[Contribution from the Department of Chemistry, Columbia University]

The Effect of Structure upon the Reactions of Organic Compounds. Benzene Derivatives

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The effect of a substituent in the meta or para position of the benzene ring upon the rate or upon the equilibrium of a reaction in which the reacting group is in a side chain attached to the ring may be represented by a simple formula which is valid within a reasonable precision in a surprising variety of cases. The formula is

$$-RT \ln K + RT \ln K^0 = \Delta F = A/d^2 \left(\frac{B_1}{D} + B_2\right)$$

K is a rate constant or an equilibrium constant for a substituted reactant, K^0 is the corresponding quantity for the unsubstituted reactant, ΔF is a free energy change or its kinetic analog, d is the distance from the substituent to the reacting group, D is the dielectric constant of the medium in which the reaction occurs, and the quantities A, B_1 and B_2 are constants independent of temperature and solvent. Of these A depends only upon the substituent and its position in the ring relative to the reacting group (with one exception, the two values necessary for the para nitro group), while B_1 and B_2 depend only upon the reaction.

The most important practical feature of equation (1) is the separation of the effect of a substituent into two constants, one of which depends on the substituent, the other upon the reaction. For this corollary of the equation the linear logarithmic relationships between equilibrium and rate constants which have been noted by myself[1] and in wider variety by Burkhardt, Ford and Singleton[2] offer a verification which has so far been made only qualitatively and by graphical methods. A more significant test may be made by obtaining a set of values of the constant A for various substituents from some suitable reaction or reactions, and determining quantitatively the precision with which these constants may be made to fit the data for all available reactions. For this purpose equation (1) may be rearranged to the form

$$\log K = \log K^0 + \sigma\rho \tag{2}$$

$$\text{where } \sigma = -A/2.303 \, R$$

$$\rho = \frac{1}{d^2 T}\left(\frac{B_1}{D} + B_2\right)$$

σ is a substituent constant, dependent upon the substituent; ρ is a reaction constant, dependent upon the reaction, the medium and the temperature. Since the only data available consist of values of the $\sigma\rho$ product, it is necessary to assign an arbitrary value to some one σ or ρ. The choice of a value of unity for the ρ constant in the ionization equilibrium of substituted benzoic acids in water solution at 25° was determined by the large amount of accurate data available from the recent work of Dippy and co-workers.[3] On this basis the difference between the logarithm of the ionization constant of a substituted benzoic acid and the logarithm of the ionization constant of benzoic acid gives the value of the σ constant for that substituent. With the nucleus of σ values thus provided, ρ values have been derived by least squares methods for other reactions, and from these in turn σ values have been obtained for substituents whose effects upon the ionization constant of benzoic acid are unknown or inaccurately known. After any new σ value was obtained it was used for the calculation of subsequent ρ values, so that the order of the calculations, which is that of the key numbers in the Tables, is of some significance. The criterion of the validity of equations (1) or (2) for any reaction is the precision with which the previously determined values of σ together with the experimental values of log K satisfy the linear equation (2). As a measure of this precision I have used the median deviation of the experimental points from the best straight line, the "probable error" of a point.[4]

The results of such calculations for all the reactions I have been able to find are given in Tables I, II and III. Table I contains the values of the substituent constants σ together with the symbol of the substituent, a key number to indicate the reaction from which the value was obtained, the number of reactions n for which data on the effect of this substituent are available, and the probable

(1) Hammett, *Chem. Rev.*, **17**, 125 (1935).

(2) Burkhardt, Ford and Singleton, *J. Chem. Soc.*, 17 (1936).

(3) (a) Dippy and Williams, *ibid.*, 1888 (1934); (b) Dippy, Williams and Lewis, *ibid.*, 343 (1935); (c) Dippy and Lewis, *ibid.*, 644 (1936).

(4) Wright and Hayford, "The Adjustment of Observations." D. Van Nostrand Company, New York, 1906, p. 132.

error r of the log K values calculated for this substituent for these reactions. The data on reactions 28, 35, 36, 37 and 38 were not included in calculating the probable error because there was reason in these cases to doubt the accuracy of the measurement or the theoretical applicability of equation (1). Table II contains the ρ values for the various reactions together with a key number for the reaction, the best value of log K^0 in equation (2), the number of substituents n for which data are available, and the probable error r of the calculated values of log K. Table III contains brief descriptions of the reactions and literature references under the key numbers previously used. In the descriptions E means that the data used are the equilibrium constants of the reaction described, R that they are rate constants.

