REACTIONS OF HALIDES IN SOLUTION

By E. D. Hughes, D.Sc., F.R.I.C., F.R.S.
(Professor of Chemistry, University College, London)

(1) Introduction

For the most part, this article deals with carbon derivatives, brief reference only being made to other halides, such as those of silicon. The halides are important structures in synthetic and industrial operations. The carbon–halogen bond in aliphatic structures is, on the whole, fairly readily severed and the replacement of halogen by other atoms or groups provides a convenient means of synthesising many and varied compounds, just as the reactions of the diazo-compounds are utilised in aromatic chemistry. This importance is not likely to wane in the near future for two main reasons. First, aliphatic chemistry in general is receiving considerable attention at present. Secondly, recent methods of controlled halogenation of aliphatic hydrocarbons, coupled with the efficiency of modern fractionating columns, should, in addition to other convenient methods, provide means of preparation of the halides required for syntheses.

The reactions of the halides afford an interesting and fruitful field for the study of mechanism. Our main thesis will be an attempt to elucidate the nature and course of the most important processes which are commonly employed in chemical work.

(2) Reaction Types

Let us consider the three recognised forms of bond fission,[1] namely :

$$\mathrm{R}\,|{\cdot\cdot}\mathrm{X}\ (1a),\quad \mathrm{R}{\cdot\cdot}|\mathrm{X}\ (1b),\quad \text{and}\quad \mathrm{R}{\cdot}|{\cdot}\mathrm{X}\ (2)$$

The first "heterolytic" form (1*a*) may be expected to be operative when the natures of R and X are such that the expelled atom or group (X) tends to separate with the electrons of its bond with R (represented by dots in the formulation). This being the condition obtaining in most carbon–halogen bonds, the process is commonly observed in organic halides, especially in the presence of powerful "nucleophilic" reagents which have strong affinity for positively polarised groups, *e.g.* :

$$\mathrm{Y}\!: + \mathrm{R}\,|{\cdot\cdot}\mathrm{Hal} \longrightarrow \mathrm{Y{-}R} + \mathrm{Hal}^- \qquad (S_\mathrm{N})$$

Such reactions, and analogous processes yielding olefins, are notable features of the chemistry of the alkyl halides.

The second form of heterolysis (1*b*) involves the expulsion of X without the electrons of the severed bond. This requires strong electron affinity in the attached group, R. The condition is less common than the foregoing but it is encountered in the so-called "positive halogen" compounds.

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[1] Ingold, *Trans. Faraday Soc.*, 1938, **34,** 227 ; Hughes, *ibid.*, 1941, **37,** 604.

Appropriate conditions for the " homolytic " fission (2) obtain, *inter alia*, when atomic or free-radical reagents are present to provide one electron for union with a fragment of symmetric scission. Processes of this type may occur, for example, in the reactions of halides with metals.

The following discussion deals almost entirely with heterolytic processes and mainly with reactions in which carbon–halogen bond fission of the first kind (1*a*) takes place.

(3) Nucleophilic Replacement Reactions

In the reactions of alkyl halides with nucleophilic reagents, replacement of the halogen is often accompanied by an elimination process in which a hydrogen atom in the β-position to the halogen is detached, with the formation of an olefin. Many published data on the relative ease of removal of halogen from organic halides refer to composite reactions and are difficult to interpret. In the work discussed in this review, the rates and mechanism of replacement and of elimination have been separately determined. Thus, the characteristic features of both reactions have been established and the way opened for a discussion of the question as to which of the two types will be dominant for given structures under given experimental conditions—a problem of some interest in preparative, as well as in theoretical chemistry. We proceed first to discuss the replacement processes.

(3.1) Classification.—Although the carbon–halogen links of alkyl halides are mainly covalent in character, the bonding electrons are more strongly under the influence of the halogen atom than of the carbon atom—a result to be ascribed to the stronger nuclear attraction of the halogen, and a condition which is responsible for a dipole in the carbon–halogen bond. Thus, we have a tendency to bond fission of the type R¦—Hal and in heterolysis the process is completed by the appropriation, by the halogen, of the two electrons constituting the link. Simultaneously with, or subsequently to, fission (we shall show that two types exist), a nucleophilic reagent (Y) utilises two electrons to form the new bond with the electronically deficient group R. In nucleophilic replacement, therefore, Y may be either negative or neutral, provided that it has unshared electrons, and two cases arise, as shown below, typical examples being (1) the alkaline hydrolysis of alkyl halides, and (2) the formation of alkylammonium salts from tertiary amines and alkyl halides :

$$\begin{array}{rcl} (1)\quad \text{Y}^- + \text{R—Hal} & \longrightarrow & \text{Y—R} + \text{Hal}^- \\ \textit{e.g.},\ \text{HO}^- + \text{CH}_3\text{—Br} & \longrightarrow & \text{HO—CH}_3 + \text{Br}^- \\ (2)\quad \text{Y:} + \text{R—Hal} & \longrightarrow & \overset{+}{\text{Y}}\text{—R} + \text{Hal}^- \\ \textit{e.g.},\ (\text{CH}_3)_3\text{N:} + \text{CH}_3\text{I} & \longrightarrow & (\text{CH}_3)_3\overset{+}{\text{N}}\text{—CH}_3 + \text{I}^- \end{array}$$

For such reactions, fundamental similarities of behaviour are observed, but there are also notable and understandable differences between the two types, the differences arising mainly from the distinct charge relationships, which are evident when we consider, for the two cases, the state of electrification of the reactants in relation to that in the transition state of reaction. These points will be illustrated later in our discussion.

(**3.2**) **Mechanism.**—Investigations of the mechanism of these reactions have shown that two fundamental routes are possible. Let us consider the case of the hydrolysis of alkyl halides in alkaline solution. For this common process in organic chemistry it had been generally considered that the alkali (hydroxide ion) was directly effective in the reaction, effective, that is, in regard to the facility of the change. Kinetic experiments have shown, however, that the alkali may or may not be involved in the rate-determining process, the result depending particularly on the structure of the halide.

For certain compounds (*e.g.*, the methyl halides) it is found that the rate of hydrolysis in water or aqueous alcohol is dependent on the concentration of hydroxide ions as well as on that of the alkyl halide, the reaction being of the first order with respect to each of the reactants and of the second order overall : $v = k_2[\mathrm{R{-}Hal}]\,[\mathrm{OH^-}]$. Bond fission in the carbon–halogen link does not here proceed with facility without the aid of hydroxide ions. However, in the presence of these highly nucleophilic ions, which have a strong tendency to enter into bond formation with a positively polarised carbon atom, a degree of charge separation in the dissociating bond may result in a transfer of the group R to the reagent. We may envisage a transition state of reaction in which the organic radical is partly under the influence of both the entering and the leaving entity, the negative charge, initially on the hydroxide ion and finally on the halide ion, being distributed in the transition state of this synchronous bond-forming and bond-breaking process, *e.g.*,

$$\underset{\text{Initial state}}{\mathrm{HO^- + R{-}Hal}} \quad \underset{\text{Transition state}}{\left[\longrightarrow \overset{\delta-}{\mathrm{HO}}\cdots\mathrm{R}\cdots\overset{\delta-}{\mathrm{Hal}}\right]} \quad \longrightarrow \quad \underset{\text{Final state}}{\mathrm{HO{-}R + Hal^-}} \quad (S_N2)$$

The hydrolysis of certain other halides (*e.g.*, the *tert.*-butyl compounds) in aqueous solutions is found to be of the first order, the rate being dependent on the concentration of the alkyl halide but independent of the concentration of hydroxide ions : $v = k_1[\mathrm{R{-}Hal}]$. The rates for these halides are the same in alkaline, neutral, or acidic solutions. A rate-determining stage is here involved in which hydroxide ions play no part. This stage has been identified with the fission of the carbon–halogen bond, the reagent intervening to form the product in a subsequent, comparatively rapid, reaction, *e.g.* :

$$\left.\begin{array}{lcl} \mathrm{R{-}Hal} & \xrightarrow{\text{(slow)}} & \mathrm{R^+ + Hal^-} \\ \mathrm{HO^- + R^+} & \xrightarrow{\text{(rapid)}} & \mathrm{HO{-}R} \end{array}\right\} \qquad (S_N1)$$

Although the importance of solvation in ionic dissociation is fully recognised, this mechanism is termed " unimolecular " because only one reactant, R—Hal, is undergoing covalency change in the rate-determining stage ; the designation S_N1 is intended to symbolise this property. The other mechanism is termed " bimolecular " because both reactants are simultaneously involved ; the description S_N2 indicates this molecularity.* An alternative interpretation of the first-order kinetic results on the basis of a bimolecular mechanism in which the solvent is acting as the reagent (its presence in large excess accounting for the kinetic order) cannot be upheld, because it is inconceivable that water molecules should be effective reagents for these compounds when the more powerfully nucleophilic hydroxide ions are inactive.† Many confirmatory observations relating to the S_N1 and S_N2 mechanisms have been made [2] and the concept of the duality of mechanism is widely accepted.

In this section on the mechanisms of nucleophilic substitution reactions, we may consider briefly three special cases which may be shown to be closely related to the basic types.

