Substitution.

THE TILDEN LECTURE, DELIVERED IN LEEDS ON NOVEMBER 26TH, 1945, AND IN LONDON ON JANUARY 17TH, 1946.

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THE study of substitution reactions had an early origin and has held a prominent position in the development of the chemistry of carbon compounds. The subject is an extensive one and in order to reduce it to accessible limits we shall deal mainly with recent advances regarding the kinetics and mechanism of substitution, and especially of certain types of replacement reactions occurring at a saturated carbon atom, *e.g.*, $Y + R{-}X \longrightarrow Y{-}R + X$, where Y is an atom or group which can replace a similar entity X in a molecule R—X, R being an organic radical which is saturated at the point of attachment of X. The importance of the kinetic method in the study of mechanism was foreshadowed by the work of Lapworth, Orton, and others in the early years of the present century. More recently, it has played a notable part in the rapid development which the theory of organic reactions has undergone since the enunciation of the electronic theory of valency.

The interest attached to the problem may be said to be two-fold. First, substitution processes are amongst the most common and useful of chemical reactions, and knowledge concerning their mechanism is itself of prime importance. Secondly, a substitution reaction of the type illustrated may be regarded as a comparatively simple unit process and a fruitful attack on the problem by the kinetic and other methods cannot fail to be of value as a guide and a model for the study of other changes. Though often of a seemingly complex character, many reactions can be analysed into stages, which, with regard to kinetics and mechanism, frequently bear some resemblance to a simple replacement process. On the basis of this two-fold definition of objectives, further discussion will be divided into two main sections, comprising (*a*) general principles of aliphatic substitution, and (*b*) applications of general principles.

A. GENERAL PRINCIPLES OF ALIPHATIC SUBSTITUTION.

I. *Historical Survey.*

In the early days of the development of chemical theories, the main question regarding the mechanism of substitution processes was put in the following form : " Is substitution always preceded by addition ? " In a reaction of the type $Y + R{-}X \longrightarrow Y{-}R + X$, where one bond is formed and one is broken, it is obvious that the process could be initiated either by the attack of the reagent (Y) on the molecule R—X (a process tending to form the new bond Y—R first and leading to the expulsion of X), *e.g.*,

$$Y \cdots R{-}X \longrightarrow Y{-}R + X,$$

or, alternatively, by the preliminary fission of the R—X bond (followed by the union of Y with R) :

$$R{-}X \longrightarrow R + X; \quad Y + R \longrightarrow Y{-}R.$$

Thus there emerged two types of theories of substitution reactions. One postulated addition as an essential condition for the expulsion of the group replaced; the other assumed that the primary dissociation of bonds was involved. In rudimentary form these theories had, as already implied, quite an early origin. It is not proposed to trace that origin fully at this time, but it is of interest to recall that notable advances in the development of more precise views concerning substitution reactions were made through the great impetus both to practical and to theoretical work which resulted from the discovery by Walden in 1895 of the configurational inversion which bears his name.

The first type of theory, which may be called the " addition-complex " theory, was particularly prominent in connection with the problem of the Walden inversion, which was considered from the mechanistic point of view by Fischer, Werner, Pfeiffer, Gadamer and others about the year 1911. In the early versions of the theory it was not clear how the addition took place; it was customary to speak rather vaguely of a union dependent on the " residual affinity " of the reactive carbon atom, and so on, and it is obvious that there were difficulties regarding the valency of this carbon atom, which was already saturated before the attachment of the entering atom or group. These difficulties were dispelled by the idea that addition is not previous to but synchronises with dissociation. This was first stated in an acceptable form by G. N. Lewis (" Valence and the Structure of Atoms and Molecules," 1923, p. 113). The physical basis (including the stereochemical implications) of the synchronous mechanism has been discussed by Polanyi (see especially Meer and Polanyi, *Z. physikal. Chem.*, 1932, *B*, **19**, 164; Bergmann, Polanyi, and Szabo, *ibid.*, 1933, **20**, 161; *Trans. Faraday Soc.*, 1936, **32**, 843), and by Olson (*J. Chem. Physics*, 1933, **1**, 418; Olson and Long, *J. Amer. Chem. Soc.*, 1934, **56**, 1294; 1936, **58**, 393), particularly in relation to the application of the mechanism to the reaction between an anion and a neutral molecule (see also later references to the work of these authors).

With regard to the second type of theory (the " prior dissociation " theory), development has also taken place in the direction of greater precision in its formulation; the theory has evolved, from a stage at which little attempt was made to explain how the replaced group was expelled, to its position at the present time, when we distinguish between various types of fission and specify quite precisely the circumstances in which each type will function (see Section II below).

The impression that the two types of theories were incompatible (in the sense that no degree of application could be given to both) has also undergone revision. By detailed reference to certain reactions which may be labelled " Nucleophilic Substitutions " we shall show that our present views regarding the mechanism of such processes may be said to embody the acceptable versions of both (*i.e.*, the " addition-complex " and the " prior dissociation ") theories. The concept of the duality of mechanism in substitution reactions at a saturated carbon atom has in fact become the main feature of the recent developments, which we shall now discuss.*

It is necessary first to arrive at a classification of substitution types, as indicated immediately below.

II. *Types of Substitution.*

In a substitution reaction of the general form $Y + R{-}X \longrightarrow Y{-}R + X$, it is clear that, independently of mechanism, the R–X bond must be severed in the course of reaction. There are two principal ways by which this can be accomplished, one of which requires further classification into two sub-types (cf. Ingold, *Trans. Faraday Soc.*, 1938, **34**, 227; Hughes, *ibid.*, 1941, **37**, 604). This is represented schematically in the formulæ below, where the dots represent electrons and the vertical lines illustrate the mode of fission of the bond :

$R|\cdot\cdot X$ (1*a*) and $R\cdot\cdot|X$ (1*b*) $R\cdot|\cdot X$ (2)

Dissymmetric or heterolytic fission. Symmetric or homolytic fission.

In one case, splitting of the bond occurs so that both the bond electrons separate with one of the fragments. In the other, each fragment appropriates one electron. The first type of fission is called dissymmetric or heterolytic fission, and the second is termed symmetric or homolytic fission. The question as to which of these forms will be operative in a given case will depend not only on the natures of R and X but also on the substituting agent and the experimental conditions.† The heterolytic type of fission is characteristic of a large proportion of substitution reactions in solution, which generally involve ions, or entities which readily form ions. Two principal factors determine which of the alternative sub-types will be followed (see Table below). The first is whether the natures of R and X are such that the expelled group X (we suppose that the substitution is to take place at R) tends to separate with its electrons (1*a*, *e.g.*, halogen in alkyl halides) or without its electrons (1*b*, *e.g.*, hydrogen in suitably activated C–H bonds), and the second is whether the substituting agent uses its electrons to attack the nucleus of R (1*a*, *e.g.*, $H\bar{O}$ or $R_3N\!:$) or uses its nucleus to combine with the electrons of R (1*b*, *e.g.*, H^+ or D^+). The former type of substituting agent is termed "nucleophilic " and the latter "electrophilic " and the substitution processes are named accordingly.

Replacement reactions of the homolytic type (2) obtain under conditions favourable to the existence of atomic or other neutral reagents and when there is little tendency for ionic fission in the R—X bond; they are thus common in gas-phase reactions [*e.g.*, the photo-halogenation (by halogen atoms) of paraffinic hydrocarbons in the gaseous phase].

Our main discussion will be confined to reactions of the heterolytic type.

Types of Substitution.