TABLE I
SUBSTITUENT CONSTANTS

Subst.	Constant σ	Source	No. of reactions n	Probable error r
pNH₂	−0.660	2	2	...
pCH₃O	− .268	1	21	0.077
pC₂H₅O	− .25	3	6	.105
3,4-di CH₃	− .229	4	1	...
m(CH₃)₂N	− .211	31	1	...
p(CH₃)₂N	− .205	21ᵃ	1	...
pCH₃	− .170	1	33	.046
mNH₂	− .161	2	3	.060
3,4CH₂O₂	− .159	2	3	.023
pC₂H₅	− .144	2	1	...
mCH₃	− .069	1	21	.038
pCH₃S	− .047	2	1	...
None	.000	1	36	.034
pC₆H₅	+ .009	2	3	.22
pF	+ .062	1	7	.066
mCH₃O	+ .115	1	7	.116
mC₂H₅O	+ .15	3	2	...
βC₄H₄ᵇ	+ .17	3	9	.102
pCl	+ .227	1	31	.040
pBr	+ .232	1	24	.040
pI	+ .276	2	11	.073
mF	+ .337	1	5	.083
mI	+ .352	1	8	.039
mCl	+ .373	1	19	.041
mBr	+ .391	1	17	.035
pC₆H₅N₂	+ .640	26, 27	1	...
mCN	+ .678	26, 27	1	...
mNO₂	+ .710	1	21	.069
pNO₂(b)ᶜ	+ .778	1	15	.066
pCN	+1.000	4	4	.042
pNO₂(a)ᵈ	+1.27	3	8	.052

ᵃ A statistical factor of 2 was used in calculating the value of σ. ᵇ β-Naphthalene derivatives. ᶜ To be used for the reactions of all benzene derivatives except those of aniline and phenol. ᵈ To be used for the reactions of derivatives of aniline and phenol.

TABLE II
REACTION CONSTANTS

Reaction	log K^0	Constant ρ	Probable error r	No. of substituents n
1	−4.203	+1	...	14
2	−1.294	+2.498	0.067	12
3	−4.569	+2.730	.060	14
4	−9.941	+2.008	.047	5
5	−0.963	+1.267	.026	11
6	−1.410	−0.085	.118	7
7	−0.597	− .550	.045	14
8	−1.746	+ .417	.060	10
9	−3.180	+1.394	.054	6
10	−1.009	+1.055	.035	13
11	−1.735	+0.118	.040	12
12	−9.699	+2.143	.065	14
13	−2.293	+1.529	.104	13
14	−1.585	+1.471	.065	10
15	−1.201	+1.217	.035	4
16	+0.137	−3.690	.085	6
17	−2.121	−3.190	.073	10
18	−0.604	−2.581	.160	10
19	−1.558	−2.743	.041	6
20	−1.508	−1.088	.040	5
21	−0.944	−2.382	.057	6
22	−1.772	−2.903	.038	4
23	−1.152	−2.694	.154	5
24	+0.665	−1.453	.036	11
25	−2.345	−1.219	.034	9
26	−2.946	+0.316	.055	9
27	−3.484	+1.190	.030	4
28	−1.491	+0.796	.220	9
29	−2.536	−1.799	.080	6
30	−0.698	−0.946	.043	9
31	−1.142	− .771	.046	9
32	−2.177	− .991	.016	5
33	−4.076	+ .587	.037	10
34	−1.921	+2.142	.054	7
35	−0.035	+0.824	.071	6
36	−4.288	+0.471	.026	10
37	−0.973	−1.875	.154	12
38	+0.167	+0.785	.078	11
39	−0.018	+2.240	.079	9

The verification of equation (3) is satisfactory. Out of thirty-eight reactions involving derivatives of benzoic acid, of phenol, of aniline, of benzenesulfonic acid, of phenylboric acid, and of phenylphosphine, and including both equilibrium and rate constants, there are only six for which the probable error is greater than 0.1, one only for which it is greater than 0.2, and the mean value of the probable error for the whole series of reactions is 0.067. These figures compare well with a total range in the value of log K between p-nitro and p-amino substituted derivatives which may in an extreme case (reaction 16) amount to as much as 7. Figure 1 visualizes the magnitude of the deviations because the four reac-

tions for which log K values are plotted against the σ values from Table I show probable errors not far from the mean value.
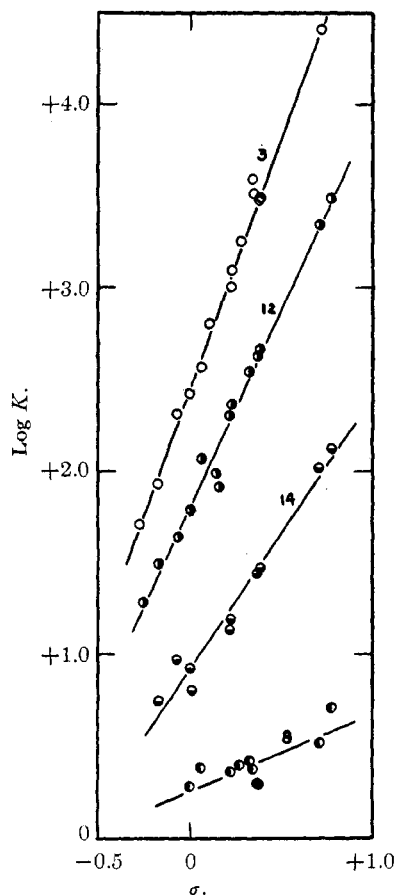

