Some Observations concerning the Theory of Aromatic Substitution.

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A relation proposed by Brown and Nelson (*J. Amer. Chem. Soc.*, 1953, **75**, 6292) between the partial rate factors for electrophilic substitution *meta* and *para* to substituents in the aromatic nucleus is discussed with reference to earlier theories.

A NUMBER of attempts have of recent years been made to develop theories which correlate the reactivities of substituted aromatic compounds in their reactions with electrophilic reagents. It is generally accepted that the effects of two substituents in the benzene ring are often nearly additive and affect principally the energy of activation of the substitution reaction (cf. Bradfield, *Trans. Faraday Soc.*, 1941, **37**, 727; Condon, *J. Amer. Chem. Soc.*, 1948, **70**, 1963; de la Mare and Vernon, *J.*, 1951, 1574). Brown and Nelson (*J. Amer. Chem. Soc.*, 1953, **75**, 6292) have discussed the differences between different reagents in aromatic substitution reactions. They suggest as an empirical generalisation that the importance of *meta*-substitution is related to the " activity " of the attacking species. They use the relative reactivity of toluene to benzene, or better the partial rate-factor f_p^{Me} for the *para*-position of toluene, as an inverse measure of the latter. A plot of $\log_{10} f_p^{Me}$ against $\log_{10}(f_p^{Me}/f_m^{Me})$, where f_m^{Me} is the partial rate factor for substitution at the *meta*-position in toluene, is approximately linear, showing that the relative amount of *meta*-substitution increases with increase in " activity."

An exactly linear relation between $\log_{10} f_p$ and $\log_{10} (f_p/f_m)$ is a direct consequence of the type of treatment used in most of the well-known attempts to treat quantitatively the theory of aromatic substitution. It simplifies the discussion to transform Brown and Nelson's relation $\log_{10} (f_p /f_m) = A + B \log_{10} f_p$ into the equivalent form :

$$\log_{10} f_m = -A + (1 - B) \log_{10} f_p \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

It should then be appreciated that, for a completely undiscriminating reagent, $f_m = f_p = 1$, whence $A = 0$, and therefore :

$$\log_{10} f_m = C \log_{10} f_p \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

where C is constant for any given substituent and independent of the substituting agent.

Consider now such a theory as that of Ri and Eyring (*J. Chem. Phys.*, 1940, **8**, 433). These authors write the equation :

$$k_y = \text{const. } [\exp - (\Delta F + e_y e_n/rD)/\boldsymbol{k}T] \quad . \quad . \quad . \quad . \quad . \quad (3)$$

Here e_y is the fractional electronic charge in excess of the normal on carbon atom C_y at which substitution occurs at rate k_y; r is the transition-state separation between the reagent and C_y; e_n is the charge on the reagent; ΔF is the free energy of activation for substitution at a carbon atom in benzene; and the other symbols have the customary significance. It follows, by taking logarithms of both sides of equation (3), that :

$$\log_e (k_y/k_H) = - (e_y e_n)/rD\boldsymbol{k}T = \log_e f_y$$

whence

$$\log_{10} f_m = (e_m/e_p) \log_{10} f_p$$

and therefore equation (2) is a consequence; and the same would be true of any modification of this theory in which one might write :

$$k_y = \text{const. } \{\exp[-\Delta F + e_y f(\text{R})/\alpha]/\beta\} \quad . \quad . \quad . \quad . \quad . \quad (4)$$

Here we are considering α and β as constants, and the effect of varying the reagent, f(R),* is multiplied by e_y in the exponent which determines the free energy of activation for the substitution.

Thus it appears that Brown and Nelson's empirical relation is a direct consequence of this type of theory, in which the free energy of activation for substitution at various positions is considered to be proportional to the electronic charge at those positions in excess of that at a carbon atom in benzene. Hence, their results, so far as these bear out the claimed relation, might be quoted in support of these theories, though Brown and Nelson consider such theories as that of Ri and Eyring (*loc. cit.*) and of C. C. Price (*Chem. Reviews*, 1941, **29**, 39; *J. Amer. Chem. Soc.*, 1951, **73**, 5833) to be unsatisfactory treatments. Brown and Nelson make incorrect use of the theory in discussing the effect of halogen and other substituents. They appear to overlook the fact that graphs of $\log_{10} f_p$ against $\log_{10} (f_p/f_m)$ must pass through the origin, since, as has been pointed out above, for a completely undiscriminating reagent, whatever the substituent, $f_p = f_m = 1$;† and so these graphs will never be parallel with that for toluene, but will diverge at different slopes from the origin.