The first concerns the reactions of organic halides with hydroxylic solvents in the presence of silver salts. Kinetic investigations [2] have shown that silver ions facilitate the separation of the halogen and that a common mechanism of the change is related to the unimolecular (S_N1) process, *e.g.* :

$$\text{R—Hal} + \text{Ag}^+ \longrightarrow \text{R}^+ + \text{AgHal}\,; \quad \text{R}^+ + \text{H}_2\text{O} \longrightarrow \text{R—OH} + \text{H}^+$$

The influence of other " electrophilic catalysts " is essentially similar in character (*e.g.*, mercuric chloride and " Lewis " acids generally). Striking similarities of behaviour between these reactions and unimolecular solvolyses have been observed, with regard, particularly, to structural influences on reaction rates, to the stereochemical consequences of the mechanisms (see later), and to the mass-law effect of halide ions in reversible ionisation (observed, for example, in unimolecular hydrolysis and in the reactions of halides with mercuric chloride in hydroxylic solvents [2, 3]). The effect of Friedel–Crafts catalysts in the alkylation, acylation, and halogenation of aromatic compounds is a closely connected function, for this may be ascribed essentially to the formation (from Y—Hal) of entities of the form $\overset{+}{\text{Y}}\text{AlCl}_4^-$(Y = Alkyl, Acyl, or Hal), followed by the interaction of these powerful electrophilic reagents with the (nucleophilic) aromatic nucleus.

The second special case concerns the reactions of halides containing a

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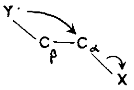
[2] For a detailed description of the development and establishment of the theory and its applications, see, especially, Hughes, Ingold, and their co-workers, *J.*, 1935, 244 ; 1936, 225 ; 1937, 1252 ; 1940, 925, 979 ; 1946, 173, 968 ; *Trans. Faraday Soc.*, 1938, **34**, 185 ; 1941, **37**, 603.

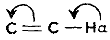
[3] Bunton, Hughes, Ingold, and AnantaRaman, unpublished.

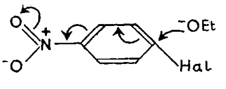
* We shall, throughout, employ the expressions " unimolecular " and " bimolecular " to denote mechanisms, as explained above. The terms " first order " and " second order " are used to indicate the type of kinetic equation which a reaction follows in given circumstances. The numerals in the representations S_N1 and S_N2 refer to mechanism, not to reaction order. Failure to appreciate this point has led to unjustified statements (see, for example, Alexander, " Principles of Ionic Organic Reactions ", John Wiley and Sons, Inc., New York, 1950, pp. 81, 84).

† The effectiveness of water molecules in reaction with structures of a different type, *e.g.*, ethylene oxide, is irrelevant to our case ; small ring structures have specific features and the reactions of epoxides, for instance, are affected by an amphoteric environment in an understandable way (cf. Hine, *J. Amer. Chem. Soc.*, 1950, **72**, 2438).

nucleophilic substituent which is suitably placed for interaction with the carbon atom bearing the halogen. In some cases of this type a substituent with unshared electrons may facilitate the separation of halogen by participating in a synchronous (S_N2 type) bond-forming and bond-breaking process (cf. inset). In other cases, such assistance to the heterolysis of the C—X bond is not operative (S_N1), though the substituent Y: may subsequently participate in an interaction with the positively charged carbon atom (C_α) in such a way as to influence the ultimate reactions, *e.g.*, the stereochemical course of substitution. In certain instances, the two types constitute two mechanisms for the formation of cyclic structures, which may be either unstable intermediates in further changes or isolated reactions products.[2] When ring closure and ring opening involve different atoms, rearrangement occurs through this route. Steric factors, the nucleophilic activity of Y:, and the ease of heterolysis of the carbon–halogen bond are important considerations in determining which of the two mechanisms (S_N2 type or S_N1) will be operative in a given instance. Though the reactions may be of the first order in both cases, there is a clear analogy between the two mechanisms and the two forms of simple replacement reactions [4] and it is important to recognise the similarity. Difficulties have arisen in the past, for example, because various investigators have attempted to place the reactions of β-halogeno-sulphides and -amines in the S_N1 category. It has been shown that the reactions of these compounds provide examples of a synchronous (internal) bond-forming and bond-breaking mechanism (S_N2 type), and that a different result obtains when substituents of a more weakly nucleophilic character are similarly situated.[4, 5] Some further aspects of the effect of neighbouring groups are discussed in Section (3.5).



The third example in the category of special cases refers to the presence of unsaturated bonds at the reaction centre. A C=C bond, as in the vinyl and phenyl halides, may be expected to induce an electrometric displacement  which, since it opposes the activation , should strongly inhibit mechanism S_N1 and also retard mechanism S_N2, although to a smaller extent. It is to be expected, therefore, that substitution in these systems never occurs by mechanism S_N1 and only with difficulty by mechanism S_N2, and this is borne out by general experience. In certain circumstances the unsaturated system may adjust itself (cf. inset) to accommodate bond formation which, by comparison with the position in substitution at a saturated carbon atom, entails reduced C–Hal bond stretching. The access of the reagent then causes ejection of the halogen atom. This is the probable explanation of the marked effect of *o*- and *p*-nitro-substituents. It may account also for the fact that the facility sequence, F > Cl, which, in this system, is sometimes observed in the



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[4] Blake, Hirst, Hughes, Ingold, and Lord, unpublished.

[5] See, especially, Bennett, *Trans. Faraday Soc.*, 1941, **37**, 794 ; Bartlett and E. S. Lewis, *J. Amer. Chem. Soc.*, 1950, **72**, 405 ; and references cited in these papers.

reactions of the halides with, for example, alkoxide ions [6a] or amines,[6b] is opposite to the usual sequence which is found in substitution at a saturated carbon atom.* A similar explanation, depending on a marked activation of the C=O bond $(\overset{\curvearrowright}{\mathrm{C{=}O}})$, may account for the ready hydrolysis of simple acid chlorides by the bimolecular mechanism.

(3.3) Medium and Temperature Effects.—The heterolytic mechanisms with which we are concerned are characterised by important electrical transferences which occur during the course of the changes. The influence of the solvent may therefore be expected to be highly important in these reactions, and, since the effect must depend on the precise manner in which the electrical transferences take place, a change of medium may be expected to affect the two main mechanisms of nucleophilic substitution both absolutely and relatively to each other. The influence of the solvent may be assessed by considering the magnitude and distribution of the charges in the transition state in relation to those in the reactants. By making the reasonable assumptions that strongly ionising solvents facilitate an increase in the magnitude of the charges, inhibit a decrease, and retard (more weakly in this case) the distribution of a given charge, the effect of solvent variation can be predicted for each of the two principal types of nucleophilic replacement reactions of alkyl halides. For mechanism S_N1, it is, of course, the rate-determining stage of reaction (the bond fission) which has to be considered and, for a given alkyl halide structure, this stage is common to the two main types discussed in Section (3.1). The predictions of the theory are collated in the following Table.

Solvent effects in the replacement of halogen in alkyl halides

Type.	Mechm.	Charges in rate-determining stage.			Predicted effects of polar media on rates.
		Reactants.	Transition state.	Products.	
1 & 2 .	S_N1	R–Hal	$\overset{\delta+}{\mathrm{R}}\text{---}\overset{\delta-}{\mathrm{Hal}}$	$\mathrm{R^+ + Hal^-}$	Strong acceleration
1 . .	S_N2	$\mathrm{Y^- + R{-}Hal}$	$\overset{\delta-}{\mathrm{Y}}\text{---}\mathrm{R}\text{---}\overset{\delta-}{\mathrm{Hal}}$	$\mathrm{Y{-}R + Hal^-}$	Weak retardation
2 . .	S_N2	$\mathrm{Y\colon + R{-}Hal}$	$\overset{\delta+}{\mathrm{Y}}\text{---}\mathrm{R}\text{---}\overset{\delta-}{\mathrm{Hal}}$	$\mathrm{Y^+{-}R + Hal^-}$	Strong acceleration

The experimental observations are wholly consistent with these deductions.[2]

For bimolecular processes of type (2), *e.g.*, the reaction of a tertiary amine with an alkyl halide, formally neutral reactants give rise to highly

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[6] (*a*) C. W. L. Bevan, Thesis, London, 1949 ; (*b*) Chapman, Parker, and Soanes, *Chem. and Ind.*, 1951, 148.

* The usual sequence here is F < Cl < Br < I, the rate ratios, F : Cl : Br : I, being of the type 10^{-3} : 1 : 30 : 80.

polar products and the stabilisation of the transition state by a polar environment is essential for facility of reaction. It is well known that the formation of alkyl 'onium salts is in fact affected in this way, a manifestation being the failure to achieve homogeneous gas-phase reactions of this type.[7] When salt formation between methyl bromide and pyridine is carried out in an unfavourable solvent, *e.g.*, benzene, the reaction is very strongly catalysed by added hydroxylic compounds, *e.g.*, methyl alcohol, and the rate is proportional to the concentration of the alcohol.[8] The importance of solvation is predicted also for mechanism S_N1 (see Table) and the facts concerning reactions for which this mechanism has been advanced are confirmatory.[2] It is claimed [8] that in the reaction of triphenylmethyl chloride with methyl alcohol in benzene solution, there is concerted solvation by two methyl alcohol molecules, one acting on carbon and the other on halogen. It is not certain, however, that the S_N1 process was under observation, for benzene is a most unfavourable environment for the mechanism.