Fig. 1.—Relationship between log K and σ for various reactions (see Table III). The position of the scale of ordinates is arbitrary.

TABLE III

1. E. Ionization of substituted benzoic acids in water at 25°.[3]

2. R. Alkaline hydrolysis of substituted benzoic esters in 87.83% ethyl alcohol at 30°.[5]

3. E. Acidity constants of substituted anilinium ions in water at 25°.[6]

4. E. Ionization of substituted phenols in water at 25°.[7]

5. R. Hydrolysis of substituted cinnamic esters, conditions as in reaction 2.[5b]

6. R. Acid catalyzed esterification of substituted benzoic esters in absolute alcohol at 25° with N HCl.[3]

7. R. Acid catalyzed bromination of substituted acetophenones in an acetic acid–water–hydrochloric acid medium at 25°.[9]

8. R. Base catalyzed bromination of substituted acetophenones in acetic acid–water medium with sodium acetate as catalyst at 35°.[10]

9. E. Ionization of 2-furoic acids substituted in the 5-position, which was considered analogous to the para position in a benzene derivative.[11]

10. R. Alkaline hydrolysis of substituted benzamides in water at 100°.[12]

11. R. Acid hydrolysis of substituted benzamides in water at 100°.[12]

12. E. Ionization of substituted phenylboric acids in 25% ethyl alcohol at 25°.[13]

13. R. Reaction of substituted benzoyl chlorides with ethyl alcohol in alcohol medium at 0°.[14]

14. R. Reaction of substituted benzoyl chlorides with methyl alcohol at 0°.[15]

15. R. Reaction of substituted benzoyl chlorides with aniline in benzene at 25°.[16]

16. R. Reaction of substituted anilines with dinitrochloronaphthalene in ethyl alcohol at 25°.[17]

17. R. Reaction of substituted anilines with dinitrochlorobenzene in ethyl alcohol at 25°.[18]

18. R. Same as 17, but at 100°.[17]

19. R. Reaction of substituted dimethylanilines with methyl iodide in an acetone–water medium at 35°.[19]

20. R. Reaction of substituted phenyldiethylphosphines with ethyl iodide in acetone at 35°.[19]

21. R. Reaction of substituted dimethylanilines with trinitrophenol methyl ether in acetone at 35°.[20]

22. R. Reaction of substituted dimethylanilines with trinitrocresol methyl ether in acetone at 25°.[21]

23. R. Reaction of substituted anilines with benzoyl chloride in benzene at 25°.[16]

24. E. Formation of substituted formanilides from substituted anilines and formic acid in a pyridine–water medium at 100°.[22]

25. R. Reaction of substituted anilines with formic acid in pyridine–water medium at 100°.[23]

26. R. Hydrolysis of substituted formanilides, conditions same as in 25.[23]

27. R. Hydrolysis of substituted benzenesulfonic ethyl esters in 30% ethyl alcohol at 25°.[24]

(5) Kindler, (a) Ann., 450, 1 (1926); (b) ibid., 452, 90 (1927); (c) ibid., 464, 278 (1928).

(6) (a) Hall and Sprinkle, THIS JOURNAL, 54, 3469 (1932); (b) Hall, ibid., 52, 5115 (1930); (c) Hammett and Paul, ibid., 56, 827 (1934); Farmer and Warth, J. Chem. Soc., 85, 1713 (1904).

(7) (a) Hantzsch and Farmer, Ber., 32, 3080 (1899); (b) Boyd, J. Chem. Soc., 107, 1538 (1915).

(8) Goldschmidt, Ber., 28, 3220 (1895).

(9) (a) Nathan and Watson, J. Chem. Soc., 217 (1933); (b) Evans, Morgan and Watson, ibid., 1167 (1935).

(10) Morgan and Watson, ibid., 1173 (1935).

(11) Catlin, C. A., 30, 935 (1936).

(12) Reid, (a) Am. Chem. J., 21, 284 (1899); (b) ibid., 24, 397 (1900).

(13) Branch, Yabroff and Bettman, THIS JOURNAL, 56, (a) 937, (b) 1850, (c) 1865 (1934).

