S 85. *Radioactive Halogens and the Mechanism of Replacement Reactions.*

By E. D. Hughes.

In investigations of the mechanisms of nucleophilic replacement reactions, useful simplifications are introduced by examining " symmetrical " exchanges of the form $\bar{X} + R{-}X \longrightarrow X{-}R + \bar{X}$, and in this connection experiments with radioactive halogens have proved of the greatest value.

For reactions with halide ions, the rates of exchange and of racemisation of optically active organic halides have been compared, and it is concluded that substitution by the bimolecular mechanism (S_N2) is accompanied by inversion of configuration. The application of the result to the general problem of the Walden inversion is considered.

It has been shown that the phenomenon of steric hindrance is associated with the bimolecular mechanism. The exchange rates for common organic halides are discussed in relation to a semi-quantitative theoretical treatment of the effect.

The existence of a one-stage, bimolecular mechanism of rearrangement in anionotropic systems (S_N2') has been demonstrated.

The substitution reactions considered in this paper generally fall into the nucleophilic class (S_N) of heterolytic processes, *e.g.*,

$$Y\!: + R\,\vdots\!{-}X \longrightarrow Y{-}R + :\!X \quad (S_N)$$

the dots representing electrons and the vertical, broken line the position of bond fission. Four types of such changes are possible, the distinction depending on the states of electrification of Y and X (Hughes and Ingold, *J.*, 1935, 244). Our discussion will be mainly concerned with the case where Y is negative and X is neutral. The alkaline hydrolysis of alkyl halides ($Y\!: = \bar{O}H$, X = halogen) is a familiar example of a reaction of this particular form.

It has been shown that there are two distinct mechanisms of nucleophilic substitution (Hughes, Ingold, and co-workers, papers published mainly in this Journal since 1933). The first is a one-stage mechanism, involving a synchronous electron transfer from Y to R and from R to X, *e.g.*,

$$H\bar{O} + R{-}Cl \longrightarrow HO{-}R + \bar{C}l \quad (S_N2)$$

Since both reactants are simultaneously involved, this mechanism is termed " bimolecular." The second mechanism is a two-stage process, wherein a rate-determining fission of R–X is succeeded by a reaction between the carbon cation formed and the substituting agent, *e.g.*,

$$\left.\begin{aligned} R{-}Cl &\xrightarrow{\text{(slow)}} \overset{+}{R} + \bar{C}l \\ H\bar{O} + \overset{+}{R} &\xrightarrow{\text{(rapid)}} HO{-}R \end{aligned}\right\} \quad (S_N1)$$

Although the importance of solvation in ionic dissociation is recognised, this mechanism is termed " unimolecular," because only one reactant, R–X, is undergoing covalency change in the rate-determining stage.

Mechanisms of this type are widespread in organic chemistry and it is important to establish as fully as possible their characteristic properties. For the purpose of investigating the basic features of the mechanisms and their application to special problems, useful simplifications are introduced by examining " symmetrical " exchanges of the form

$$\overset{-}{X} + R\text{–}X \longrightarrow X\text{–}R + \overset{-}{X}$$

and in this connection experiments with radioactive indicators have proved of the greatest value.

First, let us consider the question of the stereo chemistry of a simple replacement reaction at a saturated carbon atom, *e.g.*, CabcX ⟶ CabcY. The early concept of this, namely, the naive assumption that the new substituent (Y) would replace the extruded atom or group (X) directly, *i.e.*, without configurational change, was rudely shaken by the classical work of Walden and others (*Ber.*, 1895, **28**, 1287, and subsequent papers). For the purpose of demonstrating the existence of the phenomenon of the Walden inversion, two main methods have been employed. The first involves the conversion of an optically active compound into its enantiomorph by means of two or more reactions, *e.g.* (Walden, *Ber.*, 1896, **29**, 133):

$$(-)\text{-Chlorosuccinic acid} \xrightarrow[\&\ H_2O]{Ag_2O} (-)\text{-Malic acid} \xrightarrow{PCl_5} (+)\text{-Chlorosuccinic acid}$$

