

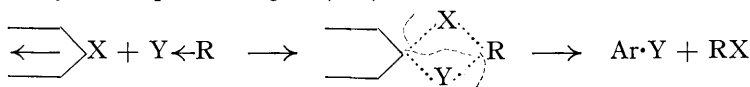
55. Mechanism of Substitution at a Saturated Carbon Atom. Part IV.
*A Discussion of Constitutional and Solvent Effects on the Mechanism,
 Kinetics, Velocity, and Orientation of Substitution.*

By EDWARD D. HUGHES and CHRISTOPHER K. INGOLD.

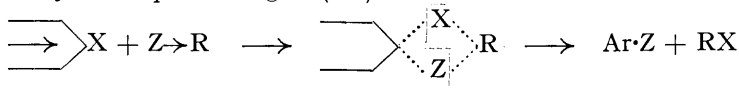
THE theories by which it has been attempted to interpret the mechanism of substitution reactions may be divided into two groups : (1) those which assume primary dissociation into ions or radicals and (2) those which postulate addition as an essential condition for the extrusion of the group replaced.

As regards aromatic substitution, theories of type (2) have an early origin, and their development in electronic schemes such as the following has yielded satisfactory explanation of this range of phenomena (Ingold and Ingold, J., 1926, 1313; Ingold, *Rec. trav. chim.*, 1929, **48**, 797). The schemes illustrated imply a classification of substitutions according to the electrical affinities of the reagents (cf. Ingold, J., 1933, 1121; *Chem. Reviews*, 1934, **15**, 225) :

Substitution by Nucleophilic Reagent (RY) :—



Substitution by Electrophilic Reagent (RZ) :—



It is characteristic of these schemes that although the *orientation* of substitution is a peculiarly aromatic phenomenon, there need be nothing exclusively aromatic in the mechanism of the substitution itself (Ingold and Ingold, *loc. cit.*). It was suggested by Ingold and Rothstein (J., 1928, 1217) that even a saturated aliphatic carbon atom must be capable of forming the partial bonds of substitution complexes quite similar to those illustrated above for aromatic substitution. These authors also recognised two kinds of complex and two corresponding types of substitution depending, as before, on the electrical affinities of the reagent (cf. Ingold and Patel, *J. Indian Chem. Soc.*, 1930, 7, 95). The formation of substitution complexes between ions and neutral molecules has been considered by Meer and Polanyi, who distinguished between substitutions brought about by positive ions and by negative ions (*Z. physikal. Chem.*, 1932, B, 19, 164; cf. Bergmann, Polanyi, and Szabo, *ibid.*, 1933, B, 20, 161; Olson, *J. Chem. Physics*, 1933, 1, 418; Olson and Long, *J. Amer. Chem. Soc.*, 1934, 56, 1294; Olson and Voge, *ibid.*, p. 1690).

All these theories belong to type (2). Olson and Voge have, indeed, objected to some existing theories of type (1) on the grounds that the assumption of primary dissociation would imply much too large a heat of activation. We use in part a form of dissociation hypothesis, and we meet this difficulty by directing attention to the important part played by solvation in ionic dissociations. The very large energy required for the formation of gaseous ions is evidently to be correlated with the circumstance that thermal ionisation does not occur in gases at relatively high temperatures. On the other hand, the spontaneity of ionisation in suitable solutions at the ordinary temperature shows that solvation must reduce both the heat of ionisation and its critical energy by an amount which is of the order of magnitude of the bond strength.

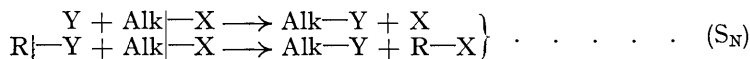
It was assumed by Ingold and Rothstein and by Ingold and Patel (*loc. cit.*) that mechanisms of both types (1) and (2) would be necessary for a complete theory of aliphatic substitution.* The first definite theory on these lines with clearly formulated consequences was advanced in Part I (Hughes, Ingold, and Patel, J., 1933, 526). This theory has been tested in considerable detail for one particular group of substitutions in Parts II and III of this series (Hughes and Ingold, J., 1933, 1571; preceding paper). It is now our object to examine from the same point of view a wider range of those aliphatic substitutions for which the necessary experimental data are available. For this purpose the fundamental considerations must be indicated in a somewhat more general form than heretofore.

The theory has reference to reactions in solution, and postulates octet-preserving electron transfers between the reagent and the seat of substitution, and between the latter and the replaced group. This assumption would not usually be true for homogeneous gas reactions for the reason given above, and there may be exceptions to the general rule even for reactions in solution. Exceptions are likely to arise in substitutions involving odd-electron reagents (*e.g.*, photochemically atomised halogens), or organic radicals in which the resonance energy is near the bond strength. We take the view, however, that special treatment should be accorded to these cases, and that the success of the electron-transfer hypothesis in the theory of aromatic substitution justifies its adoption as a basis for the general consideration of substitution at saturated carbon centres. It is an essential part of this general postulate that electron transfers may have either of two directions determined by the electronic classification of the substituting agent. According as this is nucleophilic (*e.g.*, OH⁻, NR₃) or electrophilic (*e.g.*, HNO₃, Cl₂), the reaction may be termed a "nucleophilic" or "electrophilic" substitution. In each case the reaction may involve the rupture of either one bond or two as shown in the formulæ below; and in each case the entering

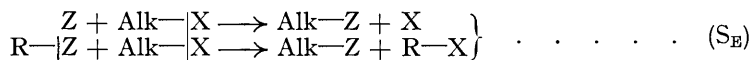
* In Carothers and Berchet's recent discussion of the mechanism of substitutions and rearrangements (*J. Amer. Chem. Soc.*, 1933, 55, 2809), the postulate "that \ddot{R} is a necessary intermediate in the meta-theoretical reactions of RX involving the formation of \ddot{X} " should have been dissociated from the names of Ingold and his collaborators. It is to this demonstrably incorrect supposition that Carothers and Berchet's difficulties are attributable, and not, as they think, to the hypothesis (for which responsibility is accepted) that a β -unsaturated ion \ddot{R} , if formed, will immediately undergo balanced electronic rearrangement.—C. K. I.

and replaced groups may be in various states of electrification as illustrated in the preceding paper and the examples considered later.

