

MECHANISM AND CHEMICAL KINETICS OF ORGANIC REACTIONS IN LIQUID SYSTEMS*

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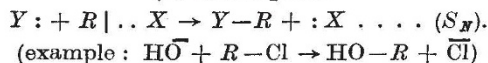
THE theory of chemical kinetics owes much of its development to the ease with which organic reactions lend themselves to convenient measurement, but the debt has been amply repaid, for kinetic studies have contributed very materially to the elucidation of the mechanism of organic processes. The importance of the kinetic method in the study of mechanism was demonstrated many years ago, particularly by Lapworth, Orton and others in the early years of the present century. More recently, it has been given enhanced value by the important advances in the physical interpretation of kinetic data (especially in liquid systems), and 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. Of the conclusions derived from investigations in this field in the last decade, one of the most important, and one which is widely illustrated in this discussion, is that a reaction may follow different mechanisms in not very drastically altered circumstances. This fact emphasizes still further the importance of kinetic control in the study of reactions. With the aid of kinetics, chemical behaviour can be related to mechanism and its determining factors, chemical structure and physical conditions, and the solution of outstanding problems can thus be greatly facilitated.

The reactions which come under review involve three main processes which are quite closely related, namely, substitution, elimination and addition. The substitution reactions may be divided into three principal types, as illustrated in the following table (the dots in the formulæ representing electrons)¹:

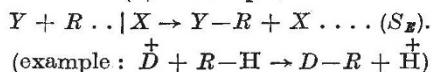
TYPES OF SUBSTITUTION.

(A) Heterolytic

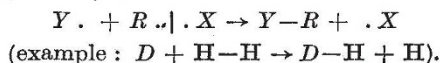
(1) Nucleophilic



(2) Electrophilic



(B) Homolytic



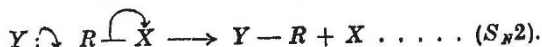
The mechanism of reactions related to the first of these types will now be discussed; reactions of the second and third type are considered in the sequel.

* This article is based on the Faraday Society's recent discussion on this subject (*Trans. Faraday Soc.*, **37**, 601, *et seq.*; 1941). References to the papers contributed to the discussion are given by noting the authors, employing the following key:

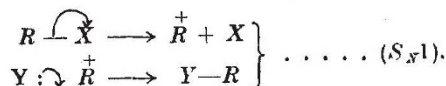
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| ¹ E. D. Hughes. | ⁹ G. M. Bennett. |
| ² E. C. Baughan and M. Polanyi. | ¹⁰ A. E. Bradfield and B. Jones. |
| ³ J. W. Baker. | ¹¹ F. Fairbrother. |
| ⁴ E. D. Hughes and C. K. Ingold. | ¹² G. Williams. |
| ⁵ J. N. E. Day and C. K. Ingold. | ¹³ W. A. Waters. |
| ⁶ H. B. Watson. | ¹⁴ J. Weiss. |
| ⁷ M. P. Balfe and J. Kenyon. | |

A full discussion of the various topics, with literature citations, is contained in these papers.

In a simple nucleophilic substitution¹, of the form $Y + R-X \rightarrow Y-R + X$, the nucleophilic reagent Y , whatever its original charge, must become one unit more positive, and the expelled group X one unit more negative; Y may therefore be either negative or neutral (for example, I^- , OH^- , NR_3 , SR_2 , etc.), and X either formally neutral or positive (for example, Cl^+ , $\overset{+}{\text{N}}\text{R}_3$, $\overset{+}{\text{S}}\text{R}_2$, etc.). The kinetics of these reactions call for the recognition of two distinct mechanisms. The first is a one-stage process, which is termed 'bimolecular' because two molecules are undergoing covalency change:



(In this formulation, and elsewhere in this article, arrows are used to show the direction of electron displacements; sign labels on X and Y have been omitted because of the various possibilities already mentioned.) The second mechanism is a two-stage process, wherein a rate-determining ionization is succeeded by a reaction between the formed carbonium ion and the substituting agent:

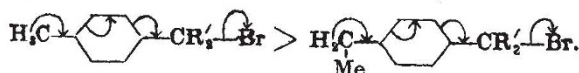


This mechanism is termed 'unimolecular', because only one molecule ($R-X$) is undergoing covalency change in the rate-determining stage. The unimolecular mechanism is favoured relatively to the bimolecular mechanism by the following principal factors: (1) low nucleophilic activity in the reagent Y , (2) large electron-release from the group R , (3) strong electron-affinity in the group X , (4) high ionizing capacity in the solvent. It may also be added that the unimolecular mechanism is less sensitive to steric inhibition by substituent groups than is the bimolecular mechanism. When the reaction centre is asymmetric, the bimolecular mechanism invariably leads to inversion of configuration, while the unimolecular mechanism may give rise, depending on structural influences, either to retention of configuration or to racemization with predominating inversion.

