarbon (benzene), the reaction is:



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.'

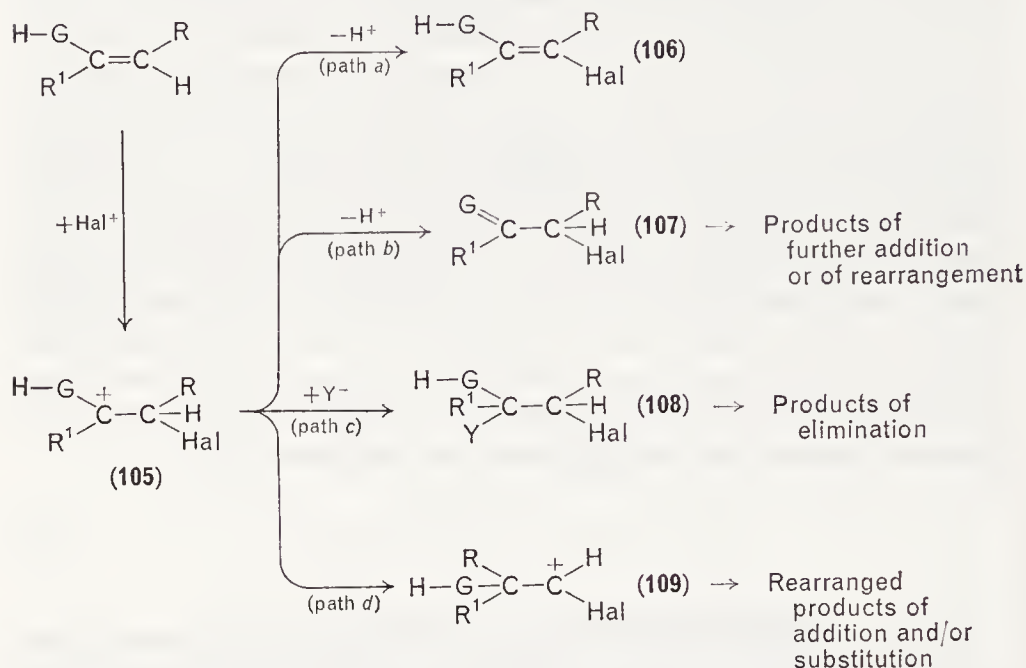
No exception need be taken to such statements, nor to the contrast on the one hand between free-radical halogenations of saturated hydrocarbons and the polar halogenations of derivatives of benzene, and on the other between additions of halogens to aliphatic unsaturated hydrocarbons and substitutions 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 mechanisms²⁴². Both free radical and polar additions of chlorine to aromatic compounds are well known, and give tetra- and hexachlorides²⁴³. Polar (electrophilic) substitutions by chlorine in simple olefinic substances are also much more widespread than is sometimes believed; an example²⁹² is the chlorination of isobutene to give 3-chloro-2-methylpropene (equation 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 pentavalent 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 years²⁴⁴, and substitution by addition-elimination also forms part of the history of chemical thought²⁴⁵, 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 halogenations²⁴⁶. 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 nitration²⁴⁷ and for other aromatic substitutions.

2. Fluorination

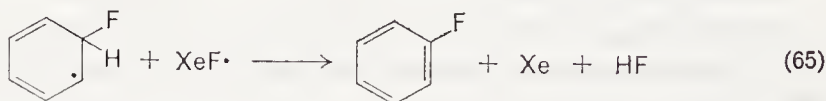
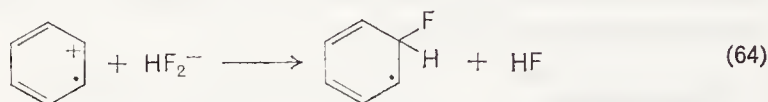
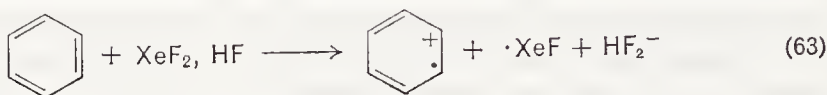
Fluorine reacts violently with most organic compounds, to give complicated mixtures of products. It is generally considered that these reactions involve chain-processes involving free-radicals, initiated easily because of the relative weakness of the F—F bond, the average bond energy of which² is 38 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 effected²⁴⁸. 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
<i>o</i> - $\text{RC}_6\text{H}_4\text{F}$ (%)	50	40	13
<i>m</i> - $\text{RC}_6\text{H}_4\text{F}$ (%)	10	10	79
<i>p</i> - $\text{RC}_6\text{H}_4\text{F}$ (%)	40	50	8

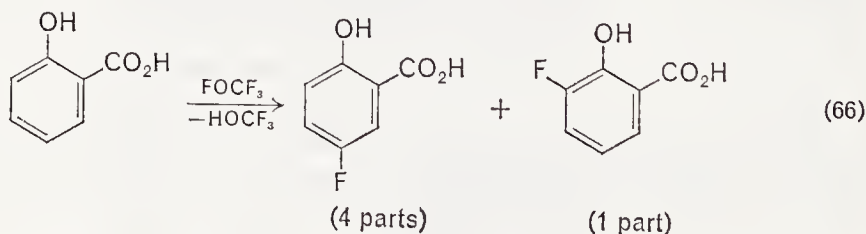
Free-radical substitutions are usually less discriminatory than this and give a rather different substitution pattern²⁴⁹, so the results suggest the operation of an electrophilic mechanism.

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 process²⁵⁰. 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)²⁵¹ has been proposed.

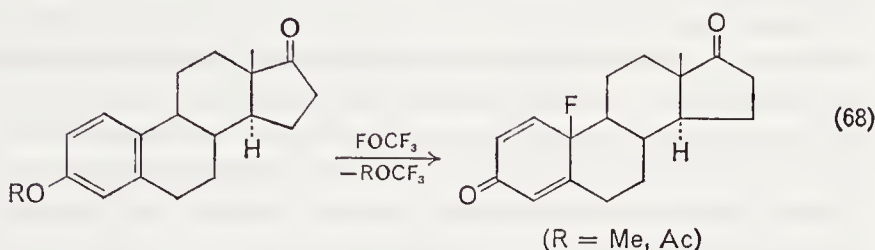
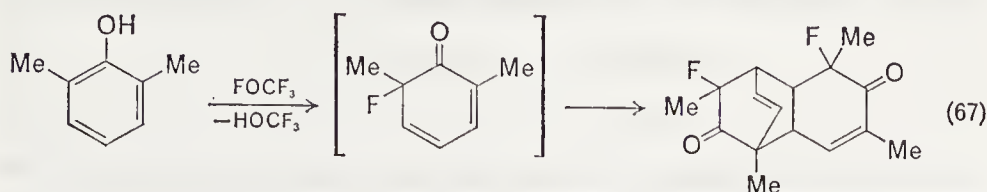


That radical-ions were involved was indicated by the development of intermediate colours.

Trifluoromethyl hypofluorite in halogenated solvents has been shown to give a variety of electrophilic fluorinations²⁵². 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



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).



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.

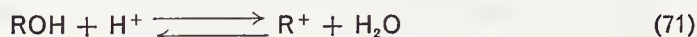
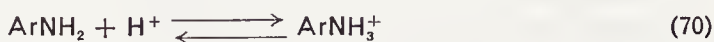
3. Chlorination, bromination and iodination

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. Berliner²⁵³ 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 cited²⁴⁶. Shilov and Kaniaev²⁵⁴ 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

$$-\text{d}[\text{BrOH}]/\text{dt} = k[\text{ArH}][\text{BrOH}][\text{H}^+] \quad (69)$$

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 acidities²⁵⁵, the rate increases more rapidly than the stoichiometric 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



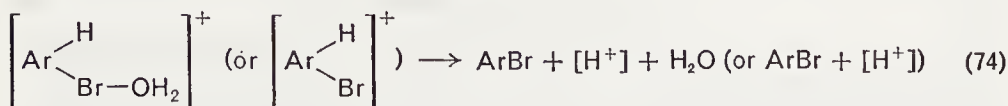
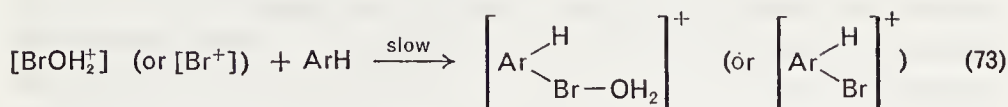
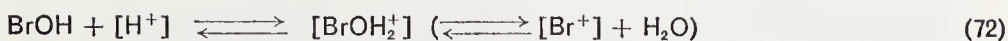
uncertainty as to whether or not a molecule of water is contained in the transition state.

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^+ substituent²⁵⁵.

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 benzene²⁵⁷. It was found that brominations showing similar kinetic behaviour could be carried out in aqueous dioxan²⁵⁷ and in aqueous acetic acid²⁵⁸.

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. Berliner²⁴⁶ discussed this possibility and recent experiments by Ridd and coworkers³⁸³ provide evidence that for the most reactive substrates at low acidities the transition state can be reached by pre-equilibrium protonation not of



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' method²⁵⁹, 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 ion²⁶⁰ 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 stoichiometric acidity²⁶¹. 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 shown²⁶² 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 $[\text{ClAgCl}]^+$.

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

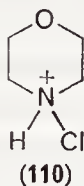
$$-d[\text{ClOH}]/dt = k[\text{ClOH}][\text{H}^+] \quad (75)$$

does not enter²⁶⁴. 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

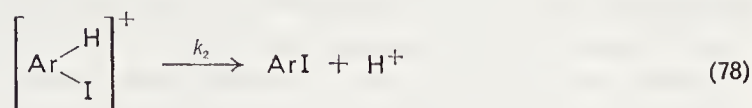
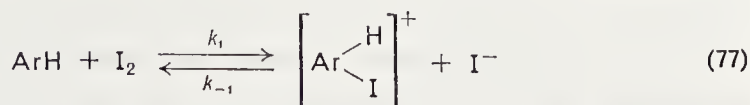


been considered, and the matter must be considered still to be open, as Berliner²⁵³ has noted.

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).

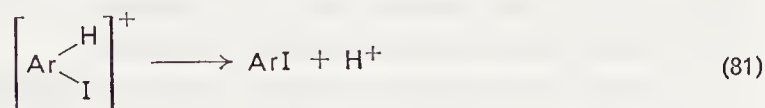
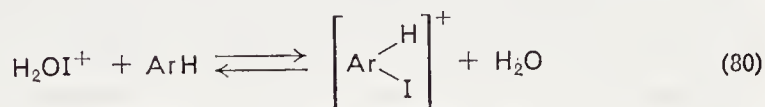
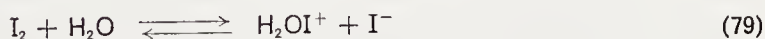


The characteristics of iodination are rather different from those of chlorination and of bromination, since the transition state usually lies later on the reaction path, and the rate-determining step more often involves the removal of the aromatic proton. Evidence in this direction comes from studies of primary isotope effects, which lie in the range $k_{\text{H}}/k_{\text{D}} = 2\text{--}5$ 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 water²⁶⁹. 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 state²⁷⁰.



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 aniline²⁶⁹, 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 ($k_{-1}[\text{I}^-]$) 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 water²⁷¹ and of aniline²⁷².

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).

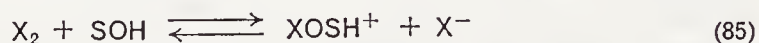
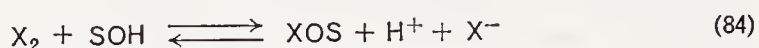
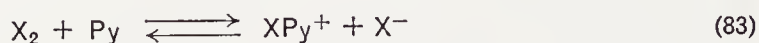


Unfortunately, solutions of HOI are rather too unstable to allow successful independent studies of the kinetics of iodination in the complete absence of iodide ions.

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

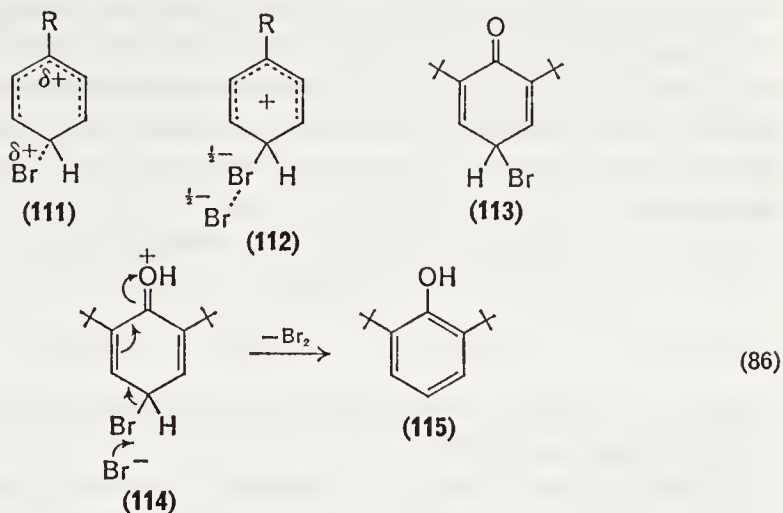
iodine, but a clear distinction between these possibilities has not been made.

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



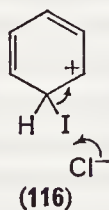
earlier examined structural effects in the halogenation of ethers and anilides²⁷⁵, it was Robertson and coworkers²⁷⁶ who first examined the kinetics of chlorination and bromination in acetic acid in sufficient detail to establish that molecular halogen in its entirety can be concerned in the transition 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 debromination²⁷⁸. 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**



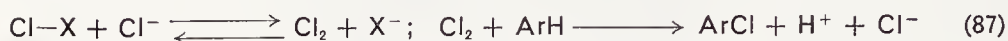
(equation 86). By the principle of microscopic reversibility, therefore, the bromination of the phenol **115** must be able to have a rate-determining stage having the same composition.

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 iodine²⁷⁹. The kinetic form for catalysis by chloride ions of the deiodination of iodo-2,4,6-trimethoxybenzene led Batts and Gold²⁸⁰ 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.



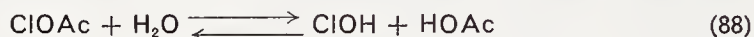
The halogen molecules and the interhalogen compounds are by no means the only potential neutral suppliers of electrophilic halogen. *N*-Halogeno-compounds, alkyl hypohalites, acyl hypohalites and other mixed anhydrides

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 known²⁸¹. 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



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 substitution²⁶⁷. 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

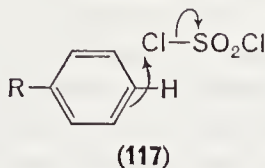


when the position of equilibrium is unfavourable, since chlorine acetate is a much more effective reagent than hypochlorous acid. It is also a much more reactive electrophile than molecular chlorine, and this feature of its chemistry is not yet fully understood. It seems likely that the explanation has to do with the properties of intermediates with expanded octets on halogen rather than with the strength or electronegativity of the Hal-X bond.

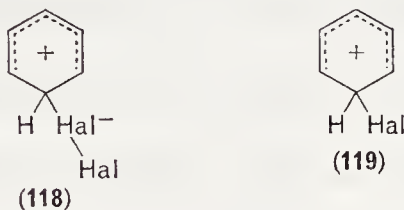
Bromine acetate can also be effective as an electrophile, and appears to resemble molecular bromine in its steric requirements²⁵⁸.

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 shown²⁸² 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 , $n\text{-Bu}_4\text{NCl}$) 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**.



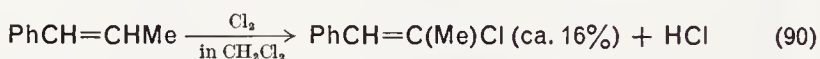
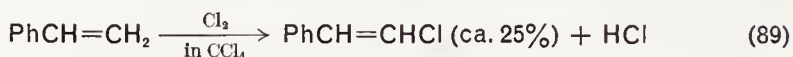
c. *The reaction sequences: displacement by the co-ordination-heterolysis pathway (Scheme 14, path a).* We have already noted that, for a number of chlorinations and brominations, studies of primary isotope effects show that proton loss in the rate-determining stage is insignificant. This makes it probable 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**.



Pfeiffer and Wizinger²⁸³ 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 systems²⁸⁴ and Wheland's use of the delocalized structure **119** as a model of the transition state for the purpose of quantum-mechanical calculations²⁸⁵, 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.

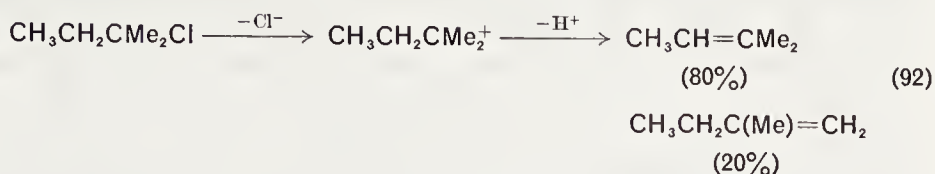
Heterolytic electrophilic substitutions by halogens in olefinic systems are quite well-known processes, though they have been investigated mechanistically very little. From a kinetic point of view, it has been documented thoroughly²⁸⁶ that the same kinetic forms are in general observed for halogenation 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}.