(14) Norris, Fasce and Staud, ibid., 57, 1415 (1935).

(15) Norris and Young, ibid., 57, 1420 (1935).

(16) Williams and Hinshelwood, J. Chem. Soc., 1079 (1934).

(17) Van Opstall, Rec. trav. chim., 52, 901 (1933).

(18) Singh and Peacock, J. Phys. Chem., 40, 669 (1936).

(19) Davies and Lewis, J. Chem. Soc., 1599 (1934).

(20) Hertel and Dressel, Z. physik. Chem., B29, 178 (1935).

(21) Hertel and Dressel, ibid., B23, 281 (1934).

(22) Davis, ibid., 78, 353 (1911).

(23) Davis and Rixon, J. Chem. Soc., 107, 728 (1915).

(24) Demé024ny, Rec. trav. chim., 50, 60 (1931).

TABLE III   (Concluded)

28. R. Hydrolysis of substituted benzoyl chlorides in acetone–water medium at 0°.[25]

29. R. Friedel–Crafts reaction of substituted benzene-sulfonyl chlorides with benzene at 30°.[26]

30. R. Reaction of substituted phenolate ions with ethylene oxide in 98% ethyl alcohol at 70.4°.[27]

31. R. Reaction of substituted phenolate ions with propylene oxide, conditions as in 30.[27]

32. R. Reaction of substituted phenolate ions with ethyl iodide in alcoholic solution at 42.5°.[28]

33. R. Acid catalyzed hydrolysis of substituted aryl sulfuric acids in water solution at 48.6°.[2]

34. R. Addition of hydrogen sulfide to substituted benzonitriles in alkaline alcoholic solution at 60.6°.[5a]

35. R. Alkaline hydrolysis of substituted phenylacetic esters, conditions as in 2.[5b]

36. E. Ionization of substituted phenylacetic acids in water at 25°.[3,29]

37. R. Hydrolysis of substituted benzyl chlorides in acetone–water medium at 69.8°.[30]

38. R. Reaction of substituted benzyl chlorides with potassium iodide in acetone at 20°.[30]

39. R. Reaction of substituted ald-chlorimines with sodium hydroxide in 92.5% alcohol at 0°.[31]

The deviations from equation (1) are undoubtedly larger than those to be expected from any reasonable error in the actual measurement of rate or equilibrium as Dippy and Watson[32] have pointed out in connection with reaction 2. It is by no means so certain that they do not in some cases result from insufficient purity of reactants. The preparation and proper purification of the numerous substituted compounds is by no means an easy task, even for a skilled organic chemist, a fact which is strongly emphasized by the discovery of Bennett and Jones[33] that the data in the previous literature on the reaction rate of substituted benzyl chlorides with iodide ion were in error by two orders of magnitude because of the presence of extremely reactive impurities. Another source of danger in the study of any organic reaction is the possibility that the product analyzed for may be produced by more than one reaction, as in the case noted by Baker,[34] or even that the same over-all reaction may result from either or both of two competing reactions which

are differently affected by substituents. Thus the hydrolysis of a halide may proceed either by a reaction with water or by a reaction with hydroxyl ion.[35] It seems hardly likely that these difficulties should account for all of the deviations noted, but they may very well be responsible for some of the worst cases.

The errors show no tendency to be larger for reactions with a large value of ρ. Consequently the probable percentage error in the prediction of an equilibrium or rate constant from Tables I and II is no greater in the case of reactions in which a substituent produces a large change in constant than it is with reactions in which a substituent has very little effect. This rather distorts the effect one gets from a graphical test, as can be seen in Fig. 1, in which all four reactions have nearly the same value of r.

In most cases the distribution of errors for a given substituent is a random one. In a few cases, notably those of the fluorine derivatives, of m-methoxy derivatives and the naphthalene compounds, there are indications that a somewhat better choice of σ values could be made, but there are hardly enough data in any of these cases to justify such a refinement.

In one case only, that of the p-nitro substituent, it has been impossible to represent all reactions with one value of σ. Even here, however, it is not a question of a range of values but of two widely different ones. One of these, listed as p-NO$_2$(a) with a value of +1.27 in Table I gives satisfactory agreement with all reactions of aniline or phenol derivatives; the other, listed as p-NO$_2$(b) with the value +0.778, applies to the reactions of all other compounds.

In addition to providing a test of equation (2), Tables I and II perform the function of compressing into a small space a large amount of experimental data, and of providing the material for a wide variety of predictions of unknown equilibrium and rate constants.

