606. *Some Observations concerning Steric Hindrance and the Effects of Substituents on the* ortho : para *Ratio in Aromatic Substitution.*

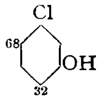
By P. B. D. de la Mare.

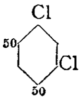
The views of Dewar (this vol., p. 463) concerning the effects of substituents on aromatic reactivity are criticised.

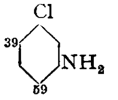
Many writers have attempted to translate into semi-quantitative terms the qualitative theory of aromatic reactivity associated with the names of Lapworth, Robinson, and Ingold. One approach, in terms only of the electrostatic effects of substituent groups, has recently been justifiably criticised by Waters (*J.*, 1948, 727), and by Dewar (this vol., p. 463). Formally a more satisfactory treatment is that of Wheland (*J. Amer. Chem. Soc.*, 1942, **64**, 900), who includes both inductive and mesomeric effects by means of molecular-orbital calculations. Dewar (*loc. cit.*) has extended these calculations, but has, in the comparison with experimental findings, chosen data which, in certain important cases, either require revision or are capable of other interpretations, as will be pointed out below.

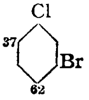
The Orienting Effect of Halogen Substituents.—Halogen substituents direct substitution into the *ortho*- and *para*-positions of the benzene nucleus, but the rates of these substitutions are usually less than those of similar substitutions in benzene. For this reason, these substituents have always been of the greatest importance and interest in theories of aromatic reactivity. De la Mare and Robertson (*J.*, 1948, 100) have recently discussed in a qualitative manner the problems raised by the available data on the halogenation and nitration of the halogenobenzenes and related compounds. On the other hand, similar, but inaccurate, data are quoted by Dewar (*loc. cit.*) to support his theoretical deductions. Thus it is stated that for each of the three types, into which he believes that substituents may be divided, the rate of substitution in a series of similarly substituted benzenes falls with increasing electron affinity of the substituent, and this is said to be shown clearly by the relative rates (Ph = 1) of nitration of the halogenobenzenes determined by Ingold and Shaw (*J.*, 1927, 2918), *viz.*: PhI, 1; PhBr, 0·36; PhCl, 0·025; PhF, 0·0107. These values are, however, taken from a much wider, though rough, survey of groups of very different types. Revised values were later recorded by Bird and Ingold (*J.*, 1938, 918) as the result of a more quantitative study of halogen substituents in particular. They found that the rate series passes through a minimum, the correct order being $F > I > Cl > Br$ both for overall and for *para*-nitration, but $I > F > Br > Cl$ for *ortho*-nitration. The minimum was confirmed by Benford and Ingold (*J.*, 1938, 929), using a different technique, and has again been obtained by Hughes, Ingold, and Reed (private communication). Bromination of the 1-halogenonaphthalenes also passes through a minimum, as shown by de la Mare and Robertson (*loc. cit.*), who also showed that chlorination of fluorobenzene is much more rapid than chlorination of chlorobenzene or of bromobenzene. Dewar's theory, therefore, does not appear to reveal the most important and characteristic feature of such reactions, namely the relatively great reactivity of the fluoro- and the iodo-substituted compounds.

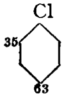
A related over-simplification of the effects of halogen substituents on the rates of aromatic substitutions is apparent in the deduction (Dewar, *loc. cit.*), from the series given below, where the figures represent the proportions of isomeric substitution products produced in nitration, that the *para*-directive power of groups decreases in the order $O > Cl > N > Br > I$, which is thought also to be the order of decreasing electron affinity.



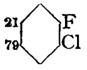


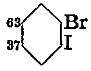






The present writer believes that to speak of bromine as "more *para*-directing" than iodine is misleading, when in fact substitution *para* to an iodine substituent appears to be more rapid than similar substitution *para* to a bromine (or even to a chlorine) substituent. Again, it seems reasonable to deduce, from the data on the *o*-halogenobenzenes given below (Ingold and Vass, *J.*, 1928, 417; Holleman, *Rec. Trav. chim.*, 1915, **34**, 204), that iodine is indeed more powerfully *para*-activating than bromine.