It is a further consequence of the type of treatment which we have been considering, that a relation of the Hammett type should apply to the partial rate factors both for *para*- and for *meta*-substitution. This has been pointed out explicitly by Price (*locc. cit.*). It is interesting, therefore, to compare the standard Hammett substituent (σ) constants (cf. Jaffe, *Chem. Reviews*, 1953, **53**, 191) with the data available for electrophilic substitution. The most accurate information for this type of comparison comes from the partial rate factors for *para*-nitration established by Ingold, Hughes, and their co-workers (cf. Ingold, " Structure and Mechanism in Organic Chemistry," G. Bell & Sons, London, 1953), but useful extension of these comes from the rates of halogenation of the substituted benzenes, compiled by Robertson, de la Mare, and Swedlund (*J.*, 1953, 782). In the Table is shown the information used to calculate the partial rate factors for these reactions, and the plots are given in Fig. 1.

It is clear from the Figure that there is no way in which the Hammett substituent

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* In Ri and Eyring's theory, the effect of the reagent is introduced by a term e_n/rD. Thus, on this theory, substituent effects would be expected to be reflected in the free energies, and hence in the rates of substitution, to a greater extent when the reagent bears a full positive charge than when the reagent bears only a partial charge, unless r and D vary with the reagent more than seems probable. Fig. 1 shows that substituent effects are on the whole smaller in nitration by the nitronium ion than in halogenation by the halogen molecule. It seems likely, therefore, that some more complicated expression [*e.g.*, (4)] is required in order to express mathematically the variation in rate with both substituent and reagent.

† Their experimental points for the methyl substituent are in fact consistent with this statement.

constants could be used to predict the rates of halogenation with any reliability. Consider, for example, the substituents H, Ph, and NHAc. All these have substituent constants near to zero: yet the phenyl group facilitates halogenation by a factor of 600, and the NHAc group has a corresponding effect of *ca.* 10^8.

Correlation of Hammett's Substituent (σ) *Constants with Partial Rate Factors for* p-*Nitration and* p-*Halogenation.*

Subst. (X)	σ (p-X) [a]	$\log_{10} f_p$ [b] (nitration)	Total relative rate of bromination [c] or chlorination (italics) of PhX (PhH = 1)	p-Halogenation (%)	$\log_{10} f_p$ (halogenation) [d]
NMe_2	−0·600	—	—	—	*ca.* 19·5 [e]
OH	−0·357	—	1·1 × 10^{11}	87 [f]	11·8
OMe	−0·268	—	1·2 × 10^9	95 [g]	9·8
CMe_3	−0·197	1·88	1·1 × 10^2 [h]	92 [c]	2·8
CH_3	−0·170	1·76	4·8 × 10^2 [i]	69 [c]	3·3
OPh	−0·028	—	1·4 × 10^7	95 [j]	7·9
NHAc	−0·015	—	2·1 × 10^8	100 [k]	9·1
Ph	0·009	—	*6·3* × 10^2 [l]	*ca.* 60 [m]	*ca.* 3·4
F	0·062	−0·10 [n]	*1·2*	90 [o]	0·8
NHBz	0·078	—	2·1 × 10^8 [p]	100 [k]	9·1
CH_2Cl	0·184	−0·02	*0·76*	*ca.* 65 [q]	*ca.* 0·5
Cl	0·227	−0·85	*0·11*	55 [r]	−0·4
Br	0·232	−0·96	*0·08*	52 [r]	−0·6
I	0·276	−0·34 [s]	—	—	—