Nucleophilic Substitutions.



Electrophilic Substitutions.



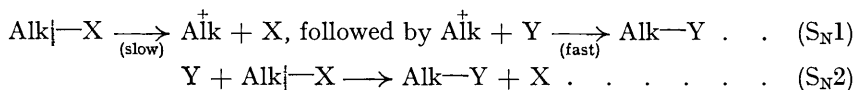
The second main postulate is that mechanisms of types (1) and (2) may operate in both categories of substitution. It is true that in the aromatic case mechanisms of type (1) never appear; but this is because the groups replaced are always held too strongly to undergo primary dissociation even in the most powerfully ionising solvents. In substitution at saturated centres, on the other hand, the more general viewpoint is required.

We envisage, in addition, the operation of steric hindrance, *i.e.*, repulsions due to the interpenetration of the atomic electron clouds at very short distances. Doubtless such effects are quantitatively important although they seldom seem to alter the direction of the broader distinctions such as those discussed in this paper.

We shall apply the theory to the deduction of constitutional effects on the kinetics and velocity of substitutions. The method has been illustrated in the preceding paper for nucleophilic substitutions; for electrophilic substitutions the method is the same in principle, although naturally many of the results are inverted. We shall also consider the deduction of solvent effects on reaction velocity. In all these aspects, attention will be directed to major distinctions of kinetics and speed; regarding small velocity differences it is recognised that there is as yet no exact theory of reaction velocity in solution.

Constitutional Effects in Nucleophilic Substitutions.

Most of the available illustrations relate to substitutions in which only one bond suffers rupture. For such reactions the two mechanisms may be formulated thus:



Reaction (S_N1) is unimolecular if, as is usual, the second stage is fast compared with the first, whereas reaction (S_N2) is bimolecular. Reaction (S_N1) is expected to be favoured relatively to reaction (S_N2) by the following factors: (1) large electron-release from the group Alk, (2) strong electron-affinity in the group X, (3) a sufficiently low nucleophilic activity in the reagent Y, (4) high ionising capacity in the solvent.

The substitutions to which these mechanisms may apply can be classified according to the states of electrification of the group X and reagent Y. There are four categories (*a*, *b*, *c*, and *d*, below).

(*a*) *Group X, Neutral. Reagent Y, Negative.*—Three groups of examples will be considered in relation to the replacement of a halogen atom: (i) hydrolysis, alcoholysis, etc., (ii) other substitutions by anions in reactive solvents, (iii) substitutions by anions in non-reactive solvents.

(i) We may consider first the hydrolysis of alkyl halides by means of alkali hydroxides in aqueous or alcoholic media: $OH' + Alk \cdot Hal \longrightarrow Alk \cdot OH + Hal'$.

The hydrolysis of methyl and ethyl iodides in water, methyl or ethyl alcohol, and various mixtures of these solvents, has been investigated by de Bruyn and Steger (*Rec. trav. chim.*, 1899, **18**, 41, 311), and the hydrolysis of ethyl halides in ethyl alcohol and aqueous ethyl alcohol by Grant and Hinshelwood (*J.*, 1933, 256). All these reactions are bimolecular, and the hydrolysis of ethyl iodide proceeds considerably more slowly than that of methyl iodide in an identical solvent. In the case of ethyl iodide the measured velocity was the total result of a hydrolysis giving ethyl alcohol and an elimination giving

ethylene, reactions which we regard as distinct decompositions of the halide; but even the total rate with the ethyl halide is less than with the methyl halide (*e.g.*, 1/10 for the iodides in 80% aqueous ethyl alcohol). The hydrolysis of *isopropyl* bromide by dilute solutions of alkali hydroxide in 60% aqueous ethyl alcohol has been studied by Hughes (*J. Amer. Chem. Soc.*, in the press): this reaction is unimolecular. The hydrolysis of *tert.*-butyl chloride is described in the following paper (*cf.* Hughes and Ingold, *Nature*, 1933, 132, 933): this reaction is also unimolecular, and is very much more rapid than that of the *isopropyl* compound. Under the conditions chosen for the hydrolysis of the secondary and tertiary compounds there is no disturbance due to olefin elimination. The following relations are thus established for a series of groups, Alk, having progressively increasing powers of electron release :

Mechanism	S_N2	S_N1
Group	$\overbrace{\text{CH}_3 \quad \text{CH}_3 \rightarrow \text{CH}_2}$	$\overbrace{\begin{array}{c} \text{CH}_3 \searrow \text{CH} \quad \text{CH}_3 \searrow \\ \text{CH}_3 \nearrow \quad \quad \quad \text{CH}_3 \nearrow \\ \text{CH}_3 \nearrow \quad \quad \quad \text{CH}_3 \nearrow \end{array} \text{C}}$
Reaction order	2 2	1 1
Velocity	— decrease —>	— increase —>

This is exactly the type of relationship which theory predicts: it is represented in Fig. 1 of Part III.

In attempting to generalise these conclusions, it should be noted that as they stand they apply primarily to strongly ionising solvents: in less strongly ionising media the mechanistic critical point should shift towards the right, so that the *isopropyl* group and even the *tert.*-butyl group could become included in the (S_N2) category. Furthermore, owing to the great loss of intensity accompanying the relay of polar effects through saturated hydrocarbon chains, the higher primary alkyl groups are likely to fall into the same class as ethyl, the higher secondary into the same class as *isopropyl*, and so on. The velocity relation in each class can readily be deduced when the mechanistic category is known. Hence, for normal alkyl groups we expect continuously diminishing differences, provided always that, when the differences really become small, they may show disturbances from factors other than that now considered.