(1) *Heterolytic.*

(*a*) *Nucleophilic.*

$$Y\!: + R|\,:X \longrightarrow Y\!:\!R + :\!X \quad (S_N)$$

$$(e.g.,\ H\bar{O} + R{-}Cl \longrightarrow HO{-}R + \bar{C}l)$$

(*b*) *Electrophilic.*

$$Y + R\,:\,|X \longrightarrow Y\!:\!R + X \quad (S_E)$$

$$(e.g.,\ D^+ + R{-}H \longrightarrow D{-}R + H^+)$$

(2) *Homolytic.*

$$Y\cdot + R\cdot|\cdot X \longrightarrow Y\!:\!R + \cdot X$$

$$(e.g.,\ Cl\cdot + R{-}H \longrightarrow Cl{-}R + \cdot H)$$

For convenience in reference the nucleophilic and electrophilic types of substitution are labelled S_N and S_E

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* For the detailed description of the development of the general theory, see especially the following papers : Hughes and Ingold, *J.*, 1935, 244; Hughes, Ingold, and Shapiro, *J.*, 1936, 225; Cowdrey, Hughes, Ingold, Masterman, and Scott, *J.*, 1937, 1252; Hughes, *Trans. Faraday Soc.*, 1938, **34**, 185, 202; Bateman, Cooper, Hughes, and Ingold, *J.*, 1940, 925; Bateman, Church, Hughes, Ingold, and Taher, *J.*, 1940, 979; Hughes, *Trans. Faraday Soc.*, 1941, **37**, 603. In connection with special points, reference to specific sections of these, and to other relevant papers, will be made in the following pages.

† The nature of the substituting agent is particularly important when it participates in a one-stage process (bimolecular mechanism, see below). When a preliminary rate-determining fission of the R–X bond is involved (unimolecular mechanism) the nature of the primary dissociation is determined independently of the substituting agent, which, nevertheless, must intervene in the formation of the substitution product.

respectively (Gleave, Hughes, and Ingold, *J.*, 1935, 236). Our attention will now be directed to the nucleophilic type, which has been more extensively studied from the mechanistic standpoint.

In nucleophilic substitution, there is a transfer of electrons from Y to R and from R to X. The reagent may therefore be either negative or neutral (provided it has unshared electrons) and the replaceable group may be either neutral or positive. Four cases thus arise, which may, for the most part, be illustrated by examples of familiar reactions in organic chemistry :

(1) Y negative and X neutral, *e.g.*, $\overset{-}{HO} + R—Br \longrightarrow HO—R + \overset{-}{Br}$

(2) Y negative and X positive, *e.g.*, $\overset{-}{Br} + R—\overset{+}{N}R_3 \longrightarrow Br—R + NR_3$

(3) Y neutral and X neutral, *e.g.*, $R_3N + R—Br \longrightarrow R_3\overset{+}{N}—R + \overset{-}{Br}$

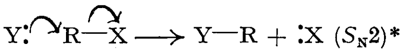
(4) Y neutral and X positive, *e.g.*, $R_3N + R—\overset{+}{S}R_2 \longrightarrow R_3\overset{+}{N}—R + SR_2$

The examples refer to (1) the hydrolysis of alkyl halides, (2) the decomposition of alkylammonium salts, (3) the formation of alkylammonium salts from tertiary amines and alkyl halides, (4) the formation of alkylammonium cations from tertiary amines and alkylsulphonium cations.

III. *Duality of Mechanism in Nucleophilic Substitution.*

We now recognise two operative mechanisms for these substitution processes. For the sake of clarity in presentation we shall first describe the mechanisms and then proceed to outline the principal observations which present strong reasons for adopting the theory of the duality of mechanism in nucleophilic substitution.

The first mechanism is a one-stage mechanism, involving a synchronous electron transfer from Y to R and from R to X, *e.g.*,



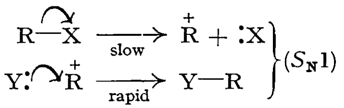
$$Y\!: R—X \longrightarrow Y—R + :X \quad (S_N2)^*$$

$$\text{Example :}\ \overset{-e}{HO} + R—Cl \longrightarrow \overset{\sim -e/2}{HO}\cdots\cdots R\cdots\cdots\overset{\sim -e/2}{Cl} \longrightarrow HO—R + \overset{-e}{Cl}$$

Initial state. Transition state. Final state.

Since both reactants are simultaneously involved, this mechanism is termed " bimolecular "; the numerical part of the designation (S_N2) is intended to symbolise this character. As an example, we may take the bimolecular alkaline hydrolysis of an alkyl halide. The anionic charge (— *e*), initially on the entering group and finally on the expelled group, becomes distributed in the transition state as indicated in the schematic representation.

The second mechanism is a two-stage process, wherein a rate-determining ionisation is succeeded by a reaction between the carbon cation formed and the substituting agent, *e.g.*,



$$\left.\begin{array}{l} R—X \xrightarrow[\text{slow}]{} \overset{+}{R} + :X \\ Y\!:\overset{+}{R} \xrightarrow[\text{rapid}]{} Y—R \end{array}\right\}(S_N1)$$

$$[\text{Example :}\ R—Cl \longrightarrow \overset{\delta+}{R}\cdots\cdots\overset{\delta-}{Cl} \longrightarrow \overset{+}{R} + \overset{-}{Cl}\ \text{(slow), followed by}\ \overset{+}{R} + \overset{-}{OH} \longrightarrow R—OH\ \text{(rapid).}]$$

In the unimolecular hydrolysis of an alkyl halide, for example, there is a partial separation of charges in the transition state of the rate-determining ionic dissociation, which is followed by a rapid reaction between the carbon cation and a hydroxide ion. Although the importance of solvation in ionic dissociation is recognized, this mechanism is termed " unimolecular " because only one reactant, R—X, is underging covalency change in the rate-determining stage. The numerical part of the designation S_N1 again indicates the molecularity of this mechanism.

The two mechanisms should clearly be characterised by distinctive kinetics and this, together with other significant properties, should be useful for purposes of diagnosis. We shall now review the principal evidence which has been derived from a study of the reactions of organic halides. In many instances supporting evidence has been obtained from parallel investigations of the reactions of ammonium or sulphonium salts.

IV. *Evidence for the Duality of Mechanism.*

(1) *Energy Requirements.*—It seems opportune to discuss this question at the outset, since the theory of the assessment of activation energies for simple reactions has reached a stage where it is at least possible to decide whether or not a given mechanism is energetically feasible. For the bimolecular mechanism, the earlier, approximate calculations of London (*Z. Electrochem.*, 1929, **35**, 552) and of Eyring and Polanyi (*Z. physikal. Chem.*, 1931, *B*, **12**, 279) have been adapted and developed for the case of an anion reacting with a neutral

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* In this formulation, and elsewhere in this lecture, arrows are used to show the direction of electron displacements. Sign labels on X and Y are omitted because of the various possibilities already mentioned.

molecule by Polanyi and his co-workers (Polanyi, *Proc. Roy. Soc.*, 1934, *B*, **116**, 203; Ogg and Polanyi, *Trans. Faraday Soc.*, 1935, **31**, 604; Baughan and Polanyi, *ibid.*, 1941, **37**, 648). The calculated activation energies (*e.g.*, for the "halogen-exchange" reaction, $\overset{-}{I} + R{-}Cl \longrightarrow I{-}R + \overset{-}{Cl}$) are found to have easily accessible values and are in fact in good agreement with the experimental results obtained under conditions for which the bimolecular mechanism is considered to be applicable. For the unimolecular mechanism, the position has seemed more controversial, mainly because some authors have given inadequate consideration to solvation effects in ionic dissociation. Olson and Voge (*J. Amer. Chem. Soc.*, 1934, **56**, 1690) objected to mechanisms of this type on the ground that primary dissociation would imply much too large a heat of activation. Hughes and Ingold (*J.*, 1935, 245) met this difficulty by drawing attention to the important part played by facilitating solvation forces in suitable solvents. In an attempt to secure evidence of a quantitative character, Ogg (*J. Amer. Chem. Soc.*, 1939, **61**, 1946) calculated that the activation energies demanded by the unimolecular mechanism would be at least 50 kg.-cals., and therefore too great to admit of measurable rates at ordinary temperatures. His calculations, however, refer primarily to the hydrolysis of the methyl halides, which are most unsuitable structures for the facile operation of the unimolecular mechanism [see sub-section (2) below]. Furthermore, it has been pointed out (Bateman, Church, Hughes, Ingold, and Taher, *J.*, 1940, 1006) that Ogg's calculations were too rough to be significant, the uncertainties introduced being of the same order of magnitude as the quantities calculated. Finally, Baughan, Evans, and Polanyi (*Trans. Faraday Soc.*, 1941, **37**, 377) deduced a much lower value ($\sim$ 30 kg.-cals.) for the activation energy of the ionisation of methyl iodide in water—a value which would accommodate an ionisation mechanism even for this halide.