The effect of temperature on the rates of the bimolecular reactions may be broadly discussed in terms of a modified Arrhenius equation of the form $k = PZe^{-E/RT}$, where E is the energy of activation, Z is the collision number, and P is a probability factor which expresses the proportion of the collisions, between sufficiently energised molecules, which actually lead to reaction. As is generally the case for reactions between an ion and a formally neutral molecule,[9] the P factor for bimolecular changes of type (1) is usually about unity. The activation energy naturally depends on the compound substituted, on the reagent anion, and on the medium. For the hydrolysis of simple primary alkyl chlorides with hydroxide ions in hydroxylic solvents, for example, E is about 23 kcals., and for the halogen-exchange reaction of chlorides with iodide ions in acetone solution, E is about 20 kcals.—a value which is increased considerably by the addition of water to the medium.

The activation energies of the bimolecular reactions of amines with alkyl halides (type 2) are generally lower, 14 kcals. being a typical value for the reaction of trialkylamines with primary chlorides in solvents of average polarity. One of the main factors involved here may be a decreased solvation of the neutral reagent in the initial state [by comparison with the anions of type (1) reactions]. The creation of charges in the transition state of these changes is reflected in low values of P for most of the solvents which have been investigated (*e.g.*, about 10^{-6} in typical cases). As may be expected on the basis of our discussion of the mechanism, there are indications that P rises with increased solvating power of the medium.

The nature of the factor B in the equation $k = Be^{-E/RT}$ is, of course, different for unimolecular reactions, and, on the whole, its significance is not so clear as is the case for bimolecular processes.[9] The values obtained

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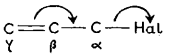
[7] Moelwyn-Hughes and Hinshelwood, *J.*, 1932, 230.

[8] Swain and Eddy, *J. Amer. Chem. Soc.*, 1948, **70**, 1119, 2989.

[9] Hinshelwood, "The Kinetics of Chemical Change", Oxford, 1940; Moelwyn-Hughes, "The Kinetics of Reactions in Solution", Oxford, 1947.

for the alkyl halides form a reasonable series in the light of the well-known statistical analysis of unimolecular reactions given by Polanyi and Wigner.[10] Further reference to the analysis of rate coefficients in terms of Arrhenius parameters will be included in later sections of this discussion.

(3.4) **Structural Factors.**—(3.41) *Polar Effects in* R. In the unimolecular mechanism, the rate-determining stage consists in the fission of the carbon–halogen bond, and this should be facilitated unconditionally by electron-release to the reaction centre. Consequently, it is found that groups which are capable of co-operating in such a demand for electrons, *e.g.*, α-methyl and α-carboxylate ion substituents, facilitate unimolecular substitution, while substituents of opposite polar influences, such as the undissociated carboxylic acid and carboxylic ester groups, have been shown to have the opposite effect. In the one-stage, bimolecular mechanism, on the other hand, one bond is formed and one bond is broken and these processes require different electronic activations. The result is that polar effects in S_N2 reactions are comparatively small. Steric effects (Section 3.6) also hinder S_N2 reactions. Most frequently, the net result is opposite to that in S_N1 but exceptions occur in regions close to mechanistic transitions ($S_N2 \rightarrow S_N1$) and when modifying structural influences are present (cf. below). In any case, the much larger effect of polar groups in unimolecular reactions often ensures a change of mechanism in a series of compounds, such as, for instance, the α-substituted series, CH_3, $Me{\cdot}CH_2$, Me_2CH, Me_3C, and CH_3, $CH_2(CO_2^-)$, $CH(CO_2^-)_2$.

Special interest attaches to the effect of a C=C substituent, as in the allyl halides (and benzyl halides to a modified extent). In this system, the conjugative electromeric polarisation  may be expected to have a very strong facilitating influence on mechanism S_N1, and a similar, though less powerful, effect on mechanism S_N2. Such halides may therefore be expected to be rather reactive under all conditions of nucleophilic substitution and this is found to be the case.[2] Here again the more pronounced effect on S_N1 is responsible for a change of mechanism in the series CH_3, $Ph{\cdot}CH_2$, Ph_2CH, Ph_3C. That the net effect of the unsaturated substituent on mechanism S_N2 is a facilitating influence has been shown in the case of allyl halides.[11] The effect of α- and γ-alkyl substituents in this system is instructive. For α-alkyl groups the results [11, 12] are similar to those for the simple α-methylated series, Me, Et, Pr^i, and Bu^t, *i.e.*, α-alkyl groups (*e.g.*, Me, Bu^t, and Me_2) have a large facilitating effect on mechanism S_N1 and an inhibiting influence on mechanism S_N2, the effect on S_N1 being largely of a polar nature, while that on S_N2 is polar and steric in character. In the case of γ-alkyl groups (*e.g.*, Me, Bu^t, and Me_2), electron release from R augments the polarisation arising from the unsaturated group , with the result that γ-alkyl substituents have a large

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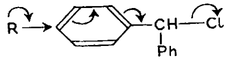
[10] Polanyi and Wigner, *Z. physikal. Chem.*, 1928, Haber Band, p. 439.

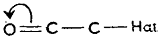
[11] (*a*) See, especially, *Trans. Faraday Soc.*, 1941, **37**, 603 ; (*b*) the results have been greatly amplified and extended by C. A. Vernon (unpublished work).

[12] de la Mare, Hughes, Ingold, Merriman, Pichat, and Vernon, unpublished.

accelerating effect on mechanism S_N1 and a smaller facilitating influence on mechanism S_N2.[11, 12] It is not surprising that the polar effect of an alkyl group is dependent, not only on the system to which it is attached, but also on its position of attachment in that system (*e.g.*, α- or γ- in the allyl structure). This is particularly the case for the bimolecular mechanism, because of the fact, already explained, that the net result for this mechanism is normally a rather finely balanced differential effect.[13] Inductive and hyperconjugative effects of alkyl groups are involved. In unimolecular hydrolysis in the system



the observed sequence (for *p*-R), $CH_3 > CH_3{\cdot}CH_2 > (CH_3)_2CH > (CH_3)_3C > H$, was one of the main items of evidence[14] which helped to establish the hyperconjugation influence from C–H bonds, first postulated by J. W. Baker and Nathan.[15] Evidence of the hyperconjugation effect has also been obtained for the alkyl-substituted allylic halides.[12]

When a carbonyl group is attached to the substitution centre, as in the α-halogeno-ketones, the usual carbonyl polarisation  favours the bimolecular mechanism. Complications readily arise in these compounds, especially if α-hydrogen atoms are present and strongly basic reagents are used. The lability of hydrogen atoms thus situated is a commonplace, and proton removal by the base, forming an incipient or actual carbanion, facilitates the ejection of the halogen.[16] This is a mode of formation of the so-called bivalent radicals which have often been postulated as intermediates in the reactions of halogeno-ketones. The strongly electron-attracting carbonyl group also facilitates " positive halogen " reactivity (see Section 6).

(3.42) *Polyhalogen Compounds.* When a second halogen is directly attached to the reaction centre, the strong electron demands of bond fission may bring into operation an electron-release process, *e.g.*, , and this should facilitate the rate-determining ionisation stage of mechanism S_N1. It is found that when a monohalide has already a moderately developed tendency to react by mechanism S_N1 (*e.g.*, benzyl chloride), then the introduction of additional α-halogen atoms (as in benzylidene dichloride and benzotrichloride) produces enhanced reactivity in solvolysis.[17] On the other hand, in a structure predisposed to react by mechanism S_N2 (*e.g.*, methyl bromide) the introduction of a second halogen atom (*e.g.*, in

[13] Cf. Webb and Young, *Trans. Faraday Soc.*, 1951, **73**, 777 and references therein cited. A. G. Evans attributes the entire effect of *a*-alkyl substituents on mechanism S_N2 to steric influences (see *Trans. Faraday Soc.*, 1951, **47**, 25 *et seq.*).

[14] Hughes, Ingold, and Taher, *J.*, 1940, 949.

[15] *J.*, 1935, 1844.

[16] Hughes, Ingold, and their co-workers, unpublished.

[17] This interpretation (Hughes and Ingold, *J.*, 1935, 244 ; Hughes, *Trans. Faraday Soc.*, 1941, **37**, 625) of the results of Olivier and Weber (*Rec. Trav. chim.*, 1934, **53**, 869) has been confirmed (Hine and Lee, *J. Amer. Chem. Soc.*, 1951, **73**, 22).

methylene dibromide) has an inhibitory effect on the replacement (bimolecular) by, for example, methoxyl.[11a, 18] The presence of further halogen atoms introduces complications. It has been shown that the alkaline hydrolysis of chloroform involves the removal of a proton [19] and that the reaction of sodium ethoxide with carbon tetrachloride and tetrabromide probably entails a rate-determining reduction.[18, 19] The reactions of bromoform and carbon tetrabromide with sodium methoxide in methyl alcohol have been shown to exhibit some of the features usually associated with homolytic processes (sensitivity to light, air, and peroxides; comparative stabilisation by quinol, etc.).[18] The " normal ", second-order reactions of these compounds in the presence of quinol are slower than the corresponding reaction of methyl bromide with sodium methoxide in methyl alcohol, but they occur more readily than the reaction of methylene dibromide in such circumstances. The question of " positive halogen " reactivity is treated briefly in Section 6. Steric factors (Section 3.6) may also play a part in some or the reactions of the polyhalides.