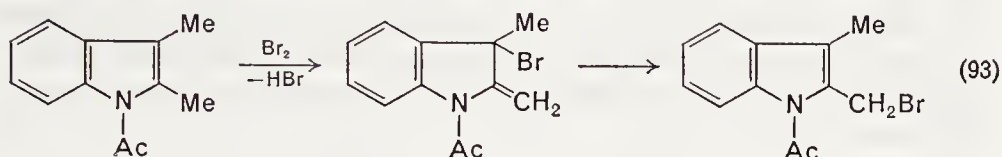
Recently, it has been shown²⁸⁸ that both *cis*- and *trans*- β -styrylpyridine-cobaloximes ($\text{PhCH=CHCo(DH)}_2\text{Py}$; DH = dimethylglyoxime mono-anion, Py = pyridine) react with elemental halogens (chlorine, bromine or iodine) in acetic acid by a process presumed to be electrophilic in character 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 *E1* reactions for example, have been much discussed; the commonly observed 'Saytzeff' orientation implies that the thermodynamically more stable of two

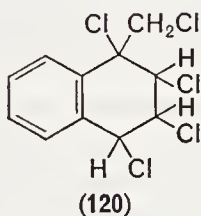
alternatively accessible olefins is often the predominant product (equation 92)⁷.



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 Tomlinson²⁸⁹ suggested that the bromination of *N*-acetyl-2,3-dimethylindole follows the course shown in equation (93).

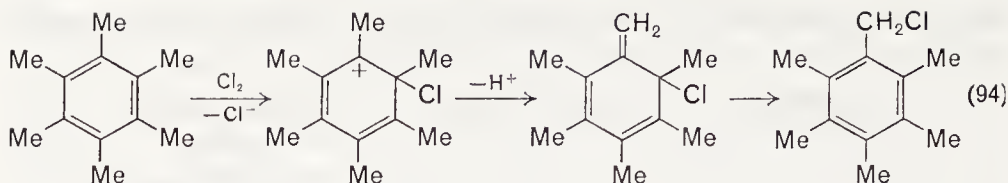


Similarly, one of the products of heterolytic chlorination of 1-methylnaphthalene is the side-chain-substituted compound **120**, for the formation of which a stage involving substitution with rearrangement is required²⁹⁰.

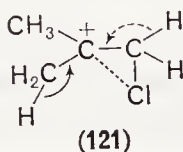


The only kinetic investigations of heterolytic side-chain substitution that we are aware of are by Illuminati and coworkers²⁹¹. They examined the side-chain chlorination of hexamethylbenzene and a number of its analogues. These reactions, which were only a little slower than correspondingly activated substitutions involving displacement of hydrogen (e.g. in pentamethylbenzene) had the usual kinetic form ($-\text{d}[\text{Cl}_2]/\text{d}t = k[\text{ArH}][\text{Cl}_2]$), 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).

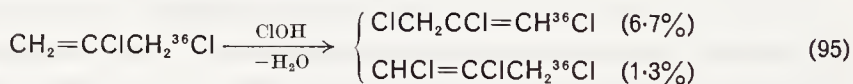
This type of reaction is not confined to aromatic systems. The chlorination of isobutylene in the liquid phase gives as the main product 3-chloro-2-methylprop-1-ene ($\text{CH}_2=\text{C}(\text{Me})\text{CH}_2\text{Cl}$), with much smaller amounts of



1-chloro-2-methylprop-1-ene ($\text{Me}_2\text{C}=\text{CHCl}$), 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 elsewhere²⁹⁴ 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**).

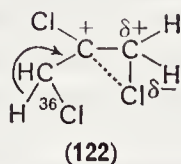


Evidence supporting the view that the geometry about the group from which the proton is to be lost can affect the ease of this loss comes from a study of the heterolytic chlorination of 2,3-dichloropropene with acidified hypochlorous acid. This reaction gives some 8% of 1,2,3-trichloropropene, and tracer 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

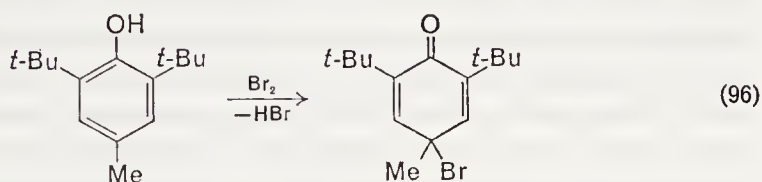


chemically but not radiochemically identical and the intermediate carbonium ion is formally symmetrical. Some factor must be responsible for the preferential loss of a proton from the 3-position, and the theory proposed for isobutene²⁹² gives a natural and consistent interpretation: in the intermediate 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

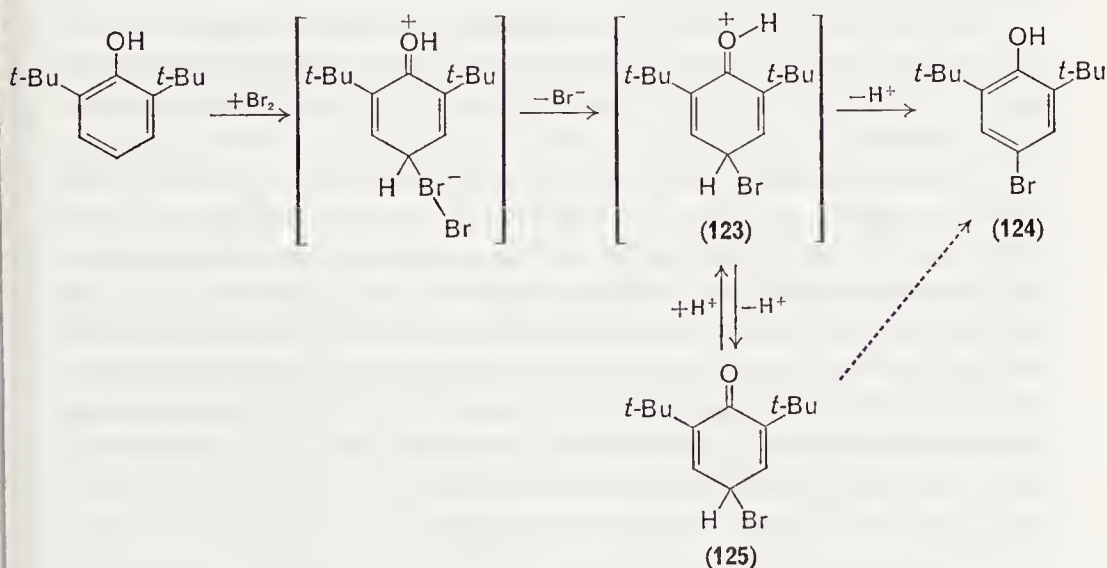
completely, proton-loss can supervene, thus giving the observed result of unsymmetrical behaviour of a formally symmetrical intermediate (122)^{292, 295}.



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}.



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.

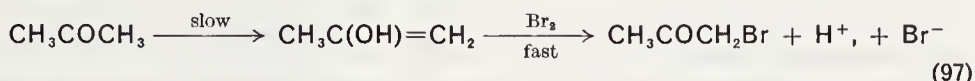
15). Several examples of this type of reaction have been examined kinetically²⁹⁷⁻²⁹⁹. The results can all be analysed in terms of second-order processes involving the phenol molecule and bromine. Little further is known about the intimate details, though these may be as complicated as those involved 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 anisoles³⁰⁰ 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 shown³⁰¹ 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 acid²⁹⁹. 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 other³⁰²; 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.

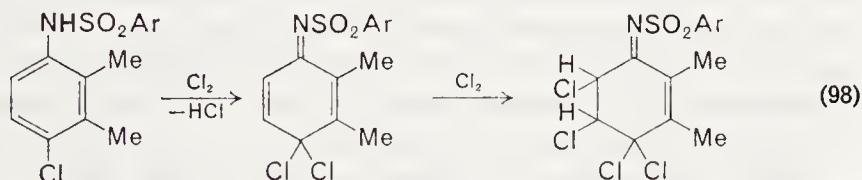
* A similar possibility, involving an *N*-halogeno-intermediate, exists in the case of the halogenation of anilides and amines; see below.

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 March³⁰³. 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



stepwise in nature. Bell and coworkers³⁰⁴ 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. Robertson³⁰⁵ has suggested that some complex examples from the chemistry of aromatic sulphonamides can be classified in this way and sequence (98) provides an example.



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 stereochemistry³⁰⁶.

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 MeNO₂—HOAc—CHCl₃ 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.

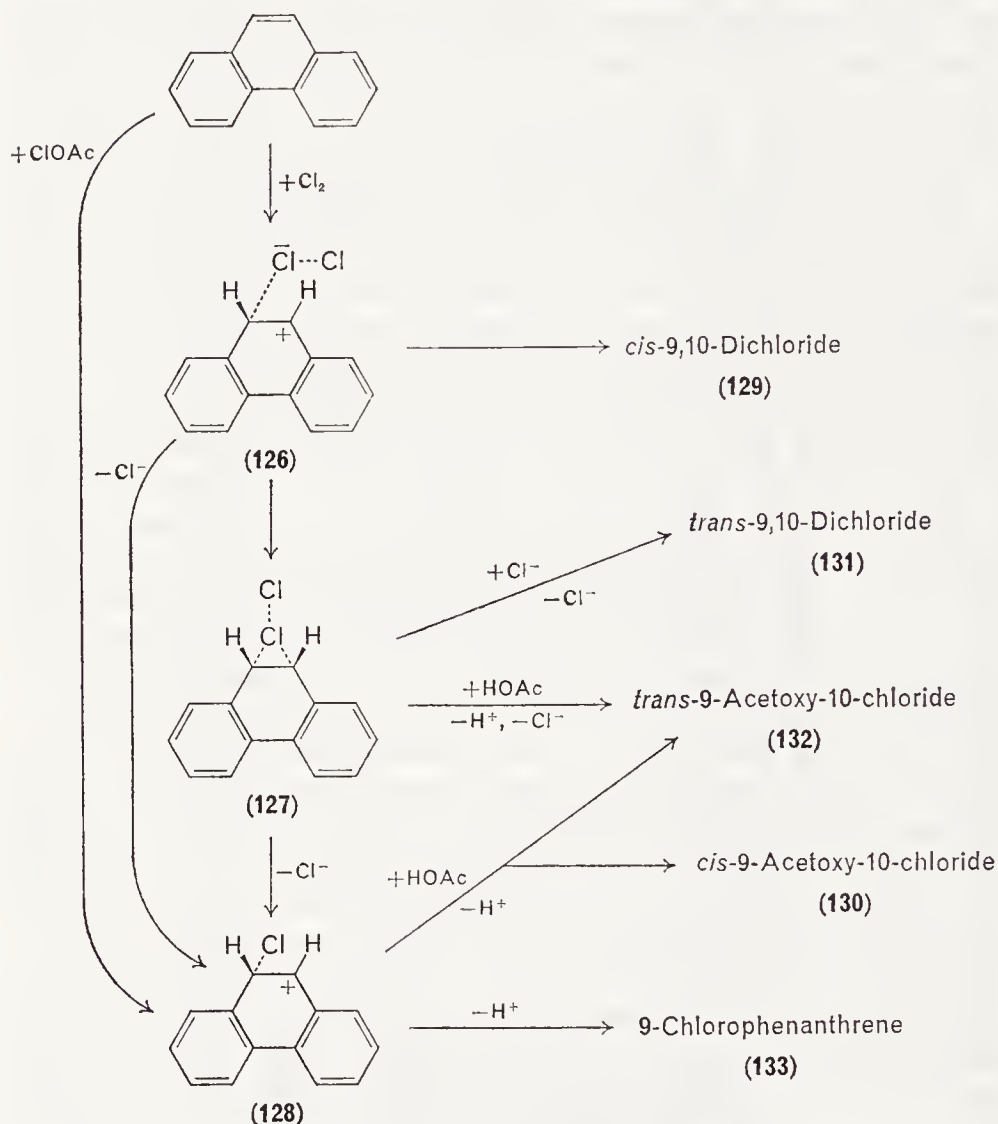
Further information is provided by study of the reaction involving chlorine acetate in the same solvent. This compound, which reacts much more rapidly than chlorine, gives the 9-acetoxy-10-chloro-9,10-dihydrophenanthrenes in a ratio quite different from that determined by molecular chlorine and unaffected by the presence of added acetate ions³⁰⁷. 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		Cl ₂		Cl ₂		Cl ₂		Cl ₂		Cl ₂	
	HOAc	HOAc + LiCl	HOAc + NaOAc	HOAc	HOAc	HOAc + NaOAc	HOAc	HOAc	HOAc + NaOAc	CHCl ₃	Cl ₂	MeNO ₂
9-Chlorophenanthrene (%)	35	36	30	40	40	40	—	—	40	41	41	66
<i>cis</i> -9,10-Dichloro-9,10-dihydrophenanthrene (%)	38	41	38	—	—	—	—	—	—	41	41	23
<i>trans</i> -9,10-Dichloro-9,10-dihydrophenanthrene (%)	10	8	7	—	—	—	—	—	—	18	18	11
<i>cis</i> -9-Acetoxy-10-chloro-9,10-dihydrophenanthrene (%)	5	4	6	30	30	30	—	—	30	—	—	—
<i>trans</i> -9-Acetoxy-10-chloro-9,10-dihydrophenanthrene (%)	12	11	19	30	30	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 considered³⁰⁷, 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 detail³⁰⁸, 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 competition between 1,2- and 1,4-addition.

Brominations of aromatic systems can also give adducts³⁰⁹⁻³¹¹ 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;

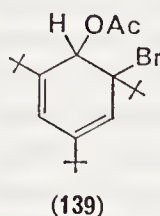
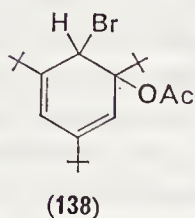
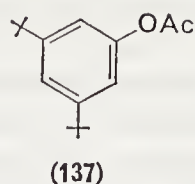
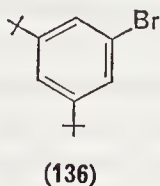
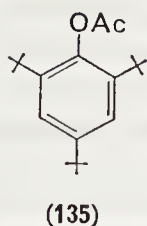
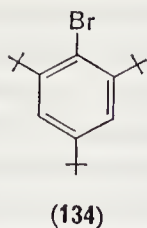
(iii) that the components of the mixture of adducts may decompose in a variety of ways to give secondary products, which can be those of substitution;

(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;

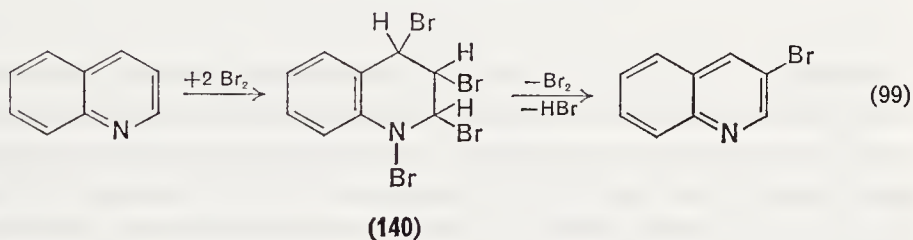
(v) that the formation of substitution products of unusual nature or orientation may often be interpretable in terms of addition-elimination sequences.

Two examples in which addition-elimination paths have been postulated are now given. In the first³¹² 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-derivatives³¹³, just as nitration by the nitronium ion in sulphuric acid gives the 5- and 8-nitroquinolines³¹⁴. Direct reaction between quinoline and bromine, on the other hand, gives first a perbromide (probably



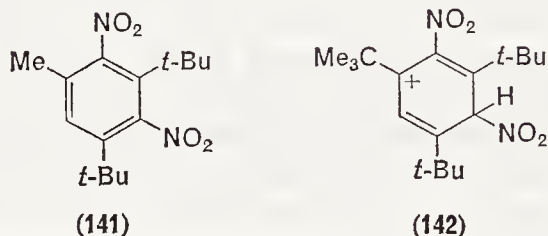
$\text{C}_9\text{H}_7\text{NBr}^+ \text{Br}_3^-$), and then 3-bromoquinoline (in pyridine) or 3,6-dibromoquinoline and 3,6,8-tribromoquinoline (in acetic acid)³¹⁵. The most natural interpretation of these results is that shown in the addition-elimination sequence (99), which indicates the route to 3-bromoquinoline; 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. Eisch³¹⁶, in a careful and scholarly review of the halogenation



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 elsewhere²⁹⁴, 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 systems²⁹⁴. 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 coworkers³¹⁷ 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.



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 work³¹⁸, 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 Berliner²⁴⁶, 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 catalysts³²⁰, 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 Stegel³²¹ showed that the silver-ion-catalysed bromination of 1,3,5-tri-*t*-butylbenzene was subject to a primary isotope effect, $k_H/k_D = 3.6$. Similarly, Berliner, Kim and Link³²² 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.

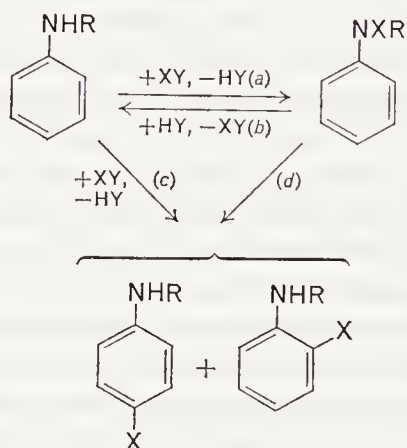
A group of Scandinavian workers³²³ have examined a number of poly-substituted benzenes, including trimethyl- and trimethoxy-benzenes, and have focused attention on the possibility that steric inhibition of resonance is also an important factor contributing to the observation of a primary isotope effect. 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 ($k_H/k_D = \text{ca. } 4$). 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 sulphonate³²⁶ 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 water³²⁵.

