292. *The Influence of Nuclear Substituents upon Side-chain Reactions. Part I.*

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It has recently been shown by the authors (this vol., p. 890) that, assuming the simple collision theory to apply, the critical energy increment of the reaction of hydrogen ion with a *p*-substituted acetophenone, $C_6H_4X\cdot CO\cdot CH_2R$, is given by the expression $E = E_0 - C(\mu - a\mu^2)$, where E_0 is the value of E for the unsubstituted compound $C_6H_5\cdot CO\cdot CH_2R$, μ is the dipole moment of C_6H_5X, and C and a are constants for the series. It was further suggested that the relationship might be applicable, *mutatis mutandis*, over a wide field of reactions.

In this series of communications it is proposed to examine the applicability of the equation $E = E_0 \pm C(\mu - a\mu^2)$ to the general problem of the influence of nuclear substituents upon side-chain reactivity. It must be emphasised that the polar influences accounted for in this equation are only those of a permanent nature, and the critical increment cannot be expected to bear any simple relationship with the dipole moment if time-variable electronic displacements occur. The classification of polar effects as " inductive " and " tautomeric " has recently been extended by Ingold (*Chem. and Ind.*, 1933, **52**, 434) to include both permanent and time-variable effects of each type. Thus, the tautomeric effect is divided into " electromeric " (time-variable) and " mesomeric " (permanent) components, and an effect differing from the inductive only in time-dependence is spoken of as " inductomeric." These terms are used in the sequel.

Reasons have already been given (Nathan and Watson, *loc. cit.*) for supposing that, in a consideration of the *relative* speeds at which a series of *similarly constituted* compounds enter into a given reaction under identical conditions, it is not necessary to take into account the free-space, phase, and steric corrections. If, therefore, such a series of compounds react at speeds which are in harmony with the simple kinetic equation, the critical increments may be expressed by $E = c - RT \log_e k/[(M_1 + M_2)/M_1M_2]^{\frac{1}{2}}[(\sigma_1 + \sigma_2)/2]^2$ [equation (4), *loc. cit.*] or $E = c - 2{\cdot}303\, RT\, E'$, where $E' = \log_{10} k/[(M_1 + M_2)/M_1M_2]^{\frac{1}{2}}[(\sigma_1 + \sigma_2)/2]^2$, and is the only variable term. This expression may be expected to apply to the side-chain reactions of a series of benzene derivatives differing only in one nuclear substituent, and the values of E' have been calculated (by the method already described, *loc. cit.*) in a number of cases where data are available (see references below) for such a series with substituents of widely different polar character. If E_0 and E_0' are the values of E and E' for the unsubstituted compound (X = H), then $E - E_0 = -2{\cdot}303\, RT\, (E' - E_0')$.

Ingold and Rothstein (J., 1928, 1217) have grouped side-chain reactions in two classes, A and B, in which the change is facilitated respectively by accession of electrons to, and by recession of electrons from, the point of attack, and it has frequently been noted that, qualitatively, a substituent which accelerates the reactions of one type retards those of the other, and *vice versa*. Thus, the order $CH_3 > H > Hals > NO_2$ holds throughout Class A, and the reversed order throughout Class B. If, therefore, the relationship between the critical increment and the dipole moment of C_6H_5X is of general application, the following expressions will hold: (1) for reactions of Class A, $E = E_0 - C(\mu - a\mu^2)$ or $E' = E_0' + x(\mu - a\mu^2)$, and (2) for reactions of Class B, $E = E_0 + C(\mu - a\mu^2)$ or $E' = E_0' - x(\mu - a\mu^2)$. Reactions 1—7 in the following table are of Class B, and 8—13 of Class A.

