

[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 myself¹ and in wider variety by Burkhardt, Ford and Singleton² 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

$$\log K = \log K^0 + \sigma \rho \quad (2)$$

where $\sigma = -A/2.303 R$

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

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

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

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

(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
<i>p</i> NH ₂	-0.660	2	2	...
<i>p</i> CH ₃ O	-.268	1	21	0.077
<i>p</i> C ₂ H ₅ O	-.25	3	6	.105
3,4-di CH ₃	-.229	4	1	...
<i>m</i> (CH ₃) ₂ N	-.211	31	1	...
<i>p</i> (CH ₃) ₂ N	-.205	21 ^a	1	...
<i>p</i> CH ₃	-.170	1	33	.046
<i>m</i> NH ₂	-.161	2	3	.060
3,4-CH ₂ O ₂	-.159	2	3	.023
<i>p</i> C ₂ H ₅	-.144	2	1	...
<i>m</i> CH ₃	-.069	1	21	.038
<i>p</i> CH ₃ S	-.047	2	1	...
None	.000	1	36	.034
<i>p</i> C ₆ H ₅	+.009	2	3	.22
<i>p</i> F	+.062	1	7	.066
<i>m</i> CH ₃ O	+.115	1	7	.116
<i>m</i> C ₂ H ₅ O	+.15	3	2	...
<i>β</i> C ₆ H ₄ ^b	+.17	3	9	.102
<i>p</i> Cl	+.227	1	31	.040
<i>p</i> Br	+.232	1	24	.040
<i>p</i> I	+.276	2	11	.073
<i>m</i> F	+.337	1	5	.083
<i>m</i> I	+.352	1	8	.039
<i>m</i> Cl	+.373	1	19	.041
<i>m</i> Br	+.391	1	17	.035
<i>p</i> C ₆ H ₅ N ₂	+.640	26, 27	1	...
<i>m</i> CN	+.678	26, 27	1	...
<i>m</i> NO ₂	+.710	1	21	.069
<i>p</i> NO ₂ (b) ^c	+.778	1	15	.066
<i>p</i> CN	+1.000	4	4	.042
<i>p</i> NO ₂ (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 substitu- ents 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.

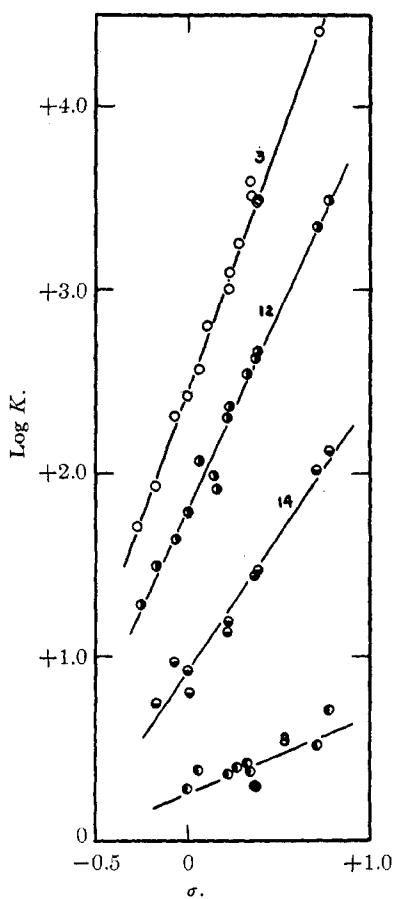


Fig. 1.—Relationship between $\log K$ and σ for various reactions (see Table III). The position of the scale of ordinates is arbitrary.

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 $N\text{HCl}$.⁸
- (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.*, **58**, 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).

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

(9) (a) Nathan and Watson, *J. Chem. Soc.*, 217 (1938); (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 Oostall, *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) Demény, *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°.²⁹
34. R. Addition of hydrogen sulfide to substituted benzonitriles in alkaline alcoholic solution at 60.6°.^{30a}
35. R. Alkaline hydrolysis of substituted phenylacetic esters, conditions as in 2.^{30b}
36. E. Ionization of substituted phenylacetic acids in water at 25°.³¹
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 Watson³² 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 Jones³³ 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

- (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.*, 1264 (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.*, 438 (1936).
 (33) Bennett and Jones, *ibid.*, 1815 (1935).
 (34) Baker, *ibid.*, 987 (1934).

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*-NO₂(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*-NO₂(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.³⁶ 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

(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

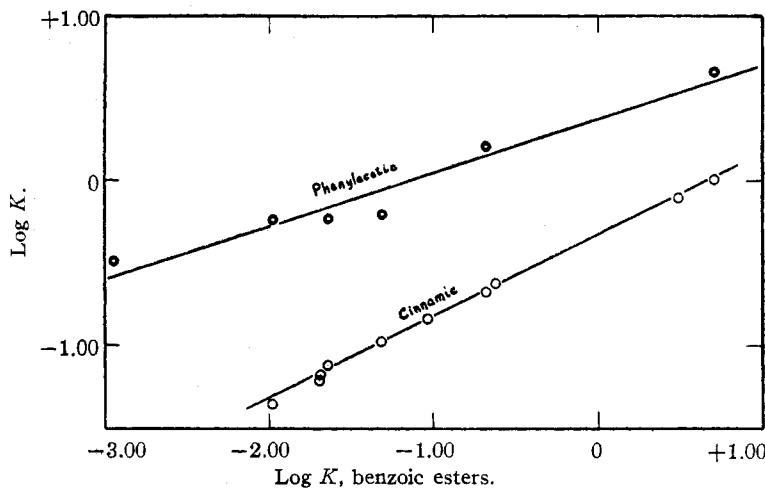


Fig. 2.—Relationships between hydrolysis constants.

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

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

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

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

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 re-

lationship 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 $D_2(B_1 + B_2 D_1)/D_1(B_1 + B_2 D_2)$. The linearity is satisfactorily verified by comparison of the results of Wooten and Hammett³⁷ 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 paper³⁸ 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

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

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 Nathan³⁹ 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

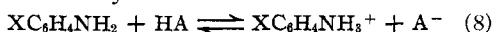
$$\Delta S = - \frac{\delta \Delta F}{\delta D} \frac{\delta D}{\delta T} \quad (7)$$

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

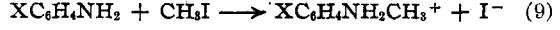
observations on the hydrolysis of cinnamic and benzoic esters demand. It is therefore an unavoidable conclusion that a substituent affects rates and equilibria essentially by a single internally transmitted mechanism.

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 Ingold⁴⁰ and to which Wheland and Pauling⁴¹ 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



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 Eyring⁴² and of Evans and Polanyi⁴³ 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



(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).

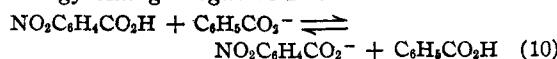
for instance the transition state is a half-reacted state in which the methyl group has not completely let loose from the iodide ion, but is already partly attached to the nitrogen atom by electrons whose source is the aniline molecule. Obviously the probability of such a transition state and hence the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



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 $\delta \ln D/\delta T = -0.005$

$$\begin{aligned} AB_1/d^2D &= -0.7 \Delta F \\ AB_2/d^2 &= 1.7 \Delta F \end{aligned}$$

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 .

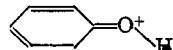
The relationships contained in equation (1) are applicable only to meta and para substituted benzene derivatives; the situation is more complicated both with ortho substituted benzene derivatives and with aliphatic or mixed aromatic-aliphatic compounds. A substituent in the ortho position to the reacting 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).²⁸ 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 Pfleiderer, *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.

Pauling⁴⁶ 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 be-

tween 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's⁴⁹ 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, Pfluger⁴⁹ 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.

NEW YORK, N. Y.

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(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.

A Survey of Hammett Substituent Constants and Resonance and Field Parameters

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Contents

I. Introduction	165
A. Field/Inductive Parameters	166
B. Resonance Effect Parameters	177
C. R^+ and R^- Values	187
D. Resonance Effect σ_R Values from NMR Chemical Shifts of Para-Substituted Fluorobenzenes Relative to Their Meta Isomers as Internal References	188
E. Calculated σ_m and σ_p Values and Shortcomings	190
II. Discussion	191
III. References	192

I. Introduction

The Hammett equation (and its extended forms) has been one of the most widely used means for the study and interpretation of organic reactions and their mechanisms. Although the Hammett methodology has been criticized by theoreticians because of its empirical foundation, it is astonishing that σ constants, obtained simply from the ionization of organic acids in solution, can frequently predict successfully equilibrium and rate constants for a variety of families of reactions in solution. Almost every kind of organic reaction has been treated via the Hammett equation, or its extended form. The literature is so voluminous and extensive that there is no complete review of all that has been accomplished.

Hammett's success in treating the electronic effect of substituents on the rates and equilibria of organic reactions^{1,2} led Taft to apply the same principles to steric and inductive and resonance effects.³ Then, more recently, octanol/water partition coefficients (P) have been used for rationalizing the hydrophobic effects of organic compounds interacting with biological systems.⁴ The use of $\log P$ (for whole molecules) or π (for substituents), when combined with electronic and steric parameters, has opened up whole new regions of biochemical and pharmacological reactions to study by the techniques of physical organic chemistry.^{5,6}

The combination of electronic, steric, hydrophobic, hydrophilic, and hydrogen-bonding⁷ parameters has been used to derive quantitative structure-activity relationships (QSAR) for a host of interactions of organic compounds with living systems or parts thereof. The binding of organic compounds to proteins,⁸ their interaction with enzymes⁹ and with cells^{10,11} and tissues,¹² their inhibition of organelles,¹¹ and as antimalarials¹³

and antitumor agents,^{10,14} their action as hypnotics^{15,16} and anesthetics,¹⁷ as well as their use in pesticide design,¹⁸ in toxicology,¹⁹ in mutagenicity²⁰ and carcinogenicity²¹ studies, their fate in metabolism,^{22,23} in environmental systems,²⁴ and their behavior in chromatographic systems^{25,26} have all been treated via QSAR.

The explosive growth of correlation analysis of biological processes via substituent constants has somewhat changed the focus in the development of σ constants. Until the 1960's the use of substituent constants was almost entirely in the hands of physical organic chemists who generally worked with "well-behaved" substituents to analyze highly refined data from reactions in homogeneous solution. Their goal was to obtain very precise correlations and understanding for clearly defined but limited organic reactions. Applications of QSAR to biological systems, drugs, pesticides, toxicology, etc. brought under consideration much wider structural variations (including less well-behaved substituents) and activity data (dependent variables) of much lower quality. Noise in the biological data in the range of 20 to 100% was common so that small errors in σ and π , became less significant for this work. Researchers in these fields required parameters for a much wider variety of structure and were willing to accept a lower precision if necessary. This shift in emphasis led Hansch and Leo to compile and publish in 1979, a truly comprehensive data base of substituent constants.⁴ During the following nine years many new substituent constants have been published, so that in this report we have been able to list both σ_m and σ_p values for 530 different substituents (Table I). With the use of values derived from F NMR shifts of meta- and para-substituted fluorobenzenes, the number is increased to over 660, including many substituents containing metallic atoms and highly interactive neutral and charged substituents. Exner² has also compiled an extensive list of σ constants including examples where only σ_m or σ_p is known, and he has attempted to evaluate their reliability. We have attempted to list all examples where both σ_m and σ_p have been reported and where more than one set of values exist we have selected the set which in our judgement is the most reliable. In some instances of very doubtful reliability we have placed the values in parentheses.