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.

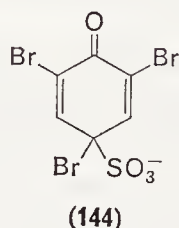
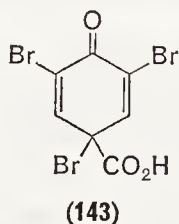
i. The reaction sequences: displacement of groups other than hydrogen. Several of the reviews already mentioned²⁴⁶ include accounts of the mechanisms established for halogenations involving the displacement of groups other than hydrogen. Although these reactions have not been investigated as systematically 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, CO₂H, COR, SO₃H, B(OH)₂, SiR₃, GeR₃ and SnR₃. 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 bromodesilylation³²⁹ 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 iododestannylation³³⁰, and positive bromine, in de-*t*-butylation²⁵⁶.

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 acid³³¹ and the bromodesulphonation of sodium 3,5-dibromo-4-hydroxybenzene sulphonate³³². 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 bromodesilylation³³³.



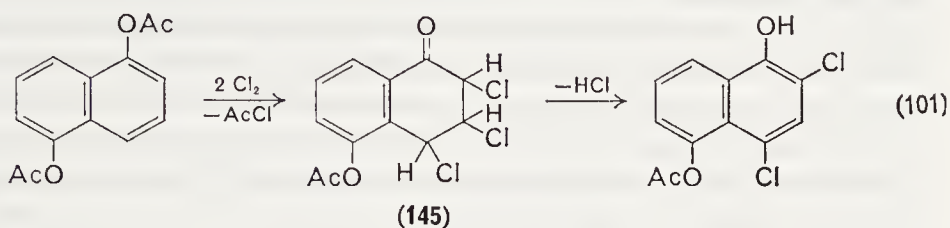
Just as in some circumstances for bromodeprotonations the final stage of the displacement may become rate-determining, so analogous situations have been recognized for the loss of other groups. Thus in bromodecarboxylation³³¹, a $^{12}\text{C} : ^{13}\text{C}$ isotope effect of up to 1.045 in the evolved 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 bromodeboronations³³⁴. The stereochemistry of desilylation³³⁵ 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

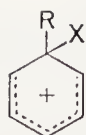


stereospecificity of this reaction and the ratios of the accompanying addition products it was concluded that the loss of CO_2 was nearly concerted with the electrophilic attack.

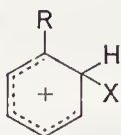
We have already noted that bromodeprotonation with rearrangement can be a first step in a reaction sequence leading to displacement of groups other than hydrogen. Halogenodealkylations and halogenodeacylations are also sometimes available as reaction paths competitive with the more usual substitutions. 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



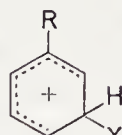
aromatic esters sometimes take the course expected, but in some cases the position of substitution is unexpected, and under these circumstances the reaction is often accompanied by deacylation, which can be catalysed by nucleophilic anions³³⁸. Formally, the overall processes leading to deacylation in such cases can be regarded as $S_{\text{E}}2'$ reactions, just as normal substitutions can be regarded as $S_{\text{E}}2$ 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, $\text{C}_6\text{H}_5\text{R}$, 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)



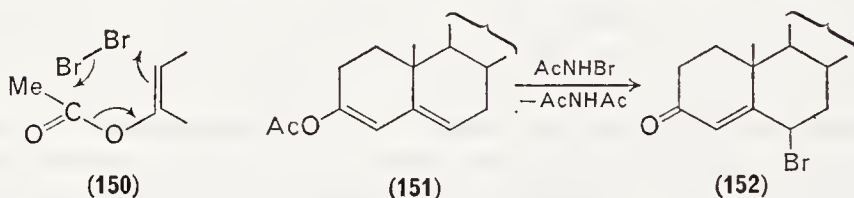
(148)



(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 Wluka³⁴² have proposed the cyclic mechanism indicated in formula **150** as one possibility; in some other circumstances³⁴³, 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 case³⁴⁴. Such sequence are difficult to disprove when the hypothetical intermediate adducts cannot be isolated.



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 Lardon³⁴⁵ 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 analogies³⁴¹.

B. Electrophilic Replacement of Halogen at Unsaturated Centres

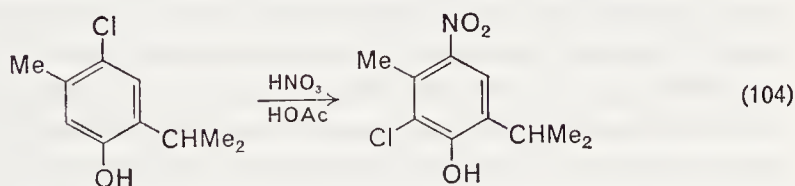
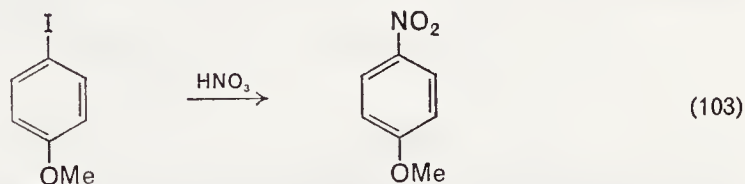
There have been a few mechanistic investigations of protodehalogenations (equation 102), which formally represent the reversal of an electrophilic halogenodeprotonation. The effects of substituents on the rates of

displacement of iodine from iodophenols are as expected for an electrophilic process³⁴⁶. The ease of removal of the different halogens is in the order $I > Cl$, and the reaction is facilitated by steric acceleration if sufficiently



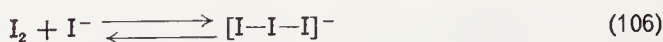
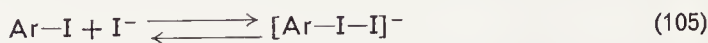
large and appropriately placed substituents are present. The kinetics of deiodination of *p*-iodoaniline show that the reaction is first-order with respect to the stoichiometric concentration of the aromatic compound and is independent of the concentration of hydrogen ion and of iodide ion³⁴⁷. The reaction 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 Nightingale³⁴⁸. 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).



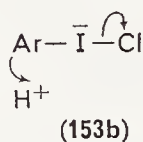
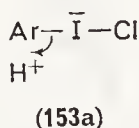
No doubt other types of dehalogenation are possible. Some recent investigations throw light on a major additional mechanistic possibility available for the electrophilic displacement of the higher halogens, particularly iodine and bromine. This involves nucleophilic catalysis, particularly by halide 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).



The likelihood of the existence of such a mechanism became apparent when it was recognized that complexes having this stoichiometry 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 accessible³⁴⁹.

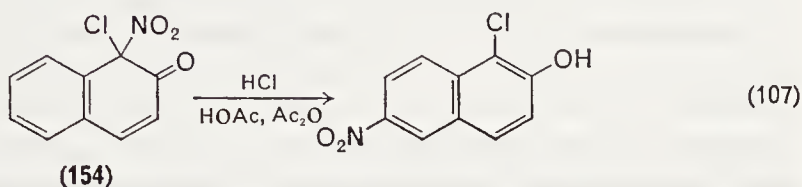
Kinetic evidence for the participation of such intermediates in the protodeiodination of iodo-2,4,6-trimethoxybenzene was presented by Batts and Gold³⁵⁰. The reaction was found to be catalysed by chloride ions, and the complex kinetic form was analysed in terms of two reaction paths, both involving hydrogen 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.



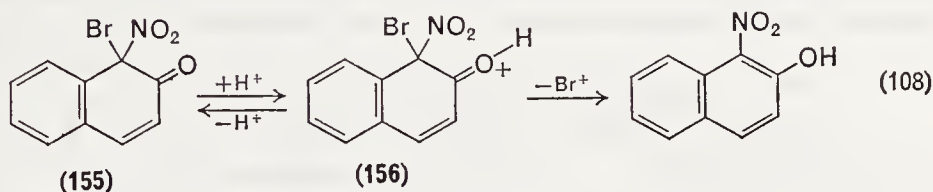
An interpretation involving similar intermediates was given of the isomerization and disproportionation of the *p*-bromophenols³⁵¹. When 3-methylphenol, for example, is brominated in an aprotic solvent at 25°C, the kinetically controlled product is, as expected, 4-bromo-3-methylphenol, with lesser amounts 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.



For the corresponding bromo-compound (**155**) on the other hand, the sole product was 1-nitro-2-naphthol (equation 108). This reaction, the

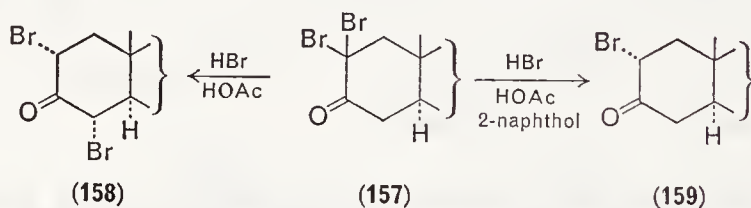


probable path for which involves the intermediate **156**, is a two-stage protodebromination with rearrangement, falling into the S_E2' classification in the sense in which we have used such terms in this article.

In discussing these reactions in terms of the relative leaving abilities of different groups, Perrin³⁵² distinguishes between those groups which he regards as generally leaving by S_N1 processes (e.g. NO_2^+ , $t\text{-Bu}^+$, 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 kind²⁴⁷. This makes it very probable that some of the nitrodehalogenations already mentioned³⁴⁸ 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 Hartshorn³⁴¹ have collected a number of cases from the chemistry of steroidal α -halogenoketones. Thus 2,2-dibromo-5 α -cholestane-3-one (**157**) rearranges with hydrogen bromide in acetic acid to give the 2 α ,4-dibromoketone (**158**), but with the same reagent in the presence of 2-naphthol to act as a scavenger for bromine gives the 2 α -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.

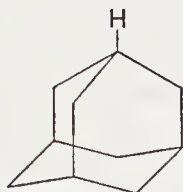
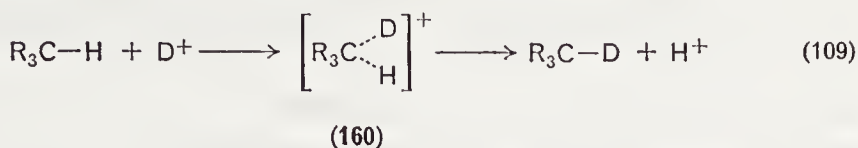


C. Electrophilic Replacement by Halogen at Saturated Centres

I. 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' treatment³⁵⁴ 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.

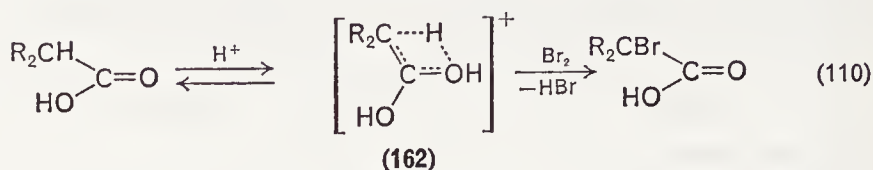


There are a number of other ways by which halogenation of saturated carbon atoms can be effected, and there is mechanistic information about some of these. The best known are the various processes by which halogen can be introduced adjacent to an electron-withdrawing substituent. We have already mentioned (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.

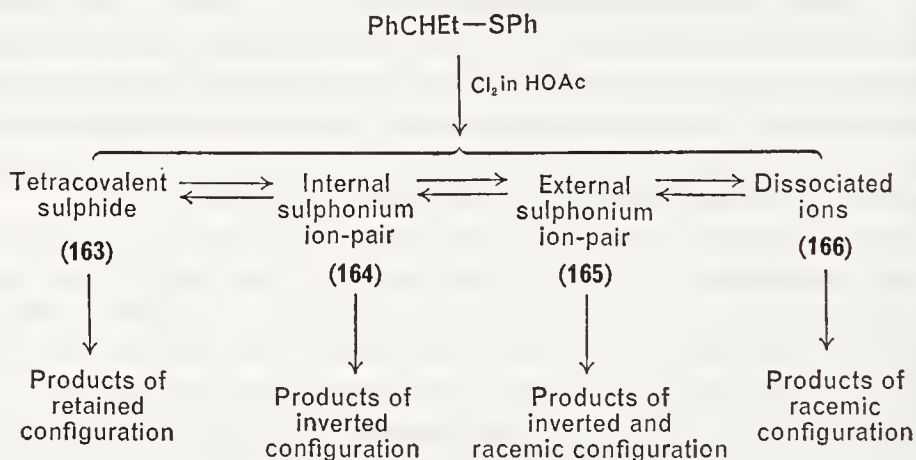
Kwart and Scalzi³⁵⁶ have measured the rates of bromination of a number of carboxylic acids in dipolar aprotic solvents. Evidence was obtained for partial dependence of the rate on the concentration of bromine. From this, from the effect of structure on the rate of reaction, and from the small magnitude 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.



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 sulphide³⁵⁷ 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

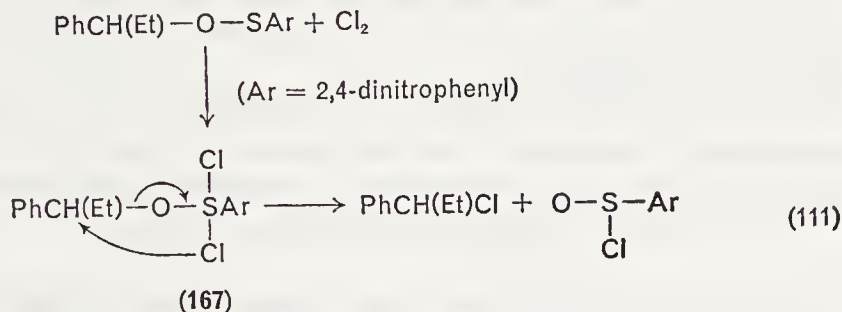


SCHEME 18. Intermediates in the chlorinolysis of arylalkyl sulphides.

(163-166). Each of the intermediates indicated in the scheme is multiple in character, depending on the anions concerned (i.e. the tetravalent sulphide could be PhCH(Et)SCl₂Ph 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 sequences³⁵⁷⁻³⁵⁹.



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 acetoxylation products accompanying nitration, first formulated as an electrophilic acetoxylation but now recognized to proceed by an addition-elimination sequence²⁴⁷ (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 lithium³⁶⁰, 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 substitutions³⁶⁰⁻³⁶³. 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 halogens³⁶⁴. The stoichiometry is that given by equation (112). The reactions are first-order in each reactant and the addition of



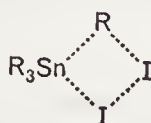
iodide ions has a negligible effect on the rate. Increase in the ionic strength of the medium, however, promotes the reaction. Some effects of structure and of solvent are shown in Table 20.

TABLE 20. Effects of structure and of solvent on the relative rates of electrophilic displacements by halogens on tetra-alkyl tins

	Reaction: Solvent:	$\text{R}_4\text{Sn} + \text{Br}_2$ PhCl	$\text{R}_4\text{Sn} + \text{Br}_2$ AcOH	$\text{R}_4\text{Sn} + \text{I}_2$ AcOH
Relative rate, R = Me		100	100	100
R = Et		1200	84	37
R = <i>n</i> -Pr		450	12	4.3
R = iso-Pr		1300	2.5	0.03

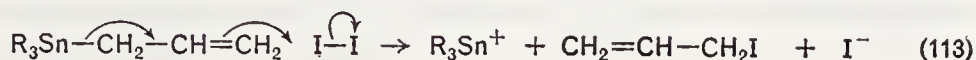
It is suggested that the reactions in acetic acid involve electrophilic displacement by halogen; the important influence of steric hindrance in diminishing the rate of reaction is evident from the effect of increasing the

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 Nasielski³⁶⁴ propose an S_E2' mechanism (equation 113) in this case.

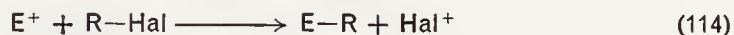


It seems likely that variants of such mechanisms are available for the reactions of halogens with many organometallic compounds³⁷².

D. Electrophilic Replacement of Halogen at Saturated Centres

I. Introduction

In the reaction of equation (114) there are two features which define that electrophilic substitution of halogen is occurring at the organic group



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



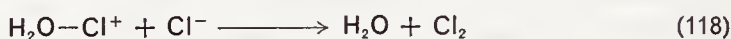
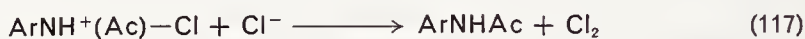
process can be regarded as nucleophilic substitution at halogen, and may be expected to occur when R is a good anionic leaving group, or when co-ordination with an electrophile occurs either prior to, or simultaneously with, nucleophilic attack.