The second method depends on the conversion of an optically active compound into enantiomorphous derivatives by the use of different reagents, *e.g.* (*idem, ibid.*, 1897, **30**, 3146) :

$$(-)\text{-Chlorosuccinic acid} \left\{ \begin{array}{l} \xrightarrow[\&\ H_2O]{Ag_2O} (-)\text{-Malic acid} \\ \xrightarrow{KOH} (+)\text{-Malic acid} \end{array} \right.$$

These and many similar cases clearly establish the occurrence of inversion, but two or more reactions are needed to provide the demonstration; and, because of the difficulty of relating sign of rotation to configuration, it is not possible to decide from such results where the inversion occurred, much less how it occurred. The identification of the configurational change with any one stage in the first method, or with any one reagent in the second, has been the subject of much speculation, mostly unfruitful (for a summary of the literature see especially *J.*, 1937, 1196, and *Trans. Faraday Soc.*, 1938, **34**, 202).

The factors which control the steric orientation of substitution must be dependent on reaction mechanism, and therefore developments in our knowledge of the kinetics and mechanism of replacement reactions were accompanied by advances in our stereochemical concepts : the stereochemical question is but a special feature of the general problem of the exact course of these changes. On the basis of considerations relating to unsymmetrical substitutions, it was suggested that replacement by the one-stage mechanism (S_N2) is invariably accompanied by inversion of configuration, while the two-stage mechanism (S_N1) may give rise, depending on structural influences, either to retention of configuration or to racemisation, possibly with a predominating inversion (Hughes and Ingold, *J.*, 1935, 244; cf. subsequent papers, especially Cowdrey, Hughes, Ingold, Masterman, and Scott, *J.*, 1937, 1252, where full references are given). It was important at this stage of the investigations to obtain conclusive evidence of inversion by the single-stage mechanism (S_N2). If we consider the reaction $\overset{-}{X} + R\text{–}X \longrightarrow X\text{–}R + \overset{-}{X}$, where X is halogen, the rates of bimolecular replacement can be directly determined by the radioactive indicator method. Optically active halides being used, the loss of activity which occurs may then be followed for the same structures under the same conditions, and the rates of replacement can be deduced on the assumption that every individual act of substitution gives inversion. If the rates of replacement calculated by the two methods are identical, the assumption made concerning the stereochemistry of the process must be correct. This test was carried out first in collaboration with Dr. B. Topley and his co-workers. For three structures, chosen to be as representative as possible, *viz.*, *sec.*-octyl iodide, 1-phenylethyl bromide, and α-bromopropionic acid, the results obtained by the two methods (for the reactions with halide ions in acetone at a given temperature) gave identical replacement rates to within the experimental errors (Hughes, Juliusburger, Masterman, Scott, Topley, and Weiss, *J.*, 1935, 1525; 1936, 1173; Cowdrey, Hughes, Nevell, and Wilson, *J.*, 1938, 209). In a detailed investigation referring to the *sec.*-octyl bromide structure at several temperatures, the previous conclusion has been fully substantiated (C. C. Evans, J. Graham, E. D. Hughes, and S. Sugden, unpublished).

For replacement reactions of the general form $Y + R{-}X \longrightarrow Y{-}R + X$, the stereochemical results have been deduced by more complicated means (Hughes, Ingold, and co-workers, *J.*, 1937, 1196 *et seq.*; *J.*, 1940, 1010) and the conclusion that the bimolecular mechanism leads to inversion of configuration has been established generally. 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; the stereochemical consequences of substitution by other reaction mechanisms, particularly the two-stage unimolecular mechanism, may then be deduced from kinetic and optical experiments. In this way, the occurrence or non-occurrence of inversion in the reciprocal replacements of halogen by hydroxyl, and similar substitutions, has been related to reaction mechanism and its determining factors, structure and experimental conditions, and a rational picture of the phenomenon has emerged (see especially Cowdrey, Hughes, Ingold, Masterman, and Scott, *loc. cit.*)

The theoretical basis of the inversion mechanism in bimolecular substitution is considered with the next example.