The hydrolysis of alkyl halides by means of alkali hydroxides in anhydrous ethyl alcohol has also been investigated by Lengfeld (*Amer. Chem. J.*, 1889, 11, 40), Wildermann and Aisinmann (*Z. physikal. Chem.*, 1891, 8, 661, and Anderson and Pierce (*J. Physical Chem.*, 1918, 22, 44). The reactions with ethoxide and other alkoxides, also in dry alcohol, have been studied by Steger (*Rec. trav. chim.*, 1899, 18, 13), Hecht, Conrad, and Brückner (*Z. physikal. Chem.*, 1889, 4, 272), and Haywood (*J.*, 1922, 121, 1904; *cf.* Goldsworthy, *J.*, 1926, 1102), whilst the reaction with phenoxide and other aryloxides, again in alcohol, have been examined by Conrad and Brückner (*Z. physikal. Chem.*, 1891, 7, 274), Segaller (*J.*, 1913, 103, 1154, 1421; 1914, 105, 106) and Cox (*J.*, 1918, 113, 666; 1920, 117, 443). These investigations establish for all these reactions the following velocity series for the normal alkyl radicals: Me>>>Et>>Pr^a> higher alkyl groups, the tendency being towards a constant value as the series is ascended. In some cases it is not quite clear to what extent results are affected by olefin elimination, which, in the reaction with hydroxides, is usually more pronounced in anhydrous than in aqueous alcohol. However, Segaller states definitely that, in the reactions of the primary halides with phenoxide, olefins are not produced (his relative rates are: Me 14.66, Et 3.03, Pr^a 1.21, Bu^a 1.15, Am^a 0.49, Hex^a 1.08, Hept^a 1.05, Oct^a 1.01, Cetyl 1.00).

The formation of olefins from halides and alkali hydroxides in anhydrous alcohol was investigated by Brussoff (*Z. physikal. Chem.*, 1900, 34, 129), who showed that, whilst it was a minor reaction of primary halides, it was the chief mode of decomposition of secondary and tertiary halides. Most of the authors mentioned in the previous paragraph do not consider the possibility of olefin elimination, but Segaller failed to detect this in his study of the reactions between secondary halides and phenoxide. His results suggest that in the dry alcoholic solvent the secondary alkyl compounds may have passed into the (S_N2)

class, or at least reached the border line : a bimolecular formula appears to fit the results, and the velocity differences obtained for homologous secondary groups are small and somewhat irregular (all within 20% of each other from *isopropyl* to *sec.-β-octyl iodide*). On the other hand, the apparent absence of olefin elimination is rather remarkable, because in Brussoff's experiments secondary alkyl halides gave more olefins than tertiary, and Segaller observed the formation of olefins in the reactions of tertiary halides with phenoxide. Hughes's results certainly suggest that, had Segaller's solutions been more dilute (to reduce the incidence of bimolecular reactions) or the solvent more ionising, a unimolecular substitution would have been observed; and this inference is supported by the analogy of benzyl chloride, the alkaline hydrolysis and alcoholysis of which had always been described as bimolecular prior to careful investigation by Olivier (see below). Lengfeld's results also confirm the above suggestion : he measured only the percentage of reaction after a fixed time, but his values show that the hydrolyses of primary bromides are much more strongly accelerated by alkalis than are the hydrolyses of secondary bromides.

Concerning tertiary alkyl halides, both Lengfeld's and Segaller's results prove that these are much more reactive than any other simple alkyl halide. Segaller tabulated a bimolecular velocity coefficient for the phenolysis of *tert.-butyl chloride*, but the values show a marked upward drift, and a unimolecular coefficient, calculated from his data, exhibits an approximately equal downward drift. Segaller observed the formation of *isobutylene*, and the assumption that a unimolecular substitution was accompanied by a bimolecular elimination gives a satisfactory interpretation of his data.

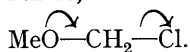
The application of the theory to the araliphyl series, $\cdot\text{CH}_3$, $\cdot\text{CH}_2\text{Ph}$, $\cdot\text{CHPh}_2$, $\cdot\text{CPh}_3$, was given by Hughes, Ingold, and Patel (*loc. cit.*) : on traversing this series towards the right, there should be a point at which the mechanism changes in the sense $(S_N2) \rightarrow (S_N1)$, after which the velocity should increase rapidly with increasing electron release.

We know that, for the reaction between halides and hydroxide ions in aqueous solvents, methyl falls into the (S_N2) class. The hydrolysis of benzyl chloride in water and aqueous acetone has recently been investigated by Olivier and Weber (*Rec. trav. chim.*, 1934, **53**, 869; Olivier, *ibid.*, p. 891). This work proves that the benzyl group is on the (S_N2) — (S_N1) border-line : the observed kinetics corresponds to no simple type, but can be approximated as the sum of two reactions of comparable speed, one independent of the reagent hydroxide and one proportional to its concentration (we regard the real mechanism as of intermediate type). The hydrolysis of benzhydryl chloride by means of alkali hydroxide in aqueous alcohol has been studied by Ward (J., 1927, 2285). This reaction proceeds in unimolecular fashion independently of the reagent hydroxide : the group $\cdot\text{CHPh}_2$ belongs definitely to the (S_N1) category.

Reference should be made to Norris and Morton's experiments on the effect of nuclear substituents on the unimolecular alcoholysis of benzhydryl chlorides (*J. Amer. Chem. Soc.*, 1928, **50**, 1795), but detailed discussion may be postponed, as the discovery that secondary halides generally belong to the (S_N1) class has shown that compounds of the type $\text{Ar}\cdot\text{CHRHal}$ ($\text{R} = \text{Me}$, etc.) form an even simpler example for a study, which will be reported later, of the effects of nuclear substituents on reactions of this class.