When, in a saturated system, the second halogen atom is in a position other than the site of reaction, the electron-release mechanism discussed above is inoperative. In this event, the electron-attracting (inductive) effect is dominant and this should retard mechanism S_N1 and probably facilitate S_N2. The inhibiting effect on the unimolecular mechanism may be illustrated by the comparative first-order rates for the solvolysis of *tert.*-butyl chloride and 1 : 2-dichloro-2-methylpropane in 80% aqueous ethyl alcohol (relative rates: $Cl{\cdot}CH_2{\cdot}CMe_2Cl = 1$; $CH_3{\cdot}CMe_2Cl = 4000$; the halogen attached to the tertiary carbon atom is eliminated in both cases).[20] For bimolecular replacement (S_N2), unambiguous data relating to isolated substitution reactions (dissociated from concomitant elimination processes) are not available and investigations of suitable systems are being undertaken.

(3.43) *The Role of the Reagent.* Since the reagent does not function in the rate-determining stage of the unimolecular mechanism but promotes reaction by the bimolecular process, the latter should be favoured by a reagent of high nucleophilic power present in high concentration. This has been abundantly confirmed.[2]

(3.5) Steric Orientation.—An early naïve assumption that, in a replacement reaction of the type under discussion, the entering atom or group replaces the extruded group directly, *i.e.*, without configurational change, was shown to be inadequate by the discovery of the Walden inversion, but the question as to when and why inversion takes place remained a mystery for many years. The problem is clearly dependent on the nature of the route which the reaction pursues and it was a natural sequel to apply the kinetic and other methods used in the clarification of reaction mechanism to the further, more detailed mechanistic question concerning the stereo-

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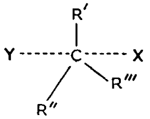
[18] Hughes, Ingold, and Peeling, unpublished; Peeling, Thesis, London, 1944.

[19] Hine, *J. Amer. Chem. Soc.*, 1950, **72**, 2438.

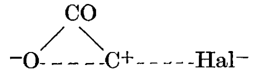
[20] Hughes, *J.*, 1935, 255; Brown, Kharasch, and Chao, *J. Amer. Chem. Soc.*, 1940, **62**, 3435.

chemical consequences of substitution.[21] Briefly, the conclusions reached are as follows : In bimolecular nucleophilic substitution, the most favourable configuration for the transition state of reaction arises when the reagent approaches the molecule on the side opposite the displaced atom or radical X. In the " linear " transition state (I), the energy of the state will be minimised because of the small interaction between the electrons of the linearly split bond and those of the full bonds. It has been established experimentally that reactions taking place by the bimolecular mechanism lead invariably to inversion of configuration. The result is so definite that it may be made the basis of a convenient method of relating sign of rotation to configuration in reactants and products.



(I.)

The unimolecular mechanism, on the other hand, leads to quite different stereochemical consequences and in this case the result is not so clear-cut, there being a marked dependence on the nature of the groups attached to the asymmetric carbon atom. When only neutral groups are attached to the reaction centre, the dominant and characteristic stereochemical result of unimolecular substitution is extensive racemisation and this is in harmony with independently derived evidence that a carbon cation will tend to take up its preferred planar configuration. The partial inversion which often accompanies the loss of optical activity may be interpreted as an effect of the shielding of the cation, by the nearby receding radical, when attack of the reagent completes the substitution process. The most striking outcome of substitution by the unimolecular mechanism occurs in the presence of a group, *e.g.*, an α-carboxylate-ion group, which has unshared electrons. As the carbon–halogen bond is severed, the group will be oriented away from the eliminated halide ion (cf. inset) and interaction between a negative oxygen atom of the substituent and the positive carbon atom may result in the entry of the new group on the opposite side, *i.e.*, on the side from which the halogen was extruded, leading, therefore, to retention of configuration. Similar effects of other neighbouring substituents with active unshared electrons have been observed.[22] Even double-bond π-electrons can exert an effect in the same direction.[23] The application to the chemistry of natural products is particularly evident in work on the steroids.[24]



A similarity of behaviour exhibited by the results for mechanism S_N1 and the silver-ion mechanism is consistent with the postulated relationship between these two processes (Section 3.2).

(3.6) Steric Retardation and Steric Acceleration.—The concept of the duality of mechanism in substitution reactions, and its application to the

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[21] Hughes, Ingold, and their co-workers, *J.*, 1935, 1525 ; 1936, 1173 ; 1937, 1196 ; 1938, 209 ; 1940, 1010 ; 1949, S 400 ; *Trans. Faraday Soc.*, 1938, **34,** 202 ; *Nature*, 1950, **166,** 178, 679.

[22] See, especially, Winstein and his co-workers, *J. Amer. Chem. Soc.*, 1948, **70,** 812 *et seq.*

[23] Davies, Hughes, and Ingold, unpublished.

[24] Shoppee, *Ann. Reports*, 1947, **44,** 170.

stereochemistry of these changes, have led to advances in our ideas of the effect of steric factors on reaction rates. In chemical reactions, the energies of links which are involved in the changes are of major importance but account should also be taken of the " non-bonding " forces between atoms which are not directly linked. These additional forces are often sufficiently weak to be neglected but, in special structural circumstances, non-bonded atoms are brought so close together that the non-bonding energy is comparable in order of magnitude to the bonding energy, and in these circumstances steric effects on reaction rates become evident. Clearly, consideration should be given in this connection to the initial and the transition state of reaction. The compression energy in the transition state may be either greater or less than that in the initial state and possible steric effects may inhibit or facilitate reaction.

The main principles underlying the connection with reaction mechanism may be briefly described as follows : In the transition state of the bimolecular mechanism, five atoms or groups are wholly or partly attached by covalency forces to a single carbon atom and in certain structural circumstances the transition state involves considerably greater compression than does the initial state. Unimolecular reactions on the other hand never entail the covalent attachment (wholly or partly) of more than four atoms or groups to the reactive centre, the additional forces engaged in the transition state of the rate-determining ionisation being of the longer-range electrostatic type associated with solvation. Consequently, steric retardation is not conspicuous in reactions which proceed by this mechanism. However, if the structural factors are such that the compression energy of the initial state is considerable, a release of compression may accompany the formation of the transition state of ionisation and steric acceleration by substituent groups which give rise to the initial state compression may be evident.

It has been shown by calculation that the steric retardation effect (for bimolecular replacement reactions) described qualitatively in the preceding paragraph is not very large for the halides of the α-methylated series, Me, Et, Pr^i, and Bu^t. It has, however, been identified as a major influence in the bimolecular reactions of other fairly simple structures. A semi-quantitative theory of steric retardation has been developed on the following lines.[25] In the transition state of bimolecular substitution, the most favourable configuration (cf. Section 3.5) arises when the nuclei of the substituting atom, of the carbon atom at which substitution takes place, and of the displaced atom, lie on or near a straight line, while the nuclei of the other three atoms to which C_α is covalently bound lie on or near a plane which passes through C_α and is perpendicular to this line. With this model of the transition states as basis, the distances between the centres of the attacking or displaced radicals and the centres of the various atoms in the reacting molecule can be calculated, and a consideration of these distances provides an estimate of the importance of the steric factor in different structures. As an example of the results of the analysis we may cite the follow-

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[25] Dostrovsky, Hughes, and Ingold, *J.*, 1946, 157 *et seq.* ; see also *J. Chim. physique*, 1948, **45**, 236, and *Quart. Reviews*, 1948, **2**, 107.

ing : For the bimolecular replacement reactions of *neo*pentyl halides (*e.g.*, $CMe_3{\cdot}CH_2Br$) the computations indicate a large steric effect comprising compressions of the order of 1Å. It was shown experimentally that these halides are markedly inert under conditions for which kinetic tests indicated a bimolecular mechanism. Under conditions favourable to the unimolecular mechanism the *neo*pentyl halides exhibit normal behaviour. The inertness referred to applies to reactions with comparatively simple reagents (*e.g.*, ^-OH). In the case of more complex reagents such as amines, steric factors may be expected to be prominent more generally and a considerable steric dependence on the nature of the attacking entity is to be expected.