(2) *The Kinetic Form of the Substitution Reaction.*—In general, the bimolecular mechanism should lead to second-order kinetics (being of the first-order with respect to each reactant), while the unimolecular mechanism should, in first approximation (see below), lead to first-order kinetics, since the substituting agent does not function in the rate-determining stage.* Many cases of each type of kinetic behaviour have been observed (for a full summary see *Trans. Faraday Soc.*, 1941, **37**, 608). In illustration of the kinetic evidence, we shall mention here but one set of observations, which refer to the hydrolysis of alkyl halides with alkali in aqueous alcohol. Kinetic investigations have shown that for certain halides (*e.g.*, the methyl halides) the reaction is of the second order, the rate being dependent on the concentration of the alkyl halide and on that of hydroxide ions. The hydrolysis of certain other halides (*e.g.*, the *tert.*-butyl halides) is, on the other hand, found to be of the first order, the rate being independent of the concentration of hydroxide ions and the same in acid, neutral, and alkaline solution. Evidently, there is a difference of mechanism between the two types and the kinetic observations are entirely consistent with the concept of the duality of mechanism. Many unsuccessful attempts have been made to find other explanations for these kinetic results. An alternative hypothesis that the first-order reactions follow a bimolecular mechanism in which the solvent is acting as the reagent (its presence in large excess accounting for the kinetic order) cannot be entertained, because a nucleophilic substituting agent is acting analogously to a base, and it is inconceivable that water molecules should be effective reagents when the more powerfully basic hydroxide ions are quite inactive.†

Furthermore, if we reduce the water concentration to small proportions comparable with the alkyl halide, then, by varying the concentration in a suitable (ionising) medium, it can be shown that the rate of hydrolysis of the type of halide for which a unimolecular mechanism is postulated is independent of the water concentration (Bateman and Hughes, *J.*, 1937, 1187; 1940, 935; cf. Koskoski, Thomas, and Fowler, *J. Amer. Chem. Soc.*, 1941, **63**, 2451). Several other criteria of mechanism (some of which are described later) have been applied to the first-order hydrolysis of alkyl halides and, in those cases for which the rate is quite independent of hydroxide-ion concentration, the evidence consistently supports an ionisation mechanism (see *Trans. Faraday Soc.*, 1941, **37**, 611). The demonstration that, while the rate of hydrolysis of some alkyl halides is sensitive to alkali, that of others is insensitive, is, without doubt, highly significant, particularly since rational predictions can be made, on the basis of the concept of the duality of mechanism (as will be shown later), concerning the types of structure which exhibit the different kinds of behaviour.

A detailed consideration of the kinetic form of the substitution reaction may provide further evidence of mechanism, particularly for unimolecular reactions, in the following way (we give here only a brief qualitative outline of the method; for a full account of the quantitative treatment see *J.*, 1940, pp. 960, 979, 1011, 1017). As already stated, in first approximation the unimolecular mechanism leads to first-order kinetics. Deviations of a highly characteristic nature may, however, arise if the rate-determining ionisation is reversible under the conditions employed. In the unimolecular hydrolysis of an appropriate alkyl halide in aqueous solvents, *e.g.*,

$$R{-}Cl \underset{(2)}{\overset{(1)}{\rightleftarrows}} \overset{+}{R} + \overset{-}{Cl} \xrightarrow[(3)]{H_2O} R{-}OH + \overset{+}{H} + \overset{-}{Cl},$$

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* We shall throughout employ the expressions "first order" and "second order" to indicate the type of kinetic equation which a reaction follows: the use of the terms "unimolecular" and "bimolecular" will be confined to the description of reaction mechanisms. There is not always a simple and exclusive correspondence between order and mechanism, and the persistent practice in current literature of interchanging and intermixing the two types of nomenclature as if the corresponding terms were completely synonymous is regrettable and confusing.

† This hypothesis was considered in our early discussions but it was found to be an inadequate explanation of our observations (cf. Hughes and Ingold, *J.*, 1935, 249). It was subsequently revived by other authors in attempts to discredit the concept of the duality of mechanism. To avoid misunderstanding, it should be added that we are, of course, aware that water (and alcohol) molecules may under favourable conditions function as substituting agents in a one-stage process; but in these circumstances reagents such as hydroxide ions act more powerfully.

reaction (2) may become of importance in certain circumstances, particularly towards the end of the hydrolysis when the concentration of chloride ions is reaching its maximum value, and this should exert a characteristic effect—a growing retardation of rate—on the kinetic form of the reaction. This deviation from simple first-order kinetics has been observed, and the disturbance shown to be quantitatively in accord with the requirements of the unimolecular mechanism. The bimolecular mechanism, *e.g.*, a one-stage hydrolysis involving solvent molecules as effective reagents, *viz.*,

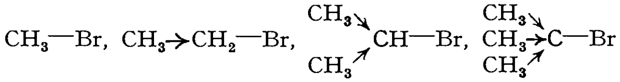
$$R{-}Cl + H_2O \longrightarrow R{-}OH + \overset{+}{H} + \overset{-}{Cl}\ (S_N2),$$

provides for no such retardation, and no effect of this kind has been observed amongst reactions regarded for other reasons as bimolecular. More elaborate, but highly distinctive evidence of mechanism has been derived from the effect of the addition of a " common-ion " salt, whose anion is identical with that formed from the alkyl halide (*e.g.*, the addition of extraneous chloride ions in the hydrolysis of an alkyl chloride) and also of " non-common-ion " salts, whose anions are different.

The effect just described may be referred to as the " mass-law " effect characteristic of the unimolecular mechanism. There is another influence associated with the presence of saline substances, namely, the " ionic-strength " effect.[*] In the hydrolysis of organic halides, the two effects are qualitatively opposite and by suitable choice of salts and experimental conditions both can be assessed quite accurately. Owing to the development of charges in the rate-determining stage of the ionisation of an alkyl halide molecule, the unimolecular mechanism may be expected to have a characteristically large " salt " or " ionic-strength " effect. This too has been observed in the hydrolysis of suitable halides. No effect of the same magnitude is found for those hydrolyses which on other evidence are considered to be bimolecular, neither would it be expected.

(3) *Structural and Environmental Effects.*—In the preceding section, it was shown that, in the hydrolysis of alkyl halides, reaction kinetics consistent with the operation of the two mechanisms previously described (S_N1 and S_N2) have been observed in different cases. The argument in favour of the concept of the duality of mechanisms would be further strengthened if the appearance of the two types of kinetic behaviour could be related in a rational manner with the structure of the reactants and the conditions of reaction. Such relationships have in fact been established. The principal evidence, bearing mainly on the effects of changes in the nature of the reagents and the reaction medium, will now be outlined in illustration of the types of relationships which can be shown to exist (for a full summary see especially *Trans. Faraday Soc.*, 1938, **34**, 187; 1941, **37**, 607).