Simple relationships are most likely to be found among the reactions of compounds where the variable substituent X stands in the *m*-position with respect to the side chain, for complications arising from electromeric effects will then be absent. An excellent test of the validity of the equation $E = E_0 \pm C(\mu - a\mu^2)$ is provided, therefore, when E' is plotted against μ for the reactions of the *m*-substituted compounds included in the table. The curves so obtained are shown in Figs. 1 and 2 (which refer to reactions of Class A and Class B respectively), and they are identical in form for all the reactions under

Values of E′.

Substituent in *m*-position.

X.	1.	2.	3.	4.	5.	8.		11.	12.	13.
						(30°.)	(83°.)			
H	14·13	14·43	14·45	16·56	—	11·50	13·64	14·86	14·43	17·81
NH_2	13·73	14·22	14·41	16·34	—	—	—	—	—	—
NMe_2	—	—	—	—	15·21	—	—	—	—	—
Me	13·96	—	14·33	—	15·49	11·59	13·76	14·94	14·46	—
MeO	14·18	—	—	—	15·84	—	—	—	—	—
Cl	14·98	—	—	16·98	16·48	10·61	13·00	14·55	14·19	17·37
Br	15·02	—	14·90	17·04	16·43	10·60	12·95	—	—	—
I	—	—	14·83	17·14	16·31	10·60	12·91	—	—	—
NO_2	15·91	15·29	15·17	17·86	17·61	10·22	12·57	14·04	13·73	17·08

Substituent in *p*-position. Class A.

X.	8.		9.	10.	11.	12.	13.
	(30°.)	(83°.)					
H	11·50	13·64	12·88	—	14·86	14·43	17·81
Me	12·45	14·64	14·08	15·65	14·98	14·55	18·01
Cl	11·15	13·42	12·48	15·18	14·58	14·18	17·56
Br	11·09	13·32	12·39	15·09	—	—	—
I	11·04	13·29	—	15·01	—	—	—
NO_2	10·12	12·48	—	14·04	13·65	13·42	17·01
MeO	—	—	15·94	15·80	—	—	—
pp′-Cl_2	—	—	12·04	—	—	—	—
pp′-Me_2	—	—	15·47	—	—	—	—

Substituent in *p*-position. Class B.

X.	1.	2.	3.	5.	6.		7.
					(55°.)	(75°.)	
H	14·13	14·43	14·45	—	14·64	—	13·08
NH_2	12·48	—	13·71	—	—	—	—
NMe_2	—	—	—	14·16	—	—	—
Me	13·78	14·27	14·25	14·95	14·55	15·32	12·88
MeO	13·44	14·03	14·11	15·19	—	15·30	—
MeS	13·99	—	—	—	—	—	—
F	14·41	14·57	—	—	—	—	—
Cl	14·75	14·73	14·71	16·34	14·97	15·77	13·26
Br	14·81	14·77	14·71	16·30	14·86	15·67	13·33
I	14·81	14·76	14·65	16·28	14·75	15·59	13·24
NO_2	16·12	15·40	15·25	—	15·15	—	14·07

The reactions referred to are as follows: Alkaline hydrolysis of (1) benzoic esters, (2) cinnamic esters, (3) benzamides, (4) phthalides; (5) prototropy of the αγ-diphenylmethyleneazomethine system; (6) reaction of β-chlorosulphides with potassium iodide, (7) substituted benzoyl chlorides with *iso*propyl alcohol.

(8) Hydrolysis of benzyl chlorides; (9) reaction of diphenylchloromethane with ethyl alcohol; (10) hydrolysis of β-chlorosulphides; (11) reaction of phenoxide ion with ethylene oxide, (12) phenoxide ion with propylene oxide; (13) *N*-chlorination of acetobenzylamides.