2. Reactions which liberate halogen

Nucleophilic attack on halogen occurs when haloketones react with acidified potassium iodide (equation 116) as in Meyer's method³⁶⁵ for

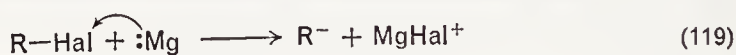


estimation of enolic content in protropic carbonyl systems. Here the leaving group involves carbon; in analogous cases, it may be a substituted nitrogen as in the chlorine-producing step of the Orton rearrangement³⁶⁶ of *N*-haloanilides (equation 117), or may be oxygen, as in equation (118).



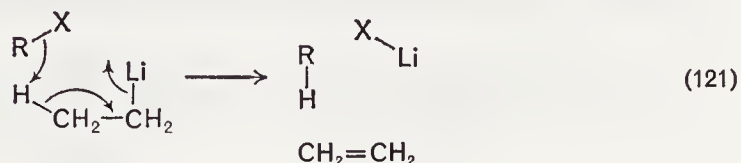
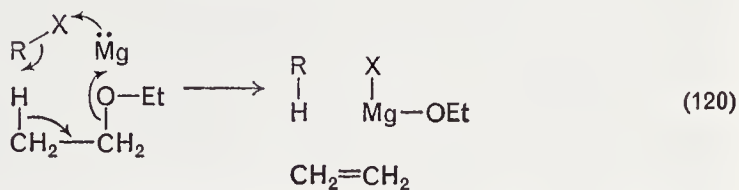
3. Metallation of halides

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,



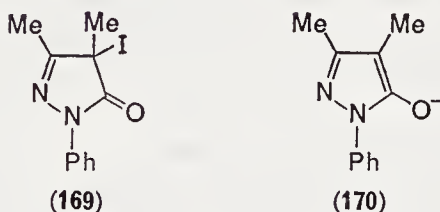
but this is a stoichiometric description and may not properly depict the mechanism, since electron transfer may be stepwise. The direct syntheses of organometallic compounds have been considered³⁶⁷, and it is notable that these reactions are frequently catalysed by electrophiles such as bromine. Metallation by magnesium has been reviewed in detail³⁶⁸. An optically active Grignard reagent has been prepared³⁶⁹. 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 proposed³⁸¹ 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 mercuriation of halides has been described in this way by Makarova and Nesmayanov³⁶².

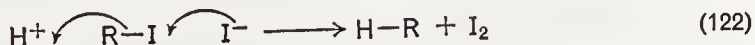


4. Iodine exchange

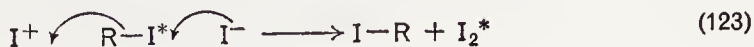
Noyes and Körös³⁷⁰ discuss iodine exchange in some heterocyclic compounds containing iodine. For 1-phenyl-3,4-dimethyl-4-iodo-2-pyrazolin-5-one (169), the enolate anion (170) would be expected to have



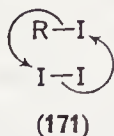
considerable stability by virtue of an aromatic sextet of electrons. In fact, iodide ion gives iodine in acid solution with this compound (equation 122).



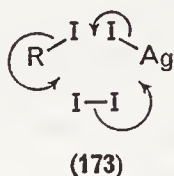
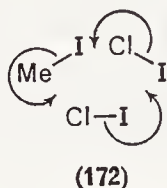
Exchange with iodide ion in neutral solution is slow, but is rapid with iodine; the mechanism of this process may be written as in equation (123).



Where, as in this case, electrophile and nucleophile are combined in the same molecule, the reaction may occur via a cyclic transition state (**171**),



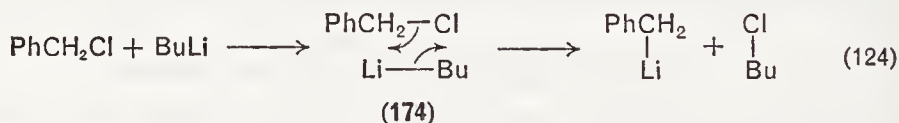
and considered in terms of electrophilic substitution at R. The transition state for such a reaction need not necessarily be electrically neutral, and for certain other heterocyclic iodides, Noyes and Körös³⁷⁰ show that the rate of iodine exchange is not altered significantly by light or oxygen, but 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 exchanges³⁷¹ may also have similar polar cyclic transition states (e.g. **172**).



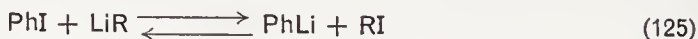
Catalysis by Hg^{2+} or Ag^+ in the reactions may be of the form **173**, although alternative possibilities involving intermediates in which R is transferred to the catalysing metal have not been excluded. Transition states of this nature have been discussed by Dessy and Kitching³⁷². Oxidative addition of alkyl and acyl halides to Group 8 metal complexes^{373, 374} show some similarities in kinetic patterns³⁷⁵ 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

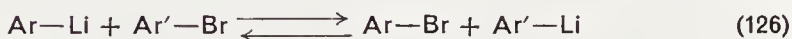


which the bases Bu^- and PhCH_2^- are competing for halogen rather than for a proton. Equilibrium constants have been determined for reaction (125),

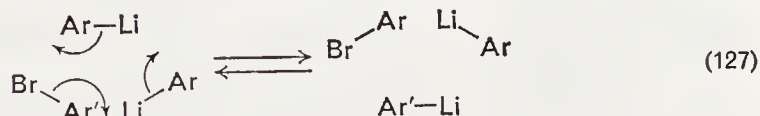


in order to derive an order of carbanionic stability³⁷⁶. The aryl and alkyl groups are clearly acting as nucleophilic centres subject to electrophilic replacement, and suitable cases would be expected to show the stereochemistry associated with electrophilic substitution at saturated carbon by the S_E2 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% racemization³⁷⁷. 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 methyldiphenylcyclopropane³⁷⁸.

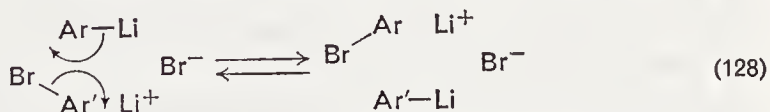
The kinetics of halogen-metal exchange reactions have been investigated by Winkler and Winkler³⁷⁹ for the reaction of equation (126). They



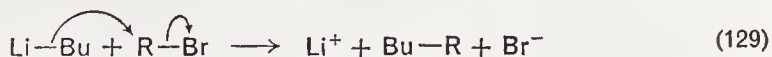
considered various mechanisms involving dimeric ArLi species, and the representation shown in equation (127) would accord with their mechanism



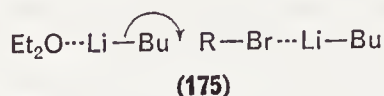
B. The value of ρ in the Hammett sigma-rho correlation is 4, a fact which indicates that an increase of negative charge in the aromatic nucleus occurs in proceeding to the transition state. The reaction involves a transition state more polar than the initial state, since the rate is increased in changing 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



interpretations are possible; Brown³⁸⁰ has considered systems involving hexamers in hydrocarbon solvents. Eastham and Gibson³⁸¹, 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



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).



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CHAPTER 8

Homolytic mechanisms of substitution

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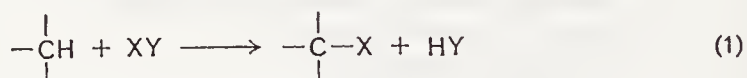
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I. INTRODUCTION

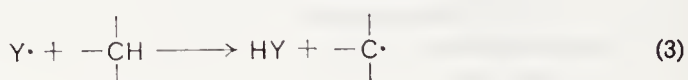
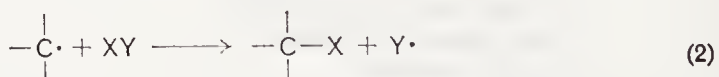
A. General Mechanism

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



sequence (2) and (3). The free radical Y^\bullet that performs the homolysis of the carbon-hydrogen bond may be either a halogen atom ($\text{X}^\bullet = \text{Y}^\bullet$) if molecular halogen is the halogenating agent ($\text{XY} = \text{X}_2$) or some free

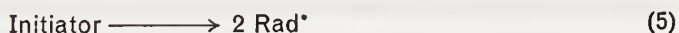


radical derived from the halogenating agent (e.g. $Y^\bullet = Cl_3C^\bullet$ if Cl_3CX is the halogenating agent). The facility with which the hydrogen atom is removed from the organic molecule depends both on the nature of Y^\bullet and the chemical environment of the hydrogen atom being abstracted 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.

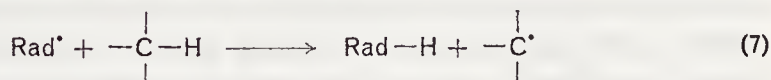
Although the stoichiometry of a halogenation reaction is determined in the chain sequence (provided the sequence repeats itself sufficiently often), other important processes are a necessary part of the overall halogenation reaction. One of these is the radical-producing or initiation reaction, the process 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



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.

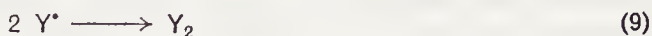
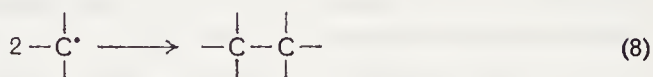


or



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



not only the initiation and chain sequence but also the particular reaction that terminates the chain sequence (see section II. C).

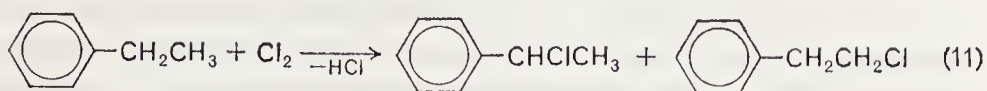
B. Scope of this Chapter

I. 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.

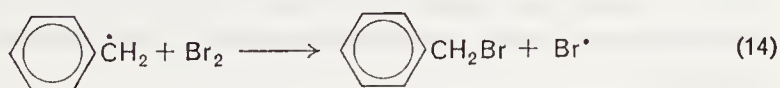
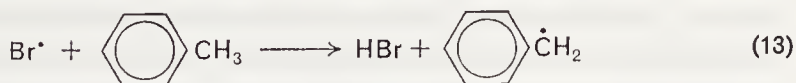
The chief disadvantages of chlorine as a halogenating agent centre around the reactivity of the chlorine atom as a hydrogen atom abstracting species. Although this characteristic is largely responsible for the long kinetic chain lengths observed for many chlorination reactions, it is also responsible 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.



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



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.



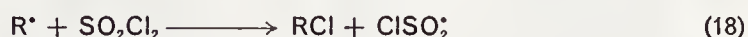
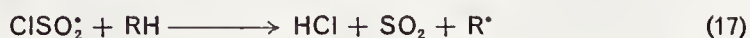
Another disadvantage of bromine is its cost. Although this is certainly not a serious limitation for most laboratory preparations, the economic disadvantage of bromine in comparison to chlorine as an industrial reagent does curtail its use to the manufacture of specialty items where either a high degree 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



display a degree of specificity greater than molecular chlorine because of characteristics of the hydrogen atom abstracting radical are $\text{Cl}_3\text{CSO}_2\text{Cl}$, Cl_3CSCl , PCl_5 , $(\text{CH}_3)_3\text{COCl}$, ICl_3 and $\text{C}_6\text{H}_5\text{ICl}_2$.

Some compounds that have been investigated as brominating agents are BrCCl_3 , $\text{BrCCl}_2\text{CCl}_2\text{Br}$, BrCl , $(\text{CH}_3)_3\text{COBr}$ 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 ₂ H ₅ —H	98	I—I	36
(CH ₃) ₂ CH—H	94.5	HO—Cl	60
(CH ₃) ₃ C—H	91	CH ₃ —Cl	84
CH ₂ =CHCH ₂ —H	85	C ₂ H ₅ —Cl	81
C ₆ H ₅ CH ₂ —H	85	(CH ₃) ₃ C—Cl	79
CH ₃ COCH ₂ —H	92	C ₆ H ₅ CH ₂ —Cl	68
H—CH ₂ CN	86	CH ₃ —Br	70
Cl ₃ C—H	96	C ₂ H ₅ —Br	69
(CH ₃) ₃ CO—H	103	(CH ₃) ₃ C—Br	63
H—Cl	103	C ₆ H ₅ CH ₂ —Br	51
H—Br	87.5	Cl ₃ C—Br	54
H—F	136	CH ₃ —I	56
H—I	71	C ₆ H ₅ CH ₂ —I	40
Cl—Cl	58	CH ₃ —F	106
Br—Br	46		

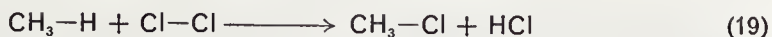
^a Bond-dissociation energies are taken from compilations given in J. A. Kerr, *Chem. Rev.*, **66**, 465 (1966) and S. W. Benson, *J. Chem. Ed.*, **42**, 502 (1965).

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.

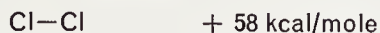
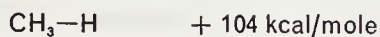
B. Reaction Enthalpies

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



Bonds broken:



Bonds made:

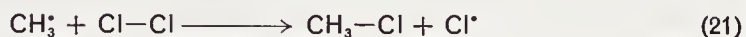


$$\Delta H = - 25 \text{ kcal/mole}$$

halogenation reactions. Examination of the reaction of methane and chlorine in this manner shows that the same value for the enthalpy is



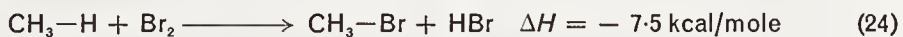
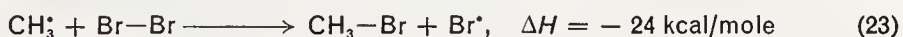
$$\Delta H = + 1 \text{ kcal/mole}$$



$$\Delta H = - 26 \text{ kcal/mole}$$

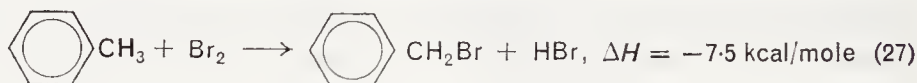
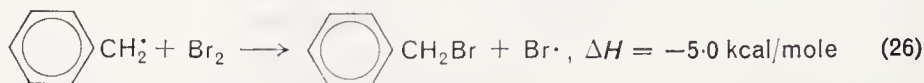
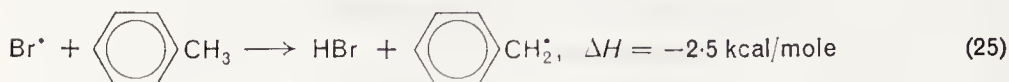
obtained (the stoichiometry of the chain reaction is the algebraic sum of the chain-propagating steps). It is obvious that essentially all of the energy evolved comes from the reaction of the methyl radical with chlorine. The hydrogen abstraction reaction, on the other hand, is an endothermic process 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



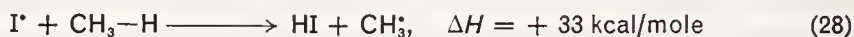
reaction is an endothermic process. The activation energy requirement for the endothermic step in the chain sequence must be at least the endothermicity of the reaction, in this case 16.5 kcal/mole, and presents a sufficiently high energy barrier to introduce a severe limitation to the overall chain 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

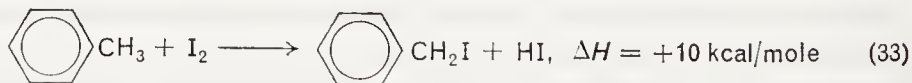
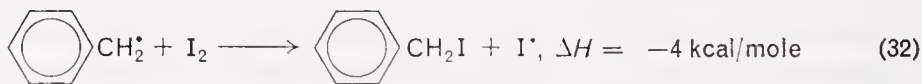


bromination of methane. The difference is encountered in that the hydrogen abstraction step in this case is exothermic and does not impose a limiting minimum for the activation energy requirement for the process.

The reactions of iodine with methane and toluene are endothermic. In both cases, the endothermicity of the hydrogen abstraction reaction

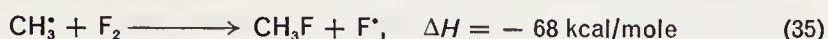


presents a severe limitation on the activation energy minimum for this step in the chain sequence.



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



fluorine with alkanes presents difficulties that render this approach to the introduction of fluorine into organic compounds unfavourable (see section V).

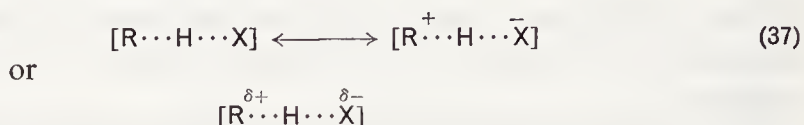
The enthalpies of the halogenation of other species with other halogenating agents can be estimated from the bond-dissociation energies listed in Table 1. Although these enthalpic relationships are informative to some degree, their principal value lies in giving information that is useful in learning 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 reactions¹. 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

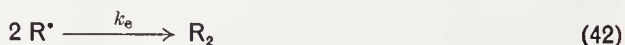
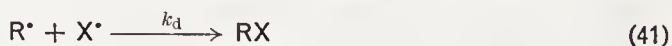
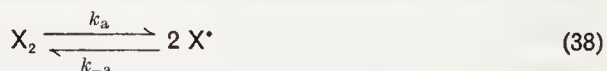
probably minimal. A different kind of polar effect involving charge separation in the transition state is observed in hydrogen atom abstractions by less energetic species (e.g. the bromine atom or trichloromethyl radical) where the transition state has considerable product-like character. These transition 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



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



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)

$$\text{Rate} = k_b \left(\frac{k_a}{k_{-a}} \right)^{\frac{1}{2}} \frac{[X_2]^{\frac{1}{2}} [RH]}{(1 + (k_{-b}[HX]/k_c[X_2]))} \quad (43)$$

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)

$$\text{Rate} = \left(\frac{k_a k_b k_c}{k_d} \right)^{\frac{1}{2}} \frac{[X_2] [RH]^{\frac{1}{2}}}{(1 + (k_{-b}[HX]/k_c[X_2]))} \quad (44)$$

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)

$$\text{Rate} = \left(\frac{k_a}{k_e} \right)^{\frac{1}{2}} k_c [X_2]^{\frac{3}{2}} \quad (45)$$

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.