The factor $1/d^2$ or some closely related function of the distance from substituent to reacting group is demanded by an important relationship noted by Kindler.[5b] This is to the effect that the quantity K/K^0 for the alkaline hydrolysis of a series of meta and para substituted cinnamic esters varies as the square root of the corresponding quantity for the similarly substituted benzoic esters. This relationship is shown in the lower

(25) Olivier and Berger, Rec. trav. chim. 46, 516 (1927).

(26) Olivier, ibid., 33, 244 (1914).

(27) Boyd and Marle, J. Chem. Soc., 105, 2117 (1914).

(28) Goldsworthy, ibid., 1254 (1926).

(29) Dippy and Williams, ibid., 161 (1934).

(30) Bennett and Jones, ibid., 1815 (1935).

(31) Hauser, Le Maistre and Rainsford, THIS JOURNAL, 57, 1056 (1935).

(32) Dippy and Watson, J. Chem. Soc., 436 (1936).

(33) Bennett and Jones, ibid., 1815 (1935).

(34) Baker, ibid., 987 (1934).

(35) Olivier and Weber, Rec. trav. chim., 53, 869; 891 (1934).

plot in Fig. 2, in which the abscissa of each point is given by the logarithm of the hydrolysis rate constant of a substituted benzoic ester, and the ordinate by the constant for a cinnamic ester
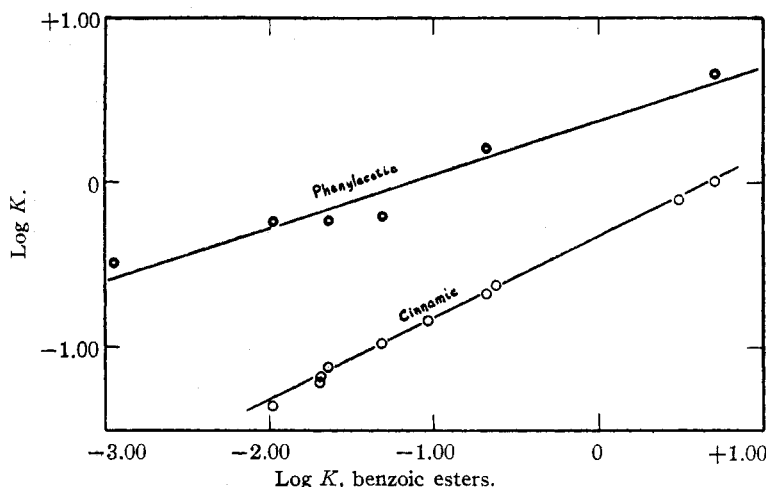

Fig. 2.—Relationships between hydrolysis constants.

carrying the same substituent. The straight line is a plot of the equation, obtained by least squares methods.

$$\log K_c = -0.331 + 0.502 \log K_b \qquad (3)$$

and the median deviation or probable error of the points is only 0.014. The slope 0.502 agrees excellently with Kindler's relationship which requires a slope of 0.5 for the logarithmic plot.

If equation (1) applies to the hydrolysis constants of both sets of esters

$$-RT \ln K_c + RT \ln K_c^0 = \frac{A}{d_c^2} \left(\frac{B_1}{D} + B_2 \right)$$

$$-RT \ln K_b + RT \ln K_b^0 = \frac{A}{d_b^2} \left(\frac{B_1}{D} + B_2 \right)$$

it follows that

$$\log K_c = \text{constant} + (d_b/d_c)^2 \log K_b \qquad (4)$$

that is to say, equation (1) predicts a linear plot in Fig. 2 with a slope equal to $(d_b/d_c)^2$. If we estimate the value of d_b to be 5 Å. and that of d_c to be 7 Å., we obtain for the slope the value of 0.51 which is in satisfactory agreement with equation 3.

The agreement vanishes when, as in the upper plot in Fig. 2, Kindler's values for the hydrolysis constants of phenylacetic esters are plotted against the benzoic ester values. The median deviation of the points from the best straight line is 0.069, five times greater than in the cinnamic ester case, and the line has a slope of 0.325, smaller than the slope for the cinnamic esters, in-

stead of larger, as would be expected. The scantier data available for hydrocinnamic esters suffice to show that the same complicating influence which appears in the phenylacetic case is present with these compounds also. It seems probable therefore that the simple relationship of equation (1) applies only when a continuous system of conjugated double bonds exists between substituent and reacting group.

