STERIC HINDRANCE

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I. *Introduction*

THE development of the theory of organic chemistry had its origin in isolated experimental observations. In the course of time it was realised that certain of these observations were related and that they indicated special phenomena. This realisation led to additional interest in further experimental work, especially of a quantitative nature, and to hypotheses and theories concerning the connected observations. At first the hypotheses were restricted in scope and often of a vague and evanescent character, if not definitely erroneous in important respects. Later, a sufficiently wide and accurate knowledge of reactions as a whole emerged to enable the particular phenomena to be seen in clearer relation to the broader background of chemical structure and reactivity generally ; certain problems were found to be closely allied, and subsequent theories were placed on a wider and more satisfactory basis. Thus the trend of development has usually been towards a more unified and precise theory of reactions. The history of the phenomenon referred to as " steric hindrance " provides an example of progress of this description.

In this Review it is not proposed to give an exhaustive summary of the innumerable papers dealing with the problem of steric hindrance. Instead, it is intended to pick out the directions from which advance has been made, including a discussion of the difficulties which have been encountered, by reference to contributions of a representative character. In this way it is hoped to convey a clearer picture of the main path of progress in the subject.

II. *Recognition of the Effect*

Following experimental studies initiated by A. W. Hofmann in 1872 [1] and continued by many subsequent investigators, the term " steric hindrance " was adopted to describe an effect, which seemed to be indicated by a number of observations, whereby in certain structural circumstances the particular location and the spatial dispositions of atoms or groups appeared to exert an inhibitory influence on the rates of reactions at neighbouring centres. The early history is sufficiently described and summarised in the existing literature [2] to make it unnecessary to give a detailed account here, but the chief points contributing to the recognition of the effect as a distinct phenomenon may be briefly indicated.

In the first investigations leading to the concept of steric hindrance it was found that the presence of a substituent X in positions *ortho* to a

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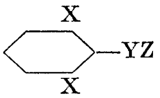
[1] *Ber.*, **5**, 704.

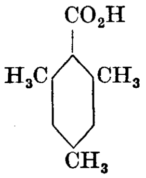
[2] See especially J. B. Cohen, " Organic Chemistry ", Fifth Edition, Edward Arnold & Co., 1928, Vol. I, Chap. V.

reacting group YZ, and especially two such substituents, *e.g.*, in the compound (I), had a retarding influence on the rates of the reactions of YZ (involving directly the atom Y adjacent to the aromatic nucleus) which was quite unequalled by effects exhibited when the substituent was other than in the *ortho*-positions. Furthermore, it was observed that an influence of this kind was exerted by atoms and groups of diverse character (*e.g.*,. by both "positive" and "negative" types), and it was concluded that the chemical nature of the substituents was less important in these circumstances than their location in the *ortho*-positions with respect to the reaction centre. The substituents examined in various investigations included halogen atoms, and nitro-, alkyl, and carboxyl groups [X (formula I) = Hal., NO_2, CH_3, CO_2H, etc.], and the reactions studied embraced the interaction of amines with alkyl halides, the hydrolysis of nitriles and their reaction with alcohols to form imino-ethers, the interaction of carbonyl compounds with reagents such as phenylhydrazine, hydroxylamine, and primary amines, the hydrolysis and alcoholysis of acid halides, the esterification of carboxylic acids, and the hydrolysis of carboxylic esters and amides [YZ = NR_2, CN, COR, COCl, CO_2R, $CONH_2$, etc. (R = H or Alk.)]. The importance of such questions as the polar influences of substituents and their transmission from the various positions in the aromatic nucleus was not fully realised when the early observations and the first attempts to interpret them were made. However, the evidence as a whole related to such a broad and representative selection of reactions and of substituents and their location as to justify the conclusion that a special effect was under observation. In anticipation of a further analysis in the light of present knowledge concerning the processes involved it should nevertheless be emphasised that many of the individual results were undoubtedly complicated by diverse factors.

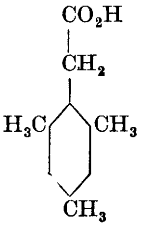


(I.)

The most extensive and significant results were obtained in studies of the esterification of carboxylic acids, for which important indications based on yield data were later followed by rate comparisons. The observations referred to the conditions governing the Fischer–Speier method of esterification in the presence of hydrogen chloride, and the investigations were initiated by V. Meyer in 1894.[3] It was shown that mesitylenecarboxylic acid (II) and other substituted benzoic acids with two methyl-, chloro-, bromo-, or nitro-substituents in the *ortho*-positions formed no ester when treated with methyl alcohol and hydrogen chloride under conditions wherein similar compounds with at least one free *ortho*-position yielded esters without ifficulty. Meyer found further that mesitylacetic acid (III), in which



(II.)



(III).

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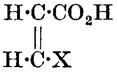
[3] *Ber.*, **27**, 510, 1580 and subsequent papers; cf. ref. 2.

the carboxyl group is removed from the proximity of the two *ortho*-methyl substituents, was esterified quite readily under the conditions for which the inertness of (II) was established. The interposition of a saturated carbon atom between the reacting group and the aromatic nucleus results, however, in fundamental effects other than the spatial separation of groups, and this familiar observation by Meyer is not as uniquely significant as is generally supposed.

In view of the results relating to the substituted benzoic acids, it was of interest to examine the acids of the aliphatic series, and evidence for a similar effect was obtained, particularly by J. J. Sudborough and his collaborators, who observed the sequence :

$$CH_3{\cdot}CO_2H > CH_2X{\cdot}CO_2H > CHX_2{\cdot}CO_2H > CX_3{\cdot}CO_2H$$

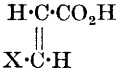
for the rates of esterification with ethyl alcohol in the presence of hydrochloric acid, the order being independent of the nature of X in the examples studied ($X = Cl$, Br, CH_3, C_6H_5).[4] Many similar, though generally less clear, indications of a "steric" effect in the reactions of aliphatic compounds were obtained by numerous investigators. Special mention may be made of recorded cases for which a substituent has a more marked effect in the *cis*- than in the *trans*-position to a reacting group, as, for example, in the esterification of substituted acrylic acids of the type represented in formulæ (IV) and (V).[5]



$$\begin{array}{l} H{\cdot}C{\cdot}CO_2H \\ \;\;\| \\ H{\cdot}C{\cdot}X \end{array}$$

cis

(IV.)



$$\begin{array}{l} H{\cdot}C{\cdot}CO_2H \\ \;\;\| \\ X{\cdot}C{\cdot}H \end{array}$$

trans

(V.)

While many of the results of individual investigations serve only to suggest a possible steric effect and are sometimes found to be of a somewhat ambiguous character when examined critically, the combined results of observations such as those which have been selected for illustration, though they do not establish the exact nature of the effect, indicate that a spatial factor may be of importance in chemical reactions.

III. *Importance of Quantitative Data*

The existence of a "steric" factor having been indicated, it became a matter of great interest to acquire a deeper knowledge of the effect and to develop a satisfactory theory regarding its origin and mode of operation. It was realised that one of the first necessities was to obtain more quantitative data, including particularly a comparison of the inhibiting effects of various substituents, with a view to establishing a relationship between these effects and the known properties of the substituents. Many of the earlier results to which reference has been made were based on the estimation of yields of products formed after reaction under comparable conditions.

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[4] See especially J. J. Sudborough and L. L. Lloyd, *J.*, 1899, **75**, 467 ; J. Gyr, *Ber.*, 1908, **41**, 4308.

[5] J. J. Sudborough and L. L. Lloyd, *J.*, 1898, **73**, 81.

While convincing indications of the existence of a "steric" factor were obtained in experiments which resulted, under the conditions chosen, in a more or less complete inhibition of the reactions examined (which proceeded substantially to completion in the absence of the special structural features imposed), the data were unsuitable as a basis for comparison of the inhibiting substituents amongst themselves. Clearly, conditions should be arranged whereby inhibiting effects requiring quantitative estimation and comparison should still lead to measurable reaction, and the application of the kinetic method to suitable reactions under appropriate conditions suggested itself as one of the most satisfactory means of securing comparative data. The convincing preliminary investigations of the esterification reaction by V. Meyer and his colleagues placed his flourishing school of chemistry in a favourable position to participate in the development, and notable results were obtained by Meyer and by H. Goldschmidt, A. M. Kellas, J. J. Sudborough, and others, and were described in important papers published at the turn of the century (*ca.* 1895–1905).