(3, 1) *Effects Depending on the Nature of* R.—(a) *Polar effects.* If a series of alkyl groups or substituted alkyl groups is placed in order of ability to release electrons to the reaction centre, *e.g.*



$$CH_3{-}Br,\ CH_3{\rightarrow}CH_2{-}Br,\ \begin{array}{l}CH_3\searrow\\ \qquad CH{-}Br,\\ CH_3\nearrow\end{array}\ \begin{array}{l}CH_3\searrow\\ CH_3{\rightarrow}C{-}Br\\ CH_3\nearrow\end{array}$$

it is found that from left to right in the series the rate of hydrolysis in alkaline solution at first diminishes, whilst the kinetics are of the second order; it then passes through a minimum, in the neighbourhood of which we observe a mixture of second- and first-order kinetics, either of which can be brought into prominence by suitable alteration in the concentration of hydroxide ions; finally, the rate rises steeply and the kinetics are those of the first order, the rate being now independent of the hydroxide ions. For hydrolysis with alkali in aqueous alcohol, the critical region of mechanistic change is situated at the *iso*propyl group, but it must be emphasized that the exact location depends on the conditions employed, especially the composition of the medium. The relationship exhibited is of the type to be expected from a change of mechanism near the point of minimum rate. Groups which supply electrons inhibit the approach of the nucleophilic reagent, the presence of which is necessary for reaction by mechanism S_N2 and which has affinity not for electrons but for nuclei, and they facilitate the supply of electrons to the halogen and thus favour the dissociation, which is the rate-determining stage of mechanism S_N1.[†] Steric factors also contribute to the inhibiting effect of α-methyl substituents on the rate of bimolecular substitution, as will be explained below in connection with a more striking example (cf. Meer and Polanyi, *Z. physikal. Chem.*, 1932, *B*, **19**, 164; Hughes and Ingold, *J.*, 1935, 246; Hughes, *Trans. Faraday Soc.*, 1941, **37**, 623; Evans and Polanyi, *Nature*, 1942, **149**, 608, 665; Dostrovsky and Hughes, this vol., p. 157 *et seq.*; Dostrovsky, Hughes, and Ingold, *ibid.*, p. 173).

(b) *Steric effects.* Further evidence is obtained from a study of steric factors. We shall deal with this matter briefly since a recent discussion is available for detailed reference (Dostrovsky, Hughes, and Ingold, *loc. cit.*) and some special aspects of the problem are mentioned later in this lecture. The principle involved is as follows : In the transition state of the bimolecular mechanism, wherein the bond-forming properties of the substituent group are engaged in promoting reaction, five groups are wholly or partly attached by covalency forces to a single carbon atom, a circumstance which may give rise to repulsion between the groups. Reactions taking place by this mechanism may therefore be expected to be very sensitive to steric inhibition by substi-

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[*] The polar substance exerts an influence on the reaction rate which, roughly speaking, may be compared to the effect of changing to a more highly solvating (ionising) medium [cf. sub-section (3, 4)].

[†] Exceptions to the general inhibiting effect of electron-releasing groups on the bimolecular mechanism may occur, *e.g.*, in the neighbourhood of the bimolecular–unimolecular transition region (cf. Hughes, Ingold, and Shapiro, *J.*, 1936, 225) but a difference in the magnitude of the effect on the two mechanisms persists even in these circumstances. In the bimolecular mechanism the effect is a difference, even though the separate terms cannot be associated each exclusively with the formation or rupture of a bond.

tuent groups of appropriate types. Unimolecular reactions on the other hand should never involve the covalent attachment (wholly or partly) of more than four groups to the reactive carbon atom, the additional forces entering in the transition state of the rate-determining stage being of the longer-range electrostatic type associated with solvation; consequently, steric hindrance should be minimised in these reactions.

It is now generally agreed that the most favourable configuration for the transition state of a bimolecular substitution is that in which the entering and leaving groups and the α-carbon atom lie on or near a straight line, the other attached groups being on or near a plane perpendicular to that line. With this model of the transition state as basis, the distances between the centres of the attacking or displaced radicals and the centres of 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. In our recent investigation of the reactions of *neo*pentyl compounds (*e.g.*, $CMe_3 \cdot CH_2Br$), for which a large steric effect can be shown by simple calculation to be involved, it was found that the halides are singularly inert under conditions which lead to second-order kinetics, *i.e.*, when the bimolecular mechanism is evidently operative. Under conditions favourable to the unimolecular mechanism, however, these compounds are moderately reactive. This circumstance makes it possible, under appropriate conditions, to observe a first-order reaction in the hydrolysis of the *neo*pentyl halides in alkaline solution—a result which it is impossible to achieve with other primary halides owing to the incursion of the second-order reaction [cf. sub-section (a) above].

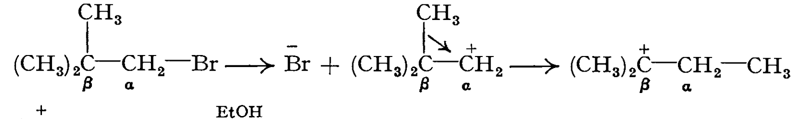
(c) *Effects observed with special forms of* R. Further evidence in support of the concept of the duality of mechanism may be derived from effects observed with special forms of the radical R, particularly effects emerging from an examination of the reaction products under kinetically controlled conditions. We shall discuss two principal cases, namely, (i) those in which R may (if liberated as $\overset{+}{R}$, as in the unimolecular mechanism) undergo rearrangement or participate in some other distinctive product-relationship, (ii) those in which R is asymmetric at the reaction centre, the molecule R—X being optically active.

(i) *Rearrangement effects.* In a qualitative sense, the reaction of an organic halogen compound (or similar structure, *e.g.*, an 'onium cation) with a nucleophilic substituting agent may, in general, be expected to give rise to the same products independently of whether the mechanism is a one-stage bimolecular process or a two-stage unimolecular process involving a preliminary ionisation. Exceptions may, however, arise in the following way : In the bimolecular mechanism the direct attachment of the reagent proceeding synchronously with the expulsion of the replaced group should always give rise to a substitution product in which the group R is the same as in the reactant. When an intermediate carbon cation is formed, however, it may in special cases undergo rearrangement, so that the products formed in a subsequent reaction with the substituting agent may contain a structure which is distinct from that of the reactant. We shall give two examples of the application of this method. In the first there is the possibility of a rearrangement of the Wagner type; in the second an anionotropic change may occur.

The second-order reaction of *neo*pentyl bromide with sodium ethoxide in dry ethyl alcohol gives ethyl *neo*pentyl ether :

$$CMe_3 \cdot CH_2 \cdot Br + EtONa \longrightarrow CMe_3 \cdot CH_2 \cdot OEt + NaBr$$

This is the direct, straightforward substitution of Br by OEt expected in a bimolecular mechanism. The first-order reaction of the same halide in aqueous ethyl alcohol on the other hand gives *tert.*-amyl derivatives (Dostrovsky, Hughes, and Ingold, *loc. cit.*). Whitmore and his co-workers have emphasized that the formation of *tert.*-amyl compounds in some of the reactions of the *neo*pentyl halides is indicative of the transitory formation of the *neo*pentyl cation in these instances (see especially Whitmore, *J. Amer. Chem. Soc.*, 1932, **54**, 3274; Whitmore, Wittle, and Popkin, *ibid.*, 1939, **61**, 1586). The cation rearranges to the *tert.*-amyl structure so that the products, *e.g.*, ethyl *tert.*-amyl ether, formed by reaction with ethyl alcohol, and amylene, formed by internal neutralisation with the loss of a proton, are derived from the *tert.*-amyl structure, *e.g.*,

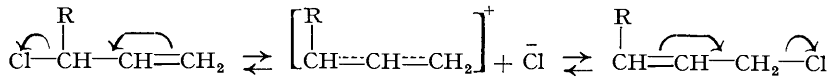


$$(CH_3)_2\overset{CH_3}{\underset{\beta}{C}}-\underset{\alpha}{CH_2}-Br \longrightarrow \bar{Br} + (CH_3)_2\overset{CH_3}{\underset{\beta}{C}}-\underset{\alpha}{\overset{+}{C}H_2} \longrightarrow (CH_3)_2\underset{\beta}{\overset{+}{C}}-\underset{\alpha}{CH_2}-CH_3$$

$$(CH_3)_2\overset{+}{C}-CH_2-CH_3 \xrightarrow{EtOH} (CH_3)_2C(OEt)\cdot CH_2-CH_3 \text{ and } (CH_3)_2C{=}CH-CH_3$$

In the rearrangement the methyl group migrates with its bond electrons, neutralizing the positive charge on the α-carbon atom (with the formation of an ethyl group attached to C_β) and creating a charge on the carbon atom (C_β) from which it leaves, thus forming the *tert.*-amyl cation. This Wagner type of rearrangement can thus be correlated with unimolecular substitution, both processes depending on a rate-determining heterolysis of the R—X bond.