[a] Jaffe, *Chem. Reviews*, 1953, **53**, 191. [b] Ingold, "Structure and Mechanism in Organic Chemistry," G. Bell and Sons, Ltd., London, 1953. [c] Robertson, de la Mare, and Swedlund, *J.*, 1953, 782. [d] The reactivity scale is necessarily compressed, so much so that, in cases in which both bromination and chlorination have been examined (*e.g.*, for alkyl groups), the points on the graph for the two processes almost coincide. Similarly, though the amount of *para*-substitution is seldom known under the conditions of the kinetic measurements, quite large deviations (*e.g.*, of 25%) from the adopted values would make insignificant differences to the positions of the plotted points. [e] Estimated indirectly (cf. ref. *c*); the value is considered to be reliable to within at least one unit. [f] Holleman and Rinkes, *Rec. Trav. chim.*, 1911, **30**, 48. [g] De la Mare and Vernon, *J.*, 1951, 1764. [h] Berliner and Bondhus (*J. Amer. Chem. Soc.*, 1948, **70**, 854) obtained this value for bromination: the value for chlorination (cf. ref. *c*) is in good agreement. [i] The value given in ref. *c*, which is for chlorination, combined with the percentage of *p*-chlorination of toluene (Wahl, Normand, and Vermuylen, *Bull. Soc. chim.*, 1922, **31**, 570) leads to a value $\log_{10} f_p$ = 3·1. [j] Cf. Suter, *J. Amer. Chem. Soc.*, 1929, **61**, 2585; Brewster and Stevenson, *ibid.*, 1940, **62**, 3144; the actual figure used has been assumed by analogy with anisole. [k] Cf. Fries, *Annalen*, 1906, **346**, 171; Huber and Weinecke, *Ber.*, 1875, **8**, 564. [l] P. W. Robertson, personal communication. [m] Chlorination gives some *o*- and much *p*-derivative (cf. Kramers, *Annalen*, 1877, **189**, 142), but there seems to be no reliable estimate of the relative proportions. The value chosen is intermediate between the values for nitration (Bennett and Chapman, *Ann. Reports*, 1930, **27**, 140) and for bromination, which appears to give almost entirely *p*-substitution (cf. Buckles, Hausman, and Wheeler, *J. Amer. Chem. Soc.*, 1950, **72**, 2494). [n] From the rate data given in ref. *b*, and the orientation data given by Holleman (*Rec. Trav. chim.*, 1904, **23**, 257). [o] Unpublished measurements. The chlorination of fluorobenzene by chlorine in acetic acid at 25° gave in 65% yield *p*-chlorofluorobenzene, f. p. −31°. Authentic material had f. p. −27°. [p] Unpublished measurements; cf. Orton and King, *J.*, 1911, **99**, 1372. [q] Estimated by analogy with the data for nitration (ref. *b*). [r] Holleman, *Chem. Reviews*, 1924, **1**, 187. [s] Roberts, Sanford, Sixma, Cerfontain, and Zagt, *J. Amer. Chem. Soc.*, 1954, **76**, 4525.

Speaking generally, it can be seen that the σ-values reflect to a greater extent the inductive than the electromeric effect of the substituent. The reasonable accordance between nitration and halogenation is of interest, and the divergences are in the direction that benzene derivatives tend to be relatively more reactive in halogenation than in nitration, particularly when the substituent has high conjugative or hyperconjugative capacity.

The above results are concerned with the effect of *ortho-para*-directing substituents on substitution at the *para*-position. The next problem concerns *meta*-substitution determined by similar groups. On this point, information in the literature is more scanty. Partial rate factors (f_m) for nitration directed by the groups Me, Bu^t, CH_2Cl (Ingold, *op. cit.*) and for Cl, Br, and I (Roberts, Sanford, Sixma, Cerfontain, and Zagt, *J. Amer. Chem. Soc.*, 1954, **76**, 4525) are plotted in Fig. 2. As the latter authors observe, there is a reasonable correlation between the σ-values and the values of $\log_{10} f_m$. We are in general agreement with their views concerning the validity of the Hammett equation as it applies to nitration processes.