The first attempt to assess the relative magnitudes of the effects of various substituents was made by Meyer,[6] who extended his observations on the esterification of di-*ortho*-substituted aromatic acids with alcohol and hydrogen chloride at 0° to higher temperatures and found that while methyl, hydroxyl, and fluorine retarded esterification in the boiling alcoholic solution, the reaction was completely arrested under these conditions by chloro-, bromo-, iodo-, and nitro-substituents. In later measurements by H. Goldschmidt,[7] more accurate comparisons of substituents were obtained by the application of kinetic measurements to the esterification of *ortho*-, *meta*-, and *para*-isomers of mono-substituted benzoic acids with excess of alcohol in the presence of hydrogen chloride (Fischer–Speier method). In the cases examined the *ortho*-isomer gave the slowest rate, as illustrated by the comparative first-order rate coefficients for the substituents and positions indicated in the appended table.

	CH_3.	Br.	NO_2.
Ortho	0·011	0·020	0·0028
Meta	0·047	0·055	0·030
Para	0·024	0·045	0·026

Benzoic acid = 0·043

The observations of Goldschmidt are typical of many results which have been recorded in the literature, such data referring to the various reactions previously mentioned, for which indications of "steric" factors had been secured. Thus, evidence of abnormal effects of *ortho*-substituents have similarly been obtained for the hydrolysis of esters, amides, and nitriles, and the reactions of aromatic amines with organic halides. In some reactions the masking effect of polar and other factors (see p. 112) is more

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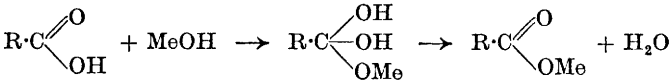
[6] *Ber.*, 1895, **28**, 1254.

[7] *Ibid.*, p. 3218.

evident than in others, particularly with the strongly polar nitro-substituent. In general the rates are found to be lower for *ortho*- than for *meta*- and *para*-compounds in the examples cited, but for some of the reactions the values for all three positions are, with certain substituents, higher than the rate for the unsubstituted structure. More ambiguous evidence is supplied by extensive data referring to other reactions, of which the hydrolysis and alcoholysis of substituted benzoyl chlorides is a notable example : here, the presence or absence of a special *ortho*-effect appears to be dependent on the chemical nature of the substituents. The data as a whole will be clarified in later discussions, but it may be mentioned now that no polar influences of the usual type can account alone for the effects of *ortho*-substituents which have been observed. The investigations have been of value, not only in establishing the " proximity factor " more definitely, but also in connection with the broader question of the influence of nuclear substituents in general on reactions at aromatic side chains.[8] Many important results of a quantitative character were also obtained for the similar reactions of purely aliphatic structures.[9] It must be admitted, however, that the data did not fulfil the highest expectations with regard to the development of precise views concerning the nature of steric hindrance.

IV. *Limitations of Interpretation*

It was inevitable that experimental studies and theoretical considerations should proceed together in the investigation of the subject of steric hindrance, and the account of practical developments will here be interrupted to record some early interpretations of the effect. The type of influence which the experimental demonstrations indicated was envisaged as being of a geometrical rather than of a chemical character, and this impression assumed more definite form through the experiments and views of V. Meyer.[6] Meyer had observed (from very limited data) that the atoms or groups which prevented esterification in hot alcoholic solutions were larger than those which produced this effect only in the cold, and he concluded that the influence of a substituent in the *ortho*-position appears to be dependent on its size, measured, as he supposed, by the sum of the weights of the atoms present. He considered that vicinal substituents occupy space near the carboxylic group and, depending on the extent of the shielding effect produced, prevent in various degrees the formation, with the alcohol, of an additive compound, which, on loss of water, gives the ester, *e.g.*,



$$\mathrm{R{\cdot}C}\begin{matrix}\nearrow\mathrm{O}\\ \searrow\mathrm{OH}\end{matrix} + \mathrm{MeOH} \longrightarrow \mathrm{R{\cdot}C}\begin{matrix}\nearrow\mathrm{OH}\\ -\mathrm{OH}\\ \searrow\mathrm{OMe}\end{matrix} \longrightarrow \mathrm{R{\cdot}C}\begin{matrix}\nearrow\mathrm{O}\\ \searrow\mathrm{OMe}\end{matrix} + \mathrm{H_2O}$$

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[8] C. K. Ingold and E. Rothstein, *J.*, 1928, 1217 ; G. Williams, *J.*, 1930, 40 ; J. W. Baker, *Trans. Faraday Soc.*, 1941, **37**, 632.

[9] For references see especially (*a*) E. D. Hughes and C. K. Ingold, *J.*, 1935, 244 ; (*b*) L. P. Hammett, " Physical Organic Chemistry ", McGraw–Hill Book Co., Inc., New York, N.Y., 1940 ; (*c*) J.N.E. Day and C. K. Ingold, *Trans. Faraday Soc.*, 1941, **37**, 686.

Similar ideas were held concerning the nature of the effects observed in other reactions.

It is now clear that such a view of the nature of the effect could not be permanently acceptable in this form. It is equally certain that some of the general difficulties which were apparent at the time, and which retarded the development of a satisfactory theory, were emphasised as a result of a lack of knowledge of the nature of other operative factors. In anticipation of a more comprehensive discussion, which is given later, special mention may be made of the polar influences of substituents and their mode of transmission, particularly from the various positions in the nucleus to reaction centres situated in aromatic side chains. It is now realised that polar factors were prominent in some of the data referring to " sterically hindered " reactions—considerably more so than in the observations of Goldschmidt, which were selected as illustrations of results of a comparatively clear character. A polar influence may appear to strengthen or weaken a " steric " retardation, depending on the nature of the substituent and the reaction investigated. In general, even if a spatial factor was not obscured completely, the additional polar effects, and other matters which will be referred to later, confused the results obtained in the quantitative investigations, which were expected to clarify the position, with the consequence that the early and immature views regarding the nature of steric hindrance neither developed satisfactorily nor were completely discarded and replaced by more appropriate interpretations. For a long time then, although further data of the same general character were obtained, the evidence as to whether the " proximity effect " was mainly of a geometrical nature, or whether it consisted of other influences, remained ambiguous, and the continued absence of any new and significant method of approach in both experimental and theoretical aspects of the problem lessened interest in the subject. The lack of progress and of a definite viewpoint had the effect also that " steric hindrance " tended to deteriorate into an omnibus term to cover a multitude of misunderstood effects, and discussion of the subject became sporadic and unco-ordinated.[10]

V. *Analysis of Difficulties*

The term " steric hindrance " was originally used to describe the spatial effects of vicinal groups, as indicated by experiments of the type illustrated in the foregoing pages. The nomenclature suggested an effect of a geometrical character, and in the absence of definite evidence that the influences under observation were of this kind it may be said to be misleading; it has been mentioned also that the term tended later to become a general label for many abnormalities. More recently, therefore, it became a frequent practice to use a more restricted and cautious nomenclature, such as the description " proximity effect " for the special influence of substituents situated near the site of reaction, and "*ortho*-effect " for the particular

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[10] For examples, see the following references in *Ann. Reports*: 1905, **2**, 150; 1907, **4**, 141, 193; 1908, **5**, 83; 1915, **12**, 98; 1916, **13**, 101, 138; 1918, **15**, 78; 1932, **29**, 21.

form relating to nuclear substituents. These terms are used in this sense in the present Review ; the expression " steric hindrance " is reserved for an effect of undoubted origin, as defined later.

In the analysis and elucidation of the proximity effect, a general difficulty, which is even more fundamental than the one already mentioned (incursion of polar effects) was due to the imperfect understanding of the mechanism of the reactions involved. This question includes and governs the special complication concerning the superposition of polar and steric factors. Space does not permit a detailed discussion of all the aspects of the difficulties which were created by the lack of sufficient knowledge of chemical processes, but it is possible to indicate by means of examples the nature of some of the obstacles. Further details will become clear later in fuller discussion of the directions in which progress was restored after the necessary background of information had been gained.

When the more extensive and quantitative phases of the investigations of the phenomenon of steric hindrance were reached it was found that the most convincing indications of the effect were obtained when certain reactions were carried out under specific conditions. The study of other similar reactions, or a change of conditions for a given reaction, often led to rather different results. It was found, for instance, that while clear evidence of a special effect was obtained for the esterification of selected acids, as already described, the results for the esterification of the same acids without the addition of the hydrogen chloride catalyst were rather contradictory,[11] and the data for analogous reactions, such as the hydrolysis or alcoholysis of benzoyl chlorides, were, as already indicated, less convincing.[12] These observations presented difficulties of interpretation which could not be solved in the absence of adequate information concerning reaction mechanism, and a confused impression remained. A particular difficulty was undoubtedly created in the minds of investigators by a persistent misconception in the annals of chemistry, namely, that an indicated mechanism represents the one and only possible route for that reaction. In anticipation of later discussion it may be mentioned here that a reaction may follow different mechanisms in not very drastically altered circumstances. It will be shown that in appropriate structures and reactions steric hindrance is a characteristic property of a certain type of mechanism, and that it is absent from the same reactions of the same compounds when other mechanisms are operative. Furthermore, even for reaction paths which are in principle subject to steric hindrance, such questions as the relative importance of polar and steric effects are closely dependent on the exact nature and dimensions of the transition state of reaction.