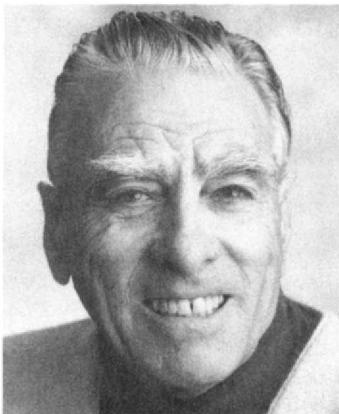
The values of σ were defined by Hammett from the ionization constants of benzoic acids as follows

$$\sigma_x = \log K_X - \log K_H \quad (1)$$

where K_H is the ionization constant for benzoic acid in water at 25 °C and K_X is the corresponding constant for a meta- or para-substituted benzoic acid. Some of the benzoic acids are so insoluble in water that mixed solvents such as 50/50 water/ethanol must be used. These secondary values have been linearly related to

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Corwin Hansch in 1944 received his Ph.D. from New York University in the field of synthetic organic chemistry, studying under Professor H. G. Lindwall. After a brief postdoctoral period with Professor H. R. Snyder at the University of Illinois, he joined the du Pont Co. and worked first on the Manhattan project at the University of Chicago and Richland, WA, and then at the experimental station in Wilmington, DE. In 1946 he joined the Chemistry Department at Pomona College, where he has remained except for two sabbatical leaves, one in Professor Prelog's laboratory in Zurich and the other in Professor Huisgen's laboratory in Munich. His main interests in research have been the high-temperature dehydrocyclization reaction and the correlation of chemical structure with biological activity.



Albert Leo was born 1925 in Winfield, IL and educated in southern California. He spent two years in the U.S. Army Infantry, serving in the ETO from 1944 to 1945. He received his B.S. in Chemistry from Pomona College (1948; Phi Beta Kappa, Magna Cum Laude) and M.S. and Ph.D. in Physical Organic Chemistry from the University of Chicago, studying reaction kinetics under Prof. Frank Westheimer. After 15 years in industrial research and development in the area of food chemistry, he returned to Pomona College to initiate and direct the Medchem Project under the leadership of his former professor, Dr. Corwin Hansch. The Project provides software and databases useful in the design of bioactive chemicals and is distributed world wide. His study of partition coefficients as a measure of hydrophobicity resulted in a 1971 paper in *Chemical Reviews* which has become a "Citation Classic". Dr. Leo was given an "Excellence in Science" award by Sigma Xi in 1980 and was chairman of the Gordon Conference on QSAR in Biology in 1981.

the water system by an appropriate scaling factor, ρ . σ values have been obtained also from various organic reactions (rates or equilibria) or from F NMR substituent chemical shifts. All of these methods have been examined in this report. However, in using the values in Table I for developing QSAR, care must be taken to see that the quality of the independent σ constant is commensurate with that of the data being correlated.

One of the early postulates of the so-called "English School of Chemists" was that the electronic effects of



Robert W. Taft is a Professor of Chemistry at the University of California, Irvine. Born in Lawrence, KS, Taft received a B.S. in Chemistry from the University of Kansas and a Ph.D. from the Ohio State University where he worked with Melvin Newman. Following a postdoctoral year with Louis Hammett at Columbia University, Taft spent 15 years at the Pennsylvania State University. He has been at the University of California, Irvine since it began in 1965. Current interests involve extensive studies of the effects of molecular structure on gas-phase proton-transfer equilibria, using ion cyclotron resonance spectroscopy. This work also includes binding studies in the gas phase with a variety of univalent cations. Additional interests include studies of structural and solvent effects on hydrogen-bond acidities and basicities and their applications to treatments of solute partitioning between bilayers and biological activities.

substituents are composed of two main parts: a field/inductive component and a resonance component.²⁷ Following Hammett's success in placing the discussion in numerical terms with σ constants, efforts were undertaken to factor σ into its component parts. Although progress has been made in showing for distant substituents that the field effect is predominate,²⁸ there remain questions to be answered³⁰ as to the magnitude of the contribution of the inductive effect. In this report, reference to either σ_I , σ_F , σ_L , or F , all of which, for present purposes, we show may be taken as essentially equivalent, (cf. Table II) assumes the operation of the combined effects.

Wider agreement has been accorded the efforts to split the electronic effect of a substituent into field/inductive (σ_I) and resonance (σ_R) components:

$$\sigma_p = \sigma_I + \sigma_R \quad \text{or} \quad \sigma_p - \sigma_I = \sigma_R \quad \text{or} \quad \sigma_p - \sigma_R = \sigma_I \quad (2)$$

These efforts have been reviewed by Charton.²⁹

A. Field/Inductive Parameters

There is general agreement that the ionization of bicyclooctane carboxylic acids³¹ (I) provides an unambiguous system for defining a field/inductive parameter because, in this rigid system, X is held firmly in place and there is little possibility for resonance or polarization interaction between X and the carboxyl functions of COOH and COO⁻. It seems safe to assume, there-



fore, that the only ways X can influence the ionization of the carboxyl group are through space (the predom-

inate field effect) and though the intervening σ bonds (inductive). Roberts and Moreland³¹ used 50% ethanol as the solvent for these rather insoluble acids and defined the electronic parameter as

$$\sigma' = \log K_X - \log K_H \quad (3)$$

Taft³² utilized a correlation between σ' and his generalized polar parameter (σ^*) to obtain additional values of σ' (called σ_I) and then calculated σ_R via eq 2. Swain and Lupton³³ used σ' to define F as a basis for separating the resonance and field inductive effects according to eq 4. The coefficients a , b , and ϵ are eval-

$$F = \sigma' = a\sigma_m + b\sigma_p + \epsilon \quad (4)$$

uated via the least squares method. The intercept ϵ , which is close to zero, can be regarded as an error term. In Swain and Lupton's derivations of F they did not attempt to place their F and R values on the same scale as Hammett constants obtained from the ionization of benzoic acids in water at 25 °C. Hansch et al. accomplished this³⁴ by scaling as follows: $F = \sigma'/1.65$ using the results of Stock et al.^{35,36} on the bicyclooctane carboxylic acids.

$$F = \sigma'/1.65 = 1.369\sigma_m - 0.373\sigma_p - 0.009 \quad (5)$$

$$n = 14, r = 0.992, s = 0.042$$

To evaluate R , Swain and Lupton made the assumptions

$$\sigma_p = \alpha F + R \quad (6)$$

and the further assumption that for $N^+(CH_3)_3$, $R = 0$. Following this procedure and substituting in eq 6 the values for $N^+(CH_3)_3$ of $F = 0.89$ and $\sigma_p = 0.82$, α was found to be 0.921.³⁴ F and R were then calculated for about 200 substituents. Since, as noted before,⁴ the α factor does not differ much from 1, little if anything is lost by using Taft's eq 2 to calculate $R = \sigma_R$ rather than eq 6. Therefore we have recalculated F and R along the lines used by Charton²⁹ to obtain his σ_L and σ_D parameters using the data in Table I.

In an extensive analysis Charton²⁹ has concluded that the scaling factor of 1.65 used in eq 5 would be better replaced by 1.56. Accordingly, we have evaluated σ_I , as did Charton, from: $\sigma_I = \Delta pK_a/1.56$, using pK_a values for the 4-X-bicyclooctane carboxylic acid (Table II, third column).

Another excellent system for establishing σ_I values is that of the quinuclidines, II, studied by Grob and Schlageter.³⁷ In this case, the ionization of the pro-



tonated amine is used to obtain σ_I , which has an advantage in that it is significantly more sensitive to X than is the carboxylate group of I. Using substituents for which σ_I can be calculated from ionization constants (entries 1–12, Table II), we have derived eq 7. There $\sigma_I(\text{Stock}) = 0.191 (\pm 0.015)\sigma_I(\text{Grob}) - 0.037 (\pm 0.031)$

$$(7)$$

$$n = 14, r = 0.992, s = 0.029$$

are only three substituents whose σ_I values were determined in the carboxylate system by both Holtz and

Stock and by Roberts and Moreland. In eq 7, $\sigma_I(\text{Stock})$ refers to the scaled values from the carboxylate parent (Roberts and Moreland data included) while $\sigma_I(\text{Grob})$ values are from unscaled quinuclidine data (Table II, fourth column).

These results in Table II allow the rederivation of eq 5 on the basis of an extended set of σ_I values. The

$$F = \sigma_I = 1.297 (\pm 0.147)\sigma_m - 0.385 (\pm 0.089)\sigma_p + 0.033 (\pm 0.026) \quad (8)$$

$$n = 38, r = 0.968, s = 0.046$$

parameters of eq 8 are only slightly different from those of eq 5 despite the inclusion of 24 more data points, the new normalization factor of 1.56, and dropping the assumption that R for $N^+(CH_3)_3$ is zero. Note that the quality of fit in eq 8 is the same as eq 5 in terms of the standard deviation. Three substituents in Table II for which σ_I could not be derived from Grob and Schlageter's data have not been used to derive eq 8: $CH_2OSO_2C_6H_4-4\text{-Me}$, $CH(OH)_2$, and CO_2^- . For the first two, σ_p and σ_m have not been reported, and hence F can not be calculated via eq 8. The value of F for the CO_2^- group obtained from eq 7 is out of line with that calculated from eq 8. For charged substituents this is not an uncommon result since the simple Hammett equation is poorly applicable.³⁸ Comparison of F values of some common substituents calculated by eq 5 and eq 8 is made in Table III.

All of the F values in Table I have been *calculated* by using eq 8. That is, we have not listed in Table I any of the experimentally based values of Table II. This seemed to be a more consistent way of presenting the results for correlation analysis although some may prefer to use the values in Tables II and IV insofar as possible.

Ideally, one would like to obtain all values of σ_I from experimentally determined pK_a values of structures like I or II where $R = 0$. This is not feasible because of the great difficulty of synthesizing the necessary structures. Even though the various approaches of evaluating the field inductive parameter from σ_m and σ_p have been criticized by some authors,^{39–41} we believe that for many applications the results are precise enough. This conclusion is supported by comparisons of σ values in Tables I, II, and IV.

Table II gives σ_F (σ_I) values obtained for many typical substituents by eight different methods. There are no large differences in the σ_I scale of field/inductive effects for common dipolar substituents, X, as obtained by eqs 5 and 6 (columns 3 and 4, respectively), or, as first obtained by Taft,³² from the relationship: $\sigma_I = \sigma' = 0.45\sigma^*_{CH_2X}$. Furthermore, there are relatively minor differences between any of these σ_I values and the σ_F values given recently by Taft and Topsom³⁰ (column 2) or F values (column 7). The individual σ_F parameters were obtained by averaging values of determinations by numerous methods^{42–44} and have been confirmed³⁰ by gas-phase proton-transfer equilibria, which are much more discriminating than most solution equilibria.

Charton's review²⁹ includes numerous examples of solution equilibria for which field/inductive effects are strongly predominant and for which there are both greater sensitivities and varieties of substituents than for the bicyclooctane carboxylic acid pK_a values.