An interesting and useful form of R is one which may give rise to two products which are tautomerides in an anionotropic system. The modern theory of tautomerism supposes that interconversion usually takes place through the formation of an ionic intermediate, *e.g.*,

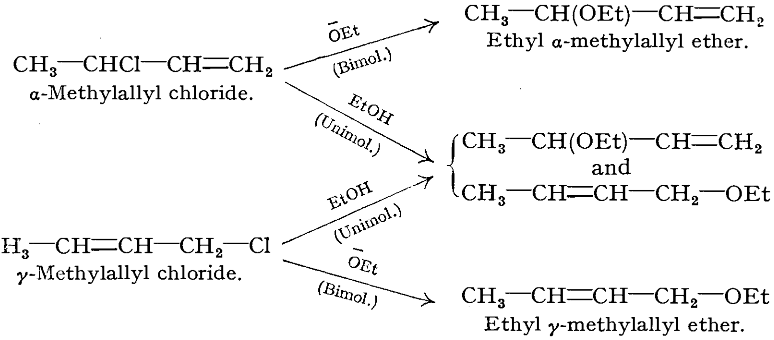


$$Cl-\overset{R}{C}H-CH{=}CH_2 \rightleftarrows \left[\overset{R}{C}H\cdots CH\cdots CH_2\right]^{+} + \bar{Cl} \rightleftarrows \overset{R}{C}H{=}CH-CH_2-Cl$$

Mesomeric ion.

Thus, in the system selected here for illustration, when the halogen is removed as halide ion there is a simultaneous distribution of electrons in the cation and the net positive charge is distributed. The " mesomeric " ion thus formed can then react with a chloride ion to form one or other of the two tautomers.

Now, for α-methylallyl chloride and γ-methylallyl chloride conditions can be found whereby both halides can eliminate halogen by two distinct mechanisms, recognised kinetically as the mechanisms we have designated " bimolecular " and " unimolecular." Under conditions leading to the bimolecular mechanism, the chlorides gave only the corresponding ethers. This is a direct, straightforward replacement and there is no isomerisation because the ion is never formed in the bimolecular mechanism. Under unimolecular conditions, however, both halides gave a mixture of the two possible ethers—a result entirely to be expected from an ionic mechanism :

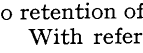


(Catchpole, Hughes, and Ingold, unpublished ; cf. *Trans. Faraday Soc.*, 1941, **37**, 629.*)

Thus theories of substitution, of rearrangement, and of anionotropic change are correlated and strengthened.

(ii) *Stereochemical effects.* Evidence of mechanism may also be obtained in special cases when R is asymmetric at its point of attachment to X, the molecule R—X being optically active. We shall describe the principles here involved only in bare outline, since a fuller discussion of work relating to the steric course of substitution can be given more appropriately in the section dealing with " Applications of General Principles " (below). The method of diagnosis (of mechanism) depends essentially on the circumstance that substitution by the bimolecular mechanism (S_N2) may be expected to lead invariably to inversion of configuration, while the unimolecular mechanism may give rise, depending on structural influences, either to retention of configuration or to racemisation with a predominating inversion.

As mentioned earlier, the most favourable configuration for the transition state of a bimolecular substitution is that in which the entering and leaving groups lie on opposite sides of the α-carbon atom and on or near a straight line passing through its centre. Thus, this mechanism leads invariably to a configurational change in the product, *i.e.*, to a Walden inversion. We shall not attempt to summarise here the theoretical and experimental work which indicates the correctness of this view; it includes a now well-known demonstration involving the use of the radioactive indicator method (Hughes, Topley, and co-workers, *J.*, 1935, 1525; 1936, 1173; 1938, 209) and the conclusion is generally accepted. The consequences of the unimolecular mechanism are not quite so clear-cut, the result depending on the nature of the groups attached to the asymmetric carbon atom, but here again the experimental observation can be satisfactorily interpreted on the basis of the adopted mechanism (S_N1). 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. Partial inversion often accompanies the loss of optical activity and this may be interpreted as an effect of the partial shielding of the cation by the receding anion, which may not be many molecular diameters away when the attack by the enveloping solvation shell or by an anionic reagent completes the substitution process before the ion has had sufficient time to assume a planar configuration. The most striking stereochemical outcome of substitution by a first-order reaction occurs in the presence of a group, such as an α-carboxylate-ion group, which can bind a cationic centre, holding it with a bond of mainly electrostatic character pending solvent attack. During the process of ionisation the charged substituent will be oriented away from the eliminated halide ion (cf. inset) and it will tend to hold the pyramidal configuration thus produced until a new group enters the position which the old one left, thus leading to retention of configuration.



With reference to the direct application of stereochemical data to the problem of establishing duality of mechanism, we shall mention but one set of experimental observations relating to the hydrolysis of the α-bromopropionate ion in alkaline solution. In this case, by suitably changing the experimental conditions, the second- and first-order reactions can be isolated and it is found that while the second-order process leads wholly to inversion, the first-order reaction gives almost quantitative retention (Cowdrey, Hughes, and Ingold, *J.*, 1937, 1208).

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* Similar results have been obtained by Young and his co-workers (*J. Amer. Chem. Soc.*, 1942, **64**, 2157; 1944, **66**, 421).

In the early work on the Walden inversion it was often found that different stereochemical results could be obtained by the use of different reagents, for example, silver oxide and potassium hydroxide in the replacement of halogen by hydroxyl. In fact, this was one of the favourite methods of demonstrating that a Walden inversion had occurred, *e.g.*,

$$l\text{-Chlorosuccinic acid} \begin{cases} \xrightarrow{Ag_2O} l\text{-Malic acid*} \\ \xrightarrow{KOH} d\text{-Malic acid} \end{cases}$$

(Walden, *Ber.*, 1897, **30**, 3146.)

In this example, it is obvious that either moist silver oxide or potassium hydroxide must have produced inversion, but, owing to the difficulty of relating the sign of rotation of the reactants and products to their configuration, it is impossible to say, in the absence of further data, which of the two reagents had this effect. In our experiments, carried out under kinetic control, two stereochemical results were obtained by the use of *one* reagent, namely potassium hydroxide, at different concentrations, these concentrations being such that one mechanism predominates at one extreme of concentrations and another mechanism at the other extreme, and further, since the optical data now refer to definite reaction mechanisms, we have clear indications as to which condition produced inversion and which produced retention of configuration (see also Section B, below). We have here an indication of a point which we shall develop in more detail later, namely, that the key to the apparent mysteries of the Walden inversion is to be found through a study of reaction mechanism (see especially Cowdrey, Hughes, Ingold, Masterman, and Scott, *J.*, 1937, 1252; Hughes, *Trans. Faraday Soc.*, 1938, **34**, 202).