One of the most serious difficulties in any general theory purporting to interpret all cases of steric hindrance as a purely geometrical effect emerged from the work of J. von Braun.[13] Tertiary aromatic amines can be con-

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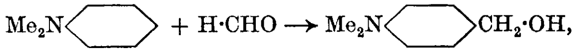
[11] A. Michael, *Ber.*, 1909, **42**, 317.

[12] See for example J. F. Norris and his co-workers, *J. Amer. Chem. Soc.*, 1935, **57**, 1415, 1420 ; 1939, **61**, 1418.

[13] *Ber.*, 1916, **49**, 1101.

densed with formaldehyde to form *para*-substituted benzyl alcohols, *e.g.*,



and a study was made of the effect produced by *ortho*-substituents. At the same time, the influence of the same substituents on the capacity of the tertiary amino-group to yield quaternary ammonium salts was examined. It would appear that the two processes could scarcely be influenced by steric hindrance to the same extent. The first takes place at the nitrogen atom, in the position adjacent to the *ortho*-substituent, while in the second the reaction centre is situated at the *para*-carbon atom, considerably removed spatially from the substituent. It was found, however, that both reactions were affected in a similar manner by the presence of the *ortho*-groups. In this connection it is of interest that the formation of a *para*-nitroso-derivative is retarded by two *ortho*-substituents[14] or by a tertiary alkyl group attached to the nitrogen atom.[15] Since the alkylation of aromatic amines was one of the reactions for which the existence of steric hindrance, as a possible factor affecting reactions rates, had been deduced from experimental observations of the inhibiting effects of *ortho*-substituents, von Braun's results tended to cast some doubt on the significance of all such demonstrations. The mechanism of these substitutions in the *para*-position is not known with certainty. The nitrogen atom may perhaps play a direct part in a preliminary reaction with the substituting reagent, and this necessary function, like the alkylation process, may be inhibited by *ortho*-substituents. Interaction between the *ortho*-substituent and the nitrogen atom and the steric inhibition of resonance—effects modifying the transmitted polar influence of the amino-group—have been suggested to account for the *ortho*-effect in these circumstances (see later).

VI. *Development of Basic Principles*

It is proposed to consider the question first in broad outline without recourse to the detailed analysis of reaction mechanism which a complete treatment will later be found to require. It will not be possible to discuss the development of general chemical theory,[16] but certain notable advances, first of a general, and then of a more special and immediately applicable character, may be recalled. The fundamental basis of recent rapid progress has been an advanced knowledge of atomic structure, leading to the modern theory of valency and molecular structure. Direct developments have resulted in the theories of polarisation and polarisability effects and of

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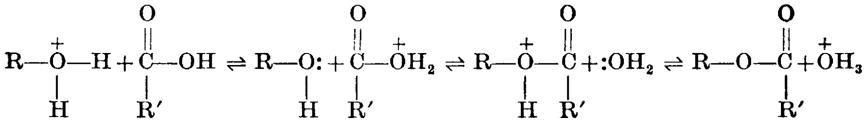
[14] J. von Braun *et al.*, *Ber.*, 1918, **51**, 282.

[15] W. J. Hickinbottom, *J.*, 1933, 946.

[16] Comprehensive text-books on the subject are now available, *e.g.*, (*a*) W. A. Waters, " Physical Aspects of Organic Chemistry ", George Routledge & Sons, Ltd., London, 1937 ; (*b*) H. B. Watson, " Modern Theories of Organic Chemistry ", Oxford University Press, 1941 ; (*c*) ref. 9*b* ; (*d*) G. E. K. Branch and M. Calvin, " The Theory of Organic Chemistry ", Prentice-Hall, Inc., New York, 1941 ; (*e*) A. E. Remick, " Electronic Interpretations of Organic Chemistry ", John Wiley & Sons, Inc., New York, 1943.

resonance phenomena, together with applications to special structural problems and the mechanism of the principal reactions of organic chemistry. The concern herewith is the nature of reactions such as the esterification of carboxylic acids and the hydrolysis of carboxylic esters, and the effect of substituents on these processes.

V. Meyer [6] accepted the current interpretation that in the esterification of a carboxylic acid there was formed with the alcohol an additive compound which, on loss of water, yielded the ester. This concept was a typical application of the " addition-complex " theory, which postulated that the addition of the reagent was an essential preliminary to group replacement ; the view was widely held in connection with various aspects of substitution processes, including particularly the problem of the Walden inversion. Certain general difficulties inherent in the theory were dispelled by the idea that addition is not previous to but synchronises with dissociation,[17] and this type of mechanism has since been firmly established as one of the most important in the field of replacement reactions (see later). In its application to the esterification of carboxylic acids and the acid hydrolysis of carboxylic esters the mechanism may be represented : [9c]



$$\mathrm{R{-}\underset{\underset{H}{|}}{\overset{+}{O}}{-}H} + \mathrm{\underset{\underset{R'}{|}}{\overset{\overset{O}{\|}}{C}}{-}OH} \rightleftharpoons \mathrm{R{-}\underset{\underset{H}{|}}{O}{:}} + \mathrm{\underset{\underset{R'}{|}}{\overset{\overset{O}{\|}}{C}}{-}\overset{+}{O}H_2} \rightleftharpoons \mathrm{R{-}\underset{\underset{H}{|}}{\overset{+}{O}}{-}\underset{\underset{R'}{|}}{\overset{\overset{O}{\|}}{C}}} + \mathrm{{:}OH_2} \rightleftharpoons \mathrm{R{-}O{-}\underset{\underset{R'}{|}}{\overset{\overset{O}{\|}}{C}}} + \mathrm{\overset{+}{O}H_3}$$

The proton transfers are regarded as effectively instantaneous, and the mechanism is formulated in a reversible manner, so that read forwards it applies to esterification, and backwards, to hydrolysis. A preliminary proton uptake weakens the C–OH bond of the acid or the C–OR bond of the ester ; the approach of the positive-centre-seeking (nucleophilic) reagent, $R\ddot{O}H$ or H_2O: (the dots representing unshared electrons), is then facilitated by the tendency of the $-\overset{+}{O}H_2$ or $-\overset{+}{O}HR$ group to appropriate electrons, and, in this particular instance, by the general attraction of the carbon atom of the " carbonyl " group for nucleophilic reagents. An analogous formulation, essentially of the general form Y: + R—X → Y—R + :X, wherein a preliminary proton transfer may not be operative (or necessary) in every case, similarly represents an important mechanism in the alkaline hydrolysis of carboxylic esters (*e.g.*, Y: = HO, R = R′·CO, X = OR″) and the reactions of amides, nitriles, organic halides, etc. The interaction with the nucleophilic reagent could be subject to steric hindrance in appropriate structures, and the reaction rate is dependent on such interaction in this mechanism. The subject is considered more closely, with simple examples, later. It should be stated at this point that, though the investigations often included no definite proof of mechanism, it may be concluded with some certainty from a critical appraisal of all available data and accumulated knowledge that the reactions here reviewed, for which considerable proximity effects

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[17] G. N. Lewis, " Valence and the Structure of Atoms and Molecules ", 1923, p. 113.

have been observed, are of this mechanistic type, now designated bimolecular nucleophilic substitutions, S_N2 (see later).