Steric retardation is, on the whole, more familiar than steric acceleration, the reason being that, while compression energy in the transition state of bimolecular replacement is considerable even for fairly simple and common structures, comparable compressions in initial states are present only in more highly ramified compounds. For instance, the steric retardation effect in the bimolecular reactions of the *neo*pentyl halides is of a very marked character (*e.g.*, ethyl/*neo*pentyl = *ca.* 10^5). On the other hand, the unimolecular reactions of compounds of the same general order of complexity exhibit no such marked steric effects, either inhibitive or accelerative. This is illustrated by the following approximate relative rates [26] of solvolysis of tertiary halides in 80% aqueous ethyl alcohol at 25° : CMe_3Cl, 1 ; CMe_2EtCl, 1·6 ; CMe_2Pr^nCl, 1·5 ; CMe_2Bu^nCl, 1·4 ; CMe_2Pr^iCl, 0·9 ; CMe_2Bu^tCl, 1·2 ; $CMeEt_2Cl$, 2·4 ; CEt_3Cl, 2·8 ; CEt_2Pr^iCl, 2·0. Brown has utilised a form of steric strain theory in a detailed discussion of results of this type, taken in conjunction with data of a more significant nature relating to open-chain halides (see below) and to cyclic compounds.[27]

Large facilitating effects of alkyl substituents have been observed in the unimolecular reactions of more complex halides: (CMe_3Cl = 1) $CMePr^i_2Cl$ 14, CEt_2Bu^tCl 48,(ref. 26e) CBu^t_3Cl 600.(ref. 28) The suddenness with which the effect enters as the density of ramification is increased is characteristic of steric effects.[25] As already indicated, the unimolecular hydrolysis rates of mono-*tert.*-butylmethyl (*neo*pentyl) chloride and simple primary alkyl chlorides are of the same order of magnitude, and the unimolecular rates for pinacolyl chloride are close to those expected for comparatively simple secondary structures.[26c] The solvolysis rates for di-*tert.*-butylmethyl chloride (3-chloro-2 : 2 : 4 : 4-tetramethylpentane) [28a]

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[26] (*a*) Hughes, *J.*, 1935, 255 ; (*b*) Cooper, Hughes, Ingold, and MacNulty, *J.*, 1937, 1183, 1280, 1283 ; (*c*) Hughes, Ingold, Martin, and Meigh, *Nature*, 1950, **166**, 679, and unpublished results ; (*d*) Shorter and Sir Cyril Hinshelwood, *J.*, 1949, 2412 ; (*e*) H. C. Brown and Fletcher, *J. Amer. Chem. Soc.*, 1949, **71**, 1845 ; cf. also H. C. Brown and Stern, *ibid.*, 1950, **72**, 5068.

[27] H. C. Brown and Gerstein, *ibid.*, p. 2926 ; H. C. Brown, Fletcher, and Johannesen, *ibid.*, 1951, **73**, 212. The importance of steric factors has also been discussed by Baddeley (see especially Baddeley and Chadwick, *J.*, 1951, 368, and references therein cited).

[28] (*a*) F. Brown, T. D. Davies, Dostrovsky, O. J. Evans and Hughes, *Nature*, in the press ; (*b*) Professor P. D. Bartlett and his co-workers reported similarly large factors at an International Colloquium in Montpellier, France (in April, 1950), where our results and conclusions were also communicated.

are greater than those for pinacolyl chloride by factors of about four only. But, as noted above, the rates for tri-*tert.*-butylmethyl chloride are very much larger than those of simple tertiary alkyl halides.

(**3.7**) **Rearrangement.**—In bimolecular replacement (S_N2), the direct attack of the reagent, proceeding synchronously with the expulsion of the replaced group, results in the conversation of the original alkyl structure. On the other hand, fission of the carbon–halogen bond without the simultaneous attachment of the reagent may in certain cases give rise to rearranged products. Two examples of the more interesting types of rearrangement will be given, namely, anionotropy and the Wagner change.

(3.71) *Anionotropy.* In the ionisation of an allylic halide (Section 3.41) the cation is mesomeric [29] and recombination with the anion may take place in either of two alternative positions, yielding one or the other of the tautomers : [30]

$$X{-}CHR{-}CH{=}CH_2 \rightleftharpoons X{:} + [CHR{\cdots}CH{\cdots}CH_2]^+ \rightleftharpoons CHR{=}CH{-}CH_2{-}X$$

Extraneous anions or other nucleophilic reagents may similarly yield tautomeric substitution products by this mechanism. In the case of non-solvolytic processes or the solvolytic reactions of cations of long life (*e.g.*, $\alpha\alpha$- and $\gamma\gamma$-dialkyl derivatives), the two isomers yield the same products by this route. In the solvolysis of halides which give reactive cations, however, reaction with solvent molecules may occur in the immediate vicinity of the eliminated halide ion and the shielding influence of the anion may slightly modify the relative reaction rates at the near (α-) or distant (γ-)carbon atoms. The effect of the expelled entity may be compared with the predominance of inversion in the unimolecular solvolytic reactions of halides (Section 3.5).

Fission of the C–X bond of an allylic compound may be catalysed by acids (Section 3.2). It has been stated that, at least in the esters of organic acids, rearrangement only occurs under acidic conditions,[31] but this conclusion is insecurely founded and the deductions made from it are unjustified.

There is an interesting bimolecular mechanism of anionotropic change in which the bond-making and bond-breaking processes at C_α and C_γ are synchronous and are accompanied by an electronic adjustment in the carbon structure,[30b] *e.g.* :

$$X{:} + CH_2{=}CH{-}CHR{-}X \rightleftharpoons X{-}CH_2{-}CH{=}CHR + {:}X \quad (S_N2')$$

Evidence for the existence of this process is outlined in the papers cited, together with a discussion of its main characteristics.

The above mechanisms apply to conditions suitable for heterolysis. In

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[29] Ingold, *Chem. Reviews*, 1934, **15**, 250.

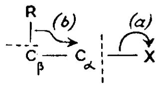
[30] See especially (*a*) Burton and Ingold, *J.*, 1928, 904 ; Burton, *J.*, 1928, 1650 ; 1934, 1268 ; (*b*) Hughes, *Trans. Faraday Soc.*, 1938, **34**, 185 ; 1941, **37**, 603 ; *J.*, 1949, S 400 ; Catchpole, Hughes, and Ingold, *J.*, 1948, *et seq.* ; Winstein, Young, and their co-workers, *J. Amer. Chem. Soc.*, 1942, **64**, 2157 ; 1944, **66**, 421 ; 1949, **71**, 115.

[31] Braude, *Ann. Reports*, 1950, **46**, 114 ; *Quart. Reviews*, 1950, **4**, 404.

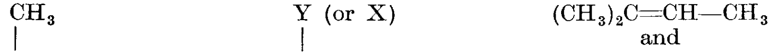
the whole range of anionotropic phenomena there are indications also of homolytic reactions, for which the following mechanism is suggested :

$$\mathrm{Br{-}CHR{-}CH{=}CH_2} + \dot{\mathrm{B}}\mathrm{r} \rightleftharpoons \dot{\mathrm{B}}\mathrm{r} + \mathrm{CHR{=}CH{-}CH_2{-}Br}$$

This process may be operative, for instance, in the isomerisation of allylic bromides in the presence of traces of oxygen and hydrogen bromide.



(3.72) *The Wagner Change.* In rearrangements of the Wagner type, the more commonly followed reaction path involves the heterolysis of the C–X bond (inset, process *a*) and the migration of R with the electrons of its bond with C_{β}* (process *b*). The accompanying deficiency of electrons on C_{β} may cause, depending on the detailed structural and environmental circumstances, one or more of the following attendant processes : (1) the attachment of X: at C_{β} (Wagner isomerisation), (2) the combination of an extraneous nucleophilic entity, Y:, at C_{β} (Wagner substitution), or (3) the ejection, with the formation of an olefin, of a proton or a positive alkyl fragment from a carbon atom adjacent to C_{β} (Wagner elimination). These changes are illustrated in the unimolecular reactions of *neo*pentyl compounds, *e.g.* :



$$\underset{\textit{neo}\text{pentyl compounds}}{(\mathrm{CH_3})_2\overset{\overset{\displaystyle\mathrm{CH_3}}{|}}{\mathrm{C}}{-}\mathrm{CH_2}{-}\mathrm{X}} \longrightarrow \underset{\textit{tert.}\text{-amyl compounds}}{(\mathrm{CH_3})_2\overset{\overset{\displaystyle\mathrm{Y\ (or\ X)}}{|}}{\mathrm{C}}{-}\mathrm{CH_2}{-}\mathrm{CH_3}} + \underset{\text{amylenes}}{\begin{matrix}(\mathrm{CH_3})_2\mathrm{C{=}CH{-}CH_3}\\ \text{and}\\ \mathrm{CH_2{=}C(CH_3){-}CH_2{-}CH_3}\end{matrix}}$$

It has been shown in the case of *neo*pentyl bromide that the process which leads to rearrangement exhibits the characteristic behaviour of ionisation in alkyl halides. However, the life of the *neo*pentyl cation, before its rearrangement to the *tert.*-amyl cation, must be very short, because it yields no detected substitution products with an unrearranged *neo*pentyl structure.[25] The general question has often been raised as to whether the migration of R accompanies or succeeds the separation of X. We shall proceed to summarise the evidence that mechanisms of two types exist, possibly as extreme cases in a graded phenomenon.[32]

If the migration of the methyl group with its bond electrons was a contributory cause, rather than a consequence of ionisation, an expected manifestation of this contribution would be an enhanced rate of reaction, by comparison with the ionisation rates of other primary halides under the same conditions. No substantial effect of this type was discernible for the solvolysis with rearrangement of *neo*pentyl bromide. Likewise, the reactions of pinacolyl halides, which also lead to rearrangement, have rates which are quite normal for the ionisation of secondary halide structures (Section 3.6).

In other cases, however, the rates of reaction of compounds which undergo rearrangement in solvolysis are definitely higher than the ionisation rates for simpler compounds of analogous constitution. In some cases it

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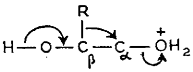
[32] F. Brown, Hughes, Ingold, and Smith, *Nature*, in the press.