(3, 2) *Variation of* X.—Convincing evidence for the concept of the duality of mechanism has also been obtained by observing the effects of changes in the group replaced (X). Since the transfer of electrons from R to X is a more uniquely fundamental feature of mechanism S_N1, the unimolecular mechanism may be expected to be facilitated relatively to the bimolecular mechanism by high electron affinity in X. Evidence bearing on this point is available. The formation of ethyl bromide from ethyl chloride and bromide ions in acetone solution is of the second order, being of the first order with respect to each of the reactants (Conant and Hussey, *J. Amer. Chem. Soc.*, 1925, **47**, 475). On the other hand, the formation of ethyl bromide from triethylsulphonium bromide (also in acetone as solvent) is a reaction of the first order, the rate being independent of the bromide-ion concentration (von Halban, *Z. physikal. Chem.*, 1909, **67**, 129) : †

$$\overset{-}{Br} + C_2H_5\text{—}Cl \longrightarrow Br\text{—}C_2H_5 + \overset{-}{Cl} \quad \text{(2nd order)}$$

$$\overset{-}{Br} + C_2H_5\text{—}\overset{+}{S}(C_2H_5)_2 \longrightarrow Br\text{—}C_2H_5 + S(C_2H_5)_2 \quad \text{(1st order)}$$

Evidently, the replacement of chlorine by the more powerful electron-attracting sulphonium group has produced a change of mechanism in accordance with expectations based on the particular mechanisms under discussion.

The effects of changes in the group replaced (X) may provide evidence for the duality of mechanism in another way, the method depending on the possible formation of two or more products of reaction, for example, substitution and elimination products (cf. Section B, V). In the unimolecular reactions, the products are formed from the intermediate cation $\overset{+}{R}$, while in bimolecular reactions they are formed directly from the molecule R—X. In first approximation, therefore, the result for unimolecular reactions (for example, the ratio in which the cation is partitioned between substitution and elimination) should be independent of X, while in bimolecular processes (for example, bimolecular substitution and elimination) the nature of the products may vary widely with variation of X. For the first- and second-order substitution and elimination reactions of alkyl halides and alkyl 'onium cations, the observed relationships are of the type predicted. Thus, the percentage of *iso*butylene formed in the first-order substitution and elimination reactions of *tert.*-butyl compounds varies but little when X is changed from Hal. to $\overset{+}{S}Me_2$, but the yield of ethylene obtained in the second-order reactions of ethyl bromide and the triethylsulphonium cation changes from about 1% in the former to about 86% in the latter (Ingold and Kuriyan, *J.*, 1933, 991; Hughes, Ingold, Masterman, and MacNulty, *J.*, 1940, 899; Hughes and Ingold, *Trans. Faraday Soc.*, 1941, **37**, 657).

(3, 3) *Variation of* Y.—The evidence of mechanism derived from observations relating to the nature of Y is similar to the evidence already discussed relating to its concentration. Since the reagent does not function in the rate-determining stage of the unimolecular process but does so in the one-stage bimolecular substitution, the rate of reaction by the unimolecular mechanism (rate of ionisation) should be independent of the nature as well as the concentration of the substituting agent, while in the bimolecular mechanism the rate must depend on the nucleophilic activity of the reagent and on its concentration. Consequently, of course, a reagent of high nucleophilic activity will favour the bimolecular mechanism. These relationships have been observed (Gleave, Hughes, and Ingold, *J.*, 1935, 236; Bateman, Hughes, and Ingold, *J.*, 1940, 1011).

(3, 4) *Solvent Variation.*—Next, we may consider the evidence derived from the observed effects accompanying solvent variation. The heterolytic substitutions with which we are concerned are characterised by important electrical transferences which occur during the course of reaction. The influence of the solvent may

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* Throughout this lecture, the symbols *d* and *l* signify sign of rotation.

† Incidentally, the solvent could not possibly function as the substituting agent in this example [cf. sub-section (2) above] and the kinetic data give unambiguous evidence of mechanism.

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 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 of each mechanism 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 correctly predicted for each of the two mechanisms in various types of reaction. The striking agreement between theory and practice may be regarded as strong evidence that the reaction mechanisms, on which the theoretical expectations are based, are firmly founded and correctly identified with respect to the observed kinetic data (Hughes and Ingold, *J.*, 1935, 252). The method is illustrated below for the reaction between an anion and an alkyl halide molecule.

Solvent Effect in the Replacement (by Anionic Reagents) of Halogen in Alkyl Halides.

	Charges in rate-determining stage of reaction.			Predicted effect of ionising media on rate.
Mechanism.	Reactants.	Transition state.	Products.	
S_N1	R–X	$\overset{\delta+}{R}\cdots\cdots\overset{\delta-}{X}$	$\overset{+}{R} + \overset{-}{X}$	Strong acceleration
S_N2	$\overset{-}{Y} + R–X$	$\overset{\delta-}{Y}\cdots\cdots R\cdots\cdots\overset{\delta-}{X}$	$Y–R + \overset{-}{X}$	Weak retardation

In mechanism S_N1, in the case of this example, a neutral reactant gives rise to an incipient formation of charges in the transition state. In mechanism S_N2, on the other hand, an existing charge in one of the reactants is dispersed in the transition state. A change to a more ionising solvent should therefore greatly facilitate the unimolecular mechanism and slightly retard the bimolecular mechanism. The facts relating to the effect of solvent variation on the rates of the first- and second-order reactions observed in the alkaline hydrolysis of appropriate alkyl halides are wholly consistent with this deduction.

The influence of the solvent in determining the mechanism should be most important in reactions of the type illustrated, in which the direction of the medium effect on rate is different for the two mechanisms. It is in such reactions that a change of kinetic form and mechanism due to a change of solvent was predicted (Hughes and Ingold, *J.*, 1935, 253) and later realised in the case of the metathetical reactions of benzhydryl halides with halide ions, which are of the second order and evidently bimolecular in acetone and of a modified first order in liquid sulphur dioxide—modified, that is, by the mass-law and ionic-strength effects characteristic of the unimolecular mechanism (Bateman, Hughes, and Ingold, *J.*, 1940, 1011, 1017).

The effect of solvent variation has also been used to establish mechanism in a somewhat different way. The method is suitable for application to those reactions ("solvolytic" reactions) in which the solvent is also the reagent. Olson and Halford (*J. Amer. Chem. Soc.*, 1937, **59**, 2644) derived a successful two-term expression for the calculation of reaction rates in binary solvent mixtures (*e.g.*, alcohol and water), namely,

$$\text{Rate} = (k_a p_a + k_w p_w) p_{\text{RX}} \quad . \; . \; . \; . \; . \; . \; . \; . \; . \; . \; . \quad (1)$$

where the subscripts *a*, *w*, and RX denote respectively alcohol, water, and the alkyl halide, the *p*'s represent partial vapour pressures, and the *k*'s are kinetic constants. Independently of mechanism, the two constants k_a and k_w, which can be derived from measurements of the rate of solvolysis at two extremes of solvent composition, will permit calculation of the rate in a mixture of any other composition. If the mechanism is bimolecular, the same two rate-derived constants should allow calculation of the composition of the substitution product, since the product is here determined in a single reaction stage the rate of which is measured. In a mixture of ethyl alcohol and water, for example, we have :

$$\text{R·Cl} + \text{H}_2\text{O} \longrightarrow \text{R·OH} + \text{HCl}, \quad \text{R·Cl} + \text{Et·OH} \longrightarrow \text{R·OEt} + \text{H·Cl}$$

and if the mechanism is of the bimolecular type, we may expect :

$$\text{R·OEt}/(\text{R·OEt} + \text{R·OH}) = k_a p_a/(k_a p_a + k_w p_w).$$

This is found to be the case for the hydrolysis and alcoholysis of *n*-butyl bromide in water–alcohol mixtures, consistently with independently derived conclusions that these reactions are bimolecular (Bird, Hughes, and Ingold, *J.*, 1943, 255). If the mechanism is unimolecular, on the other hand, the measured rates may have no connection with the composition of the product, which is formed in a separate reaction stage. For the solvolysis of *tert.*-butyl chloride in aqueous ethyl alcohol, it has been shown (Bateman, Hughes, and Ingold, *J.*, 1938, 881) that the same pair of constants could *not* be used to calculate both rates and product compositions, consistently with earlier conclusions that the solvolytic reactions of this halide are unimolecular (see also Farinacci and Hammett, *J. Amer. Chem. Soc.*, 1937, **59**, 2544; Bateman, Hughes, and Ingold, *ibid.*, 1938, **60**, 3080; Bartlett, *ibid.*, 1939, **61**, 1630).