For halogenation by the halogen molecule, values for substitution *meta* to strongly *ortho-para*-directing groups are difficult to obtain. De la Mare and Vernon (*loc. cit.*), however, deduced, from data on the relative rates of bromination of anisole, the dimethoxybenzenes, and methyl *p*-tolyl ether, that the experimental sequence of activating power, *m*-H < *m*-OMe < *m*-Me, could be written with some confidence. It is clear that this sequence could not be explained in terms of Hammett's substituent (σ) constants, which require a strongly deactivated position *meta* to the methoxyl group (MeO < H < Me). The results cannot be correlated either with the rates of *p*-substitution or with the σ_p values, which are in the order H < Me < OMe.

Pearson, Baxter, and Martin (*J. Org. Chem.*, 1952, **17**, 154) have discussed the relative rates of overall halogenation in relation to the solvolyses of substituted diphenylmethyl halides, pinacol rearrangements, and reactions of *para*-substituted acetophenones. They note the failure of the Hammett relation in predicting detailed behaviour (*e.g.*, when the alkyl group is varied), and suggest that new substituent constants, which they list for a limited number of substituents, should be used for electrophilic reactions. Their paper is valuable in that it emphasises that σ-constants often vary with the reaction (cf. also Jaffe, and Berliner and Monack, *locc. cit.*; Berliner and Liu, *J. Amer. Chem. Soc.*, 1953, **75**, 2417). It is difficult, however, to predict *a priori* which type of substituent constant should be used in any particular case. Thus the Hammett substituent constants predict the order of electron release, H > F, found in electrophilic nitration by the nitronium ion (Ingold, *op. cit.*), and electrophilic bromination by the H_2OBr^+ or Br^+ ion (de la Mare, Ketley, and Vernon, *Research*, 1953, **6**, S 15), but the opposite order is found both in electrophilic aromatic substitution by the halogen molecule, and in nucleophilic aromatic substitution by piperidine of 4-substituted 1-bromo-2-nitrobenzenes. Similarly, the last two reactions, despite their different characters, reveal the hyperconjugation order for electron release by alkyl substituents, not shown in the Hammett substituent constants. In discussing substituent effects in terms of deviations from the standard Hammett σ-constants, one is using as a basis for comparison a set of values which introduce inductive and mesomeric influences, combined in amounts which cannot be quantitatively determined and vary with the substituent. It is for this reason that some writers prefer for many purposes to use Ingold's approach (*op. cit.*), discussing reactions in terms of the separated inductive and mesomeric effects, with their time-variable analogues. This is the view taken by the present author in regard to electrophilic and nucleophilic displacements at aromatic centres; it agrees essentially with that developed independently by Dr. G. Kohnstam in his work on the solvolyses of the substituted diphenylmethyl halides (C. K. Ingold and G. Kohnstam, personal communication).

FIG. 1. *Hammett plot for electrophilic substitution* para- *to* ortho-para-*directing groups.*

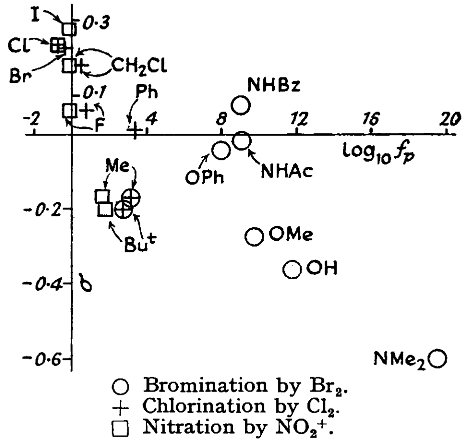
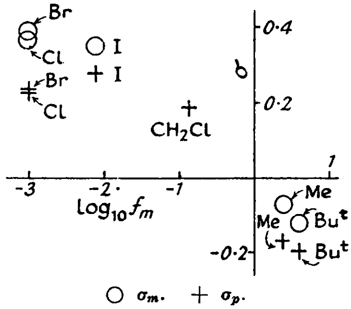


FIG. 2. *Hammett plot for nitration* meta- *to* ortho-para-*directing groups.*



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