The Function of the Reagent in Determining Aromatic Reactivity.—Different substitution reactions are affected by substituents in ways which are markedly different. Thus the ratio $k_{\text{PhMe}}/k_{\text{PhH}}$ is much greater for halogenation (*ca.* 400) than for nitration (*ca.* 25) (de la Mare and Robertson, *J.*, 1943, 279). Similarly, *para*-halogenation of fluorobenzene is more rapid, though *para*-nitration is less rapid, than that of benzene. These observations suggest that electronic polarisability is more important in halogenation than in nitration, and that thus we may regard halogenation as a more powerfully "electron-demanding" reaction than nitration when electromeric polarisability is more important than inductomeric polarisability.* The latter may, however, in some circumstances become of predominant importance, particularly when electrophilic attack is by a fully ionic reagent, as in nitration by the nitronium ion.

The nature of the reagent is, therefore, of great importance in determining the *ortho* : *para* ratio, and kinetic information concerning the character of the reagent and the course of the reaction is usually desirable. Thus the nitration of acetanilide in sulphuric acid is not necessarily that of the salt Ph·NH·CMe:OH; for a minute quantity of the free base, in equilibrium with the much less reactive salt, might well be the actual molecule undergoing reaction, and kinetic measurements are required to establish this point. It is interesting to remember that acetanilide is brominated to give almost entirely *p*-bromoacetanilide, though chlorination gives also much of the *ortho*-derivative.

Steric Hindrance in Aromatic Substitution.—In nucleophilic substitution reactions, it is now generally agreed that steric effects may be large, even for the reactions of comparatively simple molecules, provided that the reaction mechanism requires more than one molecule to participate in the rate-determining part of the reaction. Thus for the bimolecular reaction between alkyl bromides and bromide ions in acetone (as for other similar processes) the following rates (extrapolated to 25°), activation energies, and "frequency factors" have been obtained (cf. de la Mare, England, Fowden, Hughes, and Ingold, *J. Chim. physique*, 1949, **45**, 236):

Methyl bromide: $k_2 = 13{,}400 \times 10^{-5}$, $E = 15{\cdot}9$ kcals., $\log_{10} pz = 10{\cdot}8$;
Ethyl bromide: $k_2 = 165 \times 10^{-5}$, $E = 17{\cdot}6$ kcals., $\log_{10} pz = 10{\cdot}1$.

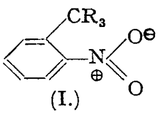
About half of such observed differences in rate and in activation energy are attributed by Dostrovsky, Hughes, and Ingold (*J.*, 1946, 173; 1948, 1283) to steric hindrance, though A. G. Evans (*Nature*, 1947, **159**, 166) prefers to ascribe the whole of this decrease in rate to steric hindrance.

Thus steric effects may account for quite large rate-differences even when structural circumstances are not particularly favourable to their operation. Very small steric hindrance to aromatic substitution reactions could, therefore, result in large changes in the *ortho* : *para* ratio. Thus if, as Dewar (*loc. cit.*) believes, steric hindrance reduces the ½-*ortho* : *para* ratio from 0·8 to almost zero in the series $Ph{\cdot}CH_3$, $Ph{\cdot}CH_2Me$, $Ph{\cdot}CHMe_2$, $Ph{\cdot}CMe_3$, then surely a large proportion of the change in the same ratio from 0·8 to 0·1 in the series $Ph{\cdot}CH_3$, $Ph{\cdot}CH_2Cl$, $Ph{\cdot}CHCl_2$, $Ph{\cdot}CCl_3$, must also be attributable to steric hindrance; and therefore to interpret this set of data as showing the effect of increasing the electron affinity of an inductive substituent is of very doubtful validity. Similarly, steric hindrance must be considered important when substitution occurs *ortho* to any bulky substituent, or when the reagent itself is large.