Benzal chloride and benzotrichloride have been shown to belong to the (S_N1) class (Olivier and Weber, *loc. cit.*). Here, however, we do not emphasise the "secondary" or "tertiary" character of the halides because the mechanism of the electron-release

necessary for ionisation is different : $\text{Cl}-\overset{\curvearrowright}{\text{C}}-\overset{\curvearrowright}{\text{C}}-\text{Cl}$; it depends on the possession of unshared electrons by the facilitating substituent, and we think it probable that even the "primary" halide, monochloromethyl ether, will also be found to belong to the (S_N1) category :



In contrast to these cases, the presence of a halogen substituent in a position other than the site of the replacement facilitates reaction by mechanism (S_N2) . This may be illustrated by Tronov and Gersevich's measurements of the velocity of the reaction between sodium methoxide and some polybromoparaffins (*J. Russ. Phys. Chem. Soc.*, 1927, **59**, 727) (relative rates : Pr^aBr , 5; Pr^bBr , 1; $\text{CH}_2\text{Br}\cdot\text{CH}_2\cdot\text{CH}_2\text{Br}$, 12; $\text{CH}_3\cdot\text{CHBr}\cdot\text{CH}_2\text{Br}$, 33;

$\text{CH}_2\text{Br}\cdot\text{CHBr}\cdot\text{CH}_2\text{Br}$, 2450). The mechanism mentioned in the previous paragraph for the electron-release which in those cases assists a primary ionisation is here unavailable, and the ordinary electron-attracting effect of halogens, which alone is now able to operate, inhibits mechanism ($\text{S}_{\text{N}}1$) and facilitates ($\text{S}_{\text{N}}2$). The effect is in direct contrast, as it should be, to that of electron-repelling alkyl substituents.

Thus the available data relating to both the kinetic type and the reaction velocity of hydrolysis and similar substitutions of alkyl halides have an unforced and unequivocal interpretation on the basis of the postulates set out above.

It is sometimes assumed that unimolecular hydrolysis is really a bimolecular reaction, occurring in a single stage, between the alkyl halide and a water molecule. However, when a water molecule does act as a direct reagent, it functions either as a base (example: hydrolysis of nitroamide), or as an acid (example: hydrolysis of acetals), or as both (example: hydrolysis of carboxylic esters), and then either the very strong base $\bar{\text{O}}\text{H}$ (Brönsted's nomenclature), or the very strong acid $\text{H}_3\bar{\text{O}}^+$, or both, as the case may be, act much more powerfully. This does not happen in the hydrolysis of *tert.*-butyl chloride, which is quite insensitive to both hydroxide and hydrogen ions. It is indeed necessary to recognise four distinct modes of action of water, which may behave (1) as solvent alone, (2) as solvent and base, (3) as solvent and acid, and (4) as solvent, base, and acid. These four modes may be distinguished experimentally by the criterion mentioned, and the hydrolysis of *tert.*-butyl chloride is found in category (1).

(ii) Two substitutions by anions in hydroxylic solvents will be referred to in this section. The first is the reaction between alkali thiosulphates and alkyl halides in water or aqueous alcohol (Slator, J., 1904, **85**, 1286; 1905, **87**, 482; Slator and Twiss, J., 1909, **95**, 93): $\text{S}_2\text{O}_3'' + \text{Alk}\cdot\text{Hal} \longrightarrow \text{Alk}\cdot\text{S}_2\text{O}_3' + \text{Hal}'$. The second is that between ethyl sodioacetate and alkyl halides in absolute ethyl alcohol (Wislicenus, *Annalen*, 1882, **212**, 232): $\bar{\text{C}}\text{HAc}\cdot\text{CO}_2\text{Et} + \text{Alk}\cdot\text{Hal} \longrightarrow \text{Alk}\cdot\bar{\text{C}}\text{HAc}\cdot\text{CO}_2\text{Et} + \text{Hal}$.

Now it is inherent in all the reactions considered in section (i) that although, according to theory, each of the mechanisms ($\text{S}_{\text{N}}2$) and ($\text{S}_{\text{N}}1$) must exist throughout a series such as Me, Et, Pr^β , Bu^γ , only one mechanism can be observed on each side of the critical point: it is impossible to trace the broken parts of the curves in Fig. 1 of Part III. The interest of the two reactions just cited is that they are of a type for which it should be possible to trace mechanism ($\text{S}_{\text{N}}2$) into the region in which it is the minor reaction. For mechanism ($\text{S}_{\text{N}}1$), if present, would not normally be observed: the carbon cation produced by a primary ionisation would react much more often with the solvent than with the ionic reagent, and the result would be a hydrolysis or alcoholysis having only an indirect effect on the consumption of this reagent. Slator established the velocity series $\text{Me} > \text{Et} > \text{Pr}^\beta$, and Wislicenus the series $\text{Me} > \text{Et} > \text{Pr}^\beta > \text{Bu}^\gamma$, the velocity for the group Bu^γ being zero. We see here a continuous fall of velocity, as mechanism ($\text{S}_{\text{N}}2$) requires, in contrast to the passage through a minimum illustrated in the reaction of section (i).

(iii) The main example to be considered in this section is the reaction between halide ions and alkyl halides in acetone as solvent: $\text{I}' + \text{Alk}\cdot\text{Cl} \longrightarrow \text{Alk}\cdot\text{I} + \text{Cl}'$. This has been studied for a large number of simple alkyl halides by Conant and Hussey (*J. Amer. Chem. Soc.*, 1925, **47**, 475), who established the following velocity series: *primary* > *secondary* ~ *tertiary*. Concerning primary chlorides, they observed the series $\text{Et} > \text{Pr}^\alpha \sim$ higher primary groups, which amongst themselves showed small irregular variations (Me was not examined). Amongst homologous secondary chlorides the differences, although rather larger, exhibited no regular trend. The two tertiary chlorides examined showed only a small difference. In all cases they recorded bimolecular velocity coefficients, but their evidence that the reactions have this order, although quite definite in the case of the primary compounds, is weak for the secondary, and non-existent for the tertiary derivatives, owing to the shortness of the ranges over which the latter reactions were traced.