The general effect of the polar influences of substituent groups on this mechanism may now be considered. Neglecting for the moment any proton transfer reactions which may be involved, the synchronous replacement consists of bond-forming and bond-breaking factors and the polar effects of a substituent in the group R of the reactant R–X will influence these in opposite directions, the attack of the reagent in the bond-making process being inhibited, while the dissociation of the expelled group is facilitated, by electron-release to the reaction centre. In most examples the bond-forming requirements are dominant, so that an electron-donating group (*e.g.*, CH_3) usually tends to inhibit reaction by this mechanism, while an electron-attracting group (*e.g.*, NO_2) facilitates it. Substituents of the latter type create a condition of electron deficiency at the reaction centre which favours the approach of the positive-centre-seeking (nucleophilic), reagent. The effects on rate vary, however, with the properties of the systems involved, depending especially on the strengths of the bonds which are formed and broken, and it is difficult to predict the result with certainty and precision.[18] With nuclear substituents we have to consider also the special feature involving the transmission of polar influences from the *ortho-*, *meta-*, and *para-*positions. In assessing this factor considerable guidance can be derived from the wealth of available knowledge concerning the " directing " influence of substituents in aromatic substitution reactions.[8, 19] The conclusion may be broadly summarised in the statement that the polarisation effect (permanent) and the polarisability influence (effective at the demand of a reagent during actual reaction) of a substituent may be transmitted strongly to a side chain from the *ortho-* or the *para-*position but more weakly (especially the polarisability effect) from the *meta-*position. In acid-catalysed reactions the situation may be complicated further by such factors as the proton affinity of the reactants (modified by substituents). The protons may come from the added catalyst (*e.g.*, hydrogen chloride in the Fischer–Speier method of esterification), or from a carboxylic acid which may either be undergoing self-catalysed esterification or formed in ester hydrolysis. If the carboxyl group is involved as a proton donor, its acid strength may be an important factor. Favourable circumstances for the clear demonstration of steric hindrance may arise in appropriate structures when, *inter alia*, the over-all polar effects on rate are weak. The esterification reaction under the conditions of the Fischer–Speier method appears to be especially suitable in this respect. A complex position results when the bond-forming and bond-breaking factors are such that either the one or the other may become dominant, depending particularly on the nature of the substituents. This seems to be the case in the

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[18] Cf. especially (*a*) E. D. Hughes, C. K. Ingold, and U. G. Shapiro, *J.*, 1936, 225; (*b*) C. N. Hinshelwood, K. J. Laidler, and E. W. Timm, *J.*, 1938, 848; (*c*) S. Glasstone, K. J. Laidler, and H. Eyring, " The Theory of Rate Processes ", McGraw-Hill Book Co., Inc., New York, 1941, p. 447.

[19] Cf. S. C. J. Olivier, *Rec. Trav. chim.*, 1923, **42**, 775; refs. 16*b* and *e*.

hydrolysis and alcoholysis of benzoyl halides.[12, 20] Considerations, along these lines, of polar influences superimposed on special proximity factors help to elucidate some complex effects of substituents on reaction rates and particularly of nuclear substituents on reactivity at aromatic side-chain groups.

The immediate influence of the more advanced views of reactions discussed above on the concept of steric hindrance may be noted. First, it became clear in a general way (without the detailed and more precise knowledge summarised later) that the observed dependence of the data on the types and conditions of reaction was a natural result. Secondly, the importance of accurate comparisons between *ortho-*, *meta-*, and *para-* (and especially *ortho-* and *para-*) substituents of various polar types was emphasised, and it was confirmed that no combination of polar influences of the usual kind could wholly account for results of the type obtained by Goldschmidt and others.[7] Thirdly, it became obvious that, even with the deeper knowledge of the nature of reactions and of the various polar factors involved, the combination of such effects was in general too intricate to enable a quantitative assessment of their influence on rate to be made. Thus it appeared impossible to pursue to a required degree of completeness a precise estimate of steric hindrance in various substituents (as a preliminary to a more advanced theory of the phenomenon) by a method which would give the spatial effects as a difference between the observed total effects of the substituents on rate and the estimated polar effects. It is important to note here that at this time (*ca.* 1935) the theory of substitution reactions had not advanced sufficiently to allow the calculation of steric hindrance effects from theoretical considerations (cf. later). Before a description of the most recent developments along such lines it is convenient to deal with the main directions of other approaches which have lately been made.

VII. *Directions of Further Advancement*

As a result of the theoretical developments discussed in the preceding section, the call for new approaches to the subject of steric hindrance became increasingly acute, and the advances in general theory indicated certain possible lines of enquiry. From the realisation that the phenomenon was dependent on reaction mechanism one clear avenue of approach was the consideration of data relating to reactions of a sufficiently varied character, including processes of a comparatively simple and fundamental nature. Here the accumulated results for the strengths of acids and bases of appropriate structural features are of interest. It is found that all *ortho*-substituted benzoic acids examined are stronger than benzoic and generally much stronger than the corresponding *meta-* and *para*-isomerides, as illustrated by the following thermodynamic dissociation constants, 10^5K, recorded by J. F. J. Dippy.[21] Substituents in the *ortho*-position decrease the strengths of anilines.[21] Data for the acidity constants of anilinium ions

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[20] E. D. Hughes, *Trans. Faraday Soc.*, 1941, **37**, 603.

[21] *Chem. Reviews*, 1939, **25**, 204.

are as follows, the figures representing the ratios of the equilibrium constants of the substituted and unsubstituted compounds:[22] o-CH_3 = 1·6, p-CH_3 = 0·33, o-Cl = 65, p-Cl = 3·8, o-NO_2 = 58,000, p-NO_2 = 3100.

	OH.	O·CH_3.	CH_3.	Cl.	NO_2.	O·C_6H_5.
Ortho	105·0	8·06	12·35	114·0	671·0	29·7
Meta	88·3	8·17	5·35	14·8	32·1	11·2
Para	2·9	3·38	4·24	10·5	37·6	3·00

Benzoic acid = 6·27

Earlier results of a similar, but less extensive and accurate, nature had from time to time been used to illustrate steric hindrance. It had been suggested, for example, that the strengths of *ortho*-substituted benzoic acids could be interpreted by supposing that spatial influences opposed the recombination of the ions but not their dissociation.[23] The effects in the equilibria are of a similar type to those exhibited in reaction rates and it has been lately concluded that they can hardly be attributed to the mere bulk of the substituent.[22] While spatial factors are often included in the complex effects which may contribute to the observed results relating to the strengths of acids and bases generally,[24] the view has recently been expressed that many of the special *ortho*-effects recorded in the literature may be due to chelation, to steric inhibition of resonance, to the short distances from which the inductive effects operate, or to the circumstance that the direction of the group dipole is different from that which it would have in the *meta*- or *para*-positions.[25, 26] The last two factors may possibly account for some comparatively small *ortho*-effects; the first two are, however, considered to be of more general importance where large effects are concerned, and are further discussed later. It has been suggested that similar factors (especially the chelation effect) are partly responsible for a number of proximity effects in general.[26, 27]

It has been explained that, though the kinetic method provided a valuable means of obtaining quantitative results, the analysis of the influence of vicinal substituents on reaction rates was not wholly successful; in particular, total effects expressed as changes in rate constants could not be split with certainty into component parts representing the separate influence of polar and steric factors. When this position was fully realised, the determination of rates at different temperatures and the analysis of rate constants in terms of the parameters of the Arrhenius equation, $k = Ae^{-E/RT}$, was yielding interesting results in other connections, and it was a natural development to apply the method later in the further investigations of steric hindrance.

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[22] Cf. ref. 9*b*, p. 204.

[23] B. Flürscheim, *J.*, 1909, **95**, 725.

[24] See especially important publications by H. C. Brown and his collaborators, *J. Amer. Chem. Soc.*, 1944, **66**, 435, and subsequent papers.

[25] Ref. 16*d*, p. 257.

[26] Ref. 16*b*, p. 241.

[27] H. B. Watson, *Ann. Reports*, (*a*) 1938, **35**, 243; (*b*) 1939, **36**, 215; (*c*) 1940, **37**, 229.

For convenience in discussion the Arrhenius equation may be written in the form $k = PZe^{-E/RT}$, where E is the energy of activation, Z is the collision number, and P is a probability factor which expresses the proportion of the collisions between sufficiently energised molecules which actually lead to the formation of the products of reaction. The collision frequency varies but little from one reaction to another, and it is clear that the marked effects of constitutional changes such as the introduction of polar substituents may be due to differences in E, in P, or in both. Initially, proximity factors had deliberately been avoided in the analysis of the effects of substituents, and it was found that the influence of atoms and groups comparatively far removed from the reaction centres often affected reaction rates mainly by changing the activation energies, the result being particularly evident when the polar effects were relayed powerfully from the distant location of the substituent to the site of reaction, as, for instance, in *para*-substituted aromatic compounds. The modified Arrhenius equation may be expressed in the logarithmic form, $\log_e k = \log_e PZ - E/RT$, and it is evident that if PZ remains constant a plot of E against $\log_{10} k$ for a given temperature is a straight line of slope $-2{\cdot}303RT$. It is found that the effects of *meta*- and *para*-substituents approximate to this behaviour in some reactions,[28] particularly the halogenation of phenolic ethers,[29] the benzoylation of anilines,[30] the alkaline hydrolysis of benzoic esters,[31] and the reaction of methyl iodide with dimethylanilines.[32] In others, however, appreciable changes in P are caused by substituents in the *meta*- or *para*-positions, notable examples being the acid hydrolysis of ethyl benzoates,[33] the alcoholysis of benzoyl halides,[34] and the hydrolysis of arylsulphuric acids.[35] Even in these cases the variations of P are not sufficiently great to outweigh the changes in E.