* A theoretical explanation of the importance of electromeric polarisability in halogenation may be that halogenation involves the formation of a reactive intermediate which is more stable than the corresponding entity produced in nitration. This is suggested by the existence of bromination processes of high order with respect to halogen, and by the effectiveness of acids as catalysts for bromination and for chlorination; the latter is associated by de la Mare and Robertson (*loc. cit.*) with the necessity of breaking the halogen–halogen link for completion of the reaction. On the other hand, removal of a proton seems kinetically to be unimportant both in nitration, as shown by the work of Melander (*Nature*, 1949, **163**, 599), and in halogenation, as shown by the absence of appreciable catalysis by bases (cf. Robertson, Dixon, Goodwin, McDonald, and Scaife, this vol., p. 294).

The Transition State of Aromatic Substitution.—A satisfactory theory of *ortho* : *para* ratios will, therefore, necessitate assessment of quite small steric effects. The simplest type of bimolecular electrophilic replacement is likely to occur when the reagent is a positive ion, as perhaps in nitration by the NO_2^+ ion. An estimate of compressions between non-bonded atoms in the transition state of such a reaction would, however, involve too many assumptions to be profitable at present.* Thus a possible model of the transition state for nitration has been proposed by Hughes, Ingold, and their co-workers (cf. *J.*, 1937, 1257; 1941, 608), and is supported by Waters (*loc. cit.*). The incoming reagent attacks from above the plane of the aromatic ring, displacing the proton downwards; and the resulting configuration of the product contains a nitro-group in which the nitrogen and the two oxygen atoms are approximately in the plane of the ring.

To estimate the bond-lengths and bond-angles in the transition-state configuration, with both nitrogen and hydrogen partly bonded to carbon, and including the energetically most favoured positions for the oxygen atoms of the nitro-group, presents great difficulty. A qualitative solution of the problem whether or not such effects will be of major importance in determining *ortho* : *para* ratios can, however, be reached from consideration of the steric effects existent in the substitution products themselves. It has often been assumed that such steric compressions are not of importance except in very complicated molecules. Evidence is beginning to accumulate, however, that even in comparatively simple molecules compressions exist, which may not be of importance or easily detectable by studies of isomerism or of bond angles, but which need to be considered in studies of those small energy changes which are revealed in comparisons of chemical reactivity. Thus Heath and Linnett (*Trans. Faraday Soc.*, 1948, **44**, 561) have shown that the properties of compounds such as carbon tetrachloride are best explained by assuming compressions between the chlorine atoms. The fact that the *o*-nitro-groups in picryl iodide are at 80° to the plane of the ring (*J.*, 1940, 1398) indicates considerable interaction between them and the iodine atom. Even *m*-dinitrobenzene appears to have a structure in which the nitro-groups are distorted out of the plane of the benzene ring (Archer, *Proc. Roy. Soc.*, 1946, *A*, **188**, 51), which suggests that there may be appreciable steric interaction between a nitro-substituent and the hydrogen atom *ortho* to it; and approximate estimate of the distance, in the normal state of the *o*-alkyl-substituted nitrobenzene (I) between the *ortho*-carbon atom and the oxygen atom of the nitro-group, gives the C—O distance as 2·5 A. The radius of the smallest such *ortho*-substituent, namely the methyl group, is probably about 2·0 A., and that of oxygen about 1·4 A. (Pauling, "The Nature of the Chemical Bond," Cornell University Press, N.Y., 1945, p. 189); so there would appear to be a compression, in *o*-nitrotoluene, of about 0·9 A. This compression would have to be overcome for completion of *ortho-*, as compared with *para-*, nitration, and though it might be relieved by bond-bending and would probably be smaller in the transition state of the reaction than in the final product, yet it seems unlikely that it is a negligible factor in determination of the proportions of isomerides found in the nitration even of toluene. All the more important, therefore, is it to consider steric hindrance of substitution *ortho* to groups larger than the methyl group (*e.g.*, the CCl_3 group).