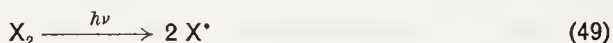
$$\text{Rate} = k_b \left(\frac{k_a}{k_{-a}} \right)^{\frac{1}{2}} [X_2]^{\frac{1}{2}} [RH] \quad (46)$$

$$\text{Rate} = \left(\frac{k_a k_b k_c}{k_d} \right)^{\frac{1}{2}} [X_2] [RH]^{\frac{1}{2}} \quad (47)$$

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

$$(\text{Rate of initiation})^{\frac{1}{2}} = (k_a[X_2])^{\frac{1}{2}} \quad (48)$$

Most often, the initiation process for halogenation reactions is the photolysis of the halogenating agent. This being the case, the intensity of



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

$$\text{Rate of initiation} = I\epsilon[X_2] \quad (50)$$

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 $k_i[\text{Init.}]$



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

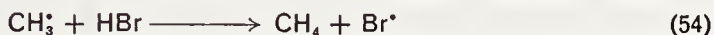
(52)². As the reaction proceeds, the rate is inhibited by the presence of HBr

$$\text{Rate} = k'[\text{CH}_4][\text{Br}]^{\frac{1}{2}} \quad (52)$$

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

$$\text{Rate} = \frac{k'[\text{CH}_4][\text{Br}]^{\frac{1}{2}}}{1 + k''[\text{HBr}]/[\text{Br}_2]} \quad (53)$$

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).



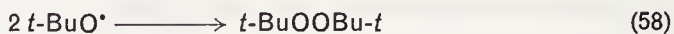
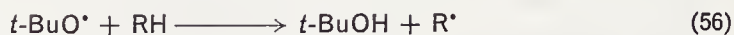
The observed rate laws for chlorinations with molecular chlorine are complex because the concentrations of the chain-carrying chlorine atoms and alkyl radicals are about the same and all three possible termination reactions are operative. Since the reactions of alkyl radicals with hydrogen chloride are 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

$$\text{Rate} = k'[\text{toluene}]^{0.92} [t\text{-BuOCl}]^{0.65} \text{I}^{0.55} \quad (55)$$

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



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

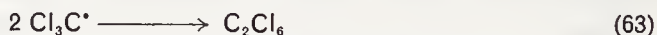
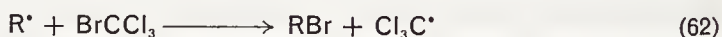
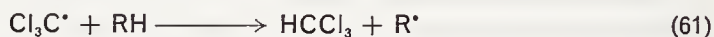
$$\text{Rate} = [t\text{-BuOCl}]^{1.30} \text{I}^{0.5} \quad (59)$$

mainly by coupling of two R^\bullet radicals ($\text{Cl}_3\text{C}^\bullet$ 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

$$\text{Rate} = k'[\text{RH}]^{0.98} [\text{Bz}_2\text{O}_2]^{0.58} [\text{BrCCl}_3]^{0.13} \quad (60)$$

(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



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 reviewed⁵. 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

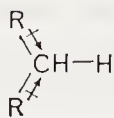
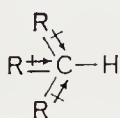
A useful set of rules for the chlorination of alkanes with molecular chlorine was formulated by Haas, McBee and Weber⁶. Most pertinent of these to the following discussion are the statements given here:

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 (hyperconjugative) 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
$\begin{array}{c} 1.0 \\ \text{CH}_3-\text{CH}_2-\text{CH}_3 \\ 3.7 \end{array}$	25	7
$\begin{array}{c} 5.6 \\ \text{CH}_3-\text{CH}-\text{CH}_3 \\ \quad 1.0 \\ \text{CH}_3 \end{array}$	25	7
$\begin{array}{c} 3.7 \quad 1.0 \\ \text{CH}_3-\text{CH}-\text{CH}-\text{CH}_3 \\ \quad \\ \text{CH}_3 \quad \text{CH}_3 \end{array}$	55	8
$\begin{array}{c} 1.0 \quad 2.6 \\ \text{CH}_3-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{CH}_3 \\ 2.45 \end{array}$	20	9
$\begin{array}{c} 0.83 \quad 2.16 \quad 1.0 \\ (\text{CH}_3)_2\text{CH}-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{CH}_3 \\ 2.48 \quad 1.45 \quad 2.10 \end{array}$	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 latter⁸.

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. $E_{\text{pri}} - E_{\text{tert}} = \sim 0.54$ kcal/mole for isobutane¹¹; $E_{\text{pri}} - E_{\text{tert}} = 0.7$ kcal/mole for 2,3-dimethylbutane⁷; $E_{\text{pri}} - E_{\text{sec}} = 0.4$ 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 mixture¹³. 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 C₅, C₆, C₇ and C₈ cycloalkanes at 40° is 1.04 : 1.00 : 1.11 : 1.59¹⁴. 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 C₅, C₆, C₇ and C₈ cycloalkanes towards abstraction by Cl₃C• 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 solvents⁸. Examination of these data shows that

some solvents have a remarkable effect on the selectivity of the chlorine atom as a hydrogen atom abstractor.

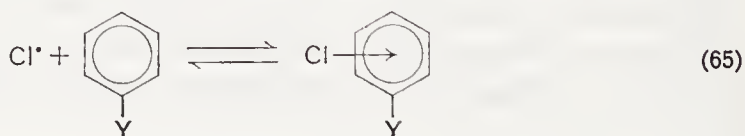
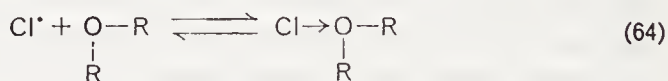
The halocarbons have essentially no effect on the reactivity of the chlorine atoms as a hydrogen abstractor. Oxygen-containing compounds, on the other hand, do increase the selectivity of the chlorine atom to some

TABLE 3. Solvent effects in chlorinations of 2,3-dimethylbutane^a

Solvent (molar concentrations)	k_t/k_p^a	
	25°C	55°C
2,3-Dimethylbutane (7.6)		3.7
Cl ₄ C (4.0)		3.5
Cl ₂ C=CHCl (4.0)		3.6
(CH ₃) ₃ COH (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.

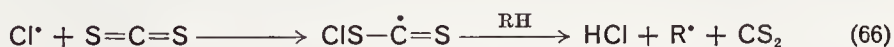
degree as do the aromatic compounds. The free chlorine atom is in equilibrium with the complexed species, both of which can apparently function as hydrogen abstractors. The complexed chlorine atom, being less energetic than the free chlorine atom, participates in the abstraction reaction in a process having a transition state with a considerable amount



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 NO₂) 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.



B. Alkylaromatics

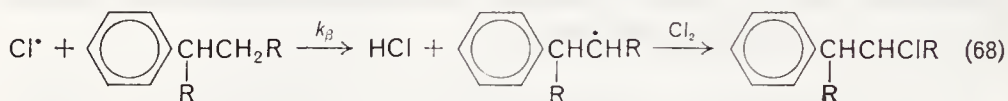
Toluene can be chlorinated in the side-chain to yield a single product, namely benzyl chloride, in high yield. Chlorination of most other alkylaromatics presents the same problems encountered in the chlorination of alkanes, namely, substitution occurs on each carbon of the alkyl chain. As might be expected, 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 cumene¹⁶

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



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.

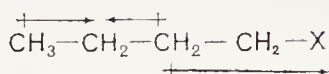
C. Alkyl Halides and Aliphatic Acid Derivatives

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
$\begin{array}{ccc} 4.2 & & 0.7 \\ \text{CH}_3-\text{CH}_2-\text{CH}_2-\text{CH}_2\text{Cl} \\ 1.0 & & 2.2 \end{array}$	35	17
$\begin{array}{ccc} 4.0 & & 0.5 \\ \text{CH}_3-\text{CH}_2-\text{CH}_2-\text{CH}_2\text{Br} \\ 1.0 & & (-) \end{array}$	35	17
$\begin{array}{ccc} 3.7 & & 0.8 \\ \text{CH}_3-\text{CH}_2-\text{CH}_2-\text{CH}_2\text{F} \\ 1.0 & & 1.6 \end{array}$	35	17
$\begin{array}{ccc} 4.3 & & 0.04 \\ \text{CH}_3-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{CF}_3 \\ 1.0 & & 1.2 \end{array}$	75	18
$\begin{array}{ccc} 4.2 & & 0.7 \\ \text{CH}_3-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{CO}_2\text{CH}_3 \\ 1.0 & & 2.2 \end{array}$	75	19
$\begin{array}{ccc} 3.9 & & 0.2 \\ \text{CH}_3-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{COCl} \\ 1.0 & & 2.1 \end{array}$	75	19
$\begin{array}{ccc} 4.2 & & 0.08 \\ \text{CH}_3-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{COF} \\ 1.0 & & 1.5 \end{array}$	60	20
$\begin{array}{ccc} 4.4 & & \\ \text{CH}_3-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{CN} \\ 1.0 & & \end{array}$	(-)	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.



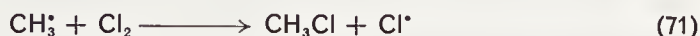
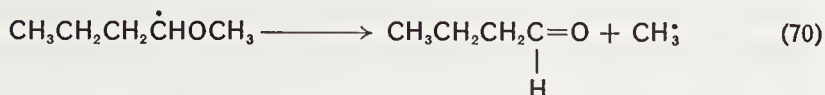
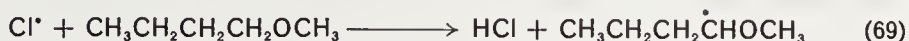
The lack of any significant amounts of hydrogen abstraction from the α -carbons of the acids and their derivatives again points out the reactant-like character of the transition states of hydrogen atom abstractions by chlorine atoms. The α -carbonyl- and α -cyano-radicals formed in these abstractions 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 : 3²². 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 chloride²³.

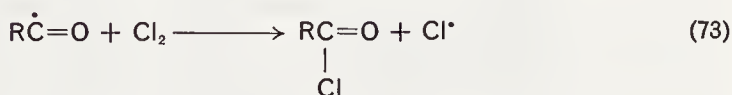
Chlorination of ethers generally yields an α -chloroether²⁴. A side reaction that may occur in the course of the chlorination is the fragmentation of the intermediate ether-derived free radical before it reacts with

molecular chlorine. For example, *n*-butyl methyl ether may yield a mixture of *n*-butyraldehyde and methyl chloride as reaction products²⁵. Fragmentations of the α -alkoxyalkyl radicals occur most readily at higher temperatures²⁶ and for that reason, successful photochlorinations of the ethers



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 products²⁹.

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



hydrogen by a chlorine atom followed by reaction of the resulting acyl radical with molecular chlorine³⁰. Other halogenating agents, namely carbon tetrachloride³¹, sulphuryl chloride³⁰ and *t*-butyl hypochlorite²⁸ 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



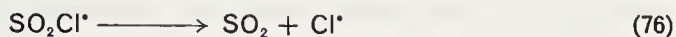
chloride is a facile process and yields the chlorosulphonyl radical which is a more specific hydrogen atom abstracting species than the chlorine atom. In Table 6, the relative reactivities of tertiary hydrogens with respect to

TABLE 6. Reactions of 2,3-dimethylbutane with chlorine and sulphuryl chloride³²

Condition	Temperature (°C)	$k_{\text{tert}}/k_{\text{pri}}$	
		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 ($k_{\text{tert}}/k_{\text{pri}}$) 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 ($\text{SO}_2\text{Cl}^{\bullet}$). 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

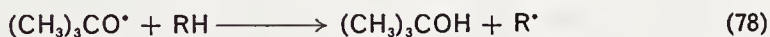
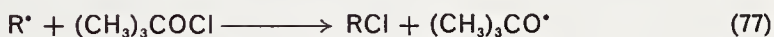
which do part of the hydrogen atom abstracting. The relative reactivity



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.

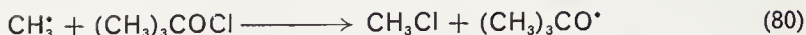
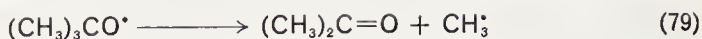
2. *t*-Butyl hypochlorite

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 species³³. The reagent itself is very reactive towards chlorine abstraction by alkyl radicals but, from the kinetic analysis of the chlorination of chloroform³ with *t*-butyl hypochlorite, it is apparently less



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.



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



function as the chlorinating agent, a complication that becomes serious if the halogenating chain sequence is short and much initiation is required.



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 ($\rho = -0.83$ 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 hypochlorite³⁴

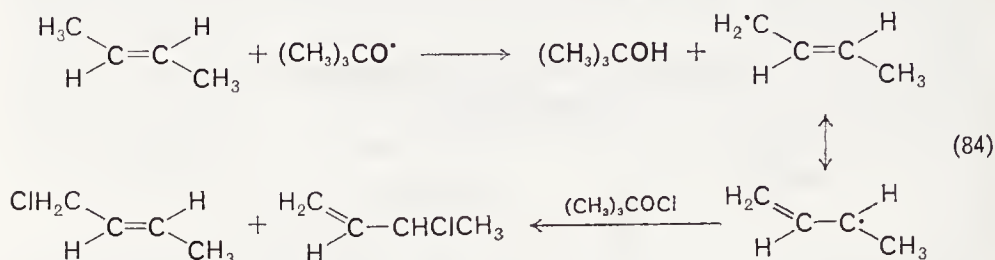
Solvent	$k_{\text{tert}}/k_{\text{pri}}$					$E_{\text{pri}}^{\ddagger} - E_{\text{tert}}^{\ddagger}$ ^a
	100°	70°	40°	25°	0°	
None	—	—	44	54	68	1.85
Benzene ^b	—	—	55	70	89	1.99
Chlorobenzene ^b	—	35	54	66	94	2.58
Acetone ^b	20	30	51	76	128	3.77
Acetonitrile ^b	10	17	33	47	—	4.57

^a kcal/mole.

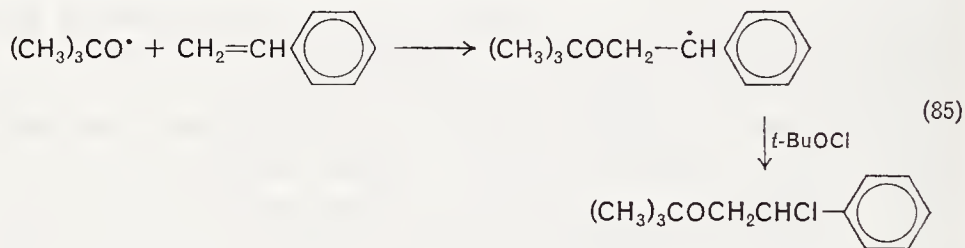
^b [2,3-Dimethylbutane] = 0.8 molar and [*t*-BuOCl] = 0.2 molar.

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

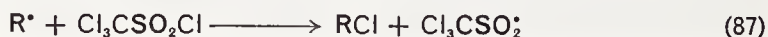


at 40°. The most striking feature of these allylic chlorinations is that the hybrid allylic radical retains its configuration³⁵. Chlorinations of other *cis* and *trans* isomeric alkenes with the same reagent also yield allylic chlorides with the same configuration as the alkene indicating the preservation 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.



3. Trichloromethanesulphonyl chloride and trichloromethanesulphenyl chloride

Alkanes and alkylaromatics have been chlorinated with trichloromethanesulphonyl chloride ($\text{Cl}_3\text{CSO}_2\text{Cl}$) in light- and peroxide-induced reactions³⁷. The chain sequence for the chlorination reaction most likely involves hydrogen atom abstraction by the trichloromethanesulphonyl radical ($\text{Cl}_3\text{CSO}_2^\bullet$)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 ($k_{\text{tert}}/k_{\text{sec}} = 20$) or primary ($k_{\text{tert}}/k_{\text{pri}} = 20\text{--}30$) and only the benzylic

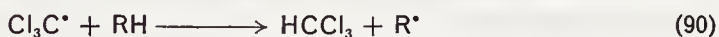


hydrogens of alkylaromatics. Trichloromethanesulphinic acid is the product formed in the hydrogen atom abstraction reaction but this species is not stable and decomposes to chloroform and sulphur dioxide, the observed by-products of the chlorination reaction. The kinetic chain



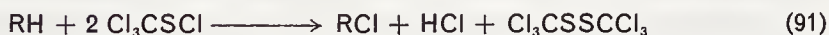
lengths of the reaction sequence are short compared to those of chlorinations with molecular chlorine, sulphuryl chloride or *t*-butyl hypochlorite.