References. (1) and (2) Kindler, *Annalen*, 1926, **450**, 1; 1927, **452**, 90; 1928, **464**, 278. (3) Reid, *Amer. Chem. J.*, 1900, **24**, 397. (4) Tasman, *Rec. trav. chim.*, 1927, **46**, 653, 922. (5) Shoppee, J., 1931, 1225; 1932, 696. (6) Baddeley and Bennett, this vol., p. 261. (7) Norris and Gregory, *J. Amer. Chem. Soc.*, 1928, **50**, 1813. (8) Olivier, *Rec. trav. chim.*, 1922, **41**, 301, 646; 1923, **42**, 516, 775. (9) Norris, Banta, and Blake, *J. Amer. Chem. Soc.*, 1928, **50**, 1802, 1808. (10) See (6). (11) and (12) Boyd and Marle, J., 1914, **105**, 2117. (13) Williams, J., 1930, 37.

The following values of dipole moments (e.s.u. $\times 10^{-18}$) are employed: Me, 0·39; Cl, − 1·56; Br, − 1·53; NO_2, − 3·97 (Tiganik, *Z. physikal. Chem.*, 1931, *B*, **13**, 452); NH_2, 1·52 (*idem, ibid.*, **14**, 139); F, − 1·45; I, − 1·30 (Bergmann, Engel, and Sandor, *ibid.*, 1930, *B*, **10**, 114); MeS, − 1·27 (*idem, ibid.*, p. 397); MeO, − 0·8 (Estermann, *ibid.*, 1928, *B*, **1**, 141); NMe_2, 1·58 (Fogelberg and Williams, *Physikal. Z.*, 1931, **32**, 28).

consideration. It is evident that the equation holds throughout, except when the substituent is a halogen. Other groups capable of a $+T$ effect do not cause a similar deviation, and the relationship is therefore a general one for the influence of *m*-substituents upon side-chain reactions, halogens being excluded.

For halogens, the values of E' always indicate an inductive effect (the only permanent effect here transmitted) corresponding with a dipole moment exceeding two units; *e.g.*, for reaction 5, which obeys the equation exceptionally well [$E' = 15{\cdot}58 - 0{\cdot}288\ (\mu - 0{\cdot}194\mu^2)$], the necessary value of μ for Cl is about $-2{\cdot}2$. The simplest interpretation is that, although the inductive effects of the halogens are actually of this magnitude, yet these atoms give rise also to permanent electronic displacements in the reversed direction, this effect being included in the experimentally determined dipole moment but not transmitted from the *m*-position. This additional factor may be identified with the " mesomeric " effect. The experimental dipole moment will then be a measure of the sum total of the inductive and the mesomeric effect, which are of opposite sign; hence its relatively low value. In the case under consideration, the mesomeric effect is not transmitted, and the full influence of the inductive effect is observed. Confirmation of the above view is found in the fact that, whereas, for other $-I$ groups the measured dipole moment of ArX is numerically greater than that of AlkX, the reverse is the case when X is halogen. This was pointed out by Sutton (*Proc. Roy. Soc.*, 1931, **133**, 686), who states that " the aryl halides have numerically smaller moments than the alkyl halides, which proves that some other process besides polarisation occurs in these."

FIG. 1.

Class A *reactions :* m-*substituents.*

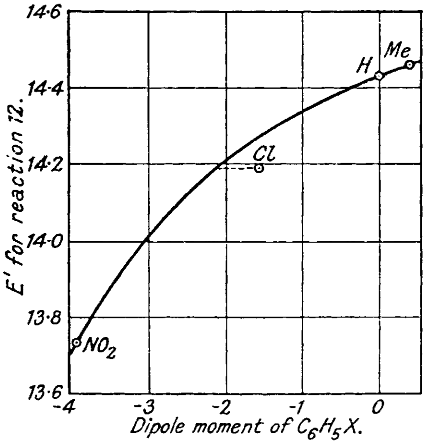
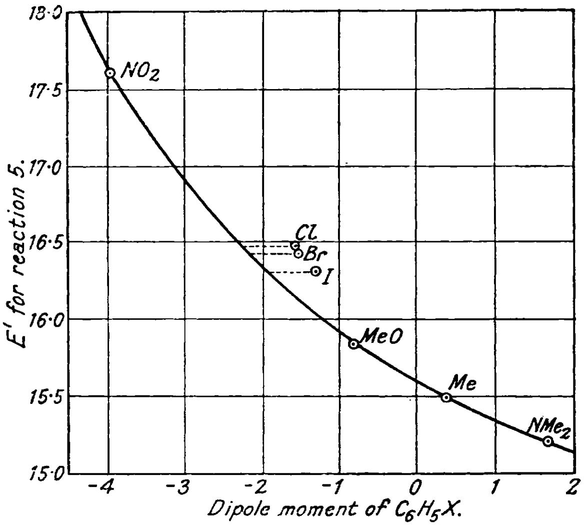