Our interpretation of the results is as follows. The series *primary* > *secondary* ~ *tertiary* shows indirectly that the reactions of both the primary and the secondary chlorides belong to the ($\text{S}_{\text{N}}2$) class, whilst those of the tertiary chlorides are either on the ($\text{S}_{\text{N}}2$)-

(S_N1) border-line or only just beyond it. The assumed dominance of mechanism (S_N2) in the primary series is consistent with the strong facilitating effects of electron-attracting substituents such as carboxy and benzoyl (Conant and Kirner, *ibid.*, 1924, **46**, 235; cf. Conant, Kirner, and Hussey, *ibid.*, 1925, **47**, 448; Bennett and Berry, J., 1927, 1676). The implied displacement of the mechanistic critical point from the position in the alkyl series in which we found it for the reactions occurring in aqueous solvents is attributed entirely to the employment in this instance of the feebly ionising solvent acetone: we think it almost certain that had the substitutions been conducted in a better ionising solvent, such as sulphur dioxide, the tertiary chlorides, and perhaps the secondary ones also, would have shown unimolecular dynamics, and the rates for the former would have been much greater than for the latter.

Lateral evidence in favour of this view is afforded by Bergmann and Polanyi's observations on the racemisation of α -chloroethylbenzene in liquid sulphur dioxide, alone and in the presence of extraneous chloride ions (*Naturwiss.*, 1933, **21**, 378). This is a reaction of the type formulated above, except that iodide ions are now replaced by chloride ions; furthermore, the alkyl group is secondary, so that the halide belongs to the general class of those which have been shown to exhibit unimolecular hydrolysis (Ward, J., 1927, 445). The racemisation in sulphur dioxide was indeed unimolecular, its speed being unaffected by the addition of the extraneous chloride ion. As a contrast, reference may be made to Bergmann, Polanyi, and Szabo's experiments (*loc. cit.*) on the racemisation of *sec.*- β -amyl and *sec.*- β -hexyl iodides by means of iodide ions in acetone: these racemisations were bimolecular, in agreement with what we have assumed concerning the reactions in this solvent of the secondary halides studied by Conant and Hussey.

(b) *Group X, Neutral. Reagent Y, Neutral.*—The substitutions falling within this category are those which lead to the formation of "onium" salts, e.g., NR₃ + Alk·Hal \longrightarrow Alk·NR₃⁺ + Hal⁻. The reaction between alkyl halides and triethylamine has been studied by Menschutkin (*Z. physikal. Chem.*, 1890, **5**, 589). Using acetone and benzene as solvents, he established the velocity series Me >> Et >> Pr ^{β} and Et > Pr ^{α} ~ higher primary groups, for which the values tended to a constant (relative rates: Me 100, Et 8.8, Pr ^{β} 0.18; and Et 8.8, Pr ^{α} 1.7, Bu ^{α} 1.2, Hept ^{α} 0.9, Oct ^{α} 0.9). The reactions were bimolecular. The investigation of Bu ^{γ} was frustrated by olefin elimination, and it is not impossible that part of the measured velocity for Pr ^{β} may have been due to the same cause (cf. Reboul, *Compt. rend.*, 1881, **93**, 69). The relation Me >> Et > Pr ^{α} has been confirmed by Preston and Jones for the reaction of alkyl iodides with dimethylaniline and triisooamylamine in absolute ethyl alcohol (J., 1912, **101**, 1930). Having regard to the character of the solvents employed, the above results are consistent with expectation, but the reaction obviously requires investigation (and we propose to make one) in more strongly ionising solvents.

A remark may be interpolated here which applies to the reactions of both sections (a) and (b). The vinyl halides (and phenyl halides are similar) contain a *mesomeric* system

$\overset{\curvearrowright}{\text{C}}=\overset{\curvearrowleft}{\text{C}}-\text{Hal}$ which must strongly inhibit mechanism (S_N1) and also must oppose mechanism (S_N2), since it makes the halogen atom considerably less negative and renders the α -carbon atom more negative, although to a smaller extent. Actually, substitutions never occur by mechanism (S_N1) and only with difficulty by mechanism (S_N2). On the other hand, allyl halides (and benzyl halides are similar) have the possibility of *electromeric* polarisation

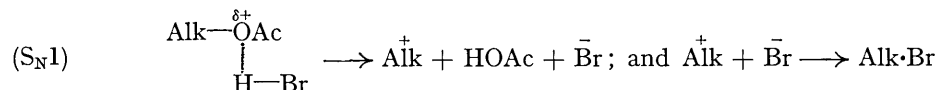
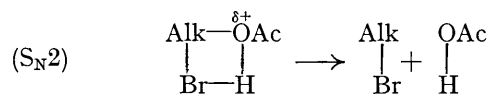
of two types, one, $\overset{\curvearrowright}{\text{C}}=\overset{\curvearrowleft}{\text{C}}-\overset{\curvearrowright}{\text{C}}-\text{Hal}$, which assists mechanism (S_N1), and the other, $\overset{\curvearrowright}{\text{C}}=\overset{\curvearrowleft}{\text{C}}\leftarrow\text{C}-\text{Hal}$, which facilitates mechanism (S_N2), although to a smaller extent. Hence under *all* conditions such halides are highly reactive in nucleophilic substitutions. The literature already cited contains numerous instances of these generalisations (cf. also Juvala, *Ber.*, 1930, **63**, 1989).

(c) *Group X, Positive. Reagent Y, Negative.*—Substitutions of this class are encountered in the degradations of "onium salts," e.g., OH⁻ + Alk·SR₂ \longrightarrow Alk·OH + SR₂⁻. They are the reactions by which the theory has already been illustrated in Parts I, II, and III (*loc. cit.*). Accordingly, discussion in this section will be confined to those reactions in

which the ejected group acquires its positive charge through the action of the reagent itself.