The $1/D$ factor in equation (1) is in agreement with Wynne-Jones'[36] observation that, in the case of the ionization of organic acids, the quantity $\log K - \log K^0$ is linear in $1/D$, a relationship which applies to all organic acids, and not merely to those here under discussion. Data are not available for a test of the corresponding relationship on other reactions. It is a further corollary of the presence of this factor that a plot of the $\log K$ values obtained in a medium of dielectric constant D_1 against the values for the same reaction in a medium of dielectric constant D_2 should be linear with the slope $D_2(B_1 + B_2D_1)/D_1(B_1 + B_2D_2)$. The linearity is satisfactorily verified by comparison of the results of Wooten and Hammett[37] on ionization constants in butyl alcohol with the ionization constants of the same acids in water.[3] From data on eight substituents a slope of 1.48 with a median deviation of 0.025 is obtained. As was explained in a previous paper[38] the magnitude of the slope is not predictable because of the high salt concentration in the butyl alcohol experiments.

The effect of temperature upon the relative strengths of carboxylic acids has been discussed in a previous paper,[38] but the treatment needs minor modifications. In terms of equation (1) the quantity ΔF varies with temperature only because of the temperature dependence of the dielectric constant. Consequently ΔS, the difference between the entropies of reaction or of activation for the substituted and for the unsubstituted reactants, is given by

$$\Delta S = -\frac{\delta \Delta F}{\delta T} = \frac{AB_1}{d^2 D^2} \frac{\delta D}{\delta T}$$

(36) Wynne-Jones, Proc. Roy. Soc. (London), A140, 440 (1933).
(37) Wooten and Hammett, This Journal, 57, 2289 (1935).
(38) Hammett, J. Chem. Phys., 4, 613 (1936).

If the constant B_2 is negligible, this becomes

$$\Delta S = \Delta F \, \delta \ln D / \delta T \qquad (6)$$

a result with which the available data on the ionization of meta and para substituted benzoic acids are in agreement.[38] The quantity $\delta \ln D/\delta T$ is in general negative in sign, is equal to -0.005 for the solvent water, and is of the same order of magnitude for many organic liquids. If, on the other hand, the quantity B_1 is negligible, ΔF should be independent of temperature. This is very nearly the case for the alkaline hydrolysis of esters, for which the work of Ingold and Nathan[39] leads to a mean value of the ratio $\Delta S/\Delta F$ equal to only 0.00028 ± 0.00007.

In any case there should be a direct proportionality between ΔS and the quantity $\delta \Delta F/\delta D$, the change in ΔF per unit change in dielectric constant, since

$$\Delta S = - \frac{\delta \Delta F}{\delta D} \frac{\delta D}{\delta T} \qquad (7)$$

The existence of this proportionality has been demonstrated for the ionization of benzoic acids, but data are not available for the comparison of observed and calculated values of the proportionality constant.[38]

The existence of the relationships embodied in equation (1) must to a considerable extent determine the nature of any theory which may be adopted to account for the effect of substituents upon rates and equilibria. The theory of a dipole field transmitted through the medium can, as previously indicated,[38] account for the observed dependence of ΔF for the ionization of benzoic acids upon dielectric constant and temperature, but fails by an order of magnitude to account for the actual values of ΔF in this reaction or for the fact that a given substituent may have a several times larger ΔF in other reactions. If the latter difficulty is avoided by the hypothesis that there is an internally transmitted effect as well as the one transmitted through the medium, it becomes necessary to admit that this additional effect is of an entirely different sort, and not merely an internally transmitted dipole field, because such a field could have no greater effect in the hydrolysis of a benzoic ester than in the ionization of benzoic acid. It then becomes quite inconceivable that the two effects should be linearly related in different reactions, as equation (2) demands, and especially that they should show so exactly the same dependence upon distance as Kindler's
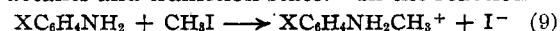
observations on the hydrolysis of cinnamic and benzoic esters demand. It is therefore an unavoidable conclusion that a substituent affects rates and equilibria essentially by a single internally transmitted mechanism.

The only reasonable theory of such an internal effect seems to be the one of an internal displacement of electrons which has been much discussed by Ingold[40] and to which Wheland and Pauling[41] have given a more definite mechanism and description in terms of quantum mechanical ideas. According to this theory a substituent alters the average density of electron charge in every part of the molecule. This may be either because the substituent directly attracts or repels electrons more than does the hydrogen atom it replaces, or because the substituent permits the construction of alternative electronic distributions of a highly polar nature which resonate with the non-polar one, or from some combination of these effects. In any case the altered concentration of electrons on the atom by which the substituted molecule enters into the reaction under consideration must alter both equilibrium and rate constant for the reaction because both depend upon an energy of bond formation which is itself a function of the electron density. Consider the reaction

$$XC_6H_4NH_2 + HA \rightleftharpoons XC_6H_4NH_3^+ + A^- \qquad (8)$$
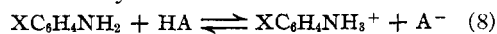
by which aniline derivatives act as bases. When the reaction proceeds to the right a new bond between hydrogen and nitrogen is formed, which depends upon electrons originally present on the nitrogen. This bond will be more stable the greater the concentration of available electrons, consequently a substituent which increases the electron density on the nitrogen atom must increase the equilibrium constant of the reaction, that is to say, it must increase the basicity of the aniline.