It has been suggested (Winstein, *ibid.*, p. 1635) that Olson and Halford's rate formula should be applied on the basis of an assumed one-stage termolecular or quadrimolecular mechanism, involving two or three solvent molecules in the transition state of reaction. It is claimed that this proposal brings rates and product compositions into harmony in the case of *tert.*-butyl chloride. However, the approximate agreement obtained between theory and experiment is of little significance here in view of the latitude which the method allows in the selection of the several additional constants now introduced, and the mechanistic model for the termolecular or quadrimolecular reactions is not impressive (see Bateman, Church, Hughes, Ingold, and Taher, *J.*, 1940, 1008).

B. *Applications of General Principles.*

I. *Introduction and Remarks on Steric Hindrance, the Wagner Rearrangement, and Anionotropy.*—We now proceed to discuss some applications of the general principles, noting instances of experimental investigations and theoretical ideas which have developed as a result of the guidance which may be derived from the study of the kinetics and mechanism of nucleophilic substitution reactions. A full discussion of the applications which have been made in recent years is not possible but we may indicate a few of these in brief outline. It will be appreciated that we have already introduced some important examples, such as those relating to steric hindrance, the Wagner type of rearrangement, anionotropy, and the Walden inversion. In all these instances the key to the situation has been the study of mechanism. With the aid of kinetic data the occurrence or non-occurrence of the phenomena mentioned has been related to mechanism and its determining factors, structure and experimental conditions, with the result that a more rational and precise understanding of these matters has emerged. We surmise, for instance, that in future it may not be quite as fashionable as it was at one period in the past to invoke steric hindrance as an explanation for all the misunderstood eccentricities of chemical substances and their reactions. There is, of course, a proper place, and a very important place, for steric hindrance amongst the effects controlling reactivity, and a start has been made (cf. p. 972) towards a fuller and a more quantitative appreciation of its function in chemical reactions and of its scope and limitations. The new outlook on this question has already led to interesting applications in esterification, ester hydrolysis, and other reactions (see sub-section III below).

Most instances of the Wagner type of rearrangement and of anionotropic changes (p. 973) are related to the unimolecular ionisation mechanism of substitution, but this may be a suitable opportunity for emphasizing another outcome of the kinetic study of nucleophilic substitution reactions, namely, that one and the same reaction may follow different mechanisms in not very drastically altered circumstances.

II. *The Walden Inversion.*—In the example of the Walden inversion two major difficulties have been jointly responsible for the delay in the development of our understanding of the phenomenon. The first was the difficulty, already referred to, of relating the sign of rotation of the reactants and products to their configuration, which made it necessary to carry out two or more reactions in order to demonstrate the occurrence of inversion. Thus the reactions

$$l\text{-Chlorosuccinic acid} \xrightarrow{Ag_2O} l\text{-Malic acid} \xrightarrow{PCl_5} d\text{-Chlorosuccinic acid} \quad . \quad . \quad . \quad . \quad (1)$$

clearly demonstrate the occurrence of inversion (Walden, *Ber.*, 1896, **29**, 133), but it is impossible to specify without further data in which single reaction inversion has occurred, much less how it occurred. Some ingenious methods of identifying an inversion with a particular reaction have been developed in special cases, particularly by Kenyon and his co-workers, but in general this difficulty has been a serious and persistent obstacle (see *Trans. Faraday Soc.*, 1938, **34**, 202). The second difficulty was the following : The conditions which control the steric orientation of substitution must be intimately dependent on the mechanism of substitution, and until recently this had not been fruitfully studied in aliphatic compounds. We shall now attempt to describe briefly how the position has been advanced by kinetic studies.

The statement that the occurrence or non-occurrence of inversion must be closely dependent on mechanism has been amply confirmed. Bimolecular substitution invariably leads to inversion of configuration, as already explained (p. 974), and this result is so definite that it can be used as a means of relating sign of rotation to configuration in reactants and products. The stereochemical consequences of single reactions can then be deduced. For example, in bimolecular hydrolysis with aqueous potassium hydroxide, *l*-chlorosuccinic acid gives *d*-malic acid ; the change of sign of rotation in this reaction therefore indicates inversion, and the retention of sign $(l \longrightarrow l)$, which, under certain conditions, is observed in hydrolysis with moist silver oxide, signifies retention of configuration ; and since an over-all inversion of configuration is involved in the course of the reactions with silver oxide and phosphorus pentachloride [equation (1) above] the inversion can now be assigned to the phosphorus pentachloride reaction (see *J.*, 1937, 1252). Thus, with the aid of further kinetic work on the reactions with silver salts, and so on, it becomes possible to discover the stereochemical consequences of mechanisms other than the bimolecular mechanism, particularly the unimolecular process and the analogous " silver-ion " reaction. In hydrolysis reactions in the presence of silver salts, silver ions facilitate the separation of the halogen, *e.g.*,

$$R{\cdot}Cl + \overset{+}{Ag} \xrightarrow{\text{(slow)}} \overset{+}{R} + Ag{\cdot}Cl \qquad\qquad \overset{+}{R} + H_2O \xrightarrow{\text{(fast)}} R{\cdot}OH + \overset{+}{H}$$

The process is therefore analogous to the unimolecular (S_N1) mechanism of hydrolysis and it is found to have similar stereochemical consequences. In this way, a good start has been made towards a fuller understanding of the problem of the Walden inversion and its broader implications regarding the stereochemical course of reactions generally.

III. *Carboxylic Esterification and Hydrolysis.*—The theory of aliphatic substitution can also be applied to the problem of carboxylic esterification and hydrolysis. The application is very similar in both cases; we shall illustrate it for the case of hydrolysis which is slightly simpler to represent.

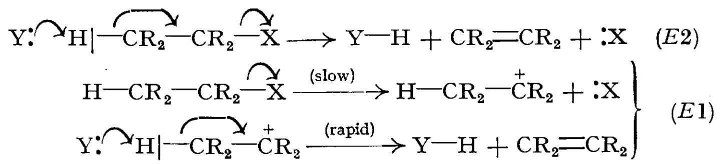
It is necessary in the first place to distinguish between " basic " reactions (*i.e.*, hydrolysis in neutral or alkaline solutions) and " acidic " reactions (*i.e.*, acid-catalysed hydrolysis). In the former the carboxylic entity which suffers reaction is R′·CO·OR, while in the latter it is $(R'{\cdot}CO{\cdot}OHR)^+$. Secondly, there are two distinct modes of bond-fission, namely, " acyl–oxygen fission " and " alkyl–oxygen fission," and, in both basic and acidic reactions, either the one or the other may take place according to circumstances. There are thus four main types of reactions as shown below :

	Basic reactions.	Acidic reactions.
Acyl–oxygen fission......................	R′·CO|—O—R	$(R'{\cdot}CO|{-}OH{-}R)^+$
Alkyl–oxygen fission	R′·CO—O—|R	$(R'{\cdot}CO{-}OH{-}|R)^+$

Finally, for certain of these reactions, two mechanisms exist which are related to each other just like the unimolecular and bimolecular mechanisms of simple nucleophilic substitution (see especially Datta, Day, and Ingold, *J.*, 1939, 838; Hughes, Ingold, and Masterman, *ibid.*, p. 840; Day and Ingold, *Trans. Faraday Soc.*, 1941, **37**, 686). With the recognition of these mechanisms and with full appreciation of their relationship with the substitution processes, it is possible to make rationally-based predictions as to the effect of chemical constitution and physical conditions on the reactions. Thus, to give but one example, it may be expected, and it is found, that here also the bimolecular type of mechanism only is sensitive to steric hindrance.