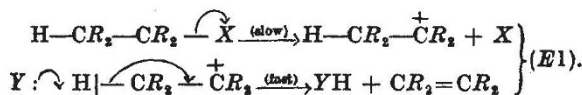
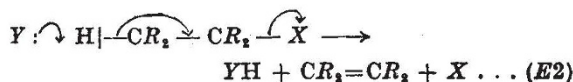
For certain simple substitutions of the type now considered, Polanyi and others have calculated the activation energies to be expected on the basis of the above mechanisms. The values thus deduced are in reasonably good agreement with the experimental results. In the case of the 'symmetrical' halogen-exchange reactions (bimolecular), for example, $\text{Cl}^- + \text{CH}_3\text{Cl} \rightarrow \text{Cl} \cdot \text{CH}_3 + \text{Cl}^-$, a very simple method of calculation has now been described². In first approximation, the activation energy is taken as the energy necessary to extend the carbon-halogen bond until it has the length corresponding to a carbon atom and a halide ion in contact, and it is shown that the introduction of various refinements into this procedure does not materially affect the result.

The same fundamental mechanisms operate in aromatic side-chain substitution³, but interesting differences of behaviour are sometimes observed when the polar effects of certain substituents in the nucleus are compared with the effects of the same substituents when attached to a saturated system. With alkyl groups, for example, the predominating influence with respect to a reaction in a saturated system, such as the replacement of halogen in an organic

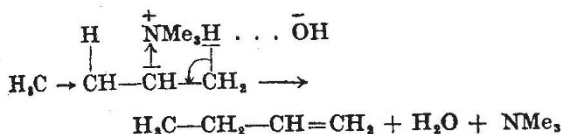
halide, $R-CR'_2-Br$, by the usual mechanisms (S_N1 and S_N2), is the general 'inductive' effect, which increases from left to right in the series, $R = CH_3, CH_3CH_2, (CH_3)_2CH, (CH_3)_3C$; thus $CH_3 \rightarrow CH_2 \rightarrow CR'_2 \rightarrow Br > CH_3 \rightarrow CR'_2 \rightarrow Br$. When the unsaturated aromatic nucleus is interposed between the alkyl group and the reaction centre, however, another effect gains in importance and occasionally becomes the dominant influence; this is the 'electromeric' effect, which arises from suitably placed C-H bonds and decreases as the operative hydrogen atoms are replaced; for example:



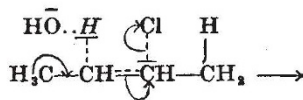
Substitution and elimination occur together so often as to suggest that the duality of mechanism established for substitution might have a parallel in the mechanism of elimination. This is found to be the case⁴. Employing the nomenclature and schematic representation already explained in connexion with nucleophilic substitution, the bimolecular ($E2$) and unimolecular ($E1$) mechanisms of elimination may be illustrated as follows ($Y = \bar{O}H, \bar{O}Ac, NR_3, H_2O$, etc.; $X = .Hal, .SO_2R, .\overset{+}{S}R_2, .\overset{+}{N}R_3$, etc.):



With the recognition of these mechanisms, and with full appreciation of their relationship with the substitution processes, the apparently inconsistent observations of the older literature fall into place, and it is possible to make rationally based predictions as to the effect of chemical constitution and physical conditions on the phenomenon. Special interest is attached to the analysis of the factors governing the contrary tendencies implied in two well-known empirical rules, namely, the Hofmann and Saytzeff rules, which indicate the preferred direction of olefin elimination in alkyl 'onium salts and in branched-chain alkyl halides respectively. (The Hofmann rule refers to the preferential formation of that ethylene which bears the smallest number of alkyl groups; Saytzeff's rule, on the other hand, predicts the production of the most' alkylated of the possible alkyl ethylenes.) It is found that bimolecular 'onium salt reactions are subject to the Hofmann rule, while the bimolecular reactions of halides, and the unimolecular reactions of both 'onium salts and halides, are governed by the Saytzeff rule. Furthermore, the Hofmann and Saytzeff influences are shown to be manifestations of the operation of the inductive and electromeric effects, respectively, of alkyl groups (compare preceding paragraph); for example:

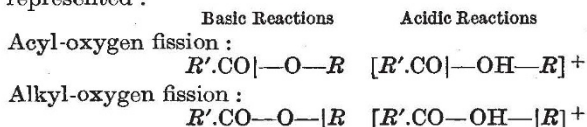


The inductive effect of the β -methyl group *inhibits* the removal of a β -proton (Hofmann influences).