TABLE I. Hammett and Modified Swain-Lupton Constants^{a,d}

	substituent	σ_m	σ_p	F^b	R^c	ref(s)
1.	BF ₂	0.32	0.48	0.26	0.22	109
2.	Br	0.39	0.23	0.45	-0.22	183
3.	GeBr ₃	0.66	0.73	0.61	0.12	139
4.	SiBr ₃	0.48	0.57	0.44	0.13	139
5.	Cl	0.37	0.23	0.42	-0.19	183
6.	HgCl	0.33	0.35	0.33	0.02	74
7.	SO ₂ Cl	1.20	1.11	1.16	(-0.05)	134
8.	SCl	0.44	0.48	0.42	0.06	74
9.	ICl ₂	1.10	1.11	1.03	0.08	110
10.	P(O)Cl ₂	0.78	0.90	0.70	0.20	74
11.	PCl ₂	0.54	0.61	0.50	0.11	164
12.	P(S)Cl ₂	0.70	0.80	0.63	0.17	74
13.	GeCl ₃	0.71	0.79	0.65	0.14	139
14.	SiCl ₃	0.48	0.56	0.44	0.12	139
15.	F	0.34	0.06	0.45	-0.39	183
16.	HgF	0.34	0.33	0.35	-0.02	74
17.	SOF	0.74	0.83	0.67	0.16	74
18.	SO ₂ F	0.80	0.91	0.72	0.19	142
19.	IF ₂	0.85	0.83	0.82	0.01	110
20.	POF ₂	0.81	0.89	0.74	0.15	164
21.	PF ₂	0.49	0.59	0.44	0.15	109
22.	GeF ₃	0.85	0.97	0.76	0.21	139
23.	SF ₃	0.70	0.80	0.63	0.17	110
24.	SiF ₃	0.54	0.69	0.47	0.22	164
25.	IF ₄	1.07	1.15	0.98	0.17	110
26.	PF ₄	0.63	0.80	0.54	0.26	110
27.	SF ₆	0.61	0.68	0.56	0.12	179
28.	I	0.35	0.18	0.42	-0.24	183
29.	IO	0.58	0.62	0.55	0.07	63
30.	IO ₂	0.68	0.78	0.61	0.17	170
31.	NO	0.62	0.91	0.49	0.42	107
32.	NO ₂	0.71	0.78	0.65	0.13	183
33.	ONO ₂	0.55	0.70	0.48	0.22	74
34.	N≡N ⁺	1.76	1.91	1.58	0.33	182
35.	N≡N ^{+(BF₄)⁻}	1.65	1.79	1.48	0.31	88
36.	NO ₂ ⁻	0.00	-0.43	0.20	-0.63	112
37.	N ₃	0.37	0.08	0.48	-0.40	130
38.	O ⁻	-0.47	(-0.81)	-0.26	(-0.55)	181
39.	SO ₂ ⁻	-0.02	-0.05	0.03	-0.08	135
40.	SO ₃ ⁻	0.30	0.35	0.29	0.06	81
41.	S ⁻	-0.36	-1.21	0.03	-1.24	74, 97
42.	AsO ₃ H ⁻	0.00	-0.02	0.04	-0.06	74, 87
43.	H	0.00	0.00	0.03	0.00	-
44.	NHNO ₂	0.91	0.57	0.99	-0.42	112
45.	OH	0.12	-0.37	0.33	-0.70	183
46.	S(O)OH	-0.04	-0.07	0.01	-0.08	74
47.	PO ₃ H ⁻	0.20	0.26	0.19	0.07	183
48.	OPO ₃ H ⁻	0.29	0.00	0.41	-0.41	74
49.	SH	0.25	0.15	0.30	-0.15	183
50.	B(OH) ₂	-0.01	0.12	-0.03	0.15	170
51.	NH ₂	-0.16	-0.66	0.08	-0.74	183
52.	NHOH	-0.04	-0.34	0.11	-0.45	87
53.	SO ₂ NH ₂	0.53	0.60	0.49	0.11	170
54.	PO(OH) ₂	0.36	0.42	0.34	0.08	74
55.	PH ₂	0.06	0.05	0.09	-0.04	74
56.	B(OH) ₃ ⁻	-0.48	-0.44	-0.42	-0.02	90
57.	GeH ₃	0.00	0.01	0.03	-0.02	74, 280
58.	NH ₃ ⁺	0.86	0.60	0.92	-0.32	181
59.	NHNH ₂	-0.02	-0.55	0.22	-0.77	87
60.	SiH ₃	0.05	0.10	0.06	0.04	110
61.	CBr ₃	0.28	0.29	0.28	0.01	165
62.	CClF ₂	0.42	0.46	0.40	0.06	74
63.	5-chloro-1-tetrazolyl	0.60	0.61	0.58	0.03	165
64.	COCl	0.51	0.61	0.46	0.15	164
65.	N=CCl ₂	0.21	0.13	0.26	-0.13	165
66.	CCl ₃	0.40	0.46	0.38	0.09	170
67.	OCCl ₃	0.43	0.35	0.46	-0.11	74
68.	COF	0.55	0.70	0.48	0.22	110
69.	OCF ₂ O	0.36	0.36	0.36	0.00	153
70.	CF ₃	0.43	0.54	0.38	0.16	183
71.	HgCF ₃	0.29	0.32	0.29	0.03	74
72.	HgSCF ₃	0.39	0.42	0.38	0.04	74
73.	I-NSO ₂ CF ₃	1.30	1.35	1.20	0.15	63
74.	N=NCF ₃	0.56	0.68	0.50	0.18	74
75.	OCF ₃	0.38	0.35	0.39	-0.04	145
76.	SOCF ₃	0.63	0.69	0.58	0.11	163
77.	SeOCF ₃	0.81	0.83	0.76	0.07	74

TABLE I (Continued)

	substituent	σ_m	σ_p	F^b	R^c	ref(s)
78.	SO_2CF_3	0.83	0.96	0.74	0.22	70
79.	SeO_2CF_3	1.08	1.21	0.97	0.24	74
80.	OSO_2CF_3	0.56	0.53	0.56	-0.03	118
81.	SCF_3	0.40	0.50	0.36	0.14	178
82.	SeCF_3	0.44	0.45	0.43	0.02	167
83.	HgCN	0.28	0.34	0.27	0.08	74
84.	CN	0.56	0.66	0.51	0.15	183
85.	NC	0.48	0.49	0.47	0.02	74
86.	$\text{CN}(\text{BBr}_3)$	0.61	0.48	0.64	-0.16	164
87.	$\text{CN}(\text{BCl}_3)$	0.95	0.86	(0.93)	(-0.05)	164
88.	$\text{CN}(\text{BF}_3)$	0.72	0.66	(0.71)	(-0.05)	164
89.	$\text{N}=\text{C}=\text{O}$	0.27	0.19	0.31	-0.12	165
90.	OCN	0.67	0.54	0.69	-0.15	74
91.	SO_2CN	1.10	1.26	0.97	0.29	74
92.	$\text{N}=\text{C}=\text{S}$	0.48	0.38	0.51	-0.13	156
93.	SCN	0.51	0.52	0.49	0.03	85, 183
94.	SeCN	0.61	0.66	0.57	0.09	173, 87
95.	N=N CN	0.71	1.03	0.56	0.47	72
96.	N(O)=CN	0.78	0.89	0.70	0.19	281
97.	$\text{C}(\text{NO}_2)_3$	0.72	0.82	0.65	0.17	74, 190
98.	5-azido-1-tetrazolyl	0.54	0.54	0.53	0.01	165
99.	CO_2^-	-0.10	0.00	-0.10	0.10	183
100.	CHBr_2	0.31	0.32	0.31	0.01	74
101.	CHCl_2	0.31	0.32	0.31	0.01	74
102.	OCHCl_2	0.38	0.26	0.43	-0.17	74
103.	CHF_2	0.29	0.32	0.29	0.03	110
104.	OCHF_2	0.31	0.18	0.37	-0.19	146
105.	SOCHF_2	0.54	0.58	0.51	0.07	140
106.	SO_2CHF_2	0.75	0.86	0.67	0.19	146
107.	SCHF_2	0.33	0.37	0.32	0.05	170
108.	S(O)(=NH)CF_3	0.72	0.84	0.64	0.20	62
109.	NHSO_2CF_3	0.44	0.39	0.45	-0.06	74
110.	CHI_2	0.26	0.26	0.27	-0.01	74
111.	NHCN	0.21	0.06	0.28	-0.22	158
112.	1-(1 <i>H</i>)-tetrazolyl	0.52	0.50	0.52	-0.02	165
113.	5-(1 <i>H</i>)-tetrazolyl	0.64	0.56	0.65	-0.09	166
114.	5-hydroxy-1-tetrazolyl	0.39	0.33	0.41	-0.08	165
115.	5-mercaptop-1-tetrazolyl	0.45	0.45	0.44	-0.01	165
116.		0.30	0.19	0.35	-0.16	158
117.	CHO	0.35	0.42	0.33	0.09	87, 174
118.	COOH	0.37	0.45	0.34	0.11	183
119.	CH_2Br	0.12	0.14	0.14	0.00	170
120.	CH_2Cl	0.11	0.12	0.13	-0.01	170
121.	OCH_2Cl	0.25	0.08	0.33	-0.25	74
122.	CH_2F	0.12	0.11	0.15	-0.04	110
123.	OCH_2F	0.20	0.02	0.29	-0.27	74
124.	SCH_2F	0.23	0.20	0.25	-0.05	74
125.	CH_2I	0.10	0.11	0.12	-0.01	170
126.	NHCHO	0.19	0.00	0.28	-0.28	156
127.	CONH_2	0.28	0.36	0.26	0.10	87, 187
128.	CSNH_2	0.25	0.30	0.24	0.06	283
129.	$\text{CH}=\text{NOH}-t$	0.22	0.10	0.28	-0.18	129
130.	3,4-N=CHNH-	-0.15	-0.15	-0.10	-0.05	116
131.	N(O)=NCONH ₂	0.59	0.63	0.56	0.07	281
132.	OCH_2O^-	-0.16	-0.16	-0.11	-0.05	188
133.	Me	-0.07	-0.17	0.01	-0.18	183
134.	$\text{CH}_2\text{SO}_2\text{R}$	0.15	0.17	0.16	0.01	170
135.	SiMeCl_2	0.31	0.39	0.29	0.10	74
136.	SiMeF_2	0.29	0.23	0.32	-0.09	74
137.	HgMe	0.43	0.10	(0.55)	(-0.45)	164
138.	NHCH_2SO_3	-0.10	-0.57	0.12	-0.69	89
139.	NHCONH_2	-0.03	-0.24	0.09	-0.33	156
140.	$\text{N}(\text{Me})\text{NO}_2$	0.49	0.61	0.43	0.18	112
141.	NHCSNH_2	0.22	0.16	0.26	-0.10	158
142.	OMe	0.12	-0.27	0.29	-0.56	183
143.	CH_2OH	0.00	0.00	0.03	-0.03	133
144.	SOMe	0.52	0.49	0.52	-0.03	183
145.	S(OMe)	0.21	0.17	0.24	-0.07	74
146.	$\text{OS}(-\text{O})\text{CH}_3$	0.44	0.45	0.43	0.02	74
147.	$\text{S}(\text{O})\text{OMe}$	0.50	0.54	0.47	0.07	74
148.	SO_2Me	0.60	0.72	0.53	0.19	183
149.	SSO_2Me	0.43	0.54	0.38	0.16	74

TABLE I (Continued)