FIG. 2.

Class B *reactions :* m-*substituents.*

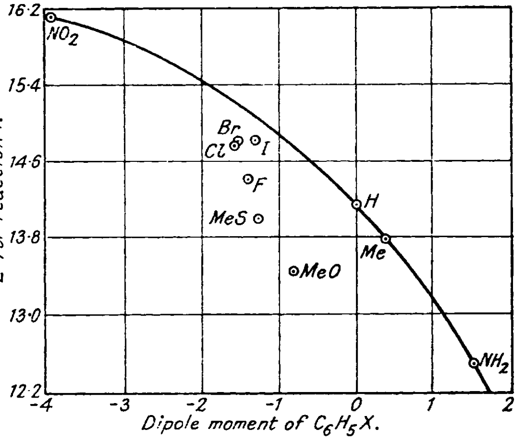


Mention has frequently been made of the inversion of the order of the halogens in reactions 1, 4, and 8, and the divergence from the expected sequence appears to be beyond the limit of experimental error. Walden and Werner (*Z. physikal. Chem.*, 1929, *B*, 2, 25) have deduced theoretically the order I > Br > Cl > F for the values of the dipole moments of the halogenobenzenes, but there is overwhelming evidence that the inductive effects follow the order F > Cl > Br > I (*e.g.*, dissociation constants of carboxylic acids; % of *m*-derivative in nitration of benzyl halides), and the halogens stand in this order in reactions 3 and 5. The present work provides no explanation of the anomaly, but it is clear that no conclusions can be drawn from the dipole moments of the halogenobenzenes, which do not give a true measure of the inductive effects.

It may be stated, then, with some degree of confidence, that the equation $E = E_0 \pm C(\mu - a\mu^2)$ is generally applicable to the reactions of the side chain of a *m*-substituted benzene derivative, provided that the existence of a mesomeric effect be assumed for the halogens. A similar treatment of *p*-substituted compounds leads, however, to less definite results, the issue being frequently obscured, as would be anticipated, by electromeric effects. The critical increments of the reaction of hydrogen ion with *p*-substituted acetophenones are given by the expression $E = E_0 - C(\mu - a\mu^2)$, the halogen compounds showing no deviation (see curve, this vol., p. 892). In the light of the suggestion made above, this fact indicates that the mesomeric effect of halogen is transmitted, while the electromeric effect does not operate, *i.e.*, the polar influence of the halogen is exactly as measured in the dipole moment. The same remarks apply to reactions 11, 12, and 13. In all these reactions the controlling stage is an addition process, and the failure of the electromeric effect to operate may be due either to the absence of demand, sufficient unshared electrons already existing at the point where addition is to occur, or to the improbability that a collision will occur simultaneously with the momentary electromeric disturbance. It is difficult to visualise the operation, in the phenoxide ion (reactions 11 and 12), of a permanent effect which involves a covalency increase. Perhaps the mesomeric effect differs from the electromeric in mechanism as well as in time-dependence. The activation of the α-carbon atom in acyl halides would receive a very simple explanation if the " tautomeric " effect to which it has been ascribed (Watson and Yates, this vol., p. 221) were in reality a " permanent component " or mesomeric effect, not involving covalency increase, and peculiar to the halogens. In the remaining reactions of Class A (8, 9, and 10) the rate-determining stage is the elimination of a negative ion, and here the curve is, in general, of the usual form, with $+T$ groups lying above. This is to be anticipated, but the transmission of the electromeric effect through the side chain of a β-chlorosulphide is peculiar, as is also the exceptionally high velocity of reaction of the *p*-methyl compound in reaction 8, which might be attributed to errors in experiment were there not an analogy in the *N*-chlorination of aceto-*p*-toluidide (Williams, J., 1930, 37).