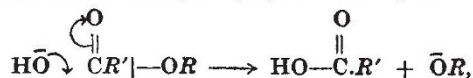
The electromeric effect of the β -methyl group *facilitates* the removal of a β -proton (Saytzeff influences).

The theory of aliphatic substitution can also be applied to the problem of carboxylic esterification and hydrolysis⁵. In this instance, it is necessary, in the first place, to distinguish between 'basic' reactions (hydrolysis in neutral or alkaline solutions) and 'acidic' reactions (acid-catalysed hydrolysis and esterification). In the former the carboxylic entity which suffers reaction is $R'.CO_2R$, while in the latter it is $[R'.CO_2HR]^+$. (In general, hydrolysis and esterification may be treated similarly; in esterification ($R = H$), however, the basic reaction is suppressed.) 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, which, with respect to the carboxylic entity and its mode of fission, may be represented:

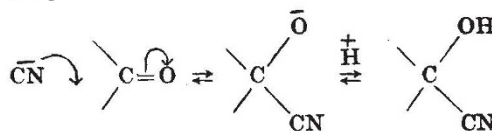


In esterification ($R = H$), there is a corresponding fission in the alcohol, that is, $R-O^+-|H$ (in acyl-oxygen fission) and $R|-O-H$ (in alkyl-oxygen fission). Finally, it would appear, from the rather limited amount of suitable kinetic data, that, for certain of these reactions, two mechanisms exist which are related to each other just like the unimolecular and bimolecular mechanisms of simple nucleophilic substitution.

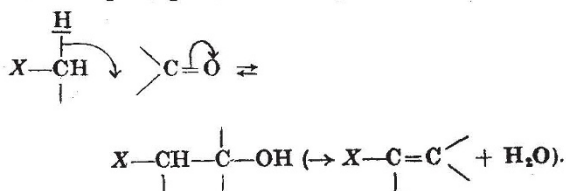
As in certain of the reactions involved in carboxylic esterification and hydrolysis, for example,



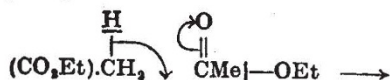
the addition and condensation reactions of carbonyl compounds⁶ are dependent on the reactivity, towards nucleophilic reagents, of the carbon atom of the carbonyl group. A simple example is to be found in cyanohydrin formation, the mechanism of which was clearly indicated by Lapworth's classical kinetic investigations:



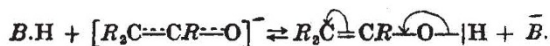
while reactions of the Aldol, Claisen, Knoevenagel and Perkin type follow a similar, though somewhat more complex, plan, for example:



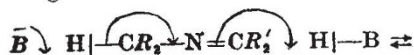
The Michael and the Thorpe reactions typify a quite analogous addition of a nucleophilic reagent to suitably activated C=C and C≡N bonds respectively.) All these reactions have certain features in common; thus they generally exhibit both alkaline and acid catalysis, and, while one of the reactants is a carbonyl compound, the second component contains a labile hydrogen atom which is activated by at least one electron-attracting substituent (X). The function of the basic catalyst is to remove the proton, thereby creating a more powerful nucleophilic reagent, and there is kinetic evidence that this reaction may, in certain cases, constitute the rate-determining stage of the process. An acid catalyst, on the other hand, probably activates the carbonyl component by forming an oxonium complex, >C=O⁺H. Reactions of the type of the acetoacetic ester condensation are also similar, and the analogy with the alkaline hydrolysis of esters is even more striking in this case:



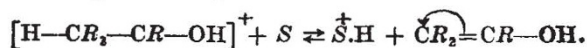
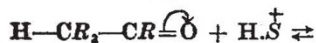
The prototropic changes of carbonyl compounds⁷, like the reactions discussed in the preceding paragraph, are catalysed both by bases and by acids. In terms of the ionic theory of prototropy, this circumstance is easily explained, for, according to this theory, the change involves the removal of a proton and the addition of a proton, processes which will obviously be facilitated by bases and by acids respectively. In the base-catalysed reaction, it is generally accepted that the first step involves the transfer of a proton to the catalyst, a 'mesomeric' anion being produced, which, by accepting a proton (for example, from the medium or the conjugate acid of the base), can form either the one or the other component of the tautomeric system:



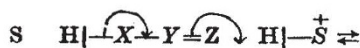
The equality of the rates of halogenation, of protium-deuterium exchange and of racemization, which has been demonstrated for certain ketones (asymmetric at the α-carbon atom), thus receives a simple interpretation if it be assumed that the rate-determining stage in all these reactions is the formation of the mesomeric anion. Similar ideas can be applied to other prototropic systems, but in certain cases (for example, methyleneazomethines) there is evidence that the anion never attains kinetic freedom, the removal of one proton and the addition of another being simultaneous:



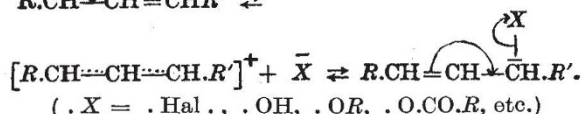
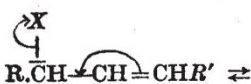
In acid catalysis, the preliminary addition of a proton to the tautomeric system may facilitate the subsequent transfer of another proton from the latter to the solvent (S):



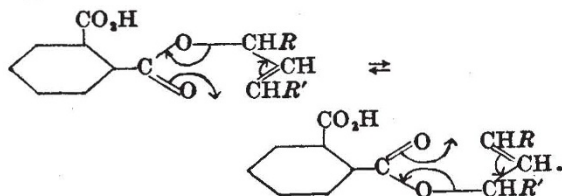
Alternatively, the proton addition and elimination may take place simultaneously:



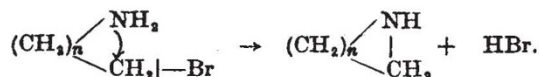
Anionotropic change⁸ is, in some respects, similar to prototropic change, and it is also related to nucleophilic substitution. In anionotropy we are concerned with the movement of negative groups, and there is evidence that the interconversion may proceed through the intermediate formation of a positive mesomeric ion and a complementary negative ion; for example,



It has been shown that the mobility of the system is increased by the following factors: (1) Strong electron-affinity in the group X, (2) large electron-release from the group R, (3) high ionizing capacity in the medium. These are the relationships to be expected if ionization is involved, and it will be recalled that the same factors assist the ionization mechanism of nucleophilic substitution (S_N1). All the facts relating to the phenomenon cannot, however, be explained on the basis of this mechanism alone. It has been shown, for example, that the anionotropic rearrangement of optically active hydrogen phthalates of substituted allyl alcohols is often accompanied by a high degree of retention of optical activity, and an intramolecular mechanism has been suggested to account for this and similar observations:

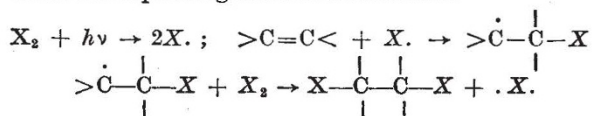


In the study of the kinetics and mechanism of ring-closure⁹, the reactions which have yielded the most profitable results are mainly those which involve an internal nucleophilic substitution; for example:

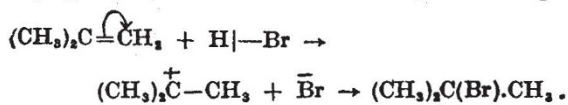


Since the intermolecular processes which generally accompany the cyclization involve two such molecules, and are therefore of a higher order, the best yields of cyclic derivatives are obtained in dilute solutions. This principle has been widely exploited both in synthetic work and in the simplification of kinetic experiments. The most important aspect of this subject concerns the effect of homology, and of the notable results which have been obtained in this connexion perhaps the most interesting relate to the great ease of formation of three- and five- (but not four-) membered rings, the special difficulty of forming rings of about nine to eleven atoms, and the

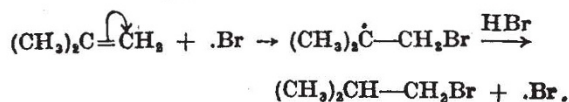
(cf. following paragraph), and this may also be true of the corresponding reaction in solution :