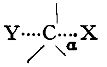
Our second illustration of the use of radiohalogens in studies of reaction mechanisms concerns steric hindrance. The term " steric hindrance " has often been used as an omnibus representation for a variety of phenomena, and a clarification of the position is desirable. The combined factors which have been thus described include ortho-group chelation, specific transmission effects of polar influences from various positions in the aromatic nucleus, and, especially, inhibition of mesomerism effects (cf. *Quart. Reviews*, 1948, **2**, 107). These factors are being studied in researches in progress at University College, London, but initially it was considered desirable to eliminate such special effects. Thus, it was advisable to begin the study in the aliphatic system, and an important feature of the method adopted was to include in the investigation alkyl groups for which steric effects could be considerable while polar factors were minimised by relay through a saturated carbon atom. Here again, our main thesis was that the operation of steric effects must be intimately connected with reaction mechanism (Dostrovsky, Hughes, and Ingold, *J.*, 1946, 173).

The rates of nucleophilic replacement of halogen by the two principal mechanisms were determined for graded series of the type:

$$\mathrm{MeBr,\ CH_2MeBr,\ CH_2Me{\cdot}CH_2Br,\ CHMe_2{\cdot}CH_2Br,\ CMe_3{\cdot}CH_2Br}$$

and, whilst no indication of an appreciable steric factor could be found for the unimolecular mechanism, evidence of considerable effects was obtained for the bimolecular one-stage mechanism, and a relation between the magnitudes of the steric influences and the structural features of the examples was traced. A qualitative theoretical interpretation is not difficult to conceive. In the transition state of the bimolecular mechanism 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. Unimolecular reactions on the other hand never entail the covalent attachment (wholly or partly) of more than four groups to the reactive carbon atom, the additional forces involved in the transition state of the rate-determining ionisation being of the longer-range electrostatic type associated with solvation.

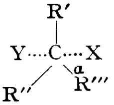
It was clear from these results that further advance lay in the direction of a detailed examination of data for the one-stage mechanism, and a more precise analysis was made in the following way, subsequent measurements with radioactive halogens being a feature of the treatment. In a process occurring through a transition state of the type



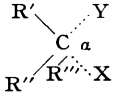
$$Y\cdots C_{\alpha}\cdots X$$

the energies of the links $Y{-}C_\alpha$ and $C_\alpha{-}X$ will be important 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 of comparable order of magnitude to the bonding energy, and in these circumstances steric hindrance may be said to be in operation. It can be shown that non-bonding energies of initial states are usually less important, and that steric factors can generally be estimated in terms of the compression energies between non-bonded atoms in the transition state of reaction. Failure to realise that transition-state models are more important than the familiar molecular models of the organic chemist has been one of the obstacles in the development of precise ideas of steric hindrance.

A more quantitative treatment is then developed along the following lines :



(I.)



(II.)

The linear transition state (I), leading to configurational inversion, will have a smaller energy than states such as (II), which correspond to retention of stereochemical form, mainly because of the small interaction between the electrons of the linearly split bond and those of the full bonds. The most favourable state 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, whilst 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. For atoms or groups attached to C_β an orientation about the C_α–C_β bond is assumed such that the non-bonded internuclear distance which falls furthest below the corresponding van der Waals distance will be a maximum. All single bonds are assumed to have normal length, corresponding to summed covalent radii. The lengths of the bonds Y–C_α and C_α–X are estimated in first approximation by adding the covalent radius of carbon to the mean of the covalent and negative ionic radii of Y or X. If models consisting of an exact straight line and a perpendicular plane are assumed, which is strictly appropriate only for the transition states of symmetrical halogen-exchange reactions involving " trigonally symmetrical " structures of the form R_3CX, the distances (" model distances ") between the nuclei of the entering or displaced atoms and those of the other atoms of the alkyl structures can be calculated. By substracting the " model distances " from the " touching distances," *i.e.*, from the sum of appropriately determined van der Waals radii for the pairs of atoms involved, the " compressions " relating to the transition states are obtained in respect of the model distances which are shorter than the touching distances.