(I.)

Factors Important in Determining the ortho : *para Ratio.*—The main features of the experimental data on *ortho* : *para* ratios seem to the author to be interpretable in the following way.

(1) For most *ortho–para*-directing substituents, the $\frac{1}{2}$-*ortho* : *para* ratio is less than unity. Two factors contribute to this effect :

(*a*) Steric considerations favour *para*-substitution. Steric hindrance is probably appreciable even *ortho* to the methyl group, and is important for all larger substituents, as is shown by the decrease in the $\frac{1}{2}$-*ortho* : *para* ratio from toluene to *tert.*-butylbenzene.

(*b*) The greater stability of *para-* than of *ortho*-quinonoid structures favours *para*-substitution, since the transition states for the reaction are analogous to such quinonoid forms. The importance of this factor has recently been stressed by Waters (*loc. cit.*), and by other writers (cf. *J.*, 1941, 608; *Trans. Faraday Soc.*, 1941, **37**, 746).

(2) Substitution is favoured *ortho* to groups polarisable by induction, and occasionally this factor is sufficient to reverse the order expected on steric grounds, as shown in nitration by the increase in the $\frac{1}{2}$-*ortho* : *para* ratio from fluorobenzene to iodobenzene.

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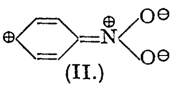
* Halogenation processes, under preparative conditions or indeed in any circumstances in which the kinetics have been adequately studied, do not seem to involve the ions Cl^+ or Br^+ (cf. de la Mare and Robertson, *loc. cit.*; Robertson, Dixon, Goodwin, McDonald, and Scaife, *loc. cit.*; Bradfield and Jones, *Trans. Faraday Soc.*, 1941, **37**, 726; Bradfield, Davies, and Long, this vol., p. 1389).



(II.)

(3) For many *meta*-directing substituents in which a mesomeric deactivation of the aromatic ring is important, the $\frac{1}{2}$-*ortho* : *para* ratio rises much above unity (cf. Dewar, *loc. cit.*, Table IV). Here quinonoid structures [*e.g.* (II)] may again be more important in transferring charge to the *para*- than to the *ortho*-position, and thus, in this case, in deactivating the *para*- relatively to the *ortho*-position by electrostatic repulsion of the reagent (or otherwise).

(4) *ortho*-Substitution depends, for some compounds, markedly on the reagent. Three distinct circumstances may be recognised :

(*a*) Substitution *ortho* to a polarisable group should be favoured by an ionic, as compared with a neutral or dipolar, reagent, as has elsewhere (de la Mare and Robertson, *loc. cit.*) been suggested to explain the differences between the effects of halogen substituents on the nitration and halogenation of aromatic compounds.

(*b*) *ortho*-Substitution should be favoured by a small, as compared with a large, reagent.

(*c*) *ortho*-Substitution should be favoured by chelation in the transition state between the reagent and the *ortho*-substituent, as has in certain cases been suggested (*e.g.*, by Dewar, *loc. cit.*).

(5) Similar considerations apply to substitution in the polysubstituted benzenes. It is usual to assume that groups affect additively the energy of activation, as is shown to be reasonable, in favourable circumstances, by Bradfield and Jones (*loc. cit.*). Similarly Condon (*J. Amer. Chem. Soc.*, 1948, **70**, 1963) has correlated the rates of halogenation of the methylbenzenes on such a basis. It is necessary, however, to make appropriate allowance for steric effects and to allow for the mutual interaction of the various substituents. The latter influence is of profound importance, as has been pointed out by Dewar (*loc. cit.*), when two groups of opposite mesomeric character (*e.g.*, OMe and NO_2) are situated *ortho* or *para* to each other. In such circumstances, these groups interact, and, in doing so, affect their own directive power and also partly localise the remaining unsaturation electrons.

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