The groups $\cdot\text{OR}$ and $\cdot\text{NR}_2$ are typically cationogenic, and their ease of separation from carbon in reactions involving electron transfers in solution is given by the sequence $(\text{F} <) \text{OR} < \text{NR}_2$. We shall express the charged modifications, the electron-attraction of which assists replacement, by the formulæ $\cdot\overset{+}{\text{OHR}}$ and $\cdot\overset{+}{\text{NHR}}_2$, although the absence hitherto of identified Raman lines for the entity $\text{H}_3\overset{+}{\text{O}}$ suggests that this conception may have to be partly replaced by that of a formally neutral group deriving its positive charge from a protonic atmosphere.

The fission of alkyl acetates by means of hydrogen bromide in glacial acetic acid has been studied by Tronov and Sibgatullin (*Ber.*, 1929, **62**, 2850). The products are the alkyl bromide and acetic acid, and having regard to the character of the solvent and the known mechanism of the hydrolysis of esters by hydrogen ions, it seems clear that the substitution is of the type for which two links have to suffer fission. The mechanisms ($\text{S}_{\text{N}}2$) and ($\text{S}_{\text{N}}1$) must be formulated thus :



Tronov and Sibgatullin have established a velocity minimum in the series $\text{Me} > \text{Et} \sim \text{Pr}^\beta < < \text{Bu}^\gamma$ (relative rates: 65, 11, 11, 2×10^6), and have shown that amongst primary groups the speed is decreased by increased chain length and by branching (relative rates: Et 11, Pr^α 9, Bu^α 6, Hex $^\alpha$ 7; *iso*amyl 5; *iso*butyl 1). Our interpretation is that methyl and primary esters use mechanism ($\text{S}_{\text{N}}2$) only, that secondary esters employ both mechanisms, and tertiary esters mechanism ($\text{S}_{\text{N}}1$) only, in their reactions with hydrogen bromide. A closely similar view may be applied to the fission of ethers by means of hydrogen bromide in acetic acid (above equations with Ac replaced by Ph, etc.), for which Tronov and Ladigina have established a minimum velocity in the series $\text{Me} > \text{Et} < \text{Pr}^\beta < < \text{Bu}^\gamma$, and a velocity diminishing with ascent of the primary series (*Ber.*, 1929, **62**, 2844). Yet another analogous reaction is the conversion of alcohols into alkyl chlorides by the action of hydrogen chloride in benzene (above equations with Ac replaced by H, and Br by Cl), for which Petrenko-Kritschenko, who did not examine methyl chloride, found the series *primary* < *secondary* < *tertiary* (*Z. physikal. Chem.*, 1925, **115**, 289; cf. also Norris, Watt, and Thomas, *J. Amer. Chem. Soc.*, 1916, **38**, 1071). The acid hydrolysis of acetals (Skrabal, Schifferer, and Mirtl, *Z. physikal. Chem.*, 1921, **99**, 290; 1924, **111**, 98) provides an example of ionic fission promoted by electromeric polarisations of the type already illustrated in relation to the hydrolysis of benzal and benzotri-chloride: $\text{RO}-\overset{\curvearrowright}{\text{C}}\text{H}_2-\overset{+}{\text{OHR}}$.

The C-N bond is less vulnerable, and examples of its fission by a substitution reaction in amines are scarce. Kharasch and Howard, however, have shown that triphenyl-methylamine is hydrolysed by acids (*J. Amer. Chem. Soc.*, 1934, **56**, 1374), and they could not observe a similar reaction with other amines; the triphenylmethyl group is the most favourable in our alkyl series for the observation of mechanism ($\text{S}_{\text{N}}1$). Hickinbottom has stated that *tert.*-butylaniline is hydrolysed by aqueous acids to *tert.*-butyl alcohol (*J.*, 1934, 1702) although the reason for assuming the production of this rather than of *iso*-butylene is not clear. We should regard this hydrolysis also, if confirmed, as an exemplification of the principles developed in these papers.

(d) *Group X, Positive. Reagent Y, Neutral.*—Substitutions of this type, which may be illustrated by the equation $\text{NR}_3 + \text{Alk}\cdot\overset{\cdot}{\text{S}}\text{R}_2 \longrightarrow \text{Alk}\cdot\overset{\cdot}{\text{N}}\text{R}_3 + \text{SR}_2$, have not yet been discovered, but we include them for the sake of completeness, and because theory not only

shows that they must exist, but also predicts in considerable detail the kinetic phenomena with which they will be found to be associated.

The remarks at the conclusion of section (b) concerning allyl and similar groups apply equally to the reactions of sections (c) and (d), and numerous confirmatory examples are to be found in the literature cited in section (c). On the other hand, the remarks relating to vinyl and similar groups have no application in sections (c) and (d) for obvious reasons.

Solvent Effects in Nucleophilic Substitutions.

The views expressed above may readily be developed to yield a theory of solvent action which probably has considerable generality, although we shall illustrate it by reference to nucleophilic substitutions, restricting the treatment for simplicity to those substitutions in which only one bond is broken and only one is formed.

In mechanism (S_N1) the speed is determined by an ionisation, and this implies the existence of a critical energy of ionisation. A condition which would lead to such a critical energy is that, beyond a certain degree of extension of the polarised link, the increasing solvation due to the separating electric charges contributes a fall of energy which is more rapid than the rise that would have occurred in the absence of solvation; this condition satisfied, a slow ionisation results. With full recognition of the circumstance that the process of separation is continuous, the degree of extension referred to may be said to characterise a "critical complex." For a bimolecular process, such as mechanism (S_N2) implies, the conception of a critical complex is now a commonplace. It is obvious that for either mechanism the reduction of the energy of activation by a given solvent is equal to the reduction of the energy of the critical complex, *minus* the reduction of the energy of the factors (cf. Polanyi, *Z. Elektrochem.*, 1929, **35**, 561).

We now introduce the following plausible assumptions concerning the degree of solvation arising in any given solvent from the presence of electric charges: (i) solvation will increase with the magnitude of the charge; (ii) solvation will decrease with increasing distribution of a given charge. We have then only to consider the magnitude and distribution of the charges in the "critical complex" in relation to those in the factors, in order to deduce the effect of solvation on the energy of activation and the velocity; and, whatever the direction of the effect may be, its magnitude will be greater in strongly solvating (ionising) than in feebly solvating solvents.