Interesting relationships have also been traced in certain instances between energies of activation and free energies of ionisation. For such substituents as those mentioned above, a plot of log k values referring to a given reaction of a series of aromatic compounds (*e.g.*, the hydrolysis of substituted benzoic esters) against the values of log K for the corresponding members of the related series of acids (*e.g.*, substituted benzoic acids) gives a straight line. Furthermore, when the values of log k for one reaction of a series of aromatic compounds (with *meta*- or *para*-substituents) are plotted against the values for the same members of the series in another reaction, a linear relationship is again indicated.[36] The energy changes due

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[28] See, for example, ref. 16*b*, p. 75.

[29] A. E. Bradfield and B. Jones, *J.*, 1928, 1006, 3073; A. E. Bradfield, W. O. Jones and F. Spencer, *J.*, 1931, 2907.

[30] E. G. Williams and C. N. Hinshelwood, *J.*, 1934, 1079.

[31] C. K. Ingold and W. S. Nathan, *J.*, 1936, 222; D. P. Evans, J. J. Gordon, and H. B. Watson, *J.*, 1937, 1430.

[32] (*a*) K. J. Laidler, *J.*, 1938, 1786; (*b*) D. P. Evans, H. B. Watson, and R. Williams, *J.*, 1939, 1345.

[33] E. W. Timm and C. N. Hinshelwood, *J.*, 1938, 862.

[34] G. E. K. Branch and A. C. Nixon, *J. Amer. Chem. Soc.*, 1936, **58**, 2499.

[35] G. N. Burkhardt, C. Horrex, and D. I. Jenkins, *J.*, 1936, 1649.

[36] L. P. Hammett, *Trans. Faraday Soc.*, 1938, **34**, 156.

to a given substituent in two separate processes being represented by ΔE_1 and ΔE_2, the relationship may be expressed in the form $\Delta E_1 = \alpha \Delta E_2$, where α is independent of the substituent. This may be interpreted to mean that for a given reaction a constant fraction of the polar influences of different substituents is transmitted and brought into effect as a factor modifying the activation energy.[37] The range of application of these linear laws is, no doubt, limited to those cases for which the electrical requirements of the different reactions are similar in nature, while the various substituents have analogous polar influences which the structure superposed between them and the reaction centre must be capable of transmitting without undue loss or modification. The relationships break down when the operating factors in the comparisons are of differing types [38] and notably when the substituents are situated near the reaction centre (see later). Quantitative relationships between group dipole moments and the effects of substituents on the dissociation constants of acids and on the activation energies of reactions have also been established in special cases where only the permanent polar influences, which alone are reflected in the dipole moments of normal molecules, are transmitted to the reaction centre, as, for example, with *meta*-substituents.[39]

It will be appreciated that the relationships discussed above give more quantitative form to ideas which were inherent in the electronic theory of organic reactions and particularly in the theory of the influence of the polar effects of substituent groups on reactivity. With this background it is clear that the analysis of reaction rate data at different temperatures might provide useful information concerning the influence of vicinal substituents and the nature of the factors responsible for proximity effects. It should be emphasized at the outset that the method loses some of its general diagnostic value because of the fact that *meta*- and *para*-substituents, which may be assumed to act mainly through their usual polar influences, are found to depart from the relationships in some reactions (see above). It should clearly be most applicable to the case of *ortho*-substituents participating in reactions for which the quantitative relationships were found to express the behaviour of the *meta*- and *para*-isomerides. It will also be obvious from the foregoing discussion that the method cannot be applied with the same quantitative significance to the reactions of aliphatic compounds.

Some results applicable to the type of analysis indicated were available in the literature in a scattered form before special investigations were instituted for the specific purpose of elucidating proximity effects. The data show that when the variable group is close to the reaction centre simultaneous variations in E and P usually occur, the changes in the P factors being generally more pronounced than with *meta*- and *para*-substituents for which P changes with E. For aliphatic structures this behaviour has been confirmed, by recent accurate measurements, in, for example, the

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[37] Cf. C. N. Hinshelwood, *Trans. Faraday Soc.*, 1938, **34**, 172.

[38] J. F. J. Dippy and H. B. Watson, *J.*, 1936, 436.

[39] H. B. Watson, *Trans. Faraday Soc.*, 1938, **34**, 165.

reactions of alkyl halides with tertiary bases.[40] No correlations of the type described for *meta*- and *para*-substituents are observed for *ortho*-groups, and the deviations from the linear relationships provide an estimate of the magnitude of the proximity effects.[36] Among reactions recently examined in detail, the most significant results have been obtained for the esterification of carboxylic acids [41] and the reaction of dimethylanilines with methyl iodide.[42] The analysis of large decreases of rate, which could be regarded as significant *ortho*-effects, showed that P is actually increased in these cases, the low rates being due to high values of E. It was thus concluded that steric hindrance is energetic rather than geometrical in character.[41] It is not uncommon for large values of E to be correlated with large values of P.[43] For the reaction of dimethylanilines with methyl iodide, substituents in the *meta*- or *para*-positions change only the energy of activation, leaving P practically constant.[32] The effect of moving a given substituent from the *para*- to the *ortho*-position is shown in the table below, where $E_o - E_p$ represents the difference in the energies of activation and P_o/P_p the ratio of the values of the non-exponential factors of the Arrhenius equation for the reactions of isomeric *ortho*- and *para*-substituted compounds :

	F.	$O{\cdot}C_6H_5$.	$O{\cdot}CH_3$.	Cl.	CH_3.	C_6H_5.
$E_o - E_p$ . . .	400	1100	1900	3700	6600	6200
P_o/P_p	1	3	9	40	250	400

It is concluded that the *ortho*-effect increases in the order F < OPh < OMe < Cl < CH_3 < Ph, a sequence which is unconnected with the sizes or polar characteristics of the groups. The effect is ascribed mainly to an interaction, in the transition complex, between the substituent and the unshared electrons of the nitrogen atom—a condition which would suppress the nucleophilic activity of the amine in reactions with alkyl halides and in analogous processes. The interaction postulated, which is related to chelation phenomenon, is expected also to reduce the electron-release capacity of the nitrogen atom in reactions occurring at, for instance, the *para*-carbon atom, and the interpretation could account for the results of J. von Braun.[13, 14] A similar explanation is suggested for other proximity effects.[26, 27] It is pointed out that the *ortho*-effect operates only when the reacting group contains an electron-donating atom (*e.g.*, NR_2, COR, CO_2R) and that, while it is manifested, for example, in the case of benzoyl chlorides, it is absent from the reactions of benzyl halides. The *ortho*-substituents must be capable of acting as electron-acceptors, and it is argued that the interaction with the unshared electrons of nitrogen or of carbonyl oxygen atoms in the transition complex may increase in importance in the same

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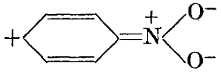
[40] C. A. Winkler and C. N. Hinshelwood, *J.*, 1935, 1147 ; cf. ref. 18*a*.

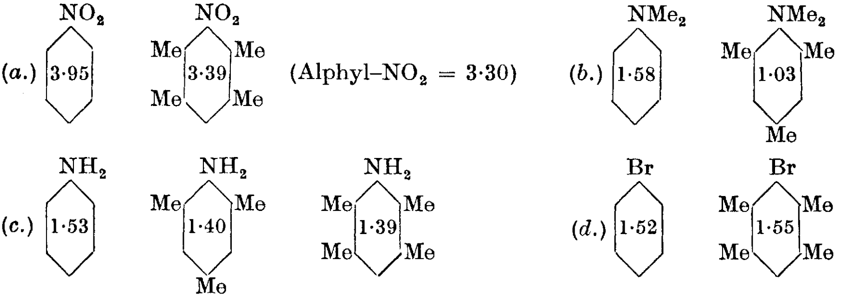
[41] C. N. Hinshelwood and A. R. Legard, *J.*, 1935, 587.

[42] D. P. Evans, H. B. Watson, and R. Williams, *J.*, 1939, 1348.

[43] See especially C. N. Hinshelwood, *Trans. Faraday Soc.*, 1938, **34,** 138.

order as that observed for the increasing magnitude of *ortho*-effects in the reaction of dimethylaniline with methyl iodide.