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



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 ($k_{\text{cyclohexane}}/k_{\text{toluene}} = 1.86$) and for bromotrichloromethane ($k_{\text{cyclohexane}}/k_{\text{toluene}} = 0.20$), a halogenating agent known to involve the trichloromethyl radical as the hydrogen atom abstracting species.

Trichloromethanesulphenyl chloride (Cl_3CSCI) reacts in light- and peroxide-induced reactions with alkanes according to the following stoichiometry³⁹:



The mechanism proposed for the reaction involves hydrogen atom abstraction by a trichloromethanethiyl radical, a species having a degree of

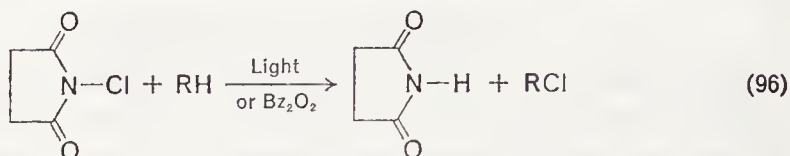


selectivity in this capacity similar to that of the trichloromethyl radical. For example, at 0° the $k_{\text{tert}}/k_{\text{pri}}$ for 2,3-dimethylbutane is 110 and the $k_{\text{sec}}/k_{\text{pri}}$ for *n*-pentane is 33. The disulphide formed as a by-product in the reaction can be isolated and converted back to the starting material by treatment with chlorine.

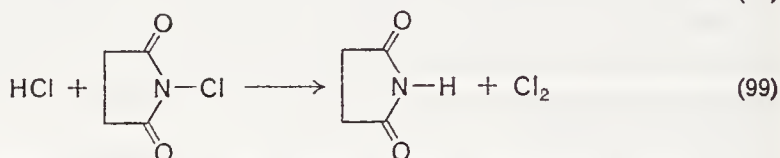


4. *N*-Chloroamides

N-Chlorosuccinimide can be used to chlorinate hydrocarbons in reactions that are either light-induced or initiated with benzoyl peroxide⁴⁰. The mechanism of the chlorination reactions with this is probably similar to



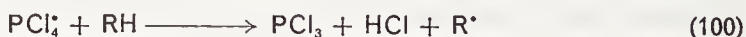
that of the brominations with *N*-bromosuccinimide in that the actual halogenating agent is the molecular halogen generated by interaction of the *N*-haloamide and the hydrogen halide produced as a product of the halogenation chain sequence. Since the site of chlorination is determined by a chlorine atom, little advantage in terms of selectivity is gained in using this reagent.



N-Chlorosulphonamides have been used to chlorinate alkanes⁴¹. 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.



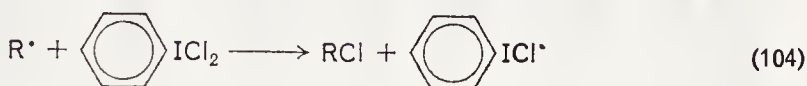
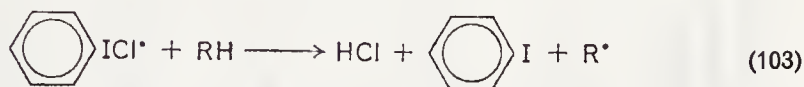
A similar selectivity is noted in the chlorinations of alkanes with molecular chlorine in the presence of phosphorus trichloride, suggesting that the chlorine atom may be effectively complexed with this reagent⁴⁴. The complex is not extremely stable since competition reactions of



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 chloride⁴⁵. 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 $\text{C}_6\text{H}_5\text{ICl}^\bullet$:



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 monochloriodobenzene 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}

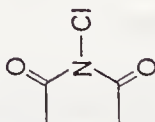
Reagent	Conditions	Substrate	Product distribution (%) ^a
Cl ₂	Light, 20°	<i>n</i> -Octane	$\begin{array}{l} 14.3 \qquad 28.4 \\ \text{CH}_3-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{C}_4\text{H}_9-n \\ 30.4 \qquad 26.7 \end{array}$
(CH ₃) ₃ COCl	Light, 20°	<i>n</i> -Octane	$\begin{array}{l} 6.3 \qquad 28.7 \\ \text{CH}_3-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{C}_4\text{H}_9-n \\ 38.2 \qquad 26.2 \end{array}$
Cl ₃ CSO ₂ Cl	Bz ₂ O ₂ , 98°	<i>n</i> -Octane	$\begin{array}{l} 1.9 \qquad 30.2 \\ \text{CH}_3-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{C}_4\text{H}_9-n \\ 42.0 \qquad 25.9 \end{array}$
Cl ₃ CSCl	Light, 98°	<i>n</i> -Octane	$\begin{array}{l} 4.7 \qquad 32.8 \\ \text{CH}_3-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{C}_4\text{H}_9-n \\ 31.5 \qquad 30.4 \end{array}$
	Bz ₂ O ₂ , 98°	<i>n</i> -Octane	$\begin{array}{l} 15.0 \qquad 28.5 \\ \text{CH}_3-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{C}_4\text{H}_9-n \\ 30.9 \qquad 25.4 \end{array}$
PCl ₅	Bz ₂ O ₂ , 98°	<i>n</i> -Octane	$\begin{array}{l} 1.5 \qquad 35.1 \\ \text{CH}_3-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{C}_4\text{H}_9-n \\ 28.4 \qquad 35.0 \end{array}$
Cl ₂	Light, 20°	2-Methylheptane	$\begin{array}{l} 11.6 \qquad 11.2 \qquad 9.2 \\ \text{CH}_3-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{CH}(\text{CH}_3)_2 \\ 32.4 \qquad 16.7 \qquad 19.1 \end{array}$

TABLE 8—continued

Reagent	Conditions	Substrate	Product distribution (%) ^a
SO ₂ Cl	Bz ₂ O ₂ , 85°	2-Methylheptane	$ \begin{array}{ccccccc} 8.5 & & & & 11.6 & & 13.0 \\ \text{CH}_3-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{CH}(\text{CH}_3)_2 & & & & 18.9 & & 14.0 \\ 34.1 & & & & & & \end{array} $
$ \begin{array}{c} \text{CH}_3\text{SO}_2\text{N}-\text{Cl} \\ \\ \text{C}(\text{CH}_3)_3 \end{array} $	Bz ₂ O ₂ , 85°	2-Methylheptane	$ \begin{array}{ccccccc} 10.8 & & & & 10.5 & & 11.5 \\ \text{CH}_3-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{CH}(\text{CH}_3)_2 & & & & 14.1 & & 14.4 \\ 38.8 & & & & & & \end{array} $
Cl ₂	Light, 20°	2,3,4-Trimethylpentane	$ \begin{array}{ccccccc} 50.8 & & 17.9 & & & & \\ (\text{CH}_3)_2\text{CH}-\text{CH}-\text{CH}-\text{CH}(\text{CH}_3)_2 & & & & 20.4 & & \\ & & \text{CH}_3 & & & & \\ & & 10.9 & & & & \end{array} $
Cl ₃ CSO ₂ Cl	Bz ₂ O ₂ , 85°	2,3,4-Trimethylpentane	$ \begin{array}{ccccccc} 4.9 & & 23.8 & & & & \\ (\text{CH}_3)_2\text{CH}-\text{CH}-\text{CH}-\text{CH}(\text{CH}_3)_2 & & & & 71.3 & & \\ & & \text{CH}_3 & & & & \end{array} $
$ \begin{array}{c} \text{CH}_3\text{SO}_2\text{N}-\text{Cl} \\ \\ \text{C}(\text{CH}_3)_3 \end{array} $	Bz ₂ O ₂ , 85°	2,3,4-Trimethylpentane	$ \begin{array}{ccccccc} 52.6 & & 19.1 & & & & \\ (\text{CH}_3)_2\text{CH}-\text{CH}-\text{CH}-\text{CH}(\text{CH}_3)_2 & & & & 19.2 & & \\ & & \text{CH}_3 & & & & \\ & & 9.1 & & & & \end{array} $

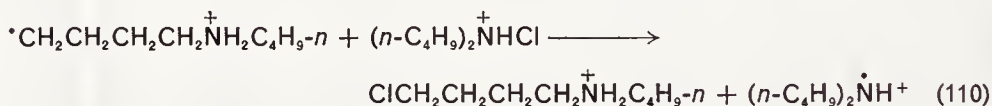
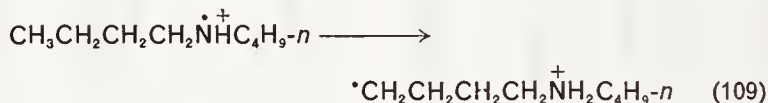
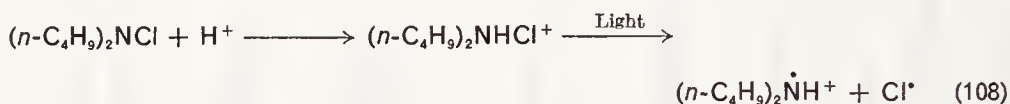
^a Actual observed percentages of monochlorinated products.

lack of specificity and the non-chain character of the reaction render the reagent of limited value as a chlorinating agent⁴⁶.

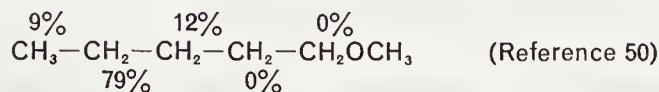
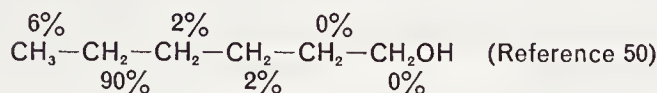
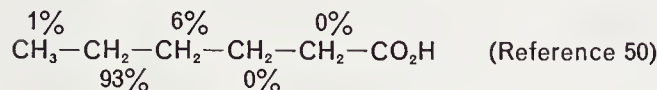
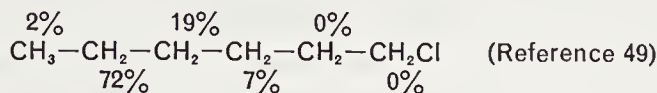
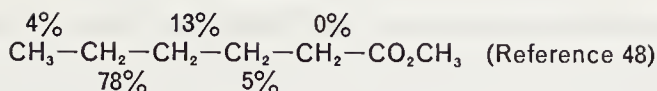


8. *N*-Chloroamines

The Hoffmann-Löffler reaction is an intramolecular chlorination involving protonated *N*-chloroamines⁴⁷. 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*-chloroamine⁴⁷.



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 ($\text{R}_2\dot{\text{N}}\text{H}^+$) 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.



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 >> primary >> methyl, it is not surprising that bromine atoms abstract



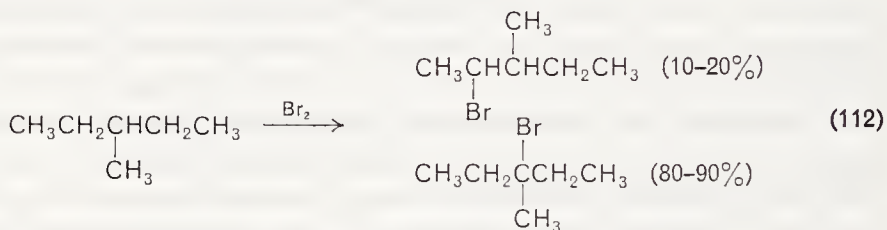
tertiary hydrogens considerably more readily than primary or even secondary hydrogens. Relative reactivities of various hydrogens have been calculated from available rate data and are given in Table 9. It can be deduced from these data that if a tertiary hydrogen is available along with primary and secondary 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 ₃ CH ₂ -H (1.00)	(CH ₃) ₂ CH-H (88) ^b	(CH ₃) ₃ C-H (1980) ^b
CH ₃ CH ₂ -H (1.00)	CH ₃ CH ₂ CH(CH ₃)-H (43) ^b	(CH ₃) ₃ C-H (1980) ^b
CH ₃ CH ₂ CH ₂ CH ₂ -H (1.00)	CH ₃ CH ₂ CH(CH ₃)-H (82) ^c	(CH ₃) ₃ C-H (1640) ^c

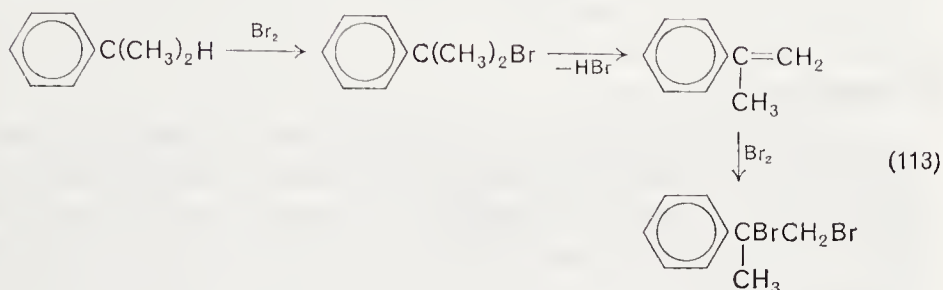
^a Statistically corrected.^b Relative to the hydrogens of ethane.^c Relative to the primary hydrogens of *n*-butane.

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.



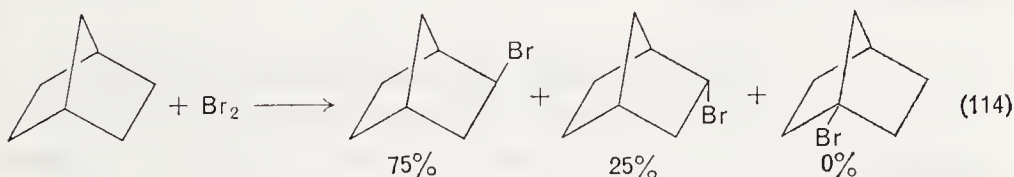
Although dibromides could be obtained by further bromination of the monobromides (see section IV. C), the amounts of dibromide are often observed to be greater than might be expected on the basis of the available monobromides. Formation of excessive amounts of dibromides is particularly evident in branched 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-dimethylbutane⁵³. Similarly, 2-methylpentane yielded 17.5% of 2,3-dibromo-2-methylpentane along with 76% of the tertiary bromide⁵³. 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.



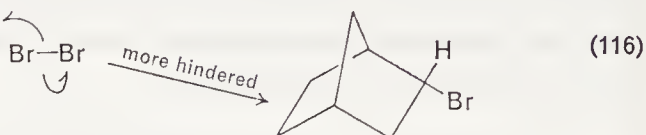
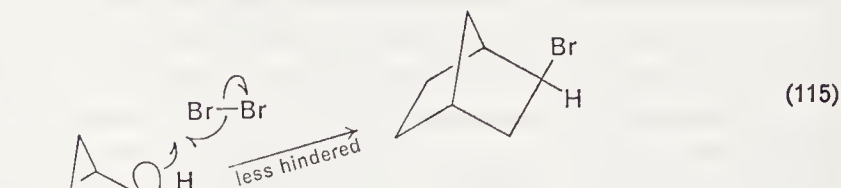
The mechanism for the dehydrohalogenation reaction is not precisely clear but may involve heterolysis of the bromide promoted by either the available hydrogen bromide or molecular bromine. Loss of the hydrogen on the carbon atom adjacent to the carbonium ion site would follow the Saytzev rule producing 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 norbornane⁵⁴, for example, yields a mixture of the *endo*- and *exo*-2-bromonorbornanes in a 1 : 3 ratio but none of the 1-bromonorbornane that would result from abstraction of a tertiary hydrogen. In this case the tertiary bridgehead hydrogen is not abstracted since, owing to the



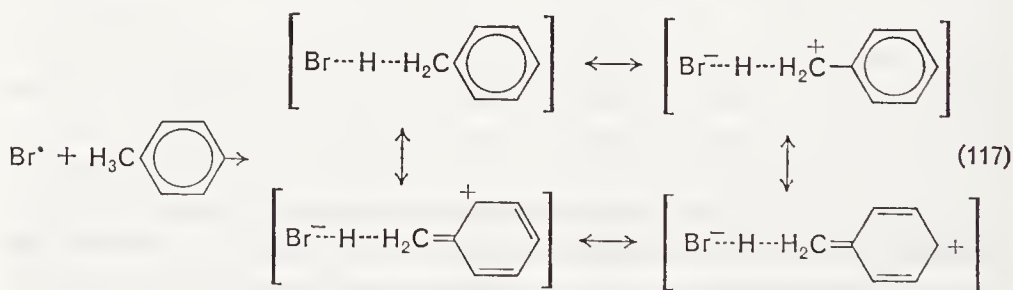
inability of the bridgehead carbon to assume the coplanarity of an sp^2 -hybridized carbon, the resulting tertiary alkyl radical is unstable. The predominant formation of the *exo*-2-bromonorbornane reflects the less

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 atoms⁵⁵. 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.