Homolytic reactions involving free radicals¹³ (compare Table of Types of Substitution) exhibit some similarity to the heterolytic processes in which electrophilic reagents are concerned, because free radicals generally have depleted electron shells and tend to share an extra electron: for example, $C_6H_5 \cdot + Cl-CCl_3 \rightarrow C_6H_5-Cl + \cdot CCl_3$. Their electrophilic character is most clearly shown in the addition reactions with olefins. In the so-called 'normal' addition of hydrogen bromide to the alkyl-ethylenes, the proton adds preferentially to the unsaturated carbon atom bearing the smaller number of alkyl groups (cf. Markownikoff's rule), for example,



Likewise, in the peroxide-catalysed reaction ('abnormal' addition), the addition is initiated by the attack of a bromine atom at the point of higher electron density :



It must be emphasized, however, that this analogy between neutral radicals and electrophilic reagents has definite limitations. Thus, it is well known that aromatic substitution reactions of neutral radicals, for example, $Ph \cdot + H.C_6H_4R \rightarrow Ph.C_6H_4R + \cdot H$, do not exhibit the usual orientation effects associated with the heterolytic reaction. This is understandable, for the 'orienting' influence of a substituent group is due to its transmitted polar effects, which are largely dependent on the demands of the reaction involved, and it is reasonable to suppose that the electron displacements which are a necessary condition for an oriented heterolysis are of less importance in homolysis.

It has been shown that the Cannizzaro reaction¹⁴ exhibits peroxide catalysis and other characteristics of a radical process, and the observations can be satisfactorily accounted for on the basis of a mechanism involving the radicals $RCO \cdot$ and $RCHOH \cdot$, both of which are formed from the aldehyde $RCHO$ by univalent oxidation and reduction respectively.

USE OF SCIENCE AND SCIENTIFIC WORKERS IN THE WAR

THE sessions during the morning and afternoon of the last day of the Conference organized by the Association of Scientific Workers and held in London during January 10-11 dealt with the two related topics: the utilization of scientific personnel, and the application of scientific knowledge to production and Services problems.

After an introductory address by Prof. S. Chapman, in which he compared the use of science in the War

of 1914-18 and in this War, Prof. W. Wardlaw spoke on the working of the Central Register. He stated that the Register has come in for a good deal of criticism but that it should be borne in mind that nearly all the persons enrolled on the Register are already in useful work from which they can only move to more important posts. The Register is intended to be a complete record of the higher administrative, professional and technically qualified personnel of Great Britain, whether employed or not. The number of engineers and scientific workers on the Register has risen from 65,000, in May 1940, to 167,000, in December 1941. It has never been the function of the Register to determine how scientific and technical knowledge should best be used in the prosecution of the War; its purpose is to meet demands for technical personnel for war purposes and to allocate the available supply in cases of scarcity. He pointed out that technical officers of full professional standing are now at the head of each section, and referred to the formation of the Technical Personnel Committee under the leadership of Lord Hankey.

Prof. Wardlaw then dealt with the new procedure of progressive de-reservation being conducted by the District Manpower Boards of the Ministry of Labour. He stated that steps are being taken to ensure that anyone with technical qualifications of Central Register standard, if not already deferred by virtue of his work, will be dealt with by the Register and placed in work which makes full use of his technical capacity, whether in the Forces or not.

Mr. E. D. Swann, of the executive committee of the Association of Scientific Workers, presented the results of inquiries by the Association into the position in the main industries in the country. It has been found that many scientific workers and engineers are not being used on war work but are engaged instead on development and design for the period of post-war competition. Others who are nominally engaged on war work have insufficient to occupy their time fully. He stated that the Essential Works Order is being used to hold redundant staff, that no mechanism exists for providing partly occupied laboratories with further problems, and that there is considerable duplication of work in laboratories and design departments of similar undertakings. He pointed out the need for provision for the proper pooling of information, including trade secrets. Another weakness is the notable lack of contact between the design departments of the Ministries and the design and production departments in industry. It has been found that criticism of designs from the point of view of speed and economy of manufacture is not encouraged. The Association has collected enough evidence of this sort to press for an investigation into the utilization of our technical resources by the Select Committee on National Expenditure.

Mr. Swann then dealt with the Association's proposal that a Technical Planning Committee should be set up under the Production Executive. This Committee would deal with the technical resources of Great Britain in the same manner as the existing Industrial Capacity and Materials Committees deal with their respective resources. In this scheme it is essential that this Committee be given executive powers. The Association of Scientific Workers, as it is composed of working men of science and technicians, is in a position to know how effective is the present organization in practice, and it knows that it is not