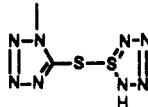
	substituent	σ_m	σ_p	F^b	R^c	ref(s)
150.	OSO_2Me	0.39	0.36	0.40	-0.04	156
151.	SMe	0.15	0.00	0.23	-0.23	183
152.	SSMe	0.22	0.13	0.27	-0.14	74
153.	SeMe	0.10	0.00	0.16	-0.16	183
154.	NHMe	-0.21	-0.70	0.03	-0.73	164
155.	CH_2NH_2	-0.03	-0.11	0.04	-0.15	74
156.	NHSO_2Me	0.20	0.03	0.28	-0.25	156
157.	CH_2NH_3^+	0.59	0.53	0.59	-0.06	88
158.	$\text{N}(\text{COF})_2$	0.58	0.57	0.57	0.00	109
159.	HgOCOCF_3	0.50	0.52	0.48	0.04	74
160.	COCF_3	0.63	0.80	0.54	0.26	110
161.	SCOCF_3	0.48	0.46	0.48	-0.02	74
162.	OCOCF_3	0.56	0.46	0.58	-0.12	74
163.	$\text{N}(\text{CF}_3)_2=\text{O}(\text{F})$	0.50	0.50	0.49	0.01	109
164.	$\text{CF}_2\text{OCF}_2^-$	0.81	0.81	0.77	0.04	153
165.	CF_3CF_3	0.47	0.52	0.44	0.08	172
166.	OCF_2CF_3	0.48	0.28	0.55	-0.27	74
167.	$\text{SO}_2\text{CF}_2\text{CF}_3$	0.92	1.08	0.81	0.27	76
168.	SCF_2CF_3	0.44	0.48	0.42	0.06	76
169.	$\text{N}(\text{CF}_3)_2$	0.40	0.53	(0.35)	0.18	145
170.	$\text{S}(\text{CF}_3)=\text{NSO}_2\text{CF}_3$	1.18	1.28	1.07	0.21	62
171.	$\text{SO}(\text{CF}_3)=\text{NSO}_2\text{CF}_3$	1.23	1.40	1.09	0.31	62
172.	$\text{N}(\text{SO}_2\text{CF}_3)_2$	0.61	0.83	0.50	0.33	103
173.	$\text{P}(\text{CF}_3)_2$	0.60	0.69	0.55	0.14	109
174.	$\text{P}(\text{CN})_2$	0.82	0.90	0.75	0.15	74
175.	$\text{C}\equiv\text{CH}$	0.21	0.23	0.22	0.01	171
176.	OCF_2CHFCl	0.35	0.28	0.38	-0.10	146
177.	NHCOCF_3	0.30	0.12	0.38	-0.26	156
178.	$\text{CH}=\text{NSO}_2\text{CF}_3$	0.76	1.00	0.63	0.37	63
179.	OCF_2CHF_2	0.34	0.25	0.38	-0.13	178
180.	SCF_2CHF_2	0.38	0.47	0.35	0.12	178
181.		0.63	0.64	0.60	0.04	165
182.	$\text{SC}\equiv\text{CH}$	0.26	0.19	0.30	-0.11	74
183.	$\text{SCH}=\text{CHCl}$	0.31	0.24	0.34	-0.10	105
184.	$\text{SeCH}=\text{CHCl}$	0.28	0.26	0.30	-0.04	105
185.	CH_2CF_3	0.12	0.09	0.15	-0.06	109
186.	CH_2SOCF_3	0.25	0.24	0.27	-0.03	162
187.	$\text{CH}_2\text{SO}_2\text{CF}_3$	0.29	0.31	0.29	0.02	162
188.	CH_2SCF_3	0.12	0.15	0.13	0.02	162
189.	CH_2CN	0.16	0.18	0.17	0.01	170
190.	$\text{CH}=\text{CHNO}_2-t$	0.32	0.26	0.35	(-0.09)	184
191.	CH_2CO_2^-	0.07	-0.16	0.19	-0.35	88
192.	CH_2SCN	0.12	0.14	0.14	0.00	74
193.	$\text{CH}=\text{CH}_2$	0.06	-0.04	0.13	-0.17	85
194.	NHCOCH_2Cl	0.17	-0.03	0.27	-0.30	156
195.	$\text{N}(\text{Me})\text{SO}_2\text{CF}_3$	0.46	0.44	0.46	-0.02	74
196.	HgOCOCH_3	0.39	0.40	0.39	0.01	74
197.	$\text{C}(\text{Me})(\text{NO}_2)_2$	0.54	0.61	0.50	0.11	74
198.	oxiranyl	0.05	0.03	0.09	-0.06	74
199.	$\text{OCH}=\text{CH}_2$	0.21	-0.09	0.34	-0.43	96
200.	COMe	0.38	0.50	0.33	0.17	183
201.	SCOMe	0.39	0.44	0.37	0.07	183
202.	OCOMe	0.39	0.31	0.42	-0.11	183
203.	COOMe	0.37	0.45	0.34	0.11	175
204.	2-thiacyclopropyl	0.04	0.01	0.08	-0.07	74
205.	$\text{SCH}=\text{CH}_2$	0.26	0.20	0.29	-0.09	99, 105
206.	$\text{SeCH}=\text{CH}_2$	0.26	0.21	0.29	-0.08	105
207.	1-aziridinyl	-0.07	-0.22	0.03	-0.25	74
208.	2-aziridinyl	-0.06	-0.10	-0.01	-0.09	74
209.	N -methyl-3-oxaziridinyl	0.09	0.12	0.10	0.02	74
210.	NHCOOMe	-0.02	-0.17	0.07	-0.24	68
211.	NHCOMe	0.21	0.00	0.31	-0.31	183
212.	CONHMe	0.35	0.36	0.35	-0.01	154
213.	$\text{CH}=\text{NOMe}$	0.37	0.30	0.40	0.10	93
214.	CH_2CONH_2	0.06	0.07	0.08	-0.01	74
215.	NHCSMe	0.24	0.12	0.30	-0.18	154
216.	CSNHMe	0.30	0.34	0.29	0.05	154
217.	$\text{CH}=\text{NNHCSNH}_2$	0.45	0.40	0.46	-0.06	93
218.	$\text{OCH}_2\text{CH}_2\text{O}^-$	-0.12	-0.12	-0.08	-0.04	74
219.	Et	-0.07	-0.15	0.00	-0.15	183
220.	$\text{CH}=\text{NNHCONHNH}_2$	0.22	0.16	0.26	-0.10	93
221.	OCH_2CH_3	0.10	-0.24	0.26	-0.50	183

TABLE I (Continued)

	substituent	σ_m	σ_p	F^b	R^c	ref(s)
299.	GeMe ₃	0.00	0.00	0.03	-0.03	74
300.	N ⁺ (Me) ₃	0.88	0.82	0.86	-0.04	183
301.	CH ₂ NH ⁺ (Me) ₂	0.40	0.43	0.39	0.04	74
302.	Si(Me) ₂ OMe	0.04	-0.02	0.09	-0.11	74
303.	OSiMe ₃	0.13	-0.27	0.31	-0.58	74
304.	SiMe(OMe) ₂	0.04	0.10	0.05	0.05	74
305.	Si(OMe) ₃	0.09	0.13	0.10	0.03	74
306.	P ⁺ Me ₃	0.74	0.73	0.71	0.02	123, 122
307.	SiMe ₃	-0.04	-0.07	0.01	-0.08	183
308.	SnMe ₃	0.00	0.00	0.03	-0.03	74, 183
309.	1-(1,2-(BH) ₁₀ -C ₂ Me)	0.50	0.65	0.43	0.22	111
310.	CH ₂ -1-(1,7-(BH) ₁₀ -C ₂ H)	0.00	0.01	0.03	-0.02	67
311.	CH ₂ -1-(1,2-(BH) ₁₀ -C ₂ H)	0.12	0.12	0.14	-0.02	67
312.	1-(1,2-(BH) ₁₀ -C ₃ H ₃ HgCH ₃)	0.86	0.85	0.82	0.03	111
313.	2-(hydroxymethyl)carboran-1-yl	0.38	0.49	0.34	0.15	111
314.	I(OCOCF ₃) ₂	1.28	1.34	1.18	0.16	110
315.	cyclo-C ₄ F ₇	0.48	0.53	0.45	0.08	109
316.	COCF ₂ CF ₂ CF ₃	0.63	0.79	0.55	0.24	110
317.	C(CF ₃) ₃	0.55	0.55	0.53	0.02	76
318.	(CF ₂) ₃ CF ₃	0.47	0.52	0.44	0.08	172
319.	SO ₂ C(CF ₃) ₃	0.96	1.13	0.84	0.29	76
320.	SC(CF ₃) ₃	0.51	0.58	0.47	0.11	76
321.	C(SCF ₃) ₃	0.51	0.53	0.49	0.04	74
322.	SeC(CF ₃) ₃	0.49	0.54	0.46	0.08	76
323.	C(CN) ₃	0.97	0.96	0.92	0.04	165
324.	cyclo-1-(OH)C ₄ F ₆	0.36	0.37	0.36	0.01	109
325.	CH=C(CN) ₂	0.66	0.84	0.57	0.27	93
326.	2-(5-bromofuryl)	0.15	0.00	0.23	-0.23	94, 95
327.		0.33	0.27	0.36	-0.09	108
328.	3-chloro-1-pyrrolidine-2,5-dione	0.47	0.46	0.47	-0.01	108
329.	3-pyridazinyl	0.28	0.48	0.21	0.27	61
330.	3,4-CH=CHCH=CH-	0.04	0.04	0.07	-0.03	183
331.	C(Me)(CN) ₂	0.60	0.57	0.59	-0.02	74
332.	4-pyrimidinyl	0.30	0.63	0.18	0.45	277
333.	2-pyrimidinyl	0.23	0.53	0.13	0.40	277
334.	5-pyrimidinyl	0.28	0.39	0.25	0.14	277
335.	2-furyl	0.06	0.02	0.10	-0.08	114
336.	2-thienyl	0.09	0.05	0.13	-0.08	159
337.	3-thienyl	0.03	-0.02	0.08	-0.10	159
338.	2-selenienyl	0.06	0.04	0.10	-0.06	84
339.	2-tellurienyl	0.06	0.03	0.10	-0.07	84
340.	1-pyrryl	0.47	0.37	0.50	-0.13	93
341.	1-pyrrolidine-2,5-dione	0.34	0.31	0.36	-0.05	108
342.	CH=CHCOMe	0.21	-0.01	0.31	-0.32	155
343.	I(OCOMe) ₂	0.85	0.88	0.80	0.08	110
344.	N(COMe) ₂	0.35	0.33	0.36	-0.03	74
345.	cyclobutyl	-0.05	-0.14	0.02	-0.16	85
346.	COCHMe ₂	0.38	0.47	0.35	0.12	74, 119
347.	(CH ₂) ₄	-0.48	-0.48	-0.40	-0.08	87
348.	NHCOC(Me) ₂	0.11	-0.10	0.21	-0.31	156
349.	C(Me) ₃	-0.10	-0.20	-0.02	-0.18	183
350.	CH(Me)Et	-0.08	-0.12	-0.02	-0.10	74, 87
351.	CH ₂ CH(Me) ₂	-0.07	-0.12	-0.01	-0.11	176, 87
352.	(CH ₂) ₃ CH ₃	-0.08	-0.16	-0.01	-0.15	174, 87
353.	O(CH ₂) ₃ CH ₃	0.10	-0.32	0.29	-0.61	183
354.	CH ₂ C(OH)Me ₂	-0.16	-0.17	-0.11	-0.06	74, 102
355.	C(OMe) ₃	-0.03	-0.04	0.01	-0.05	74
356.	AsEt ₂	0.22	0.00	0.32	-0.32	77
357.	As(O)Et ₂	0.57	0.44	0.60	-0.16	77
358.	As(S)Et ₂	0.52	0.44	0.54	-0.10	77
359.	NH(CH ₂) ₃ CH ₃	-0.34	-0.51	-0.21	-0.30	87, 85
360.	N(Et) ₂	-0.23	-0.72	0.01	-0.73	113, 82
361.	PO(Et) ₂	0.37	0.47	0.33	0.14	79
362.	N=NPO(OEt) ₂	(0.16)	0.74	(-0.05)	(0.79)	72
363.	PO(OEt) ₂	0.55	0.60	0.52	0.08	143
364.	P(Et) ₂	0.10	0.13	0.11	0.02	124
365.	P(S)Et ₂	0.39	0.46	0.36	0.10	79
366.	CH ₃ N(Me) ₃ ⁺	0.40	0.44	0.38	0.06	74
367.	CH ₃ CH ₂ NH(Me) ₂ ⁺	0.24	0.14	0.29	-0.15	74
368.	CH ₃ OSi(CH ₃) ₃	-0.04	-0.05	0.00	-0.05	74
369.	CH ₃ Si(Me) ₃	-0.16	-0.21	-0.09	-0.12	183
370.	PO(N(Me) ₂) ₂	0.30	0.40	0.27	0.13	78