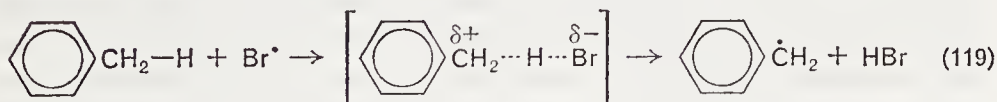
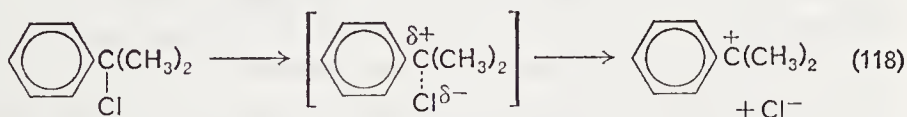


It is interesting that hydrogen atom abstraction from toluene by bromine atoms is only about three times faster than abstraction of the tertiary hydrogen from isobutane. In the latter case, the contribution of the polar canonical structure to the hybrid transition state is significant because of extensive 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 substituents⁵⁶, 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.



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 -1.07 and -1.36 at 80° and 19° , respectively, for reactions involving slow addition of bromine and -1.36 and -1.76 at 80° and 19° , respectively, for rapid reactions involving an excess of bromine⁵⁷.

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.

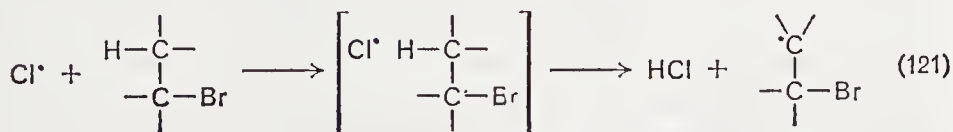
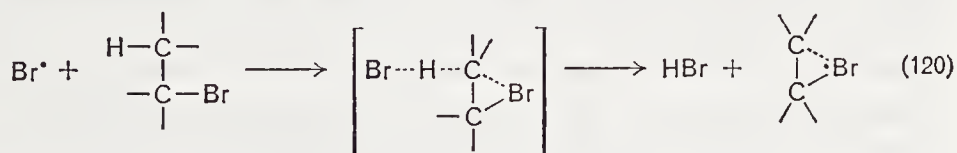
The most striking anomaly is the enhanced reactivity of the hydrogen atoms on the β -carbon relative to the bromine towards abstraction by bromine atoms. This effect is noted both in the reactions of 1-bromobutane

TABLE 10. Relative rates of hydrogen abstraction by bromine and chlorine atoms from butyl halides at 60°⁵⁸

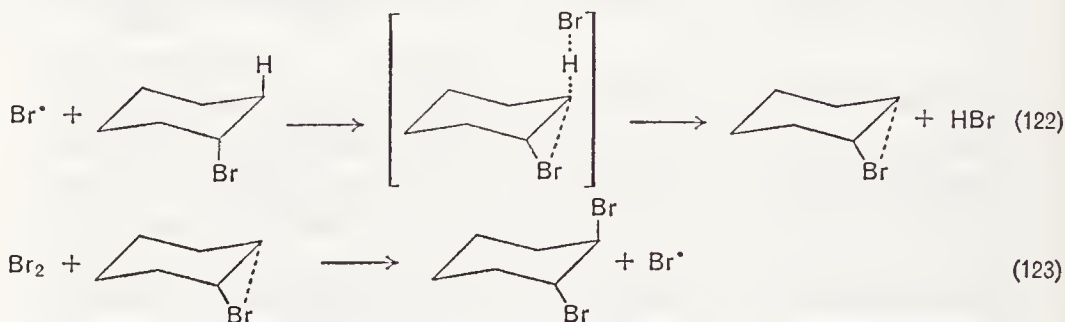
Butyl halide	Halogenating agent	Relative reactivities ^a
1-Chlorobutane	Chlorine	$\begin{array}{ccc} 0.397 & & 0.478 \\ \text{CH}_3 - \text{CH}_2 - \text{CH}_2 - \text{CH}_2 - \text{Cl} \\ 1.00 & & 0.158 \end{array}$
1-Chlorobutane	Bromine	$\begin{array}{ccc} & & 0.488 \\ \text{CH}_3 - \text{CH}_2 - \text{CH}_2 - \text{CH}_2 - \text{Cl} \\ 1.00 & & 0.439 \end{array}$
1-Bromobutane	Chlorine	$\begin{array}{ccc} 0.455 & & 0.434 \\ \text{CH}_3 - \text{CH}_2 - \text{CH}_2 - \text{CH}_2 - \text{Br} \\ 1.00 & & 0.093 \end{array}$
1-Bromobutane	Bromine	$\begin{array}{ccc} & & 5.78 \\ \text{CH}_3 - \text{CH}_2 - \text{CH}_2 - \text{CH}_2 - \text{Br} \\ 1.00 & & 0.62 \end{array}$
2-Chlorobutane	Bromine	$\begin{array}{ccc} & & 1.00 \\ \text{CH}_3 - \text{CH}_2 - \text{CHCl} - \text{CH}_3 \\ 0.086 & & \end{array}$
2-Bromobutane	Bromine	$\begin{array}{ccc} & & 1.00 \\ \text{CH}_3 - \text{CH}_2 - \text{CHBr} - \text{CH}_3 \\ 5.13 & & \end{array}$

^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.

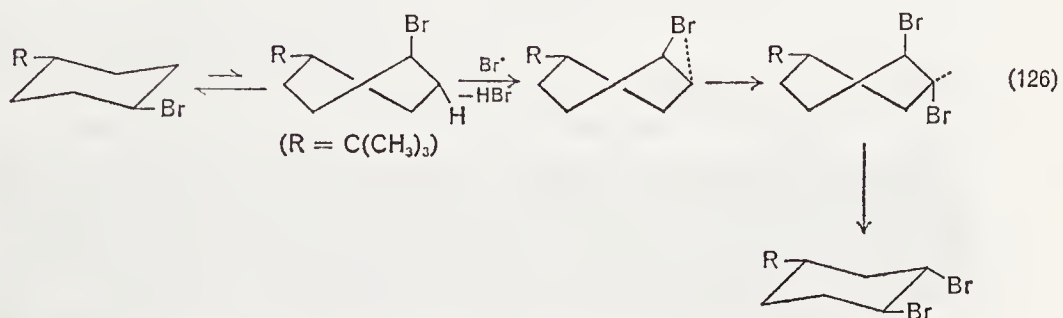
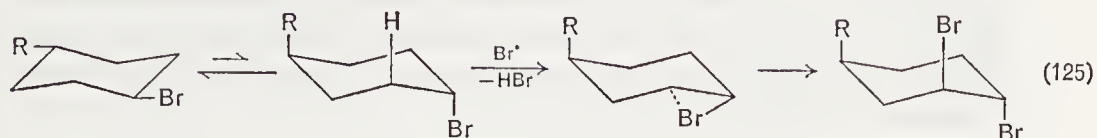
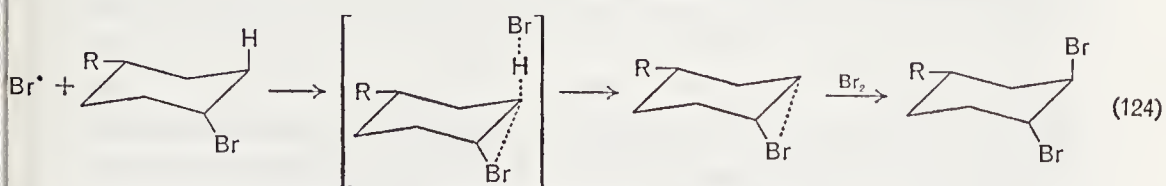


Evidence for the bridged radical is also found in the products resulting from its interaction with molecular bromine yielding the dibrominated alkane. For example, both bromocyclohexane and bromocyclopentane yield predominantly *trans*-1,2-dibromocycloalkanes on photobromination⁵⁹. Not only is the site 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 bromides⁶⁰ 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

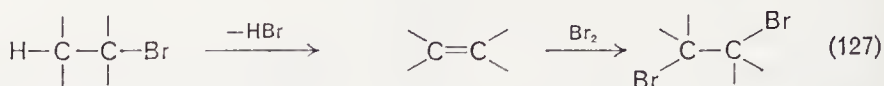
also by the fact that the *trans*-isomer yields a mixture of dibromides. The latter, of course, is the consequence of hydrogen atom abstraction from other sites on the cyclohexane ring.



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 alkanes⁶¹. 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-dibromoalkane⁶¹. This mechanism not only explains the preference for formation of vicinal dibromides but also

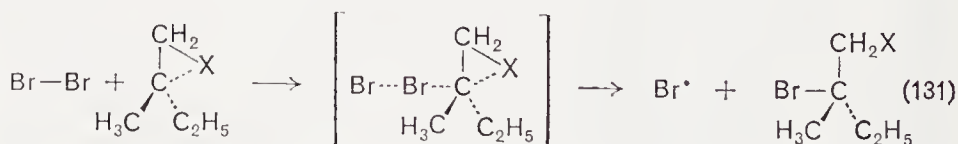
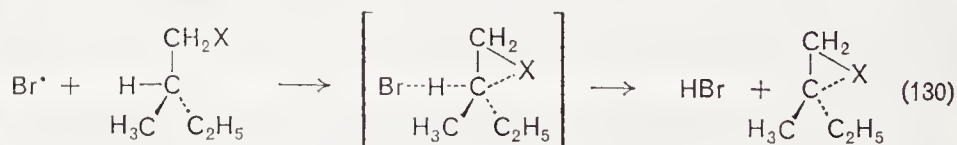
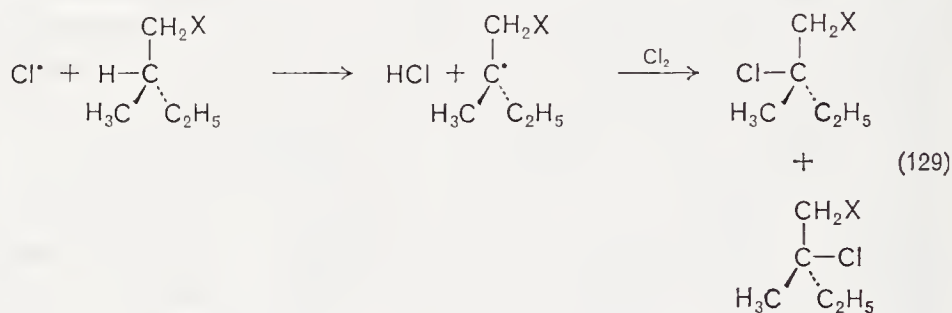
accounts for the stereospecificity noted in both the reactivities of the isomeric *t*-butylcyclohexyl bromides and in the formation of the *trans*-diaxial bromides from the *cis*-isomer and from the bromocycloalkanes.



Dehydrohalogenation of the cycloalkyl bromides having the bromine in an axial position would be expected to occur more readily by an *E2* 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.



Although the argument against the bridged radical is not without merit and at the time of the writing of this article is actively being investigated⁶², 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



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

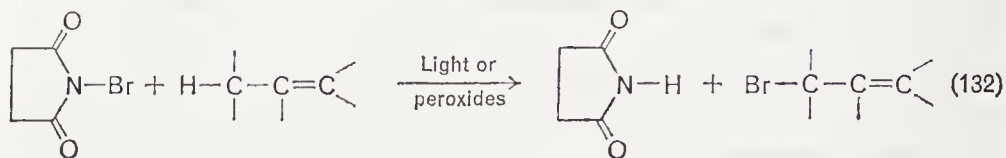
The lack of specificity of the chlorine atom as a hydrogen atom abstracting radical makes the search for chlorinating agents with more selective abstracting radicals of interest. The bromine atom, on the other hand, is selective in its role as a hydrogen abstractor and the use of brominating agents other 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.

I. *N*-Bromosuccinimide and related compounds

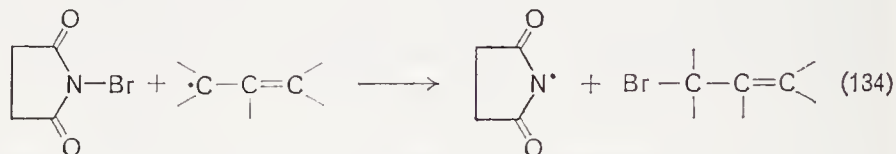
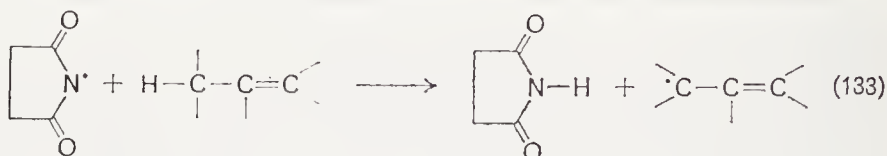
The bromination of an alkene in the allylic position by an *N*-bromoamide has been known as a valuable synthetic procedure for some time. The first report of such a reaction was made by Wohl in 1919⁶⁴. The synthetic potential of the reaction was not appreciated until the 1940's when Ziegler and coworkers published their investigations⁶⁵. 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 agents⁶⁶.

N-Bromosuccinimide is generally employed in synthetic work for the allylic bromination reactions and serves well as a model for the reactions of

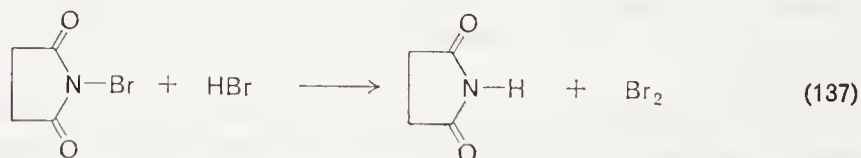
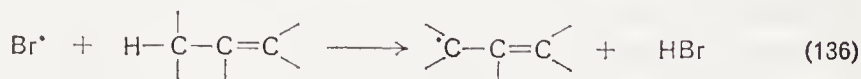
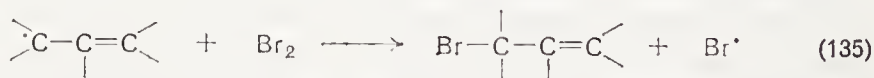
the *N*-bromoamides. The stoichiometry of the reaction indicates a simple substitution of an allylic hydrogen of the unsaturated compound with the nitrogen-bonded bromine of the *N*-bromosuccinimide. A free-radical chain mechanism for this substitution seems plausible in view of the observations



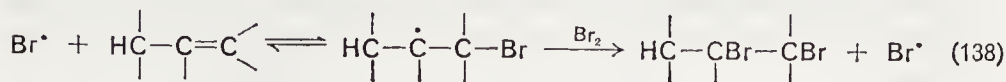
that the reaction rate is accelerated by free-radical initiation procedures such as decomposition of peroxides and illumination of the reaction mixture. The obvious mechanism for the reaction, namely that shown in the chain sequence below, involves abstraction of the allylic hydrogen atom by the *N*-succinimidyl radical followed by reaction of the resulting allylic radical with the brominating agent. This mechanism was first postulated by Hey⁶⁷ and Bloomfield⁶⁸ in 1944. Subsequent investigations showed,



however, that this mechanism was not correct. The presently accepted mechanism for the reaction was suggested by Goldfinger in 1953⁶⁹, 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



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



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.

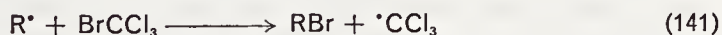
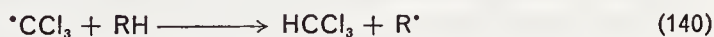
The most compelling evidence supporting the Goldfinger mechanism is the similarity observed in the relative rates of bromination of alkanes, alkylaromatics and substituted toluenes with bromine and with *N*-bromosuccinimide⁷⁰. Both reagents require the bromine atom as the hydrogen atom abstracting radical. 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 maintained⁷¹.

2. Polyhaloalkanes

Bromotrichloromethane reacts with alkylaromatics⁷² and, to a lesser extent, with alkanes⁷³ 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

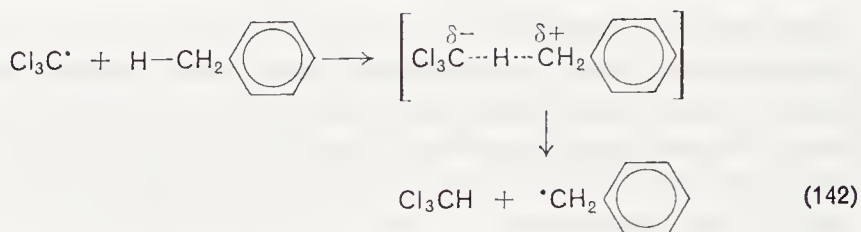


in this capacity similar to those of a bromine atom. While benzylic hydrogens are readily abstracted by both bromine atoms and trichloromethyl radicals, only alkanes with tertiary hydrogens are reactive enough

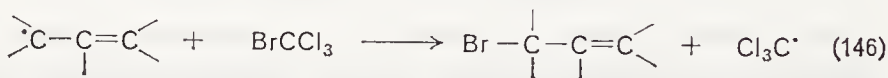
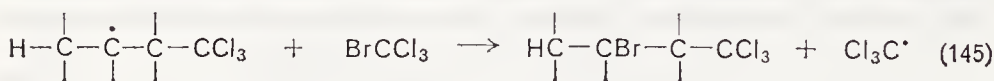
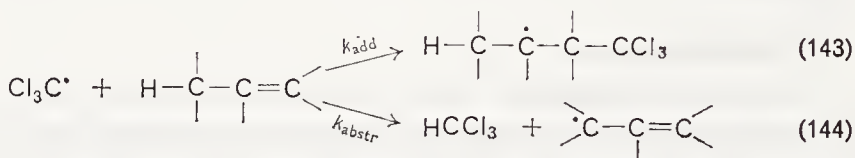


to participate readily in chain reactions with either bromine or bromotrichloromethane. Similarities are also observed in the reactivities of the benzylic hydrogens of substituted toluenes towards attack by bromine,

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 ($\rho = -1.46$ at 50°) than when plotted against the σ -values⁷². 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.