The reaction rate problem is most satisfactorily treated in terms of the illuminating idea of Eyring[42] and of Evans and Polanyi[43] according to which the rate of a reaction is proportional to the concentration of a transition state of maximum energy, which concentration can be calculated by the same statistical mechanical methods as if there were reversible chemical equilibrium between reactants and transition state. In the reaction

$$XC_6H_4NH_2 + CH_3I \longrightarrow XC_6H_4NH_2CH_3^+ + I^- \qquad (9)$$

(39) Ingold and Nathan, *J. Chem. Soc.*, 222 (1936).

(40) See for instance Ingold, *Chem. Rev.*, **15**, 225 (1934).

(41) Wheland and Pauling, THIS JOURNAL, **57**, 2086 (1935).

(42) Eyring, *J. Chem. Phys.*, **3**, 107 (1935).

(43) Evans and Polanyi, *Trans. Faraday Soc.*, **31**, 875 (1935).

for instance the transition state is a half-reacted state in which the methyl group has not completely let loose from the iodide ion, but is already partly attached to the nitrogen atom by electrons whose source is the aniline molecule. Obviously the probability of such a transition state and hence the rate of reaction will be increased by a substituent which increases the density of electrons on the nitrogen atom.

Clearly this picture is qualitatively in agreement with the effect represented by the second term in equation (1), although it does not immediately suggest the simplicity of the actual relationship. The factor A measures the tendency of the substituent to displace electrons, the factor B_2/d^2 measures both the displaceability of the electrons on the reacting group and the dependence of the free energy of reaction or of activation upon the change in electron density.

The first term in equation (1), AB_1/d^2D, may be accounted for in terms of the energy of a charged body in a dielectric medium, $e^2/2Da$ where e is the charge and a the radius of the body. By far the greater part of this energy in the case of a substance like benzoate ion must derive from that portion of the charge which is concentrated on the carboxylic group. Any charge distributed over the benzene nucleus can contribute little to the energy because of the large dimensions of the structure over which it is distributed. A substituent like the nitro group which attracts electrons must draw some of the charge off the carboxylic group, and even though this charge is again concentrated on a small structure, the nitro group, the electrostatic energy must decrease, because the effect depends upon the square of the charge. Thus if the energy due to the charge on the CO_2^- group in benzoate ion is given by $e^2/2Da$ and if the NO_2 group shares the charge equally with the CO_2^- in nitrobenzoate ion, the energy of the latter becomes

$$2(e/2)^2/2Da = 1/2(e^2/2Da)$$

which is one-half as great as the energy of the benzoate ion. This effect alone would make the free energy change negative in the reaction

$$NO_2C_6H_4CO_2H + C_6H_5CO_3^- \rightleftharpoons$$
$$NO_2C_6H_4CO_2^- + C_6H_5CO_2H \quad (10)$$
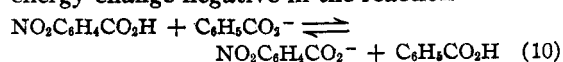
and increase the equilibrium constant above unity. An additional favorable factor is the fact that the wave function for nitrobenzoic acid must contain a considerable contribution from a dipolar configuration with a negative charge on the NO_2

group and a positive charge on the CO_2H, whose electrostatic energy would also contribute to increasing the energy of the left-hand side of equation (10). Both of these energy changes will have a magnitude proportional to $1/D$, in agreement with equation (1).

Since the quantities B_1 and B_2 depend upon quite different phenomena, they are independently variable from reaction to reaction, and may even differ in sign. This is the case in the hydrolysis of aryl sulfuric acids (reaction 33) studied by Burkhardt, Ford and Singleton.[2] Here the mean value of the ratio $\Delta S/\Delta F$ is found to be 0.0035 ± 0.0001, and from equations (1) and (5) we have, using $\delta \ln D/\delta T = -0.005$

$$AB_1/d^2D = -0.7\Delta F$$
$$AB_2/d^2 = 1.7\Delta F$$

B_1 presumably will have its largest values when reactants, products or transition state contain electrically charged molecular species, it need not however be zero in the absence of these because of the possible presence of dipoles with widely separated charges. The sensitivity to structure of reactants exhibited by ρ of equation (2), which represents the total effect of the B_1 and B_2 terms is surprisingly large. Thus the value of ρ for reaction 30, the reaction of a series of substituted phenolate ions with ethylene oxide is -0.946, while the value for the reaction of the same substances with propylene oxide (reaction 31) is -0.771.