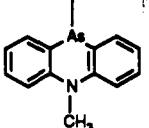
TABLE I (Continued)

	substituent	σ_m	σ_p	F^b	R^c	ref(s)
371.	$P(N(Me)_2)_2$	0.18	0.25	0.17	0.08	164
372.	2-(methylcarbonyl)carboran-1-yl	0.40	0.63	0.31	0.32	111
373.	2-[(carboxyloxy)methyl]carboran-1-yl	0.70	0.74	0.66	0.08	111
374.	$CH_2\cdot 1\cdot(1,2\cdot(BH)_{10}\cdot C_2Me)$	0.10	0.11	0.12	-0.01	67
375.	$C(CN)=C(CN)_2$	0.77	0.98	0.65	0.33	74, 165
376.	2-(5-cyanofuryl)	0.25	0.10	0.32	-0.22	94, 95
377.	2-(5-formylfuryl)	0.22	-0.05	0.34	-0.39	94, 95
378.	2-pyridyl	0.33	0.17	0.40	-0.23	93
379.	3-pyridyl	0.23	0.25	0.24	0.01	71
380.	4-pyridyl	0.27	0.44	0.21	0.23	71
381.	2-(4,6-dimethyl-s-triazinyl)	0.25	0.39	0.21	0.18	121
382.	1-cyclopentenyl	-0.06	-0.05	-0.03	-0.02	127
383.	$CH=CHCOOEt$	0.19	0.03	0.27	-0.24	155
384.	cyclopentyl	-0.05	-0.14	0.02	-0.16	85
385.	$CO(CMe)_3$	0.27	0.32	0.26	0.06	74, 119
386.	$NHCO_2(CH_2)_3CH_3$	0.06	-0.05	0.13	-0.18	126
387.	$C(Et)(Me)_2$	-0.06	-0.18	0.03	-0.21	85
388.	$CH_2C(Me)_3$	-0.05	-0.17	0.03	-0.14	85
389.	$(CH_2)_4CH_3$	-0.08	-0.15	-0.01	-0.14	174
390.	$O(CH_2)_4CH_3$	0.10	(-0.34)	0.29	(-0.63)	183
391.	$CH_2PO(OEt)_2$	0.12	0.06	0.17	-0.11	85
392.	$CH_2CH_2N(Me)_3^+$	0.16	0.13	0.19	-0.06	74, 189
393.	$CH_2CH_2Si(Me)_3$	-0.16	-0.17	-0.11	-0.06	74, 132
394.	$Si(Me)_2OSi(Me)_3$	0.00	-0.01	0.04	-0.05	160
395.	C_6Cl_5	0.25	0.24	0.27	-0.03	151
396.	C_6F_5	0.26	0.27	0.27	0.00	151
397.	$P(O)(C_3F_7)_2$	0.95	1.10	0.84	0.26	64
398.	$OP(O)(C_3F_7)_2$	0.66	0.56	0.67	-0.11	64
399.	$NHP(O)(C_3F_7)_2$	0.28	0.18	0.33	-0.15	64
400.	$CH_2Co(CN)_3^-$	-0.53	-0.68	-0.39	-0.29	150
401.	$CH_2Mn(CO)_5$	-0.14	-0.44	0.02	-0.46	150
402.	$C_6H_2\cdot 2,4,6\cdot(NO_2)_3$	0.26	0.30	0.26	0.04	170
403.	$C_6H_4\cdot 3\cdot Br$	0.09	0.08	0.12	-0.04	161
404.	$C_6H_4\cdot 4\cdot Br$	0.15	0.12	0.18	-0.06	85
405.	$C_6H_4\cdot 3\cdot Cl$	0.15	0.10	0.19	-0.09	85
406.	$C_6H_4\cdot 4\cdot Cl$	0.15	0.12	0.18	-0.06	85
407.	$C_6H_4\cdot 3\cdot F$	0.15	0.10	0.19	-0.09	85
408.	$C_6H_4\cdot 4\cdot F$	0.12	0.06	0.17	-0.11	85
409.	$OC_6H_4\cdot 4\cdot F$	-0.08	-0.10	-0.03	-0.07	106
410.	$C_6H_4\cdot 3\cdot I$	0.13	0.06	0.18	-0.12	85
411.	$C_6H_4\cdot 4\cdot I$	0.14	0.10	0.18	-0.08	85
412.	$C_6H_4\cdot 3\cdot NO_2$	0.21	0.20	0.23	-0.03	85
413.	$C_6H_4\cdot 4\cdot NO_2$	0.25	0.26	0.26	0.00	85
414.	$SC_6H_4\cdot 4\cdot NO_2$	0.32	0.24	0.36	-0.12	85
415.	$SOC_6H_4\cdot 4\cdot NO_2$	0.58	0.60	0.55	0.05	85
416.	2-benzotriazolyl	0.49	0.51	0.47	0.04	74
417.	C_6H_5	0.06	-0.01	0.12	-0.13	183
418.	$N(O)=NSO_2C_6H_5$	0.69	0.79	0.62	0.17	281
419.	$N=NC_6H_5$	0.32	0.39	0.30	0.09	175
420.	OC_6H_5	0.25	-0.03	0.37	-0.40	183, 87
421.	SOC_6H_5	0.50	0.44	0.51	-0.07	85
422.	2-(5-acetylfuryl)	0.24	0.08	0.31	-0.23	94, 95
423.	2-(6-methylpyronyl)	0.38	0.43	0.36	0.07	115
424.	$SO_2C_6H_5$	0.62	0.68	0.58	0.10	85
425.	$OSO_2C_6H_5$	0.36	0.33	0.37	-0.04	156
426.	SC_6H_5	0.23	0.07	0.30	-0.23	85
427.	NHC_6H_5	-0.02	-0.56	0.22	-0.78	173, 85
428.	$HNSO_2C_6H_5$	0.16	0.01	0.24	-0.23	156
429.	$SO_2NHC_6H_5$	0.56	0.65	0.51	0.14	74
430.	2-(5-ethylfuryl)	0.09	-0.13	0.20	-0.33	94, 95
431.	1-(2,5-dimethylpyrryl)	0.49	0.38	0.52	-0.14	93
432.	1-cyclohexenyl	-0.10	-0.08	-0.07	-0.01	127
433.	cyclohexyl	-0.05	-0.15	0.03	-0.18	85
434.	$N(C_3H_7)_2$	-0.26	-0.93	0.06	-0.99	113
435.	$(CH_2)_4NMe_2$	-0.08	-0.16	-0.01	-0.15	74
436.	$PO(isopropyl)_2$	0.37	0.41	0.36	0.05	79
437.	$P(isopropyl)_2$	0.02	0.06	0.04	0.02	69
438.	$P(O)(OPr)_2$	0.38	0.50	0.33	0.17	152
439.	$Ge(Et)_3$	0.00	0.00	0.03	-0.03	74, 183
440.	$(CH_2)_3N(Me)_3^+$	0.06	-0.01	0.12	-0.13	74
441.	$Si(OEt)_3$	0.02	0.08	0.03	0.05	74
442.	$P(Et)_3^+$	0.99	0.98	0.94	0.04	78
443.	$Sn(Et)_3$	0.00	0.00	0.03	-0.03	74, 183
444.	$P(=NSO_2CF_3)(C_3F_7)_2$	1.24	1.37	1.11	0.26	63
445.	$Si(NMe_2)_3$	-0.04	-0.04	0.00	-0.04	74
446.	2-benzoxazolyl	0.30	0.33	0.30	0.04	138
447.	2-benzthiazolyl	0.27	0.29	0.27	0.02	138

TABLE I (Continued)

	substituent	σ_m	σ_p	F^b	R^c	ref(s)
448.	CO ₂ C ₆ H ₅	0.34	0.43	0.31	0.12	180
449.	OCOC ₆ H ₅	0.21	0.13	0.26	-0.13	156
450.	COOC ₆ H ₅	0.37	0.44	0.34	0.10	128
451.	N=CHC ₆ H ₅	-0.08	-0.55	0.14	-0.69	156
452.	CH=NC ₆ H ₅	0.35	0.42	0.33	0.09	136, 137
453.	NHCOC ₆ H ₅	0.02	-0.19	0.13	-0.32	156
454.	CONHC ₆ H ₅	0.23	0.41	0.17	0.24	74, 175
455.	C ₆ H ₄ -4-Me	0.06	-0.03	0.12	-0.15	85
456.	CH ₂ C ₆ H ₅	-0.08	-0.09	-0.04	-0.05	170
457.	N=NC ₆ H ₃ -5-Me-2-OH	0.27	0.31	0.26	0.05	156
458.	C ₆ H ₄ -4-OMe	0.05	-0.08	0.13	-0.21	85
459.	CH(OH)C ₆ H ₅	0.00	-0.03	0.05	-0.08	74, 175
460.	CH ₂ OC ₆ H ₅	0.06	0.07	0.08	-0.01	128, 282
461.	CH ₂ SO ₂ C ₆ H ₅	0.15	0.16	0.17	-0.01	128, 282
462.	C(Et) ₃	-0.07	-0.20	0.02	-0.22	85
463.	(CH ₂) ₆ CH ₃	-0.07	-0.16	0.00	-0.16	85
464.	SiMe(OSi(Me) ₃) ₂	-0.02	-0.01	0.01	-0.02	160
465.	CF ₃ CF ₂ C ₆ H ₄ -4-F	0.34	0.39	0.32	0.07	109
466.	C≡C ₆ H ₅	0.14	0.16	0.15	0.01	170
467.	CH=NCOC ₆ H ₅	0.39	0.51	0.34	0.17	74
468.	CH=CHC ₆ H ₅	0.03	-0.07	0.10	-0.17	186
469.	CH ₂ Fe(CO) ₂ (π -C ₅ H ₅)	-0.26	-0.49	-0.11	-0.38	150
470.	CH=NNHCOC ₆ H ₅	0.39	0.51	0.34	0.17	93
471.	N=CHC ₆ H ₄ -4-OMe	-0.07	-0.54	0.15	-0.69	156
472.	NHCOC ₆ H ₄ -4-OMe	0.09	-0.06	0.17	-0.23	156
473.	SCH=NSO ₂ C ₆ H ₄ -4-Me	0.65	0.70	0.61	0.09	74
474.	C ₆ H ₄ -4-Et	0.07	-0.02	0.13	-0.15	85
475.	CH ₂ CH ₂ C ₆ H ₅	-0.07	-0.12	-0.01	-0.11	74
476.	N=C(Me)NHC ₆ H ₅	0.29	0.08	0.38	-0.30	133
477.	Si(C ₆ H ₅)(Me) ₂	0.04	0.07	0.06	0.01	74
478.	S(Me)=NSO ₂ C ₆ H ₄ -4-Me	0.65	0.70	0.61	0.09	205
479.	2,4,6-trimethylpyridinium	0.62	0.58	0.61	-0.03	73
480.	PO(CMe ₃) ₂	0.31	0.41	0.28	0.13	79
481.	PO(C ₆ H ₅) ₂	0.35	0.49	0.30	0.19	152
482.	PO(OC ₆ H ₅) ₂	0.41	0.57	0.35	0.22	85
483.	P(CMe ₃) ₂	0.01	0.15	-0.01	0.16	69
484.	C ₆ H ₅ Cr(CO) ₃	0.29	0.14	0.36	-0.22	104
485.	2-benzo-4-thiopyronyl	0.34	0.35	0.34	0.01	115
486.	2-(benzothiopyronyl)	0.48	0.45	0.48	-0.03	115
487.	2-(benzo-1,4-pyronyl)	0.41	0.40	0.41	-0.01	115
488.	CH=CHCOC ₆ H ₄ -4-NO ₂	0.15	0.05	0.21	-0.16	155
489.	CH ₂ Mo(CO) ₃ (C ₆ H ₅)	-0.21	-0.45	-0.07	-0.38	150
490.	CH=CHCOC ₆ H ₅	0.18	0.05	0.25	-0.20	155
491.	C ₆ H ₄ -4-CHMe ₂	0.08	0.01	0.13	-0.12	85
492.	Si(OSiMe ₃) ₃	-0.09	-0.01	-0.08	0.07	160
493.	ferrocenyl	-0.15	-0.18	-0.09	-0.09	141
494.	ferricenium ⁺	0.29	0.29	0.30	-0.01	100
495.	ferrocenonium ⁺	0.05	0.29	-0.01	0.30	101
496.	C ₆ H ₄ -4-CMe ₃	0.07	0.01	0.12	-0.11	85
497.	1-adamantyl	-0.12	-0.13	-0.07	-0.06	149
498.	1-dibenzarsenyl	0.19	0.13	0.23	-0.10	65
499.	1-dibenzoarsoxyl	0.17	0.09	0.22	-0.13	65
500.	1-dibenzoarsazinyl	0.14	0.09	0.18	-0.09	66
501.	As(C ₆ H ₅) ₂	0.03	0.09	0.04	0.05	125
502.	AsO(C ₆ H ₅) ₂	0.54	0.64	0.49	0.15	81
503.	P(C ₆ H ₅) ₂ (BCl ₃)	0.67	0.72	0.62	0.10	164
504.	N(C ₆ H ₅) ₂	0.00	-0.22	0.12	-0.34	168, 169
505.	PO(C ₆ H ₅) ₂	0.38	0.53	0.32	0.21	144
506.	P(C ₆ H ₅) ₂	0.11	0.19	0.10	0.09	144
507.	PS(C ₆ H ₅) ₂	0.29	0.47	0.23	0.24	144
508.	P(N(C ₆ H ₅) ₂)C ₆ H ₄ -3-F	0.20	0.24	0.20	0.04	122, 123
509.		0.37	0.38	0.37	0.01	61
510.		0.38	0.38	0.38	0.00	61
511.		0.17	0.21	0.17	0.04	138