The following table illustrates the deduction by this method of the directions of the solvent effects to be expected for the types of nucleophilic substitution considered under the headings (a), (b), and (c) in the previous section. Similar deductions could easily be made for the undiscovered reactions of class (d). We may anticipate that effects on velocity due to the dispersal in the critical complex of a given charge are likely to be less than the effects caused by the creation or disappearance of charges.

Type and mechanism.	Charges concerned in rate-determining stage of reaction.			Effect on charges of forming complex.		Expected effect of ionising media.
	Factors.	Complex.	Products.	Magnitude.	Distribn.	
1. (a) (S_N1)	RX	$\overset{\delta+}{R} \dots \overset{\delta-}{X}$	$\overset{+}{R} + \overset{-}{X}$	Increase	—	Accelerate
2. (S_N2)	$\bar{Y} + RX$	$\overset{\delta-}{Y} \dots R \dots \overset{\delta-}{X}$	$YR + \bar{X}$	No change	Dispersed	Retard
3. (b) (S_N1)	RX	$\overset{\delta+}{R} \dots \overset{\delta-}{X}$	$\overset{+}{R} + \overset{-}{X}$	Increase	—	Accelerate
4. (S_N2)	$Y + RX$	$\overset{\delta+}{Y} \dots R \dots \overset{\delta-}{X}$	$\overset{+}{Y}R + \overset{-}{X}$	Increase	—	Accelerate
5. (c) (S_N1)	$R\bar{X}$	$\overset{\delta+}{R} \dots \overset{\delta+}{X}$	$\overset{+}{R} + X$	No change	Dispersed	Retard
6. (S_N2)	$\bar{Y} + R\bar{X}$	$\overset{\delta-}{Y} \dots R \dots \overset{\delta+}{X}$	$YR + X$	Decrease	—	Retard

Five of these deductions can be tested by reference to the literature: all are correct. Hughes has shown (following paper) that the rate of hydrolysis of *tert.*-butyl chloride (a, 1) is increased on increasing the proportion of water in an aqueous alcoholic solvent. De Bruyn and Steger (*loc. cit.*) proved that the speeds of hydrolysis of methyl and ethyl iodides (a, 2) are decreased on increasing the proportion of water in aqueous alcohol;

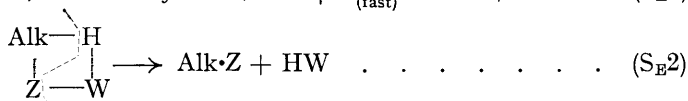
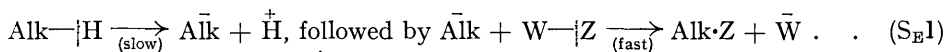
and furthermore, Bergmann, Polanyi, and Szabo (*loc. cit.*) found the rate of racemisation of secondary iodides in acetone (*a*, 2) to be decreased on addition of a small proportion of water. Menschutkin (*loc. cit.*) found the combination of ethyl iodide with triethylamine (*b*, 4) to proceed more rapidly in alcohols than in hydrocarbons (*e.g.*, MeOH > EtOH > Me₂CO > C₆H₆ > C₆H₁₄), and the same general sequence has been confirmed for other primary alkyl, or methyl, halides and other amines, or sulphides (*b*, 4), by a number of subsequent investigators (Carrera, *Gazzetta*, 1894, **24**, i, 180; Hemptinne and Bekaert, *Z. physikal. Chem.*, 1899, **28**, 225; von Halban, *ibid.*, 1913, **84**, 128; Cox, J., 1921, **119**, 142; Hawkins, J., 1922, **121**, 1170; Muchin, Ginsberg, and Moissejera, *Ukraine Chem. J.*, 1926, **2**, 136; McCombie, Scarborough, and Smith, J., 1927, 802; Essex and Gelormini, *J. Amer. Chem. Soc.*, 1926, **48**, 882). Von Halban proved (*Z. physikal. Chem.*, 1909, **67**, 29) that the decomposition of triethylsulphonium iodide (*c*, 5) takes place more slowly in alcohols than in acetone, and we have shown (Part II, *loc. cit.*) that the rate of hydrolysis of the dimethyl-*tert.*-butylsulphonium cation (*c*, 5) is decreased on increasing the proportion of water in an aqueous alcoholic solvent. Finally, we have found with Gleave (Part III) that the speed of hydrolysis of the trimethylsulphonium cation (*c*, 6) is also decreased by the same change of solvent.

Reference has already been made (cf. also Hughes, *J. Amer. Chem. Soc.*, in the press) to the possibility of changing even the order of a reaction by changing the solvent. A radical alteration such as this is likely to be realised most easily in reactions, such as those of class (*a*), in which not only the magnitude but also the direction of the solvent effect on velocity is different for the two possible mechanisms. For this group of reactions, more extensively ionising solvents should favour the change (S_N2) → (S_N1). Very recently an alteration of this type has been observed by Olivier (*loc. cit.*), who found that the hydrolysis of benzyl chloride, which in 50% acetone is approximately bimolecular, became much more nearly unimolecular when the solvent was water alone.

Doubtless, the considerations advanced are likely to constitute the chief factor in the determination of solvent effects on reaction velocity only in reactions in which ions are produced or destroyed. A general theory of solvent effects must also envisage other factors, such as the specificity of energy exchanges between solute and solvent.

Electrophilic Substitutions.

The principal examples relate to the replacement of hydrogen in substitutions in which two bonds are broken, and for such cases the two typical mechanisms may be formulated thus :



Reaction (S_E1) will be favoured in comparison with reaction (S_E2) by (i) strong electron-attraction by the group Alk (if this contains substituents which endow it with such an effect), and (ii) strong proton affinity in the medium. The more important electrophilic reagents include nitric and sulphuric acids and the halogens.