Information concerning a factor which is probably included in the influences designated *ortho*-effects has emerged from another direction. It is now well known that for many substituents, X, the dipole moments of aromatic compounds, Aryl–X, differ appreciably from those of the corresponding aliphatic compounds, Alphyl–X, because of the contribution of mesomerism.[44] In nitrobenzene, for example, the moment is considerably larger than the value for alkyl nitro-compounds (see figures below) because of resonance involving structures such as  In order that resonance of this type may occur, giving partial double-bond character to the links joining the aromatic nucleus and the attached substituents, it is considered that the molecule should be approximately coplanar. If the planar configuration is modified by repulsion forces involving adjacent groups, the effect should be detectable as, *inter alia*, a change of dipole moment. Evidence for such effects has been obtained,[45] as illustrated by the data shown below (*a*, *b*, and *c*), the figures in the centre of the formulæ being the dipole moments in Debye units (10^{-18} e.s.u.):



It is reasonable that the effect should be reduced when the critical group is comparatively small (cf. *b* and *c*) and that it should be non-existent for cylindrically symmetrical substituents such as the halogens (*d*). There is similar evidence that *ortho*-methyl groups inhibit the mesomeric effect of the carbonyl group in, for example, acetophenone. On the other hand, *ortho*-methyl groups produce no diminution of the moment of benzaldehyde, and models show that group interference is negligible in benzaldehyde but not in acetophenone.[46]

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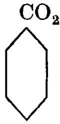
[44] (*a*) C. K. Ingold, *Ann. Reports*, 1926, **23**, 144; *Chem. Reviews*, 1934, **15**, 225; (*b*) L. E. Sutton, *Proc. Roy. Soc.*, 1931, *A* **133**, 668.

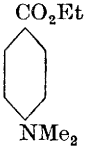
[45] See especially (*a*) R. H. Birtles and G. C. Hampson, *J.*, 1937, 10; C. E. Ingham and G. C. Hampson, *J.*, 1939, 981; (*b*) L. Pauling, "The Nature of the Chemical Bond", Cornell University Press, 1940, p. 221; (c) H. B. Watson, *Ann. Reports*, 1941, **38**, 124; (*d*) G. W. Wheland, "The Theory of Resonance", John Wiley & Sons, Inc., New York, N.Y., 1944, pp. 136, 160, 185, 272.

[46] R. G. Kadesch and S. W. Weller, *J. Amer. Chem. Soc.*, 1941, **63**, 1310.

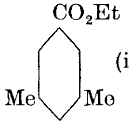
It has been suggested [47] that this factor is responsible for some of the peculiarities exhibited by compounds having *ortho*-substituents. It is a possible explanation, for instance, of results of the type obtained first by J. von Braun,[13, 14] who observed that *ortho*-groups render the *para*-carbon atom of dimethylaniline less reactive in substitution processes. The mesomeric effect of the dimethylamino-group is a facilitating influence in aromatic substitution and this may be reduced by the steric effect on resonance. In this connection, the results of F. H. Westheimer and R. P. Metcalf [48] are of special interest. These authors observed that a considerable inhibiting effect of a *para*-dimethylamino-substituent on the rate of alkaline hydrolysis of ethyl benzoate (a reaction of opposite polar requirements from the foregoing example) is largely eliminated by the presence of methyl groups in the *ortho*-positions to the deactivating (NMe_2) substituent [rates : (i)/(ii) = 34 ; (iii)/(iv) = 1·8].



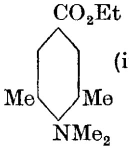
(i.)



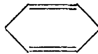
(ii.)



(iii.)



(iv.)

H. B. Watson [26] has expressed the view that his results for the reaction of dimethylaniline with methyl iodide cannot be attributed to steric effects on mesomerism since the alkylation process depends on the availability of electrons at the nitrogen atom itself and should, therefore, not be retarded by steric hindrance of resonance involving structures such as $\bar{:}$  $=\overset{+}{N}R_2$. He also recalls the fact that no connection with the sizes of the groups was discernible in his results. Watson suggests further that the formation of hydrogen bonds between the methyl substituents and electron-donating atoms in the adjacent groups (*e.g.*, nitrogen in NH_2 or NR_2) appears to furnish an alternative explanation of some of the data attributed to steric effects on resonance, but he concludes that, in addition to his chelation hypothesis, effects such as those postulated by V. Meyer and G. C. Hampson may find a place in a complete and comprehensive interpretation of all the phenomena associated with *ortho*-compounds.[26, 27b, 45c]

VIII. *Steric Hindrance in Relation to Reaction Mechanism*

It has been indicated that one of the principal reasons for delayed progress in the analysis of proximity effects was a lack of sufficient knowledge of reaction mechanism. As in other instances of effects accompanying chemical changes, including, for example, the stereochemical consequences, the phenomenon is intimately dependent on reaction mechanism, and it is only in comparatively recent years that appropriate advances have been made in the study of this basic subject. In the preceding sections it has been shown

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[47] See especially G. Baddeley, *Nature*, 1939, **144**, 444 ; and refs. 45*b*—*d*.

[48] *J. Amer. Chem. Soc.*, 1941, **63**, 1339.

how progress in the elucidation of the problem of steric hindrance closely followed developments in general chemical theory. Indications were obtained that the processes in which large *ortho*-effects were exhibited could be included in a certain category of reactions, and considerable advances were made in attempts to separate the polar influences of groups from special proximity factors and to elucidate the nature of the latter. It will be realised, however, that no general relationship with reaction mechanism had been established by the methods described, and that the background of knowledge regarding the course of reactions was not then sufficiently advanced to indicate crucial investigations concerning the problem of proximity effects generally.

The advanced development of fundamental principles which most closely affects the problem relates to replacement processes. Recent advances in the field of substitution reactions at saturated carbon centres in aliphatic compounds are particularly important here for two main reasons. First, progress in the study of the nature of proximity effects by the methods already described was especially lacking in the purely aliphatic examples. Secondly, the usefulness of the application of the principles of reaction mechanism may be expected to be most clearly demonstrated when the special features connected with reactions at aromatic side chains are, in the first instance, absent. Historically, developments in the study of the basic problem were already afoot when interest in the steric question was beginning to wane through lack of sustained progressive results. The ultimate realisation of the very close connection between the two problems has revived interest in the phenomenon of steric hindrance, added further significance to the study of substitution reactions, and provided a good example of the importance of the interdependence of various aspects of chemical change in the establishment of a comprehensive theory of reactions.

The substitution reactions of chief concern here are of the " nucleophilic " class (labelled S_N for convenience in reference) [9a], *e.g.*,

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

As indicated by the position of the dotted line in the representation, the type of replacement reaction considered is characterised by the condition that there is a transfer of electrons (represented by dots in the formulation) from Y to R and from R to X. The reagent may be either negative or neutral (provided it has unshared electrons), and the replaceable group may be either neutral or positive. The following three typical examples are from familiar reactions in organic chemistry; they refer to (1) the hydrolysis of alkyl halides, (2) the formation of alkylammonium salts from tertiary amines and alkyl halides, and (3) the decomposition of alkylammonium salts.

$$\text{(1)}\quad \overset{-}{\mathrm{HO}} + \mathrm{R{-}Cl} \longrightarrow \mathrm{HO{-}R} + \overset{-}{\mathrm{Cl}}$$

$$\text{(2)}\quad \mathrm{R_3N} + \mathrm{R{-}Br} \longrightarrow \mathrm{R_3}\overset{+}{\mathrm{N}}\mathrm{{-}R} + \overset{-}{\mathrm{Br}}$$

$$\text{(3)}\quad \overset{-}{\mathrm{Br}} + \mathrm{R{-}}\overset{+}{\mathrm{N}}\mathrm{R_3} \longrightarrow \mathrm{Br{-}R} + \mathrm{NR_3}$$

It has been shown that there are two distinct mechanisms for these substitution processes. The first is a one-stage mechanism, involving a synchronous electron transfer from Y to R and from R to X, *e.g.*,

$$\mathrm{Y{:}} + \mathrm{R{-}X} \longrightarrow \mathrm{Y{-}R} + \mathrm{{:}X}(S_{\mathrm{N}}2)$$

$$\left[\text{Example: } \underset{\substack{\text{Initial}\\ \text{state}}}{\overset{-e}{\mathrm{HO}} + \mathrm{R{-}Cl}} \longrightarrow \underset{\substack{\text{Transition}\\ \text{state}}}{\overset{\sim -e/2}{\mathrm{HO}}\cdots\cdots\mathrm{R}\cdots\cdots\overset{\sim -e/2}{\mathrm{Cl}}} \longrightarrow \underset{\substack{\text{Final}\\ \text{state}}}{\mathrm{HO{-}R} + \overset{-e}{\mathrm{Cl}}}\right]$$

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

$$\mathrm{R{-}X} \xrightarrow[\text{(slow)}]{} \overset{+}{\mathrm{R}} + \mathrm{{:}X},\ \text{followed by}\ \mathrm{Y{:}} + \overset{+}{\mathrm{R}} \xrightarrow[\text{(rapid)}]{} \mathrm{Y{-}R} \quad (S_{\mathrm{N}}1)$$