TABLE I (Continued)

	substituent	σ_m	σ_p	F^b	R^c	ref(s)
512.	$\text{CH}(\text{C}_6\text{H}_5)_2$	-0.03	-0.05	0.01	-0.06	74, 102
513.		0.12	0.07	0.16	-0.09	66
514.	$\text{PO}(\text{C}_6\text{H}_5)\text{C}_6\text{H}_4\text{-4-Me}$	0.13	0.30	0.09	0.21	91
515.	$\text{CH}_2\text{PO}(\text{C}_6\text{H}_5)_2$	0.14	0.01	0.21	-0.20	85
516.	$\text{PS}(\text{C}_6\text{H}_5)\text{C}_6\text{H}_4\text{-4-Me}$	0.09	0.30	0.03	0.27	91
517.	$\text{P}^+(\text{Me})(\text{C}_6\text{H}_5)_2$	1.13	1.18	1.04	0.14	91
518.	$\text{Si}(\text{Me})(\text{C}_6\text{H}_5)_2$	0.10	0.13	0.11	0.02	74
519.	$\text{COOCH}(\text{C}_6\text{H}_5)_2$	0.36	0.56	0.28	0.28	175
520.	$\text{PO}(\text{C}_6\text{H}_4\text{-4-Me})_2$	0.17	0.30	0.14	0.16	91
521.	$\text{PS}(\text{C}_6\text{H}_4\text{-4-Me})_2$	0.20	0.23	0.20	0.03	91
522.	$\text{P}^+(\text{Me})(\text{C}_6\text{H}_5)(\text{C}_6\text{H}_4\text{-4-Me})$	1.09	1.11	1.02	0.09	91
523.	$\text{P}^+(\text{Me})(\text{C}_6\text{H}_4\text{-4-Me})_2$	1.13	1.18	1.04	1.14	91
524.	$\text{Ge}(\text{C}_6\text{H}_5)_3$	0.05	0.08	0.07	0.01	98
525.	2-methyl-4,6-diphenylpyridinium	0.65	0.70	0.61	0.09	61
526.	$\text{N}=\text{P}(\text{C}_6\text{H}_5)_3$	-0.33	-0.77	-0.10	-0.67	83
527.	$\text{Si}(\text{C}_6\text{H}_5)_3$	-0.03	0.10	-0.04	0.14	132
528.	$\text{Sn}(\text{C}_6\text{H}_5)_3$	(0.53)	(0.27)	(0.62)	(-0.35)	164
529.	$\text{C}(\text{C}_6\text{H}_5)_3$	-0.01	0.02	0.01	0.01	131
530.	2,4,6-triphenylpyridinium	0.34	0.33	0.35	-0.02	73

^aValues in parentheses are suspected of being inaccurate. ^bCalculated from eq 8. ^cCalculated from eq 2. ^dSubstituents are arranged by molecular formula, C_xH_y ; other elements in alphabetical order.

TABLE II. Substituent Field/Inductive Parameters for Primary Dipolar Substituents Obtained from Various Sources

substituent X	$\sigma_I = 0.45\sigma^*$			σ_I			F^e	σ_I (F NMR) Taft ^h
	CH_2X	Stock ^c	Grobb ^d	Charton ^e	Taylor ^f			
	Taft ^a	Taft ^b						
NO_2	0.63	0.65	0.68	0.63	0.67	0.64	0.65	0.64
H	0.00	0.00	0.00 ^{b,c}	0.00	0.00	0.00	0.00	0.00
CH_3	-0.05	0.00	-0.01	-0.02	-0.01	0.01	0.01	-0.01
C_2H_5	-0.05	0.00	-0.01		-0.01	-0.03	0.00	0.06
CH_2OH			0.05	0.09	0.11		0.03	0.13
OH	0.27	0.30	0.26 ^{b,c}		0.24		0.33	
OCH_3	0.23	0.25 (0.28)	0.30 ^b	0.31	0.30	0.29	0.29	0.30
OC_6H_5	0.38				0.40		0.37	0.42
$\text{CO}_2\text{C}_2\text{H}_5$	0.31	0.24 (0.31)	0.29 ^{b,c}	0.29	0.30	0.31	0.34	0.19
Cl	0.47	0.45	0.47 ^b	0.44	0.47		0.42	0.43
Br	0.45	0.45	0.45 ^{b,c}	0.47	0.47		0.45	0.49
CN	0.59	0.60	0.54 ^c	0.55	0.57	0.63	0.51	(0.53)
$\text{CH}(\text{CH}_3)_2$				-0.05	0.01		0.04	
$\text{C}(\text{CH}_3)_3$	-0.07	0.00		-0.07	-0.01		-0.02	0.09
CH_3OCH_3			0.14		0.09	0.11	0.13	0.09
$\text{CH}_3\text{OCOCH}_3$					0.13	0.15		0.07
tosylmethyl					0.21	0.23		
CH_2Cl	0.17	0.23			0.15	0.17	0.13	0.23
CH_2Br					0.16	0.20	0.14	0.23
CH_2I					0.16	0.17	0.12	0.26
$\text{CH}(\text{OH})_2$					0.20	0.22		
$\text{CH}=\text{CH}_2$			0.06		0.07	0.11	0.13	0.07
$\text{C}(\text{CH}_3)=\text{CH}_2$					0.08	0.10	0.13	
$\text{C}\equiv\text{CH}$			0.23		0.28	0.29	0.22	(0.15)
C_6H_5	0.10	0.10			0.15	0.12	0.12	0.14
COCH_3	0.27	0.26 (0.30)	0.26	0.29	0.30	0.26	0.33	0.25
COC_6H_5		0.28				0.30	0.31	0.29
CONH_2					0.30	0.28	0.26	0.23
NH_2	0.10	0.14 (0.19)			0.15	0.17	0.14	0.09
NHCH_3			0.12		0.12	0.13		-0.03
$\text{N}(\text{CH}_3)_2$	0.10	0.10 (0.19)			0.15	0.17		0.15 (0.17)
NHCOCH_3	0.28				0.27	0.28	0.27	0.31
$\text{NHCO}_2\text{C}_2\text{H}_5$					0.26		0.23	
OCOCH_3					0.37	0.38	0.42	0.34
SCH_3	0.25	0.25			0.28	0.30	0.23	0.24
SO_2CH_3	0.59	0.59 (0.65)			0.58	0.59	0.53	0.61
SO_2CF_3		0.84				0.71	0.74	0.83
F	0.50	0.44			0.46	0.54	0.45	(0.57)
I	0.38				0.41	0.40	0.42	(0.47)

^aReference 32. ^bReference 30. ^cCalculated as $\Delta pK_a/1.56$. ^dCalculated from refs 35 and 36. ^eCalculated from eq 8. ^fReference 45. ^gCalculated as $0.0415 \Delta pK_a$ for $\text{XHN}=\text{C}(\text{NH}_2)_2^+$. Reference 41. ^hFrom Table I. ⁱCalculated from the meta-substituted fluorobenzene F NMR shift (relative to fluorobenzene). Reference 43 using eq 10. Values in parentheses are thought to involve magnetic or other complications.

TABLE III. Comparison of *F* Values Calculated via Eq 5 and 8

	<i>F</i> calcd via eq 5	<i>F</i> calcd via eq 8	eq 5 - eq 8
1. F	0.43	0.45	0.02
2. Br	0.44	0.45	0.01
3. CF ₃	0.38	0.38	0.00
4. C≡CH	0.19	0.22	0.03
5. CONH ₂	0.24	0.26	0.02
6. NO ₂	0.67	0.65	0.02
7. NH ₂	0.02	0.09	0.06
8. NHCONH ₂	0.04	0.09	0.05
9. OH	0.29	0.33	0.04
10. OCH ₃	0.26	0.29	0.03
11. SO ₂ NH ₂	0.41	0.49	0.08
12. SCH ₃	0.20	0.23	0.03
13. CN	0.51	0.51	0.00
14. CH ₃ C ₆ H ₅	-0.08	-0.04	0.04
15. OCOCH ₃	0.41	0.42	0.01

In a different approach to evaluating σ_I , Charton elected to use ionization constants of substituted acetic acids (XCH_2COOH) as a basis for its definition.²⁹ As he notes, this does not constitute a method beyond reproach, but it does allow the definition of σ_I for 294 substituents whose pK_a 's have been measured. A limitation of this method is that of the 294 substituents, only 125 have known values of σ_p so that only 125 σ_I values can be estimated via eq 2.

Despite the quite different methods used to obtain secondary σ_I values by Charton and the method of obtaining *F* values via eq 7, there is generally satisfactory agreement between the two types of field/inductive constants as shown by the comparison of the fifth and seventh columns of Table II or by eq 9. Equation 9

$$F = 0.888 (\pm 0.054) \sigma_I (\text{Charton}) + 0.017 (\pm 0.017) \quad (9)$$

$$n = 129, r = 0.944, s = 0.067$$

is based on 129 substituents common to both data sets. Bear in mind that not only are the two approaches for obtaining inductive constants grossly different, but also the individual values come from a variety of different laboratories and hence, have different degrees of reliability. Given these conditions, one could hardly expect a better correlation. Table VIII contains σ_I from the acetic acid system by Charton for substituents not contained in Table I.

A recent report by Taylor and Wait⁴⁵ of substituent effects based on ΔpK_a for N-substituted guanidinium ions, H₂O at 25 °C, is of particular importance with respect to biologically important substituents. For 15 common substituents with known σ_F values,³⁰ $\sigma_I = 0.0415\Delta pK_a$, $r = 0.996$, $s = 0.03$. Values of σ_I calculated from this equation are given in the sixth column of Table II. The very great sensitivity of these particular aqueous solution proton transfer equilibria is shown by the very small (0.0415) coefficient to their ΔpK_a . This value is even smaller than the coefficient obtained in the gas phase for the relative acidities of nine 4-substituted bicyclooctane carboxylic acids³⁰ (for these, $\sigma_F = 0.106\Delta pK_a$).

The eighth column of Table II lists σ_F values calculated from the meta substituent F NMR shielding effect, \int_{H}^{m-X} for meta-substituted fluorobenzene, in dilute hydrocarbon solvents.⁴³ A correlation obtained herein for 33 substituents with well-established σ_F values³⁰

(C(CF₃)₃, C(CN)₃, CH₂Cl, CH₂CF₃, CH₂OMe, CH₃, C₂H₅, CH₂SO₂CF₃, CHCl₂, CHF₂, CF₃, CH=CH₂, C₆H₅, CO₂R, COMe, COC₆H₅, CHO, COCF₃, COCN, NH₂, NO₂, NO, OMe, OC₆H₅, Cl, Br, Si(Me)₃, SCH₃, SC₆H₅, SCF₃, SF₅, SO₂Me, SO₂CF₃) is

$$\sigma_F = 0.16 + 0.137 \left(-\int_{\text{H}}^{m-X} \right) \quad (10)$$

$$n = 33, r = 0.990, s = 0.034$$

Equation 10 has been utilized to obtain σ_F values listed in Tables II and IV.