IV. *Aromatic Substitution.*—In a lecture on substitution some reference should be made to the important question of aromatic replacements. The field is, however, too extensive for a discussion of all the aspects involved, and a brief mention of an application of the principles which form the main theme of this lecture must suffice at this time. In the replacement of hydrogen in the aromatic nucleus, we have normally a clear example of electrophilic substitution, and the attack of the effective reagent appears in this case to be an essential condition for the expulsion of the displaced atom. This does not, however, mean that the kinetics and mechanism are always uniform. In nitration, there is, in special cases, clear evidence of a preliminary, rate-determining stage involving the nitrating agent and not the aromatic compound. We then have the striking result that the rate of nitration is independent of the concentration and of the nature of the aromatic compound, within the boundaries of this particular mechanism. There is evidence that the rate-determining change in the reagent nitric acid is the formation of the nitronium ion, $\overset{+}{NO_2}$, which is expected to be a most effective nitrating agent. The more common result is, of course, that, in addition to a dependence on the nitrating agent, the rate is dependent on the nature and the concentration of the compound undergoing substitution just as in nucleophilic replacements. The special case is reminiscent of the unimolecular ionisation mechanism of nucleophilic substitution, and the knowledge and experience gained in the study of aliphatic replacements has been of considerable assistance in our more recent investigations of the kinetics and mechanism of aromatic substitution (cf. *Nature*, 1945, **156**, 688).

V. *Elimination Reactions.*—The theory has application also to elimination reactions (see especially Hughes and Ingold, *Trans. Faraday Soc.*, 1941, **37**, 657). 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. Employing the nomenclature and schematic representation already explained in connection with nucleophilic substitution, the bimolecular (*E*2) and the unimolecular (*E*1) mechanism of elimination may be illustrated as follows ($Y = \overset{-}{O}H$, $\overset{-}{O}Ac$, NR_3, H_2O, etc.; $X =$ Hal., SO_2R, $\overset{+}{S}R_2$, $\overset{+}{N}R_3$, etc.) :



$$Y{:}\,H|{-}CR_2{-}CR_2{-}X \longrightarrow Y{-}H + CR_2{=}CR_2 + {:}X \qquad (E2)$$

$$\left.\begin{array}{l} H{-}CR_2{-}CR_2{-}X \xrightarrow{\text{(slow)}} H{-}CR_2{-}\overset{+}{C}R_2 + {:}X \\ Y{:}\,H|{-}CR_2{-}\overset{+}{C}R_2 \xrightarrow{\text{(rapid)}} Y{-}H + CR_2{=}CR_2 \end{array}\right\} \quad (E1)$$

With $Y = \overset{-}{O}H$ and $X =$ halogen or $\overset{+}{N}R_3$ we have, for instance, a representation of olefin elimination from alkyl halides and alkylammonium salts in alkaline solution. In the bimolecular reaction, a hydroxide ion or a similar nucleophilic reagent extracts a β-proton with an accompanying separation of X with its bond electrons and the formation of the olefin—the whole process constituting a synchronous mechanism. A new proof of this mechanism, involving the use of deuterium, has recently been obtained by Skell and Hauser (*J. Amer. Chem. Soc.*, 1945, **67**, 1661). During the conversion of α-phenylethyl bromide into styrene with sodium ethoxide in $C_2H_5{\cdot}OD$, it was shown that the unreacted bromide did not accumulate deuterium, indicating that the β-proton and the bromide ion are eliminated simultaneously, as required by the bimolecular mechanism. In unimolecular olefin formation, the rate-determining stage is the same as for unimolecular substitution.

In the elimination reaction the carbon cation loses a β-proton, this eventuality being, in suitable circumstances, concurrent with substitution by the corresponding route. Although the elimination mechanisms are similar to the substitution processes there are important differences with respect to the effects of structural and environmental factors, and a full recognition of the similarities and differences, which is only possible through a detailed study of rates and mechanism, provides valuable information concerning the important reactions of alkyl halides and similar compounds. We shall give one example relating to the reactions of the ethyl, *iso*propyl, and *tert.*-butyl halides with potassium hydroxide in ethyl alcohol. Under these conditions the alcohol or the alkyl ethyl ether may result by substitution reactions and an olefin by the elimination process, *e.g.*,

$$CH_3{-}CR_1R_2{-}Br + R{-}OK \left\{ \begin{array}{l} \longrightarrow CH_3{-}CR_1R_2{-}O{-}R + KBr \\ \longrightarrow CH_2{=}CR_1R_2 + R{-}OH + KBr \end{array} \right.$$

(R_1 and R_2 = H or Me; R = H or Et.)

It is often stated that the action of alcoholic potassium hydroxide on an alkyl halide provides a good general method for the preparation of olefins. Actually, and quite understandably when the reaction mechanisms are considered, success or failure depends very markedly on the structure of the halide and the experimental conditions. Under the most favourable conditions for elimination the ethyl halides give only 1% of ethylene (the main products being substitution products), but the *iso*propyl halides may give up to 80% of propylene, while the *tert.*-butyl halides yield 100% of *iso*butylene, provided special precautions are taken to ensure that the unimolecular mechanism, which is so facile in the last case, does not intervene. If the unimolecular reaction does intervene in the case of the tertiary halide (a circumstance which will arise in this instance if the alkali concentration is low or the alcoholic medium is not sufficiently anhydrous) then *iso*butylene formation is reduced to about 25%, this being the characteristic ratio in which the carbon cation is partitioned between elimination and substitution under these conditions. It naturally follows that for tertiary halides the unimolecular mechanism is a much more profitable proposition when substitution products are required.

VI. *Reactivity as a Function of Mechanism.*—As a final example of the application of the general principles discussed in the first main section we may take one of a general character, and one which can be readily described in outline. We have seen from several examples that even within the comparatively narrow field of nucleophilic substitution the effect of structural factors on the rate of reaction may vary in a marked degree, depending not only on the type of reaction involved but also on the mechanism of the reaction. It is obvious, therefore, that such terms as " reactive " or " unreactive " as ordinarily used in describing the behaviour of organic compounds have little significance unless the processes which are used as the criterion of reactivity are carefully described. Striking examples are encountered when we look beyond the boundaries of nucleophilic replacements to the broader fields of substitution generally. Thus, recent work by Kharasch and others has emphasized the fact that the simple, saturated aliphatic hydrocarbons, which are usually considered to be inert, participate in a number of reactions (*e.g.*, halogenation) under surprisingly mild conditions, provided these conditions are suitably chosen. In these compounds the atom which has to be replaced, namely hydrogen, is quite unsuitable for high nucleophilic reactivity at the carbon centre (reactivity towards $\overset{-}{O}H$, for instance) and they lack the necessary activating influence (for example, a carbonyl group or an aromatic system) which is essential for facile electrophilic substitution of a hydrogen atom, but they are quite vulnerable to attack by atomic substituting agents (*e.g.*, chlorine atoms) which participate in a symmetric or homolytic fission of the C—H bond.

Conclusion.—In conclusion, it may be remarked that the sum total of evidence for the concept of the duality of mechanism in nucleophilic substitution is overwhelmingly strong. A considerable part of the discussion has been devoted to a consideration of the evidence, partly because it has been possible at the same time to indicate some of the principal characteristics and consequences of the mechanisms, but partly also because there is still not a sufficiently general knowledge of the principles of the concept of the duplexity of mechanism, and especially of the importance of ionisation as a mechanism of change—a mechanism which is operative even in cases in which the equilibrium proportion of ions is immeasurably small or inaccessible to measurement. In the section on "Applications of General Principles " we have indicated briefly but a few of the experimental investigations and theoretical concepts which have been assisted in their development by the knowledge and experience gained in the study of the mechanism of nucleophilic replacements. Other instances have been investigated, including examples of homolytic and addition reactions, for which the application of the same methods and principles has proved of value. It is a legitimate hope that the usefulness of the technique is not exhausted and that the study of the kinetics and mechanism of reactions will continue to play an important part in the development of a more comprehensive and, at the same time, a more precise understanding of chemical substances and their reactions.