The relationships contained in equation (1) are applicable only to meta and para substituted benzene derivatives; the situation is more complicated both with ortho substituted benzene derivatives and with aliphatic or mixed aromatic-aliphatic compounds. A substituent in the ortho position to the reacting group exerts an influence upon both equilibrium and rate of reaction, which is frequently but not always of great magnitude, and whose governing laws and mechanism are evidently entirely different from those concerned in the effect of more distant substituents.[1,5,22,44,45] One corollary only of equation (1) remains valid in the case of an ortho substituent, namely, that represented by equation (7).[38] Consequently the temperature effect upon ΔF may be described as the result of the temperature dependence of the dielectric constant even in the case of an ortho substituent.

(44) Schwarzenbach and Egli, *Helv. Chim. Acta*, **17**, 1184 (1934).
(45) Hammett and Pfluger, THIS JOURNAL, **55**, 4079 (1933).

In the case of aliphatic compounds equation (7) also fails, even as the crudest approximation.[38] It seems probable that in this case factors appear in the partition functions whose ratio determines the value of ΔF which are dependent upon the internal motions of the reacting molecules and which fail to cancel out between numerator and denominator. As a result the free energy change is not equal to the difference in potential energy between products and reactants and is dependent upon temperature.[38] On this basis the applicability of equation (1) is dependent upon a rigidity of structure which is indeed inherent in most of the reactants to which we have applied the equation, and whose absence in other cases results in some of the most striking failures of the equation.

Pauling[46] has recently pointed out that the freedom of rotation of any side chain attached to the benzene ring is limited or destroyed whenever the classical formula with a single link between side chain and ring resonates with another configuration with a double link in the same position. Thus the actual structure of phenol partakes sufficiently of such structures as
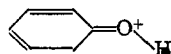
to prevent rotation around the carbon–oxygen link. The same effect must exist in the various derivatives of phenol, aniline and benzoic acid which we have considered, and it should notably ossify the structure of cinnamic ester and its derivatives, but not those of the phenylacetic and hydrocinnamic esters. The striking contrast shown in Fig. 2 between the exact correlation of the hydrolysis rates of cinnamic esters with those of benzoic esters, and the poor correlation of the rates for phenylacetic esters is therefore entirely in agreement with this hypothesis.

Since the benzyl halides are incapable of this kind of resonance, there should be free rotation of the side chain. In agreement with this prediction we find very poor correlation between our σ constants and the reaction rates of benzyl halides. This is notably true for the hydrolysis (reaction 37) for which $r = 0.15$, but the reaction with iodide (reaction 38) has an r greater than the average, and a direct comparison of the iodide reaction with the hydrolysis gives a very poor correlation, the probable error in log K for the hydrolysis predicted from the iodide reaction being 0.20. On the other hand, there is excellent correlation between hydrolysis rate and rate of reaction with a tertiary amine.[47]

Clearly, then, linear logarithmic relationships between equilibrium or rate constants of different reactions are not limited to cases to which equation (1) is directly applicable. This fact appears indeed in the prototype of all such relationships, the relation between acid or base strength and catalytic effect discovered by Brönsted and Pedersen.[48] This applies both to aliphatic and aromatic acids, to ortho substituted as well as to meta and para substituted compounds. The same thing is true of Hammett and Pfluger's[45] relationship between the rate of alkylation of an amine by the methyl ester of an acid and the strength of the acid. Evidently the factors which cause the deviations from equation (1) may have linearly related effects upon two different reactions, provided these reactions are sufficiently closely related. Yet even in the case of general basic catalysis, Pfluger[49] has found significant deviations from a straight line plot when the alterations in structure take place in the reacting group itself as when diethylaniline is substituted for dimethylaniline.

Summary

A simple formula is proposed to represent the effect of a substituent in the meta or para position of the benzene ring upon the rate or equilibrium of a reaction in which the reacting group is in a side chain attached to the ring. This formula represents not only the total effect of the substituent but also the influence of changing length of side chain, of dielectric constant of the medium, and of temperature within a satisfactory precision in a wide variety of cases. The theory that a substituent acts by internal electron displacement is in complete agreement with this formula, including the temperature and medium effects embodied in it, and accounts also for the large deviations observed in the case of non-rigid structures.

A table of substituent constants and one of reaction constants has been calculated from which the effect of many substituents upon a large number of reaction rates and equilibria may be obtained by multiplication of the constants.

(46) Pauling, THIS JOURNAL, **58**, 94 (1936).

(47) See Fig. 9 of ref. 1.

(48) Brönsted and Pedersen, Z. physik. Chem., **108**, 185 (1924).

(49) Unpublished results kindly communicated to me by Dr. H. L. Pfluger.