For ease of determination, the F NMR measurement is a method of choice for estimation of the σ_F value of a new substituent. There is adequate signal-to-noise ratio in this method, a great breadth is allowed in the permissible substituent structural variation, preparation is relatively simple, and there is essentially no dependence upon nonspecific solvent dielectric constant variation.⁴³ Nevertheless, the F NMR method has given σ_F values for some substituents which appear to involve some relatively small specific magnetic contributions (usually less than 0.10 unit of σ_F) that are not observed in proton-transfer equilibria or other reactions. (Examples are the substituents CN, C≡CH, F, and *t*-C₄H₉ and others given in parentheses in the last column of Table II). However, variations in σ_F values due to substituent H-bonding solvation assisted field effects⁴² are well established and predictable.⁴⁶ A few typical examples are given in Table II of enhanced σ_F values resulting from the hydrogen-bond acceptor substituent interacting with the HBD solvent water (cf. σ_F values given in parentheses in the second column of Table II). Another solvent effect on field/inductive parameters involves the fall-off factor for transmission of dipolar effects in a homologous straight chain. For gas-phase equilibria, the factor is 1/1.95 per methylene carbon,³⁰ but in certain solution equilibria the attenuation factor has been thought to be as large as 1/2.8 per methylene. For CH₂X type substituents in Table II, the σ_F values are generally larger than the corresponding *F* values.

In spite of these and other complications, the σ_F values from the F NMR method are in generally satisfactory agreement with *F* values obtained from eq 8. There are 146 substituents common to Tables I and IV. These 146 sets of *F* and σ_F (F NMR) are collected in Table IV. Only 10 substituents have $|\sigma_F - F|$ differences of 0.20 or greater. Excluding these substituents SO₂Cl, CN·BCl₃, HgMe, SnMe₃, N(CF₃)₂, ³P(CH₃)₃, OCF₃, CF(CF₃)₂, C(CF₃)₃ and P⁺Me(C₆H₅)₂ the standard deviation for equality between corresponding *F* and σ_F (F NMR) values (for a range of -0.12 to 1.15 in the latter), is only 0.076. Correlation by least-squares gives eq 11.

$$F = 0.924 (\pm 0.023) \sigma_F - 0.006 (\pm 0.11) \quad (11)$$

$$n = 136, r = 0.960, s = 0.067$$

These results further support the conclusion that field/inductive parameters can, with care, be obtained reliably from a number of useful sources.

It is clearly of interest to confirm this kind of agreement for many additional substituents present in one, but not the other, of Tables I and IV. We have commenced a literature search for a more complete tabulation of substituent F NMR chemical shifts for

meta- and para-substituted fluorobenzenes. The results of this search and of experimental determinations of additional substituents shifts will be reported subsequently.

B. Resonance Effect Parameters

Taft used eq 2 to obtain σ_R values. To evaluate R , Swain and Lupton³³ made the assumption that eq 6 applies in the following form

$$\sigma_p = \alpha F + R \quad \text{or} \quad R = \sigma_p - \alpha F \quad (12)$$

and that for $\text{N}^+(\text{CH}_3)_3$, $R = 0$. By using eq 12 and the values of $F = 0.89$ and $\sigma_p = 0.82$, α was found to be 0.921. By using this value for α , F and R were then calculated for about 200 substituents.³⁴ Since, as noted before,⁴ α does not differ much from 1, little, if anything, is lost by using Taft's eq 2 to calculate R ($= \sigma_p - F$) rather than eq 12. Therefore, we have recalculated F (using eq 8) and R (using eq 2). The values of R given in Table I generally compare well with Charton's σ_D as shown in eqs 13 and 14.

$$R = 0.864 (\pm 0.066) \sigma_D - 0.004 (\pm 0.018) \quad (13)$$

$$n = 117, r = 0.923, s = 0.085$$

$$R = 0.877 (\pm 0.050) \sigma_D - 0.002 (\pm 0.013) \quad (14)$$

$$n = 105, r = 0.959, s = 0.057$$

Equation 13 is based on all 117 substituents common to both data sets, and for eq 14, the 12 most poorly fit data points were dropped. The slopes and intercepts of eqs 13 and 14 are essentially identical. However, eq 14 is a sharper correlation.

Current expertise accepts the need for special parameterization for instances where strong resonance interaction occurs between reaction center and substituent. Two types of parameters σ^- and σ^+ (R^- and R^+) are widely used for such situations; however, Swain et al.⁴⁷ argue that this is unnecessary and have derived a set of optimized F and R from 14 selected reactions for all electronic substituent effects. Equations 15 and 16 compare these values of F and R based in part on reactions where π -donor and π -acceptor substituents are conjugated with the reaction centers.

$$F_{\text{Swain}} = 1.63 (\pm 0.11) F_{\text{Table I}} + 0.45 (\pm 0.033) \quad (15)$$

$$n = 43, r = 0.978, s = 0.163$$

$$R_{\text{Swain}} = 3.44 (\pm 0.43) R_{\text{Table I}} - 0.44 (\pm 1.0) \quad (16)$$

$$n = 43, r = 0.947, s = 0.455$$

The correlation between the two field/inductive parameters is fair, although the standard deviation is 3 times greater than that for either eqs 9 or 11, which apply to about 3 times as many substituents.

Swain's values were optimized for all of his selected reaction series including those involving through resonance effects that have been normally correlated by σ^+ and σ^- . Also included were charged substituents (CO_2^- , $\text{S}(\text{Me})_2^+$, PO_3H^- , SO_3^- , N_2^+ , and $\text{N}(\text{Me})_3^+$) which often correlate poorly when included in sets of neutral sub-

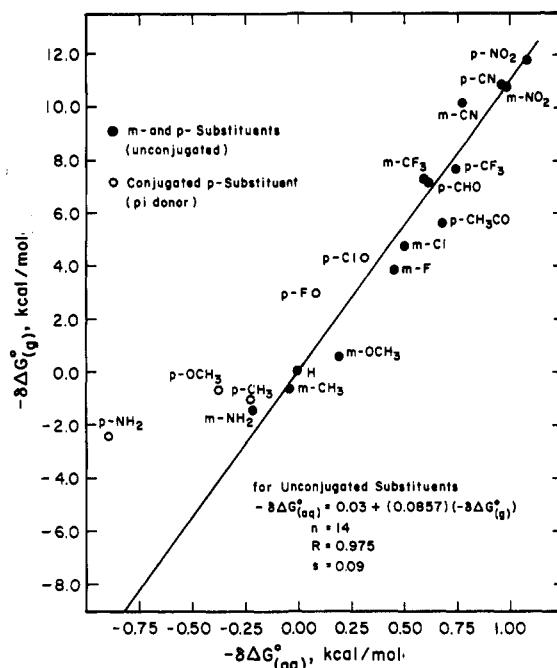


Figure 1. Meta- and para-substituted benzoic acid acidities gas phase vs aqueous.

stituents.³⁸ Thus, Swain has viewed the situation from the worst possible position so that it is perhaps surprising that the correlation is as good as it is. Still, we do not recommend using these normalized values since it is clear from many, many, examples that σ_p^- and σ_p^+ not only give better correlations, but they often afford insight into the reaction mechanism which is lost when the normalized Swain constants are used.

Gas-phase proton-transfer equilibria for a variety of reaction series have been recently reported.³⁰ The very large accompanying substituent effects have been examined for rigid substituents at a fixed carbon position in saturated and unsaturated chains or cycles.⁴⁸ The series includes substituent effects at tetrahedral, trigonal, planar, or linear carbon positions. Linear free energy relationships of good precision were found to be much less common than in solution. However, σ_F and σ_R values with proper application give generally very good correlations of the substituent field/inductive and resonance effects (substituent polarizability effects were also found to be generally important in the gas phase).^{30,48} In many series, it was found necessary to treat π -electron donor and acceptor substituents by using separate reaction constants, ρ_R^d and ρ_R^a in accord with ideas of Yukawa and Tsuno.⁴⁹ A number of gas-phase equilibria have ρ_R and ρ_F reaction constants of opposite signs.³⁰ Such reactions illustrate that although σ_p values are not applicable, the σ_F and σ_R values are. Certain reaction rate series in solution that involve conjugating para substituents have also been shown to follow this same kind of behavior.⁵⁰

The relative gas-phase acidities of meta- and para-substituted benzoic acids provide important evidence that while aqueous solution solvent effects lead to significantly enhanced negative σ_p values for strong π -donor substituents, the major features of σ_m and σ_p constants do involve inherent electronic effects. Figure 1 shows a plot of $-\Delta G_{(g)}^{\circ}$ [$= 2.303RT \log (K/K_0)_{(g)}$] vs $-\Delta G_{(aq)}^{\circ}$ ($= 1.364\sigma_{(aq)}$) for meta- and para-substituted

TABLE IV. σ_F , σ_R , $c\sigma_m$, and $c\sigma_p$ Constants from F NMR Chemical Shifts of Meta- and Para-Substituted Fluorobenzenes