* Retention of configuration in the migrating group, which has been observed in changes of this type, is doubtless a manifestation of the fact that R migrates in this precise way.

is difficult to decide whether or not the observed effects are larger than could be explained by the operation of other special facilitating influences, such as steric acceleration, but instances are available in which the presence of a " driving force " associated specifically with rearrangement seems manifest. Possibly the clearest and most striking examples have been encountered in our investigations in the terpene field.[32] For instance, while the rate for bornyl chloride in 80% aqueous ethyl alcohol is almost the same as that for pinacolyl chloride, the rate for *iso*bornyl chloride is larger by a factor of about 70,000. For ready rearrangement, the electrons of the migrating bond preferentially enter the orbit of the neighbouring carbon atom from a direction away from the expelled chlorine and synchronously with the separation of the halogen. The *iso*bornyl (*exo*) structure is a more accommodating configuration for this mechanism than is the bornyl (*endo*) isomer. The very reactive pinene hydrochloride may provide another example of a concerted process. The case of camphene hydrochloride is not clear-cut. In alcoholic solvents the rates for this compound are greater than those for *tert.*-butyl chloride by a factor of about 6000, but steric effects may be large for this tertiary halide structure.[32]

In open-chain compounds, the case of 2 : 2 : 2-triphenylethyl chloride, $(C_6H_5)_3C{\cdot}CH_2Cl$, has provided significant results.[33] For this compound in aqueous ethyl alcohol and in formic acid, the rates of reaction (leading to rearrangement) are greater than those for *neo*pentyl chloride under the same conditions by factors of the order of 10^4. Since this halide is primary and since a saturated carbon atom is interposed between the phenyl groups and the reaction centre, this effect seems larger than any possible combination of steric and polar influences, and it is concluded that the separation of the halogen is here assisted by the simultaneous migration of a phenyl group.

Transformations of the pinacol type, and rearrangements involving deamination, are analogous to the Wagner change, and the same principles may be operative for these cases also. In the pinacol–pinacone change, the prior separation of X might be expected to lead, partly at least, to the formation of an oxide ring by interaction between the remaining hydroxyl group and the positive charge at C_α. The absence of evidence for this interaction may be regarded as an indication that the migration of R usually takes place simultaneously with the separation of X in this change, *e.g.* :



The smooth transformation of *cis*-dimethyl*cyclo*pentane-1 : 2-diol into 2 : 2-dimethyl*cyclo*pentanone in acid solution supports this mechanism and provides strong evidence of the stereoelectronic requirement of a facile change, namely, that the migrating alkyl group (R) should approach the

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[33] Charlton, Dostrovsky, and Hughes, *Nature*, in the press. The substance previously listed in the literature as 2 : 2 : 2-triphenylethyl chloride is triphenylchloroethylene, $Ph_2C{=}CClPh$.

neighbouring carbon atom C_α from the side opposite to that from which the expelled group (OH) was displaced.[34]

(4) 1 : 2-Elimination Reactions

Substitution and elimination occur together so often as to suggest that the duality of mechanism established for substitution might have a parallel in the mechanism of elimination. This is found to be the case.[2, 35] Employing the nomenclature and schematic representation used in connection with nucleophilic substitution, we may illustrate the bimolecular (*E*2) and unimolecular (*E*1) mechanisms of elimination as follows ($Y = {}^-OEt$, ${}^-OH$, NR_3, H_2O, etc.) :

$$\text{Y:} + \text{H—CR}_2\text{—CR}_2\text{—X} \xrightarrow{\qquad} \text{Y—H} + \text{CR}_2\text{=CR}_2 + \text{:X} \qquad (E2)$$

$$\left.\begin{aligned} \text{H—CR}_2\text{—CR}_2\text{—X} &\xrightarrow{\text{(slow)}} \text{H—CR}_2\text{—CR}_2{}^+ + \text{:X} \\ \text{Y:} + \text{H—CR}_2\text{—CR}_2{}^+ &\xrightarrow[\text{(rapid)}]{} \text{Y—H} + \text{CR}_2\text{=CR}_2 \end{aligned}\right\} \qquad (E1)$$

In bimolecular elimination, a hydroxide ion or a similar nucleophilic reagent extracts a β-proton, with an accompanying separation of the atom or group X with its bond electrons, the olefin being thus formed in a single synchronous process. In the unimolecular mechanism, the rate-determining stage is the same as that for unimolecular substitution. In the elimination reaction the carbon cation loses a β-proton to a suitable acceptor, this eventuality being, in favourable circumstances, concurrent with the alternative reaction of the cation with an anion or a nucleophilic solvent molecule to give a substitution product. An alternative two-stage mechanism has been considered,[35] entailing a prior extraction of the β-proton by a base, and the subsequent ejection of :X from the anion :

$$\left.\begin{aligned} \text{Y:} + \text{H—CR}_2\text{—CR}_2\text{—X} &\longrightarrow \text{Y—H} + \overset{-}{\text{C}}\text{R}_2\text{—CR}_2\text{—X} \\ \overset{-}{\text{C}}\text{R}_2\text{—CR}_2\text{—X} &\longrightarrow \text{CR}_2\text{=CR}_2 + \text{:X} \end{aligned}\right\} \qquad (E1cB)^*$$

So far, no compelling evidence for this process has been obtained but it is clearly a possible mechanism of elimination reactions and it may function, for example, when stereochemical factors render mechanism *E*2 unavailable and when mechanism *E*1 is suppressed by other structural features in the compound (see below).

The synchronous, bimolecular mechanism (*E*2) has an important stereoelectronic property, namely, that the most favourable configuration of the transition state occurs when the β-CH electrons in $H—C_\beta—C_\alpha—X$ enter the octet of C_α on the side remote from X, the mechanism requiring there-

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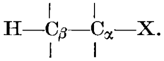
[34] Bartlett and Bavley, *J. Amer. Chem. Soc.*, 1938, **60**, 2416.

[35] Hughes, Ingold, and their co-workers, *J.*, 1935, 523, 526, 1571 ; *J. Amer. Chem. Soc.*, 1935, **57**, 708 ; *J.*, 1937, 1277, 1280, 1283 ; *J.*, 1940, 899 ; *Trans. Faraday Soc.*, 1941, **37**, 657 ; *J.*, 1948, 2038 *et seq.*

* The designation *ElcB* is intended to indicate elimination involving the conjugate base of the reactant  $H—C_\beta—C_\alpha—X$.

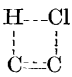
fore a *trans*-configuration of hydrogen and halogen for ready elimination.[36] Detailed kinetic investigations [37, 38] of the reactions of benzene hexachlorides with alkali in aqueous alcohol have shown that in the case of the β-isomer, where only *cis*-dispositions are available, a bimolecular mechanism, dependent on the attack of the base in the rate-determining process, is nevertheless possible. This is, however, much more difficult, and it entails a much higher activation energy, than bimolecular elimination in the α-, γ-, δ-, and ε-isomers, in which at least one pair of hydrogen and halogen atoms are *trans* to each other. The activation energies obtained in independent investigations are as follows :

Isomer :	E, kcals.				
	α.	β.	γ.	δ.	ε.
Ref. 37* . .	18·5	31·0	20·6	—	21·4
Ref. 38† . .	19·0	32·3	20·4‡, 20·1§	21·6‡, 21·1§	—

* Solvent : 76% (by wt.) EtOH. † Solvent : 90% (by vol.) EtOH.
‡§ Approx. values obtained from analyses of simultaneous first (‡) and second (§) stages of dehydrochlorination.

Throughout the series, B, in the equation $k = Be^{-E/RT}$, tends to increase with increase in E, *e.g.*, log B varies from 13·5 (α-isomer) to 18·6 (β-isomer). Except where otherwise indicated the values given for E and B refer to the first stage of elimination. The presence of a double bond confers on the subsequent process a facility which is either greater than or comparable with that of a first-stage, *trans*-elimination reaction. In two cases (γ and δ), product investigations, carried out during the course of reaction and guided by information provided by rate curves, resulted in the isolation of intermediates of composition $C_6H_5Cl_5$.[37, 38, 39] On the basis of their results, Cristol and his co-workers have concluded that, while the other isomers react with alkali by mechanism $E2$, the β-isomer utilises the mechanism here designated $E1cB$.

It should be emphasised that the above discussion refers to heterolytic mechanisms in solution. There is evidence that there is another mechanism of elimination reactions, which is operative, for example, in the gaseous phase. This may involve interaction between H_β and X in a transition state of a four-centre type (cf. inset) and it is a comparatively facile mechanism for *cis*-elimination. The stereochemical characteristics of the various mechanisms are of particular interest and importance in connection with elimination reactions in cyclic systems.[35, 36, 40]



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[36] Huckel, Tappe, and Legutke, *Annalen*, 1940, **543**, 191 ; Cristol, *J. Amer. Chem. Soc.*, 1947, **69**, 338.

[37] Cristol, Hause, and Meek, *J. Amer. Chem. Soc.*, 1951, **73**, 674.

[38] Hughes, Ingold, and Pasternak, unpublished ; Pasternak, Report to the Ramsay Memorial Fellowships Trust, 1948.

[39] Nakajima, Okubo, and Katumura, *Botyu-Kagaku*, 1949, [14], 10.

[40] Barton, *J.*, 1949, 2174.