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

In the first mechanism, both reactants are simultaneously involved, while in the second only one reactant, R—X, is undergoing covalency change in the rate-determining stage of reaction. The mechanisms are therefore termed " bimolecular " and " unimolecular " respectively, and the numerical parts of the designations $S_{\mathrm{N}}2$ and $S_{\mathrm{N}}1$ are intended to signify this fundamental difference in molecularity. The two types may be characterised by their distinctive kinetic requirements, and this, together with other significant properties, is useful for purposes of diagnosis.[49]

Concerning the application of the concept of the duality of mechanism to the problem of proximity effects, it was realised that in many of the recorded reactions of aliphatic compounds, including some for which proximity factors appeared to be in evidence, the operative mechanism was uncertain and the problem of the superposition of polar and steric effects was a complicating factor.[9a] It was therefore important to determine first the broad steric consequences of the two mechanisms.[50] Part of the technique adopted for this purpose was to select alkyl groups for which steric factors could be considerable while polar effects were reduced by relay through a saturated carbon atom ; the rates of the nucleophilic replacement of halogen in the halides of these alkyl structures were then determined for a graded series of the type Me, $\mathrm{Me{\cdot}CH_2}$, $\mathrm{Me{\cdot}CH_2{\cdot}CH_2}$, $\mathrm{Me_2CH{\cdot}CH_2}$, $\mathrm{Me_3C{\cdot}CH_2}$, the measurements being carried out under different experimental

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[49] For summaries of the development of the general theory and for full references to the literature see especially the following papers : (*a*) refs. 9*a*, 18*a*, and 20 ; (*b*) W. A. Cowdrey, E. D. Hughes, C. K. Ingold, S. Masterman, and A. D. Scott, *J.*, 1937, 1252 ; (*c*) L. C. Bateman, K. A. Cooper, E. D. Hughes, and C. K. Ingold, *J.*, 1940, 925 ; (*d*) L. C. Bateman, M. G. Church, E. D. Hughes, C. K. Ingold, and N. A. Taher, *J.*, 1940, 979 ; (*e*) E. D. Hughes, *J.*, 1946, 968.

[50] I. Dostrovsky, E. D. Hughes, and C. K. Ingold, *J.*, 1946, 157 *et seq.* ; the results and conclusions were reported in a preliminary form for the Faraday Society's discussion on " Mechanism and Chemical Kinetics of Organic Reactions in Liquid Systems " in September, 1941 (*Trans. Faraday Soc.*, 1941, **37**, 603).

conditions, chosen so that the results for the bimolecular and the unimolecular mechanisms could be separately deduced.

Below are given some of the data obtained for a series of primary alkyl bromides; the figures are the relative second- and first-order rate coefficients (Et = 1) at 55° and 95° respectively for (*a*) the reaction with sodium ethoxide in ethyl alcohol and (*b*) the solvolytic reaction with aqueous formic acid.

Bromide :	Methyl.	Ethyl.	*n*-Propyl.	*iso*Butyl.	*neo*Pentyl.
(*a*) Relative rates of bimolecular etholysis (S_N2)	17·6	1	0·28	0·030	$4{\cdot}2 \times 10^{-6}$
(*b*) Relative rates of solvolysis [mainly unimolecular (S_N1)]	0·64	1	0·69	—	0·57

The first reaction is bimolecular throughout the series, and it was concluded from a detailed analysis of the results (see following section) that a steric factor is operative for all members except methyl, the result being particularly marked for the last compound (*neo*pentyl), for which the steric effect completely outweighs the polar influences. The solvolytic reaction is mainly unimolecular, and there is no indication of any considerable steric effect. The demonstration here is complicated by the incursion, in all cases except *neo*pentyl, of an appreciable bimolecular reaction with solvent molecules—a result which is difficult to avoid in the solvolytic reactions of primary alkyl halides. That the unimolecular mechanism is not sensitive to steric effects was confirmed by the consideration of evidence relating to other series of alkyl compounds for which the mechanism is well developed; for example, the first-order rate coefficients (sec.$^{-1}$) for the solvolysis of *tert.*-butyl and αα-diethyl*neo*pentyl chlorides in 80% aqueous ethyl alcohol at 25° are as follows: $CH_3{\cdot}CMe_2Cl = 0{\cdot}845 \times 10^{-5}$, $CMe_3{\cdot}CEt_2Cl = 11{\cdot}7 \times 10^{-5}$.

It may be concluded with some certainty that the bimolecular process is the mechanism with which large steric effects are likely to be associated in nucleophilic replacement reactions in suitable structural circumstances, and a qualitative theoretical interpretation is not difficult to conceive. In the transition state of the bimolecular mechanism, wherein the bond-forming properties of the reagent are engaged in promoting reaction, five groups are wholly or partly attached by covalency forces to a single carbon atom, a circumstance which may give rise to repulsion between the groups. Unimolecular reactions on the other hand should 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. Lest it should be concluded that the ionisation mechanism has no stereochemical requirements of any kind it should be recalled that the preferred configuration of a free carbon cation is planar.[51] P. D. Bartlett and L. H. Knox have shown that the unimolecular mechanism

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[51] Cf. refs. 49*b* and *d*.

of substitution is not available to a structure for which the flattening of the ion cannot occur.[52]

The conclusions derived from the application of the concept of the duality of mechanism to the question of steric factors have been utilised in the solution of a number of outstanding difficulties in the interpretation of reactivity data,[50] but these may be more appropriately considered after a more quantitative treatment of steric effects in bimolecular substitutions.

IX. *Steric Factors in Relation to the Detailed Configuration and Dimensions of Transition States*

Steric effects in nucleophilic substitution reactions having been shown to be mainly confined to the bimolecular mechanism, the development of a more quantitative treatment may be reviewed. Following the idea of a synchronous bond-forming and bond-breaking process, first explained in a clear manner by G. N. Lewis [17] as a reaction leading to inversion of configuration, the physical basis of the mechanism, including the stereochemical implications, was discussed by M. Polanyi and by A. R. Olson and their co-workers, particularly in relation to the reaction between an anion and a neutral molecule, such as an organic halide.[53, 54] Polanyi and his collaborators suggested that substitutions affected by anionic reagents ("negative mechanism") involve inversion of configuration and are subject to steric inhibition, while those in which the attack is by a cation ("positive mechanism") result in retention of configuration and are not sensitive to steric effects. They pointed out that the dipole field in a link such as $\overset{\delta+}{C}—\overset{\delta-}{Cl}$ would preferentially direct an anionic reagent such as $\overset{-}{I}$ to the position leading to inversion. Olson and his co-workers employed substantially the same idea, pointing out also that, since the carbon " eigenfunction " involved in the carbon–halogen bond extends beyond the carbon atom on the side away from the halogen, there will be a tendency for bond-formation at the face of the tetrahedron opposite the halogen. E. D. Hughes, C. K. Ingold, and their collaborators did not make the net charges of the interacting species a primary basis for the classification of substitutions (preceding section), and, having observed in many structures that inversion of configuration is the rule for bimolecular substitutions (S_N2), they explained that the transition state which leads to inversion (I) will have a smaller energy than that which corresponds to retention of stereochemical form (II). The relative energies of the transition states are assessed by application of the exclusion principle. Transition states such as (II) will be less stable than

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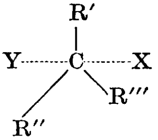
[52] *J. Amer. Chem. Soc.*, 1939, **61**, 3184.

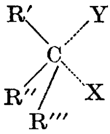
[53] See especially N. Meer and M. Polanyi, *Z. physikal. Chem.*, 1932, *B*, **19**, 164 ; E. Bergmann, M. Polanyi, and A. L. Szabo, *ibid.*, 1933, **20**, 161 ; *Trans. Faraday Soc.*, 1936, **32**, 843 ; M. Polanyi, *Proc. Roy. Soc.*, 1934, *B*, **116**, 203 ; R. A. Ogg and M. Polanyi, *Trans. Faraday Soc.*, 1935, **31**, 604 ; E. C. Baughan and M. Polanyi, *ibid.*, 1941, **37**, 648.

[54] A. R. Olson, *J. Chem. Physics*, 1933, **1**, 418 ; A. R. Olson and F. A. Long, *J. Amer. Chem. Soc.*, 1934, **56**, 1294 ; 1936, **58**, 393.

the "linear" state (I) because of the large positive exchange integrals between the electrons of the non-linearly split bond and those of the full bonds.[55]



(I.)



(II.)