FIG. 3.

Reactions 1, 2, 3, *and* 7 : p-*substituents.*



More difficulties are encountered among the Class B reactions of the *p*-substituted compounds. Reaction 6 gives a curve of the form shown in Fig. 2, except that the value of E' for the methoxy-compound is low, and, as in reaction 10, the operation of the electromeric effect is unexpected. The transmission of this effect through *one* methylene group (but not two) appears to have an analogy in the nitration of the benzyl ether of guaiacol (Allan and Robinson, J., 1926, 376; compare Allan, Oxford, Robinson, and Smith, *ibid.*, p. 407) and in the ready ionisation of halogen from chlorodimethyl ether (Cocker, Lapworth, and Walton, J., 1930, 446). Reactions 1, 2, 3, and 7 are complicated, as Shoppee points out (J., 1931, 1226), by the ability of the $+T$ effect of the *p*-substituent to compete with the $-T$ of carbonyl, and groups capable of a $+T$ effect (except possibly NH_2 in reactions 1 and 3) give low values of E'. It is surprising, moreover, that in all these reactions the remaining groups are placed in an exceptional manner (see Fig. 3), the μ^2 term changing in sign, *i.e.*, $E = E_0 + C(\mu + a\mu^2)$; *e.g.*, for reaction 1, $E' = E_0' - 0{\cdot}897(\mu + 0{\cdot}111\mu^2)$. A similar change in sign was observed when the dissociation constants of substituted acetic acids were considered (this vol., p. 894), but in that case the expression referred to the *difference* of critical increments, and a departure from the normal was perhaps not surprising.

It is clear that, if further progress is to be made in the theoretical treatment of side-chain reactivity, accurate data must be obtained for reactions where complicating factors are reduced to a minimum, and efforts are being made to acquire such data. In spite, however, of the anomalous observations referred to above, the general conclusion may be drawn that the equation $E = E_0 \pm C(\mu - a\mu^2)$ is applicable to the side-chain reactions of *p*-substituted compounds in nearly all (perhaps, indeed, all) cases where the operation of electromeric effects does not complicate the position. Reactions such as the acid hydrolysis of benzoyl chlorides (Berger and Olivier, *Rec. trav. chim.*, 1927, **46**, 516) and of benzamides (Reid, *loc. cit.*) are not included in the discussion for obvious reasons (compare Ingold, *Ann. Reports*, 1927, **24**, 157); nor has attention been given to groups of such doubtful polar character as –CN and $-CO_2H$.

It may be pointed out that, in most cases, the results noted above could have been obtained by using log *k* in place of the calculated term *E'*. For the prototropy of acetophenones, however, where the differences between the *k* values are small, no relationship would have been traced if this simplication had been adopted.

SUMMARY.

1. The simple kinetic equation being assumed to be applicable throughout, there is a quantitative relationship between the dipole moments of C_6H_5X and the critical increments of the side-chain reactions of benzene derivatives having X as nuclear substituent.

2. With X in the *m*-position, the expression is applicable in all the cases examined, except halogen substituents. The exception is attributed to a mesomeric effect, which is included in the dipole moment but not transmitted.

3. With X in the *p*-position, complications (due mainly, at least, to electromeric effects) are frequently present, but the expression appears to be applicable when the issue is not thus obscured.

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