In the first five rows of the following table, we give the compressions (in A.) for the bromine-exchange reaction, $\bar{Br} + R\cdot Br \longrightarrow Br\cdot R + \bar{Br}$, for the pairs of atoms and the alkyl groups shown (Dostrovsky, Hughes, and Ingold, *loc. cit.*). The figures in parentheses are the number of such compressed distances involved in each case :

	Me.	Et.	Pr^n.	Bu^i.	*neo*Pentyl.
H_α --- Br	0·13(6)	0·13(4)	0·13(4)	0·13(4)	0·13(4)
C_β --- Br	—	0·22(2)	0·22(2)	0·22(2)	0·22(2)
H_β --- Br	—	0·58(2)	0·58(2)	0·72(1)	—
C_γ --- Br	—	—	0·0	0·48(1)	1·05(2)
H_γ --- Br	—	—	0·0	0·34(4)	0·98(4)
10^5k_2........................	13,400	165	109	5·9	0·003

It will be observed that appreciable compressions are indicated for all members except methyl, and that the position of *neo*pentyl is particularly striking, this group alone in the series considered being involved in compressions of the order of 1 A. The last row of the table records some experimental results obtained by Dr. P. B. D. de la Mare in unpublished investigations (cf. de la Mare, England, Fowden, Hughes, and Ingold, *J. Chim. physique*, 1948, **45**, 236); k_2 is the second-order rate coefficient (in sec.$^{-1}$ g.-mol.$^{-1}$ l.) for the bromine-exchange reaction at 25°.* It seems clear even at this stage in our analysis that the marked inactivity of the *neo*pentyl halides in bimolecular substitution is to be attributed mainly to the large steric factor associated with this structure.

The next step is that of assessing compressions in terms of energy. This is a difficult development partly because of the imperfections in our knowledge of the laws of force between atoms at small distances. Using a repulsive potential-energy function due to Born and Mayer (*Z. Physik*, 1932, **75**, 1), Dostrovsky, Hughes, and Ingold obtained the following steric energies, E_S (in kcals.), for bimolecular bromine exchange :

	Me.	Et.	Pr^n.	Bu^i.	*neo*Pentyl.
E_S	0·0	0·7	0·7	2·3	11·7
E_R–E_{Me}	0	1·7	1·6	3·1	6·2

---

* In some cases the figures are calculated from experimental results at other temperatures.

In the reactions of methyl halides, the contribution of steric hindrance is negligible, as already indicated. By subtracting the observed activation energy for methyl (in bromine exchange) from those for the other alkyl groups, we obtain differences, E_R–E_{Me} (in kcals.; second row of table), which should contain the steric energy, together with possible polar factors, which are expected to exert but a small contribution to the increase of activation energy from ethyl to *neo*pentyl. The calculated values, E_S, are obtained on the basis of trigonally symmetrical models, assuming no adjustment from the strictly linear configuration described, and they are expected to be rendered too large by this simplification. In the case of the *neo*pentyl group, for example, since two of the valencies of C_α are linked to hydrogen atoms, a considerable reduction of steric energy (due to the *α-tert.*-butyl substituent) may result from a departure from the " straight line and perpendicular plane " configuration, but it is difficult to assess the advantage at present. It may be concluded from the comparisons that theory and experiment indicate a similar variation of steric hindrance energy with structure, and the differences between the calculated and observed figures may well be due largely to the absence in the calculations of any corrections for the bending factor mentioned. Extensions which are in hand are expected to refine the treatment.