(5) Factors influencing Relative Yields of Substitution and Elimination Products

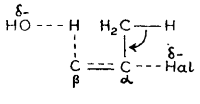
Although the main elimination mechanisms ($E1$ and $E2$) are similar to the substitution processes (S_N1 and S_N2) there are notable differences with respect to the effects of structural and environmental influences on the two changes, and the recognition of the important factors concerned provides useful information regarding the course of the reactions of alkyl halides and analogous compounds. We shall consider below the effect of the chief variables on the relative importance of the two processes in the interaction of a reagent Y with a halide R–X.[2, 25, 35]

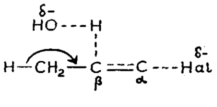
(5.1) Structural Effects.—(5.11) *Variation of* X. In the bimolecular mechanisms, the substitution and elimination processes are determined when X is attached to the system. The group to be expelled should therefore exert an important influence on the relative rates of the two reactions and this is found to be the case. For the various halides, a definite, though not very large, effect is observed, the yield of olefins increasing in the series $Cl < Br < I$ (little work has so far been carried out on the fluorides in this connection). A much more pronounced variation is observed when X is changed to $^+SR_2$ or $^+NR_3$. Thus, while ethyl bromide and alcoholic potassium hydroxide give only about 1% of ethylene, the olefin is a major product in the decomposition of the tetraethylammonium cation under the same conditions.

In the unimolecular mechanism, the products are formed after the group X has been removed, though it may be in the close vicinity of R^+ when the cation is partitioned between substitution and elimination. In first approximation, therefore, the ratio of the products should be independent of X. This is found to be the case, for instance, in the unimolecular solvolysis of the various *tert.*-butyl halides and *tert.*-butyldimethylsulphonium salts.

Incidentally, such distinctions between the bimolecular and the unimolecular mechanism constitute further evidence for the concept of the duality of mechanism in substitution and elimination reactions.

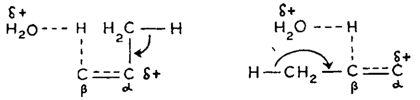
(5.12) *Variation of* R. We shall consider two main cases, namely, α-methyl substitution in the series $CH_3{\cdot}CH_2$, $(CH_3)_2CH$, $(CH_3)_3C$, and β-methyl substitution in the series $CH_3{\cdot}CH_2$, $CH_3{\cdot}CH_2{\cdot}CH_2$, $(CH_3)_2CH{\cdot}CH_2$. In both series the rates of bimolecular replacement decrease with progressive introduction of methyl groups, a combination of polar and steric factors being responsible as already described. For elimination, the attack of the reagent on the small hydrogen atom does not usually involve any considerable steric factors. Furthermore, in elimination it is found that the net effect of both α- and β-methyl groups is to facilitate the removal of the halogen by the electronic activation indicated in the transition state representations below :



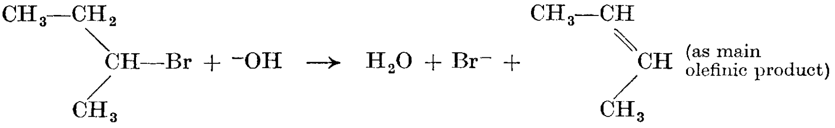


An increase in elimination rates in both series, coupled with a decrease in substitution rates, therefore results in a rather pronounced increase in the yield of olefin with progressive α- or β-methyl substitution. Typical results for the bimolecular reactions of bromides with sodium ethoxide in ethyl alcohol at 40° are appended as approximate yields (%) of olefin : Et, 1 ; Pr^i, 80 ; Bu^t, 100 ; Pr^n, 10 ; Bu^i, 60. The common text-book procedure for making ethylene (from ethyl halide and alcoholic potassium hydroxide) gives a good yield of ethyl ether. The principal reaction (R = Et) is the replacement of halogen and the effective reagent is mainly the ethoxide ion.

The primary halides do not lend themselves to ready reaction by the unimolecular mechanism and we shall consider only their general relationship to secondary and tertiary compounds, in connection, that is, with the α-methylated series. Here we are concerned with the relative ease with which the cation R^+ undergoes reaction with solvent molecules to give either substitution or elimination products. The olefin yields (%) in solvolysis in aqueous alcoholic media are Et ~ 0, $Pr^i \sim 5$, $Bu^t \sim 16$. β-Methyl substitution also increases the yield of olefin in the halides for which this mechanism is observable, *e.g.*, Bu^t 16, CMe_2Et 34%. Hyperconjugation from the methyl substituent again facilitates the formation of olefin :



These results have a direct bearing on two long-standing problems of some interest. The first concerns the basis of the Saytzeff rule which refers to the preferential production of the most alkylated of the possible olefins which may be formed from branched-chain alkyl halides, *e.g.* :



$$CH_3{-}CH_2(CH_3)CH{-}Br + {}^-OH \longrightarrow H_2O + Br^- + CH_3{-}CH{=}CH{-}CH_3 \quad \text{(as main olefinic product)}$$

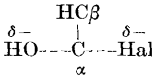
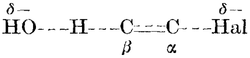
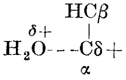
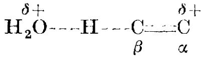
This rule has been shown to apply to unimolecular and bimolecular reactions of halides. The interpretation lies in the facilitating influence of a β-methyl substituent as explained above. [It should be mentioned here that the position in bimolecular elimination from 'onium cations is different ; in these structures the inductive effect of a β-alkyl substituent [35] is responsible for a decrease in the facility of proton removal by a base (cf. Hofmann's rule).] The second application concerns a classical controversy as to whether or not tertiary halides gave better yields of olefins than do secondary halides (in the reaction with alcoholic alkali). Provided that the reactions used in the comparison are bimolecular in both cases, or are uniformly unimolecular, it is clear from the above discussion that tertiary halides give the higher yields. However, unless the alkali used is concentrated and the solvent fairly anhydrous, the incursion of unimolecular decomposition in tertiary halides is very marked and a comparison (without kinetic control) of the olefin yield for a unimolecular reaction of a tertiary halide with the yield for a bimolecular reaction of a secondary halide would give results in favour of the secondary compound. For both secondary and tertiary halides, the unimolecular route is generally a more profitable proposition when substitution products of solvolytic reactions are required.

(5.13) *Variation of* Y. The reagent may influence the nature of the products in three main ways. First, the reagent is important in determining the question as to whether the reactions are of the unimolecular or the bimolecular type ; and the particular mechanisms which the reactions follow partly control the composition of the products. Strongly basic reagents in high concentration promote bimolecular reactions, whereas weakly basic reagents in good ionising solvents are conducive to unimolecular reactions. Then, as already indicated, the ratio of elimination to substitution in concomitant bimolecular processes is usually very much higher than the ratio for unimolecular reactions.

The second way in which the reagent may affect the ratio of products depends on its relative basicity and nucleophilic power. Nucleophilic activity towards a carbon centre and basicity towards hydrogen, though often exhibiting a very rough parallelism, also show marked divergencies. Reagents which have high basicity (and form weakly dissociated conjugate acids, Y—H) usually exhibit good nucleophilic power towards a reactive carbon centre, but reagents with high nucleophilic activity towards carbon are not always powerfully basic. For reagents which have reasonably high activities in both types of reactions, such as ethoxide or hydroxide ions, the more powerful reagent (*e.g.*, $^{-}$OEt) gives the higher yield of olefin. Of the reagents which have a well-developed activity towards a carbon centre but negligible action on hydrogen, halide ions are good examples, for, while they are quite active in substitution processes, *e.g.*, in halogen-exchange of the type $I^- + R{-}Cl \rightarrow R{-}I + Cl^-$, there is little evidence that they participate in elimination reactions. Azide ions and various sulphur compounds, *e.g.*, $^{-}$SH, $^{-}$SR, SR_2, are similar.

The third important effect depends on the steric properties of the reagent. Substitution reactions are often subject to steric retardation (Section 3.6), whereas elimination reactions are not sensitive to this factor. Complex amines of reasonably high basicity are therefore appropriate dehydrohalogenation reagents when loss of yield through replacement reactions is to be avoided.

(5.14) *Solvent Variation.* The solvent is important both as a factor controlling the mechanism and as a condition which influences the ratio of products within each mechanism. The effect on the relative importance of unimolecular and bimolecular reactions follows from the discussion in Section 3.3, and it is evident from the foregoing considerations that the ratio of products is dependent on the particular mechanism pursued. Under conditions of uniformity of mechanism, the influence of the medium on the product ratio is governed by the distribution of charge in the transition state. This is illustrated below for the bimolecular reactions with anionic reagents and for the unimolecular mechanism, the products in the latter case being derived from the organic cation :

Reactions.	Transition states.	
	Substitution.	Elimination.
S_N2 and $E2$	 $\overset{\delta-}{\mathrm{HO}}\text{---}\underset{\alpha}{\overset{\overset{\mathrm{HC}\beta}{\vert}}{\mathrm{C}}}\text{---}\overset{\delta-}{\mathrm{Hal}}$	 $\overset{\delta-}{\mathrm{HO}}\text{---H---}\underset{\beta}{\mathrm{C}}\overset{\text{---}}{=}\underset{\alpha}{\mathrm{C}}\text{---}\overset{\delta-}{\mathrm{Hal}}$
S_N1 and $E1$ . . .	 $\overset{\delta+}{\mathrm{H_2O}}\text{---}\underset{\alpha}{\overset{\overset{\mathrm{HC}\beta}{\vert}}{\mathrm{C}}}\delta+$	 $\overset{\delta+}{\mathrm{H_2O}}\text{---H---}\underset{\beta}{\mathrm{C}}\overset{\text{---}}{=}\underset{\alpha}{\overset{\delta+}{\mathrm{C}}}$

In each case there is a greater dispersal of charge in the transition state of elimination, leading therefore to the prediction that elimination should be favoured by less ionising (solvating) media. This is found to be the case.[35]

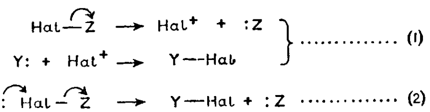
(5.15) *Temperature Variation.* For both the unimolecular and the bimolecular mechanism of the reactions of alkyl halides with alkali in aqueous alcohol, it is found that the elimination processes are favoured by increase of temperature, the activation energies of elimination being generally about 2 kcals. higher than for substitution.[35] One of the chief contributing causes may be the fact that a rather strong C–H bond is severed in elimination.