In a process of the type under discussion the nature of the "bonding" forces, associated particularly with the Y–R and R–X linkages, will clearly be a prime consideration, 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 in comparison with the bonding energies, but in special structural circumstances non-bonded atoms are brought so close together that the non-bonding energy is of the same order of magnitude as the bonding energy, and in these circumstances steric hindrance may be said to be in operation. In assessing the critical distances between the atoms, and the related non-bonding forces, it is necessary to consider not only the usual models of molecules in their normal states but also the configurations of the "activated" or "transition" states of reactions. The important quantity which determines the influence of steric factors on reaction rates is the difference between the non-bonding energy of the transition and initial states. Non-bonding energies of initial states are usually negligible, however, and steric factors can generally be estimated in terms of the compression energies between non-bonded atoms in the transition states of reactions.[50] 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 a quantitative theory of steric hindrance, and it is only recently that our knowledge of reaction mechanism has advanced far enough to provide, as a basis for computation, sufficiently detailed and accurate models of the transition-state configurations of important reactions.

It is now generally agreed that in the transition state of a bimolecular nucleophilic substitution the nuclei of the substituting atom Y, of the carbon atom C_α at which substitution takes place, and of the displaced atom X, are collinearly arranged, whilst the nuclei of the other three atoms to which C_α is covalently bound lie in directions from C_α inclined at angles of 120° to one another, and in a plane which passes through C_α and is perpendicular to the line of Y and X. With this model of the transition state as basis, the distances between the nuclei of the attacking and displaced atoms and those of all the other atoms of the structure can be calculated, and a consideration of these distances provides an estimate of the relative importance of the steric factor in different compounds. In a further evaluation of steric effects in terms of energy, any deviations from the idealised model which could reduce the total energy must be taken into account.[56] The

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[55] See especially ref. 49*b*.

[56] See especially ref. 50, p. 173.

configuration adopted fixes the directions of the bonds of C_α and the positions of atoms to which it is directly linked. The bonds of other carbon atoms are assumed to conform to the usual tetrahedral arrangement, and, with regard to the positions of atoms which are linked to β-carbon atoms, an orientation about the C_α–C_β bond is selected so 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 a normal length, corresponding to summed covalent radii. The lengths of the partial, and partially ionic, bonds YC_α and $C_\alpha X$, have to be specially assessed ;[57] in first approximation they may be estimated by adding the covalent radius of carbon to the mean of the covalent and negative ionic radii of Y or X. On the basis of these considerations detailed models are set up for different structures, and the distances (" model distances ") between the nucleii of Y or X and those of the carbon and hydrogen atoms of the alkyl groups are calculated, for both the transition states and the initial states. It is then necessary to compare these distances with the distances below which compression would occur (" touching distances "). The latter, the van der Waals distances between different pairs of atoms, are obtained by the summation of appropriately determined van der Waals radii. By subtracting the model distances from the touching distances, the " compression " relating to the initial or transition state is obtained in respect of each model distance which is shorter than the touching distance. For such groups as methyl, ethyl, *iso*propyl, and *tert.*-butyl (α-methylated series), and ethyl, *n*-propyl, *iso*butyl, and *neo*pentyl (β-methylated series) there are no appreciable compressions in the initial states. Hence, although in principle the energy of steric hindrance must be calculated as a difference of compression energy in the initial and transition states, in practice attention may be confined to the transition state.

The compressions (in A.) for various alkyl groups in the transition states of the bromine exchange reaction, $\bar{\mathrm{Br}} + \mathrm{R{\cdot}Br} \longrightarrow \mathrm{Br{\cdot}R} + \bar{\mathrm{Br}}$, are given in the table below, the figures in parentheses being the numbers of compressed distances affecting the energies of the states.

	$H_\alpha \ldots Br$	$C_\beta \ldots Br$	$H_\beta \ldots Br$	$C_\gamma \ldots Br$	$H_\gamma \ldots Br$
$CH_3{\cdot}CH_2{\cdot}CH_2$ . . .	* 0·13(4)	† 0·22(2)	† 0·58(2)	—	—
$(CH_3)_2CH{\cdot}CH_2$ . . .	,,	,,	0·72(1)	0·48(2)	0·34(4)
$(CH_3)_3C{\cdot}CH_2$	,,	,,	—	1·05(2)	0·98(4)

* Applies also to Me (6), Et (4), and *iso*Pr (2).
† ,, ,, ,, Et (2), *iso*Pr (4), and *tert.*-Bu (6).

It will be observed that appreciable compressions are indicated for all members except methyl, and that the position of the *neo*pentyl structure is particularly striking. Only the *neo*pentyl group involves compressions of

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[57] For a discussion of this point see A. G. Evans, M. G. Evans, and M. Polanyi, *J.*, 1947, 558 ; I. Dostrovsky, E. D. Hughes, and C. K. Ingold, *J.*, 1948 (in the press).

the order of 1·0 A., and the interpenetration figures alone give clear indications of the origin of the large rate decrease which is associated with this structure in bimolecular substitutions (preceding section). Owing to the rapid steepening which all repulsive energy curves exhibit when the distance is decreased beyond a certain more or less critical amount, an effect due to repulsion energy may be expected to become prominent fairly suddenly. A qualitative similarity with reference to steric effects is to be expected of many of the commoner nucleophilic substitutions, for it is found that the compressions are not very sensitive to changes in the size of the attacking and displaced groups. It is not possible to review here the more intricate and more quantitative step of evaluating the absolute significance of the compressions in terms of energy and the comparisons which have been made with experimental data. Full details of these matters are given in the original papers.[56] The main conclusion of the whole analysis is that the series of groups from ethyl to *iso*butyl (β-methylated series) or ethyl to *tert.*-butyl (α-methylated series) exert a relatively weak (though increasing) steric effect, with superposed polar effects, while the *neo*pentyl group has an outstandingly strong steric effect which completely outweighs its polar influence.

The results of the investigations summarised in the last two sections have been utilised in a review of data relating to many reactions.[56] Thus it has been shown that much of the evidence formerly held to support the Thorpe–Ingold valency-deflexion hypothesis can be consistently explained as an effect of steric hindrance, and certain reactions of alcohols [58] and of carboxyl compounds have been interpreted on the basis of the more complete picture of unimolecular and bimolecular processes which is now discernible. With both alcohols and carboxyl compounds, reaction mechanisms are available which are related to each other like the unimolecular and bimolecular mechanisms of simple nucleophilic substitution, and it is found that the bimolecular type of mechanism only is sensitive to steric hindrance. Calculations of steric effects have been applied with success to the base-catalysed addition of methyl alcohol to aryl *iso*cyanates.[59]

Analogous calculations of steric factors in some replacement reactions of alkyl halides have been made by A. G. Evans and M. Polanyi. These authors conclude, however, that the increase in repulsion energy may account for the whole of the decrease in the bimolecular reaction rates in the primary to tertiary halide series (α-methylated series). The main differences of views involved have been discussed elsewhere.[60] Calculations of steric hindrance effects have also been applied to the polymerisation of olefins.[61]

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[58] Cf. W. Gerrard and A. Nechvatal, *Nature*, 1947, **159,** 812 ; I. Dostrovsky, E. D. Hughes, and C. K. Ingold, *ibid.*, 1947, **160,** 901.

[59] J. W. Baker and J. B. Holdsworth, *J.*, 1947, 713.

[60] A. G. Evans and M. Polanyi, *Nature*, 1942, **129,** 608, 665 ; A. G. Evans, *ibid.*, 1946, **157,** 438, and **158,** 586 ; *idem, ibid.*, 1947, **159,** 166 ; *idem, Trans. Faraday Soc.*, 1946, **42,** 719, and *Mem. Proc. Manchester Lit. Phil. Soc.*, Vol. 87 ; E. D. Hughes and C. K. Ingold, *Nature*, 1946, **158,** 94 ; *idem, ibid.*, 1947, **159,** 166 ; *idem, Trans. Faraday Soc.*, 1948, **43,** 798 ; see also ref. 57.

[61] A. G. Evans and M. Polanyi, *Nature*, 1943, **152,** 738.

In a brief review of progress in a broad field with many diverse aspects, one is conscious of omissions. Special attention should be drawn to a particular development relevant to the discussion—the recent computations of the rates of racemisation of optically active derivatives of diphenyl.[62]

A basis has now been established for a more precise and fruitful era in the development of experimental and theoretical studies of steric hindrance effects generally.

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[62] F. H. Westheimer and J. E. Mayer, *J. Chem. Physics*, 1946, **14**, 733; F. H. Westheimer, *ibid.*, 1947, **15**, 252 ; see also an outline of a general method for the evaluation of steric strain (T. L. Hill, *ibid.*, 1946, **14**, 465).