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 $k_{\text{add}}/k_{\text{abstr}}$

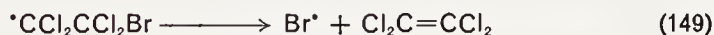
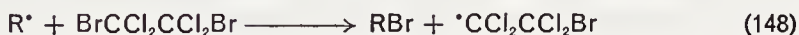


depends on the structure of the alkene both in terms of the steric effects that may retard the rate of addition and resonance and polar effects that may enhance the rate of allylic hydrogen atom abstraction. Table 11 lists $k_{\text{add}}/k_{\text{abstr}}$ ratios observed for simple alkenes. Note that 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.

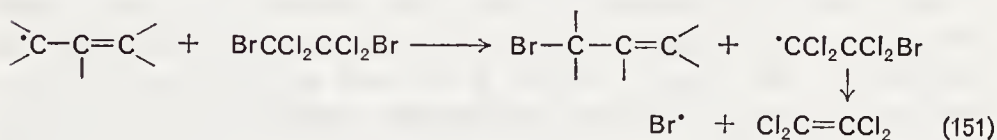
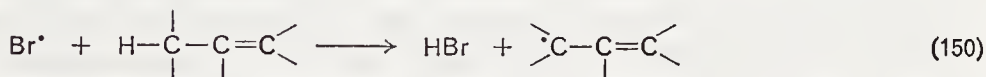
TABLE 11. Relative rates of addition with respect to allylic hydrogen abstraction by trichloromethyl radicals⁷⁴

Alkene	$k_{\text{add}}/k_{\text{abstr}}$		
	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	
<i>cis</i> -2-Butene			34
<i>trans</i> -2-Butene			26
Cyclohexene		1.20	
Cyclopentene		5.4	
Cycloheptene		5.5	

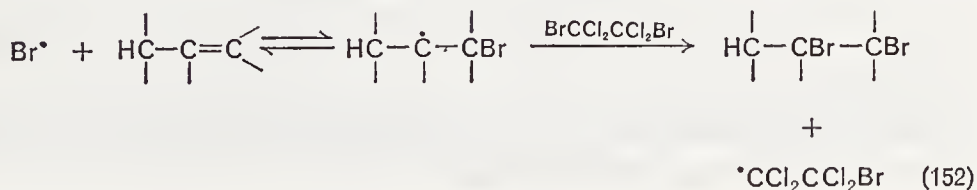
1,2-Dibromo-1,1,2,2-tetrachloroethane brominates compounds having abstractable hydrogens via the following chain sequence of reactions:



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 position⁷⁵. The bromine atom, as in the *N*-bromoamide reactions, may add to the unsaturated linkage yielding an adduct radical



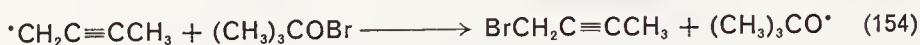
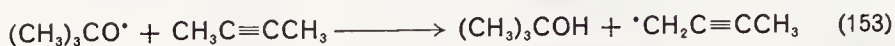
but reaction of the adduct radical with the polyhaloalkane is slower than its fragmentation. The allylic radical, on the other hand, apparently reacts



with the dibromotetrachloroethane faster than it does with the hydrogen bromide that is present in the reaction mixture.

3. *t*-Butyl hypobromite

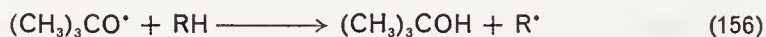
This reagent might be expected to behave in a manner similar to that of *t*-butyl hypochlorite in that the *t*-butoxy radical would be the hydrogen abstracting radical in a chain sequence resulting in substitution of a hydrogen for a bromine. However, little work has been reported on the use of this 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



abstraction by *t*-butoxy radicals relative to their addition to unsaturated linkages⁷⁶. 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 styrene⁷⁶.



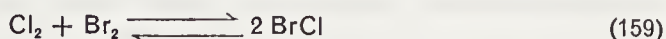
Brominations may be accomplished by the use of a mixture of *t*-butyl hypochlorite and bromotrichloromethane⁷⁷. The procedure for the use of this mixture of reagents requires an excess of bromotrichloromethane relative to the hypochlorite. This is done by slowly adding the *t*-butyl hypochlorite to an 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



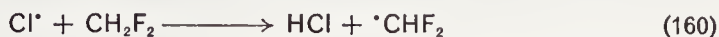
enough with bromotrichloromethane to allow it to compete effectively with the *t*-butyl hypochlorite which, although present in small amounts, is very reactive towards attack by free radicals.

4. Bromochloride

Mixtures of molecular chlorine and bromine contain the mixed halogen bromochloride⁷⁸. This mixed halogen can be used to brominate compounds

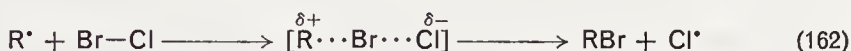


that are normally resistant to bromination. For example, methylene difluoride is brominated by bromochloride but does not react with bromine. It does, however, react with chlorine, suggesting that the mechanism for the



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.



5. Trichloromethanesulphonyl bromide

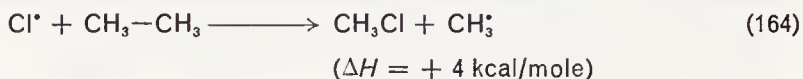
Trichloromethanesulphonyl bromide brominates alkanes and alkylaromatics in a reaction that stoichiometrically resembles that of the corresponding sulphonyl chloride. Investigation has shown that the reaction



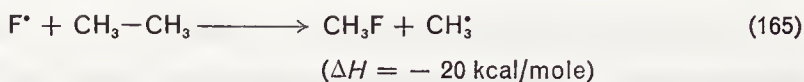
paths for the two reagents are different⁷⁹. In the case of the sulphonyl chloride (see section III. E), much, if not all, of the hydrogen atom abstraction from the substrate is accomplished by the trichloromethanesulphonyl radical. Competition reactions indicate that the trichloromethyl radical is the 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

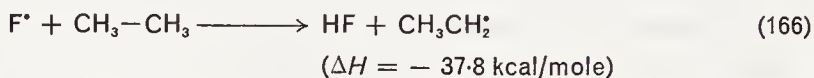
Reactions of alkanes with molecular fluorine are exothermic and often lead to complete oxidation of the alkane to carbon tetrafluoride if sufficient fluorine is present. The cleavage of carbon-carbon bonds in the fluorination of alkanes can be ascribed, at least in part, to the reactivity of the fluorine 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.



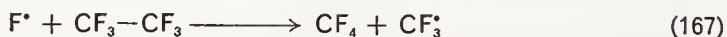
It seems unlikely that displacement on carbon by fluorine atoms would



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

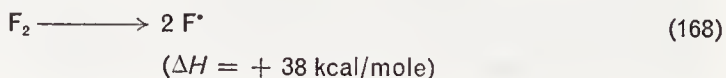


available for reaction with fluorine atoms. The accessibility of the carbon to displacement, owing to the small size of the fluorines, as well as the

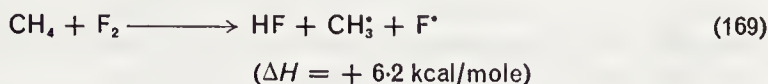


exothermicity of the formation of the carbon-fluorine bond, are probably the most significant factors that lead to carbon attack in these reactions.

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 ($\text{CF}_3\text{CF}_2\text{CF}_3$) are also found⁸⁰. 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. $2 \text{CF}_3^\bullet \rightarrow \text{CF}_3\text{CF}_3$). 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



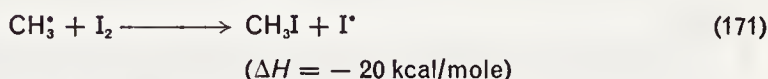
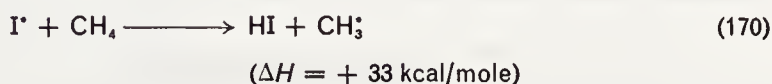
feasible at higher temperatures, would not be expected to account either for the initiation of an unusually large number of chains or for the reaction taking place at low temperatures. A bimolecular reaction of methane with fluorine, however, can occur at lower temperatures and may well be



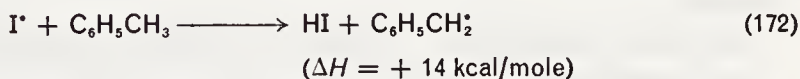
responsible both for the rapid rates of fluorination at low temperatures and the formation of radical dimerization products in unexpectedly large amounts.

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



energy requirements for hydrogen abstractions may be too high for reactions to occur at temperatures generally employed for halogenation reactions (room temperature $\pm 100^\circ$), reactions might be possible at more elevated temperatures, particularly with substrates having readily abstractable hydrogens (e.g. the reaction with toluene). There are, however,



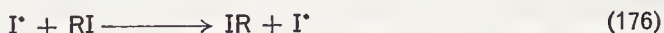
complicating features that would be encountered if the reaction does occur. One of these is the fact that the equilibrium favours reduction of alkyl iodides by hydrogen iodide. This reverse reaction becomes mechanistically



possible because of the facility of the reverse reactions of both steps in the chain sequence of the iodination reaction.



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



exchange reactions using radioactive iodine and in the racemization of optically active 2-iodobutane with iodine atoms⁸¹.

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 alkane⁸² but, unfortunately, the hydrogen chloride



formed in the chain reaction catalyses the dehydroiodination of the product.

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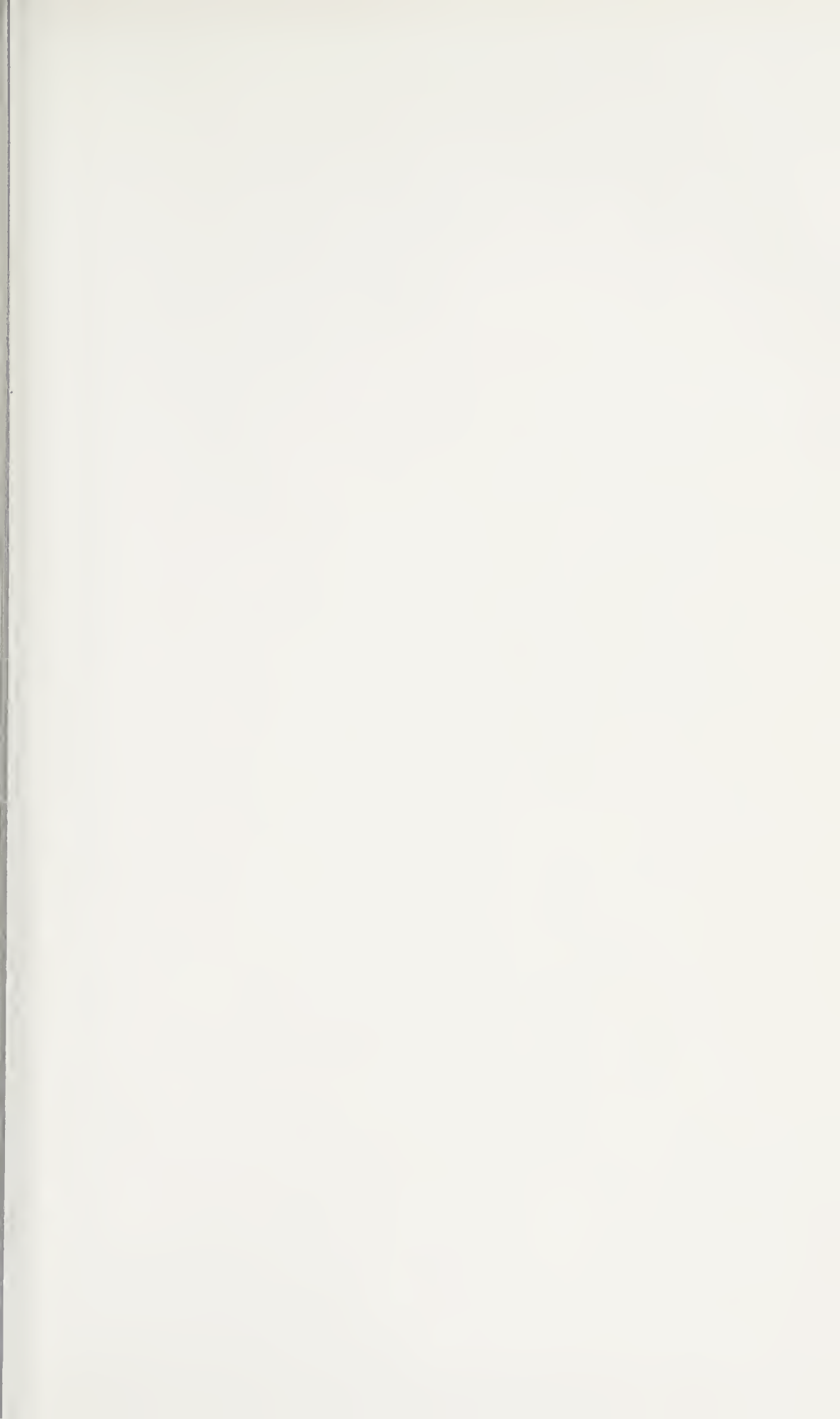
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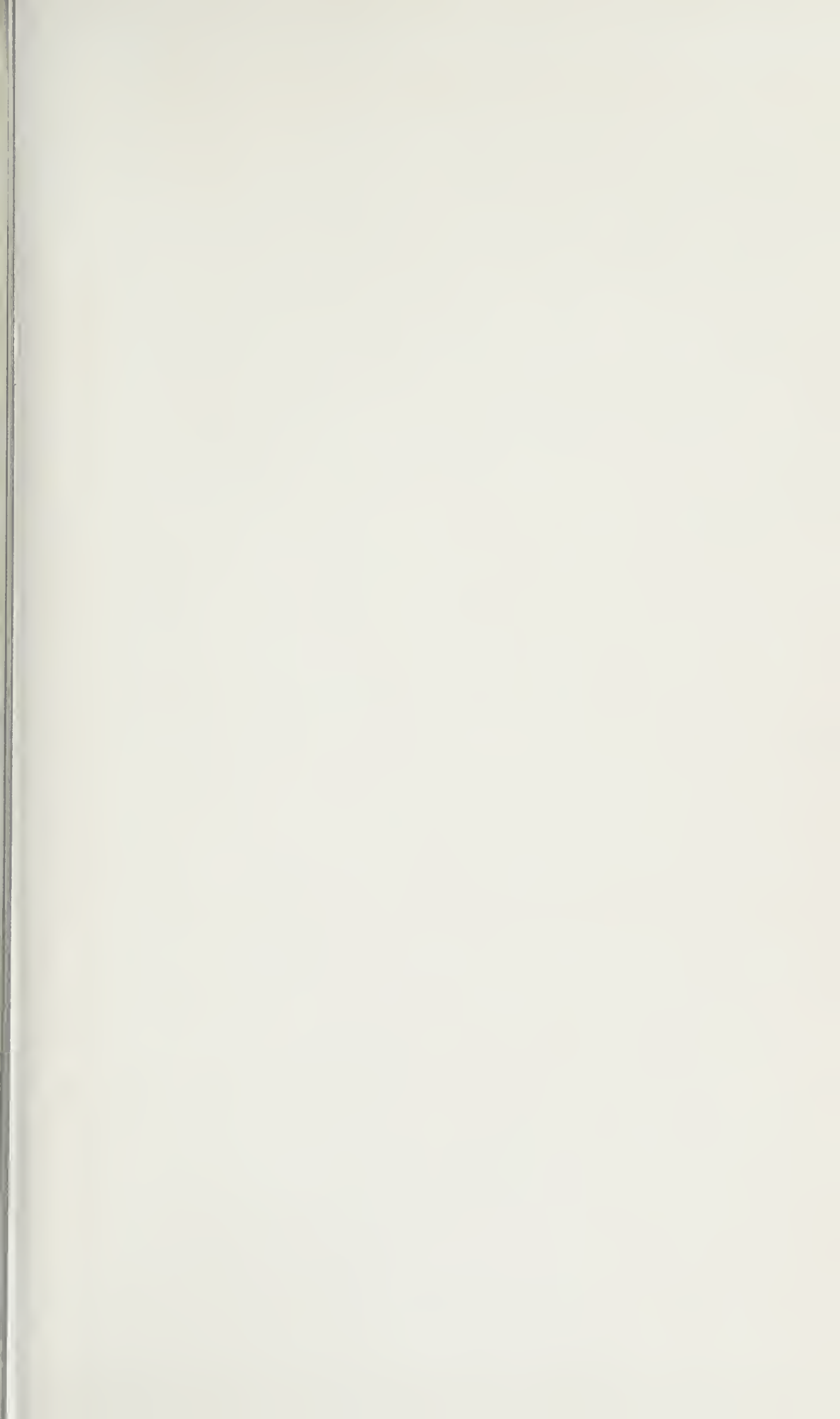
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