(6) " Positive Halogen " Fission

Only an outline of the second form of heterolysis of halides will be given at this time, the aim being to illustrate briefly the relation between the two types. The reactions with nucleophilic reagents may be formulated as follows (charges being unspecified because of the various possibilities indicated below) :

$$\mathrm{Y}\!: + \mathrm{Hal}\,|\!-\!\mathrm{Z} \longrightarrow \mathrm{Y}\!-\!\mathrm{Hal} + :\!\mathrm{Z}$$

Examples are found in the formation of Cl_2, Cl_2O, ClOAc, etc., from such compounds as hypochlorous acid and *N*-chloroamines (*e.g.*, Y: = Cl^-, ClO^-, AcO^- ; Z = OH, $^+OH_2$, $^+NHR_2$). If Y–Hal is itself a halogenating agent it may function (as does Hal–Z) as an intermediate in substitution processes. The halogenation of aromatic compounds, olefins, etc. (considered for this purpose as nucleophilic reagents), may be profitably regarded in a similar way. Some rearrangements involving halogens can also be interpreted satisfactorily on this basis. The two main mechanisms may be formulated : [41]



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[41] de la Mare, Hughes, Ingold, and Vernon, *Research,* 1950, **3,** 192, 242. and unpublished work.

The " normal ", second-order reactions of carbon tetrahalides with strongly nucleophilic reagents (Section 3.42) are probably initiated by the extraction of a positive halogen atom by the anion [process (2) ; Y: = $^{-}$OR ; Hal = Cl, Br ; Z = CCl_3, CBr_3]. The identical products obtained from the tetrahalides and the trihalides (also *via* the intermediate $^{-}CHal_3$, formed in this case by extraction of a proton) are consistent with this interpretation.[18]

The reactions of trifluoroiodomethane (Z = CF_3) with reagents such as iodide and hydroxide ions are further interesting examples of this type of fission. Indications of the first of the above mechanisms, and possibly of the second, have been obtained in this instance, and evidence of homolytic fission was detected at higher temperatures.[42] Positive halogen and homolytic reactivities often occur together. Thus, while *N*-bromosuccinimide commonly exhibits homolysis, it also acts as a source of positive halogen, especially under acidic conditions. Rearrangement reactions involving halogenoamines (*e.g.*, *N*-bromoacetanilide) also show this duality of behaviour in certain circumstances. The reactions of nitryl chloride, Cl–NO_2, suggest that all three forms of fission of the N–Cl bond (Section 2) are possible in this structure. The role of positive entities in halogenation (*e.g.*, Hal–OH_2^+ or Hal^+) has been frequently discussed and considerable work on the subject has been recently undertaken.[43]

(7) The Reactions of the Halides of the Elements

The bond-fission mechanisms which have been established for the halides of carbon provide a useful basis for consideration of the reactions of the halides of the elements generally. A modification which it is necessary to make is that, for an element (A) which is capable of octet expansion, the nucleophilic reagent may utilise its bond-making properties to assist the separation of the halogen without the occurrence of any large stretching of the A–Hal bond. A similar modification was found useful in the treatment of reactions at unsaturated carbon atoms. This type of mechanism had an early origin in chemistry. It was utilised, for example, in the " addition complex " theory of substitution reactions, often in connections for which it could not well apply (*e.g.*, in replacement processes at saturated carbon atoms). The connection with the reactions of the compounds of silicon, and other elements for which it is applicable, was developed especially by Sidgwick.[44]

It is important to determine whether the high reactivity of silicon halides is usually associated with octet expansion or with a facile ionisation process. In this connection, a comparison of the properties of the triphenylmethyl halides with those of the silicon analogues ($Ph_3Si{\cdot}Hal$) is of interest. The triphenylsilyl halides are more reactive in, for example, alcoholysis than are the triphenylmethyl halides, but, in contrast to tri-

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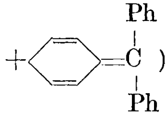
[42] Banus, Emeléus, and Haszeldine, *J.*, 1951, 60.

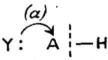
[43] See, especially, Wilson and Soper, *J.*, 1949, 706, 3376 ; Derbyshire and Waters, *J.*, 1950, 564, 574, 3694 ; *J.*, 1951 73.

[44] See especially, " The Electronic Theory of Valency ", Oxford Univ. Press, 1927.

phenylmethyl chloride, triphenylsilyl chloride exhibits no marked conductivity in liquid sulphur dioxide.[45] Spectroscopic evidence of the absence of ionisation in certain triarylsilanols, under conditions for which the corresponding carbon compounds undergo fission, has been reported by Gilman and Dunn.[46] These authors discuss the readier ionisation of the carbon compounds in relation to a possible condition of steric strain in the initial state and to resonance stabilisation of the cation (involving structures of the type 

), these being factors which are diminished in importance, or wholly eliminated, in the case of the compounds of silicon. It should be emphasised, however, that these physical properties may possibly indicate the state of equilibrium in the balanced reactions, $R_3SiX \rightleftharpoons R_3Si^+ + :X$, and it is necessary to consider also the association reactions, for which the steric and resonance factors mentioned would tend to favour readier recombination in the case of silicon. It is important, therefore, to obtain rates of fission by kinetic experiments, and investigations to this end are being undertaken.

The rates of alcoholysis [45] and hydrolysis [47] of silicon halides, including triphenylsilyl fluoride, are decreased by electron accession to the reaction centre, are facilitated but weakly by an increase in the polarity of the medium, and are increased by added ethoxide or hydroxide ions. In all cases there is a difference of behaviour, either of a qualitative or of a quantitative nature, when the results are compared with the corresponding data for triphenylmethyl halides [45, 47] and it may be concluded that the reaction mechanisms for the carbon and the silicon compounds are different. Swain and his co-workers concluded that the hydrolysis of triphenylsilyl fluoride is a two-stage reaction in which the break-down of a five-covalent intermediate into $Ph_3Si{\cdot}OH_2^+$ and F^- is the rate-determining process. Our interpretation [45] is that while the solvolytic reactions of triphenylmethyl halides in reasonably good ionising media are unimolecular (S_N1), the reactions of silicon halides follow a modified S_N2 mechanism in which bond-making influences are dominant.

In discussing such questions as the relative reactivities of the halides of related elements it is useful to consider two main mechanism of heterolysis. The essential features of these mechanisms may be represented schematically as (1) 

and (2) 

For a group of elements such as titanium, zirconium, and thorium,[48] the relative facility of process *a* may be expected to decrease with increasing atomic number, the reason being that more effective shielding of atomic nuclei by an increased number of electrons may tend to inhibit bond formation with a nucleophilic reagent.

[45] C. Eaborn, Thesis, Univ. of Wales, 1947; Dostrovsky, Eaborn, and Hughes, unpublished.

[46] *J. Amer. Chem. Soc.*, 1950, **72**, 2178.

[47] Swain, Esteve, and Jones, *ibid.*, 1949, **71**, 965.

[48] Bradley, Abd-el-Halim, and Wardlaw, *J.*, 1950, 3450; 1951, 280.

For a similar reason, process *b* should gain in importance with increasing atomic number. Thus, while the mainly covalent bonds of elements of comparatively low atomic number (A′–Hal, *e.g.*, the Ti–Cl bond) become heterolysed with considerable facility in the presence of nucleophilic reagents (*e.g.*, H_2O, EtOH), the bonds of elements of high atomic number (A″–Hal, *e.g.*, the Th–Cl bond) are ionised in their crystal forms. Heterolysis of bonds A′–Hal results in covalency formation with the reagent (giving, for example, A′–OH or A′–OEt). Covalency formation will be difficult in the case of an element A″ of much higher atomic number but co-ordination with reagent molecules (*e.g.*, H_2O or EtOH) may accompany ionisation in the solvent. The suggested mechanisms should have interesting stereochemical consequences.

Analogous considerations have similar application for other groups of elements and for bonds other than those involving halogen. In considering the position of halides in general, due regard should also be given to the " positive halogen " fission discussed in the preceding section, which probably applies, for example, to nitrogen trichloride.

Conclusion

A fitting conclusion is that the results of investigations of the reactions of the halides of carbon have extensive applications in chemistry. The most significant property of carbon is that, coupled with the fact that it is generally tetravalent in its compounds, its maximum covalency is four. This confers on the element the parentage of a great wealth of comparatively stable compounds which lend themselves to profitable studies and uses. To this fact the chemistry of carbon compounds owes its distinction and it is better regarded as a circumstance arising from the atomic structure of carbon in the array of the elements than to an entirely specialised position which is sometimes alleged to justify the complete separation of organic chemistry from chemistry as a whole.