A qualitative similarity of steric effects is to be expected of many of the common nucleophilic substitutions involving comparatively simple anionic reagents such as halide or hydroxide ions, for it is found that the calculated compressions are not very sensitive to changes in the size of the entering and displaced atoms (Dostrovsky, Hughes, and Ingold, *loc. cit.*). This is confirmed by extensive experimental results, referring to numerous alkyl structures and various symmetrical and unsymmetrical halogen exchanges, together with other simple nucleophilic replacement reactions, which have lately been carried out (de la Mare *et al.*, *loc. cit.* and unpublished investigations). In the case of larger and more complex radicals, a steric dependence on the nature of the expelled group (*e.g.*, $X = \overset{+}{N}R_3$) and the nucleophilic reagent (*e.g.*, $Y^{:} = NR_3$) is to be expected. These types of replacement reactions are also under investigation in concurrent researches at University College, London.

The third illustration, which we shall give only in outline, of the use of radio-halogens in studies of reaction mechanism in organic chemistry concerns the subject of anionotropic change. There is strong evidence that the main course of this reaction is related to the unimolecular mechanism of simple substitution, ionisation being the rate-determining process (Burton and Ingold, *J.*, 1928, 904; Burton, *ibid.*, p. 1650; 1934, 1268). In this instance a mesomeric cation is formed and recombination with an anion may take place in either of two alternative positions. Clearly, if the anion with which the carbonium ion recombines is of the same kind as that originally eliminated, an isomeric rearrangement may result:

$$\text{R–CHX–CH=CH}_2 \rightleftharpoons \bar{\text{X}} + [\text{R–}\overset{\frown}{\text{CH–CH}}\text{–CH}_2]^+ \rightleftharpoons \text{R–CH=CH–CH}_2\text{–X}$$

However, combination with another anion, $\bar{Y}$, would lead to substitution with or without rearrangement. Therefore, in this mechanism, isomeric rearrangement is to be regarded as a particular case of substitution with rearrangement, and the substitution mechanism itself is a special case of the unimolecular type (S_N1).

For substitution without rearrangement, there is an obvious alternative mechanism, namely, the common one-stage bimolecular mechanism (S_N2); and the point with which we are chiefly interested now is the suggestion (Hughes, *Trans. Faraday Soc.*, 1938, **34**, 185) that there may be a one-stage bimolecular mechanism with rearrangement (S_N2'):

$$\text{R–CHX–CH=CH}_2 + \bar{\text{Y}} \rightleftharpoons \bar{\text{X}} + \text{R–CH=CH–CH}_2\text{–Y} \quad (S_N2')$$

As written, this is a possible mechanism for substitution with rearrangement, but, when $\bar{Y} = \bar{X}$, it is also a feasible mechanism for isomeric rearrangement. Previous attempts to obtain evidence for or against this mechanism have been based mainly on the detection or isolation of substitution products formed with rearrangement (S_N2') in the presence of predominating substitution without rearrangement (S_N2). The fact that, depending on structural factors, both negative and positive evidence for the operation of mechanism S_N2' has, in this way, been obtained in different examples is not, of course, fundamentally inconsistent; the relative importance of mechanisms S_N2 and S_N2', on which the method rests, is expected to vary with structure in an understandable way (see especially, Catchpole, Hughes, and Ingold, *J.*, 1948, 8; Kepner, Winstein, and Young, *J. Amer. Chem. Soc.*, 1949, **71**, 115). The existing data are not, however, wholly convincing.

With the aid of radio-halogens, this question may be conclusively settled. Bimolecular exchange without rearrangement (S_N2) is not a complicating issue in symmetrical substitution (the product of such a reaction being identical for ordinary purposes with the reactant), while bimolecular isomerisation may be investigated directly and compared as to rate with the normal exchange (S_N2) determined by the tracer method. Unpublished work of a preliminary nature by Mr. B. D. England has shown that mechanism S_N2' exists, but it is not sufficiently facile in simple structures to compete successfully with the ordinary bimolecular mechanism of substitution without rearrangement (S_N2) and for most conditions of anionotropic change it is not as important a mechanism of rearrangement as the ionisation mechanism in the halide systems (cf. de la Mare *et al.*, *loc. cit.*).

SIR WILLIAM RAMSAY AND RALPH FORSTER LABORATORIES,
UNIVERSITY COLLEGE, LONDON, W.C.1.

[*Read, April 1st*, 1949.]