The expected kinetic relations may be indicated. In a series such as Me, Et, Pr^β, Bu^γ, the speed of reaction by mechanism (S_E2) should progressively increase. This should be true even for the substitution of paraffin hydrocarbons; for, although the differences of permanent polarity between the carbon atoms of a paraffin must be extremely small, yet those atoms will become most negative on the approach of an electrophilic reagent which would permanently have been the most negative atoms had they been attached to a negative substituent. Thus, corresponding to Fig. 1 of Part III, a diagram could be constructed in which the curve for mechanism (S_E2) would slope upwards to the right; but in a left-ward continuation of the same diagram, extended to include the effect of reversing the polarity of alkyl groups by substitution, a point should be encountered from which another curve representing mechanism (S_E1) should slope upwards to the left.

It is well known that, in the halogenation and nitration of paraffins, tertiary hydrogen is more readily replaced than secondary, and secondary than primary. This has been established, *e.g.*, for nitration by Konowalow (*Compt. rend.*, 1892, **114**, 26; *Ber.*, 1895, **28**, 1863, *et seq.*). Markownikoff has drawn a finer distinction by showing that, in a hydrocarbon containing no tertiary hydrogen, but only methylene and methyl groups, nitration will occur at the methylene group adjacent to the most highly substituted carbon atom (*Ber.*, 1900, **33**, 1907). Markownikoff generalised these results in the statement that substitution occurs at that carbon atom which is most under the influence of other carbon atoms. This rule is well substantiated, except in relation to a group of examples considered later. It seems probable that the mechanism we assume to apply to these simple hydrocarbons [*viz.*, (S_E2)] will persist even when alkyl polarity is reversed by moderately strongly electron-attracting substituents, for Ingold and Rothstein have shown (*loc. cit.*) that bromination is inhibited by the nitroxyl group in an *o*-nitroaryl substituent. On the other hand, there is one well-authenticated case in which the electron-attraction of the substituent is sufficient to bring about substitution by mechanism (S_E1); this is the halogenation of ketones in the presence of acids (Lapworth, J., 1904, **85**, 30; Dawson, *et al.*, J., 1909, **95**, 1860, *et seq.*; Watson *et al.*, J., 1931, **3323**, *et seq.*), a reaction for which we may, in agreement with Watson, ascribe the form $\cdot CR:\overset{+}{O}H$ to the electron-attracting complex.

Ionic Pre-dissociation and the Stereo-orientation of Substitution.

The evidence on which we have assumed a preliminary ionisation in mechanism (S_N1) may be summarised as follows: (1) the rate of substitution is governed by a preliminary slow change in the compound substituted; (2) this preliminary change is not accelerated by bases or acids as such; (3) its rate is affected by constitution in the manner expected for ionisation; (4) its rate also shows the expected type of dependence on the solvent.

None of these considerations implies the necessity for assuming that both the ions have a long life, or even that they attain "complete" dissociation. A lower limit to the life of the carbon cation is given in some cases by the observation of complete, or almost complete, racemisation accompanying substitution by mechanism (S_N1). This has been observed, *e.g.*, by McKenzie and Clough for the hydrolysis of α -chloroethylbenzene and of α -chloro- α -phenylpropionic acid (J., 1913, **103**, 687; 1910, **97**, 1017); and Ward has proved that the reaction of the former compound is unimolecular (*loc. cit.*), whilst Senter and Martin have established the same point for the bromo-analogue of the latter (J., 1917, **111**, 447). Doubtless, complete racemisation would be the rule in ionising, but chemically inactive, solvents such as sulphur dioxide. On the other hand, there are substitutions of type (S_N1) in which perceptible optical activity persists in the product, and this shows that decomposition of a water molecule by the cation may occur rather soon after the ionisation has passed over its energy barrier. The reaction might then be described as depending on ionic pre-dissociation.

Mechanism (S_E1) is in a similar case. An appreciable retention of optical activity during the bromination of 2-*o*-carboxybenzylindanone has been reported (Leuchs, *Ber.*, 1913, **46**, 2435; cf. *ibid.*, 1915, **48**, 1015), but the reaction was conducted in a non-ionising solvent and the kinetics obtaining under these conditions are unknown. It has, however, been shown that, when this ketone is brominated in aqueous acetic acid in the presence of a strong acid, the kinetics of the reaction correspond to mechanism (S_E1) and racemisation is complete (Ingold and Wilson, J., 1934, 773).*

When complete racemisation does not occur during a substitution, the question of the configuration of the product arises. Polanyi has suggested that inversion always accompanies substitutions by negative ionic reagents, and Olson has advanced the view that inversion is a concomitant of one-stage substitutions generally (*loc. cit.*). We think that different substitution mechanisms should be considered independently in this connexion,

* This follows from the recorded comparison of the rates of racemisation and bromination. These authors directly verified the optical inactivity of the bromo-ketone by isolating it, but, owing to an oversight, omitted to mention this observation in their paper.

and may tentatively indicate a third possibility, *viz.*, that inversion is the rule for mechanisms (S_N2) and (S_E2), whilst retention of configuration may occur in (S_N1) and (S_E1).

This question will later be discussed in its relation to the unimolecular substitutions. With regard to the bimolecular substitutions, it may be noted that the experimental evidence of inversion adduced by Polanyi and Olson applies primarily to mechanism (S_N2). Indirect evidence that inversion is also general for mechanism (S_E2) may be seen in the fact that the orientation rules for electrophilic substitutions in aliphatic compounds break down completely when applied to rigid polycyclic systems such as the camphane structure. This contains a tertiary hydrogen atom; yet there is no established instance of substitution in this position, which remains unattacked whilst halogenations, nitrations, and sulphonations occur in the methylene and even in the methyl groups of camphane derivatives. Obviously, this should be so if substitution requires inversion; for inversion in the tertiary position would necessitate a simultaneous inversion at the other bridge-head, for which there is no mechanism.

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