substituent, Y	solvent	$-\delta_{\text{H}}^{\text{F}}$	$-\delta_{\text{H}}^{m\text{-Y}}$	σ_F	σ_R	$c\sigma_m$	$c\sigma_p$
Carbon Substituents							
1. CH_2X							
1. CH_2SnMe_3	c-C ₆ H ₁₂	7.75	0.85	0.04	-0.23	-0.11	-0.35 ^a
2. CH_2GeMe_3	c-C ₆ H ₁₂	7.05	0.90	0.04	-0.20	-0.09	-0.22
3. CH_2SiMe_3	c-C ₆ H ₁₂	7.00	1.10	0.01	-0.19	-0.12	-0.28
4. CH_3	c-C ₆ H ₁₂	5.40	1.20	-0.01	-0.13	-0.11	-0.19
5. CH_2Me	c-C ₆ H ₁₂	5.05	0.75	0.06	-0.13	-0.04	-0.13
6. CH_2NH_2	c-C ₆ H ₁₂	3.75	0.58	0.08	-0.09	0.00	-0.06
7. CH_2COMe	C ₆ H ₆	3.22	0.36	0.11	-0.08	0.03	-0.02
8. CH_2NMe_2	C ₆ H ₆	3.09	0.79	0.05	-0.06	-0.02	-0.06
9. CH_2SMe	C ₆ H ₆	2.95	0.37	0.11	-0.07	0.04	-0.01
10. CH_2OMe	Cl ₃ CF	2.41	0.53	0.09	-0.05	0.03	-0.01
11. CH_2OH	c-C ₆ H ₁₂	2.15	0.18	0.13	-0.05	0.07	0.03
12. CH_2CN	c-C ₆ H ₁₂	1.07	-1.20	0.32	-0.06	0.25	0.21
13. CH_2CF_3	Cl ₃ CF	0.92	-0.43	0.22	-0.03	0.16	0.14
14. CH_2SCF_3	Cl ₃ CF	0.73	-0.92	0.29	-0.03	0.23	0.21
15. CH_2Cl	Cl ₃ CF	0.50	-0.53	0.23	-0.02	0.18	0.16
16. CH_2F	Cl ₃ CF	0.25	-0.28	0.20	0.00	0.16	0.15
17. CHBr	Cl ₃ CF	0.22	-0.50	0.23	-0.01	0.18	0.17
18. $\text{CH}_2\text{SO}_2\text{CF}_3$	C ₆ H ₆	-0.07	-0.67	0.25	0.00	0.21	0.20
19. CH_2SOCF_3	CCl ₄	-0.81	-1.28	0.33	0.00	0.28	0.28
20. $\text{CH}_2\text{SO}_2\text{CF}_3$	CCl ₄	-1.35	-2.14	0.46	-0.01	0.41	0.40
2. CHX_2							
21. $\text{CH}(\text{SiMe}_3)_2$	CCl ₄	7.47	0.84	0.04	-0.22	-0.10	-0.24
22. $\text{CH}(\text{C}_6\text{H}_5)_2$	CH ₂ Cl ₂	2.83	0.20	0.13	-0.07	0.06	0.01
23. $\text{CH}(\text{OMe})_2$	Cl ₃ CF	1.38	0.50	0.09	-0.01	0.05	0.03
24. $\text{CH}(\text{SCF}_3)_2$	Cl ₃ CF	-2.43	-2.53	0.51	0.02	0.47	0.48
25. CHBr_2	Cl ₃ CF	-2.21	-1.51	0.37	0.03	0.34	0.35
26. CHF_2	Cl ₃ CF	-3.14	-1.48	0.36	0.06	0.34	0.37
27. $\text{CH}(\text{CN})_2$	Cl ₃ CF	-2.30	-3.29	0.61	-0.02	0.55	0.53
3. CX_3							
28. $\text{C}(\text{SiMe}_3)_3$	CCl ₄	6.93	-0.30	(0.20)	(-0.23)	(0.05)	(-0.09)
29. CM_3	c-C ₆ H ₁₂	5.55	0.50	(0.09)	(-0.16)	(-0.02)	(-0.13)
30. CH_3	c-C ₆ H ₁₂	5.40	1.20	0.01	-0.13	-0.11	-0.19
31. $\text{CO}(\text{Me})_3$	Cl ₃ CF	0.62	0.41	0.10	0.01	0.07	0.06
32. CBr_3	Cl ₃ CF	-2.21	-1.26	0.33	0.04	0.30	0.32
33. CCl_3	Cl ₃ CF	-2.31	-1.51	0.37	0.03	0.34	0.35
34. $\text{C}(\text{CF}_3)_3$	n-C ₇ H ₁₆	-3.44	-3.32	0.61	0.01	0.56	0.56
35. $\text{C}(\text{SCF}_3)_3$	Cl ₃ CF	-3.99	-2.90	0.56	0.04	0.52	0.55
36. CF_3	c-C ₆ H ₁₂	-5.05	-2.18	0.46	0.09	0.45	0.50
37. $\text{C}(\text{CN})_3$	Cl ₃ CF	-6.02	-5.75	0.95	0.02	0.90	0.91
Δ							
38. Δ	CCl ₄	5.11	1.18	0.00	-0.12	-0.09	-0.17
39. Δ	CCl ₄	3.26	0.75	0.06	-0.07	-0.01	-0.06
40. Δ	CCl ₄	1.80	0.10	0.15	-0.13	0.10	0.07
41. Δ	CCl ₄	1.43	0.11	0.17	-0.02	0.12	0.10
5. CX_2Z							
42. $\text{C}(\text{C}_6\text{H}_5)_2\text{N}=\text{P}(\text{C}_6\text{H}_5)_3$	Cl ₃ CH	6.12	1.63	-0.07	-0.14	-0.17	-0.26
43. $\text{C}(\text{C}_6\text{H}_5)_2\text{OH}$	CH ₂ Cl ₂	1.31	0.05	0.09	-0.01	0.05	0.03
44. $\text{C}(\text{Me})(\text{CN})_2$	CH ₂ Cl ₂	-2.16	-3.88	0.69	-0.04	0.62	0.59
45. $\text{C}(\text{OH})(\text{CF}_3)_2$	Cl ₃ CF	-2.37	-1.88	0.42	0.02	0.38	0.39
46. $\begin{matrix} \text{OH} \\ \\ \text{CF}_2 \\ \\ \text{C} \\ \\ \text{CF}_2 \\ \\ \text{CF}_2 \end{matrix}$	Cl ₃ CF	-2.50	-1.88	0.42	0.03	0.39	0.40
47. $\text{CF}(\text{CF}_3)_2$	Cl ₃ CF	-4.14	2.93	0.56	0.05	0.53	0.56
48. CF_2Cl	Cl ₃ CF	-4.39	-2.09	0.45	0.07	0.43	0.47
49. $\begin{matrix} \text{F} \\ \\ \text{CF}_2 \\ \\ \text{C} \\ \\ \text{CF}_2 \\ \\ \text{CF}_2 \end{matrix}$	Cl ₃ CF	-4.84	-2.60	0.52	0.07	0.50	0.54
50. $\text{CF}_2(n\text{-C}_3\text{F}_7)$	Cl ₃ CF	-5.58	-2.30	0.47	0.10	0.47	0.52
6. CXYZ							
51. $\text{C}(\text{Me})\text{HOH}$	c-C ₆ H ₁₂	2.75	0.07	0.15	-0.07	0.08	0.03
7. $\text{C}=\text{C}$							
52. $\text{C}(\text{C}_6\text{H}_5)=\text{CH}_2$	CH ₂ Cl ₂	1.67	0.60	0.08	-0.02	0.03	0.01
53. $\text{CH}=\text{CH}_2$	c-C ₆ H ₁₂	1.45	0.63	0.07	-0.01	0.03	0.01
54. $\text{CH}=\text{CHCF}_3$	Cl ₃ CF	-1.69	-0.25	0.19	0.05	0.17	0.19

TABLE IV (Continued)

	substituent, Y	solvent	$-f_H^{F-Y}$	$-f_H^{m-Y}$	σ_F	σ_R	$c\sigma_m$	$c\sigma_p$
109.	3-B ₁₀ C ₁₁ H ₁₁ (1,2)	(MeOCH ₂) ₂	3. Other -1.27	0.52	0.09	0.06	0.08	0.11
Nitrogen Substituents								
			1. NHX					
110.	NH ₂	c-C ₆ H ₁₂	14.40	0.50	0.09	-0.48	-0.18	-0.72 ^a
111.	NHNH ₂	MeOH	12.25	-0.05	0.17	-0.42	-0.07	-0.50 ^a
112.	NHC ₆ H ₅	CCl ₄	9.15	-1.10	0.31	-0.35	0.10	-0.26 ^a
113.	NHCN	Cl ₃ CF	7.01	-2.06	0.44	-0.30	0.25	-0.06 ^a
114.	NHCOMe	MeOH	5.15	-1.35	0.34	-0.21	0.20	-0.04 ^a
			2. NXZ					
115.	N(COF)CF ₃	Cl ₃ CF	-3.40	-3.36	0.62	0.01	0.57	0.57
			3. NX ₂					
116.	NMe ₂	c-C ₆ H ₁₂	15.90	-0.08	(0.17)	-0.56	-0.14	-0.42 ^a
117.	—N—	n-C ₇ H ₁₆	8.52	0.10	0.15	-0.28	-0.02	-0.32 ^a
118.	N(CN) ₂	Cl ₃ CF	0.64	-5.75	0.94	-0.21	0.78	0.66
119.	N(CF ₃) ₂	Cl ₃ CF	-3.19	-2.86	0.55	0.02	0.51	0.52
120.	N(COF) ₂	Cl ₃ CF	-3.22	-3.49	0.64	0.01	0.59	0.59
			4. NX ₂ Z					
121.	NMe ₂ BCl ₃	CH ₂ Cl ₂	-0.10	-2.78	0.54	-0.08	0.45	0.40
122.	N ⁺ Me ₂ O ⁻	MeOH	-1.03	-4.03	0.71	-0.09	0.61	0.56
			5. N=Z					
123.	N=P(C ₆ H ₅) ₃	Cl ₃ CH	15.45	2.02	-0.12	-0.46	-0.37	0.86 ^a
124.	N=CCL ₂	Cl ₃ CF	3.15	-1.42	0.35	-0.14	0.24	0.15
125.	N=C=O	Cl ₃ CF	3.11	-1.92	0.42	-0.16	0.30	0.20
126.	N=NPt(Cl)(PEt ₃) ₂	Cl ₃ CF	2.27	-0.66	0.25	-0.08	0.17	0.12
127.	N=C(CF ₃) ₂	Cl ₃ CF	1.77	-1.91	0.42	-0.11	0.32	0.25
128.	N=C=S	CCl ₄	-0.53	-2.35	0.48	-0.05	0.41	0.37
129.		C ₆ H ₆	-1.61	-3.28	0.61	-0.04	0.54	0.51
130.	N=NC ₆ H ₅	c-C ₆ H ₁₂	-3.10	-0.70	0.25	0.08	0.25	0.28
131.	N=C	Cl ₃ CF	-3.21	-2.76	0.54	0.00	0.49	0.49
132.		C ₆ H ₆	-3.63	-3.44	0.63	0.02	0.59	0.60
133.	N=S=O	Cl ₃ CF	-5.99	-2.25	0.47	0.11	0.47	0.53
134.	NO ₂	c-C ₆ H ₁₂	-9.01	-3.50	0.64	0.16	0.66	0.75
135.	N=O	c-C ₆ H ₁₂	-10.50	-1.80	0.41	0.25	0.48	0.62
			6. N _n P _n F _{2n-1}					
136.	N ₃ P ₃ F ₅	Cl ₃ CF	-10.6	-3.3	0.61	0.21	0.66	0.78
137.	N ₄ P ₄ F ₇	Cl ₃ CF	-10.4	-3.2	0.60	0.21	0.65	0.77
138.	N ₅ P ₅ F ₉	Cl ₃ CF	-10.2	-3.3	0.61	0.20	0.65	0.77
139.	N ₆ P ₆ F ₁₁	Cl ₃ CF	-10.1	-3.3	0.61	0.20	0.65	0.77
140.	N ₇ P ₇ F ₁₃	Cl ₃ CF	-10.0	-3.3	0.61	0.20	0.65	0.77
141.	N ₈ P ₈ F ₁₅	Cl ₃ CF	-10.0	-3.3	0.61	0.20	0.65	0.77
Oxygen Substituents								
			1. Y					
142.	OH	CCl ₄	11.40	-1.20	0.32	-0.43	0.07	-0.38 ^a
143.	OMe	c-C ₆ H ₁₂	11.58	-1.05	0.30	-0.43	0.05	0.40 ^a
144.	O(CH ₂) ₂ Br	Cl ₃ CF	9.86	-1.90	0.42	-0.40	0.18	0.23 ^a
145.	OCH=CH ₂	Cl ₃ CF	7.55	-2.07	0.44	-0.31	0.25	-0.09 ^a
146.	OC ₆ H ₅	c-C ₆ H ₁₂	7.45	-1.95	0.43	-0.32	0.23	-0.11 ^a
147.	OCH ₂ Cl	CCl ₄	7.36	-2.28	0.47	-0.31	0.27	-0.04 ^a
148.	OCH=CHBr	Cl ₃ CF	6.64	-2.38	0.49	-0.30	0.30	-0.01 ^a
149.	OC≡CH	Cl ₃ CF	5.99	-2.94	0.56	-0.30	0.37	0.06 ^a
150.	OCOMe	c-C ₆ H ₁₂	4.55	-1.33	0.34	-0.19	0.20	0.09
151.	OCHF ₂	CCl ₄	4.32	-2.62	0.52	-0.23	0.36	0.22
152.	OCHCl ₂	CCl ₄	3.98	-2.95	0.56	-0.23	0.40	0.26
153.	OCN	Cl ₃ CF	2.46	-5.12	0.86	-0.25	0.68	0.54
154.	OCF ₃	c-C ₆ H ₁₂	2.25	-3.35	0.62	-0.18	0.48	0.37
155.	OCCl ₃	CCl ₄	1.65	-3.04	0.58	-0.15	0.46	0.37
156.	OCOCF ₃	c-C ₆ H ₁₂	1.58	-3.98	0.71	-0.18	0.57	0.46
			2. OXZ					
157.	O(Me)BCl ₃	CH ₂ Cl ₂	-1.5	-3.2	0.60	-0.06	0.52	0.48

TABLE IV (Continued)

	substituent, Y	solvent	$-\sigma_H^{p-Y}$	$-\sigma_H^{m-Y}$	σ_F	σ_R	$c\sigma_m$	$c\sigma_p$
270.	$S(Me)_2^+$	CH_3OH	-10.58	-6.19	1.01	0.13	1.01	1.09
271.	$S(Et)_2^+$	CH_3OH	-11.96	-6.5	1.05	0.16	1.06	1.16
272.	$As(Ph)_3^+$	CH_3OH	-10.9	-6.5	1.05	0.13	1.05	1.13

^a Calculated by using the enhanced σ_R value obtained from eq 18. ^b From a collection of values of F NMR substituent chemical shifts by R. W. Taft no longer kept current after ca. 1973. Both published and unpublished results are included. Results in $c-C_6H_{12}$, CCl_4 , CH_2Cl_2 , CH_3OH , and CF_3CO_2H are generally from work of Taft and co-workers, refs 43 and 55, or below. Exceptions in $c-C_6H_{12}$ and CH_2Cl_2 are principally the results with transition-metal substituents from Parshall, G. W. *J. Am. Chem. Soc.* 1966, 88, 704, and from Stewart, R. P.; Treichel, P. M. *J. Am. Chem. Soc.* 1970, 92, 2710. Results in Cl_3CF generally are from W. A. Sheppard and co-workers (below). Many of the shifts in various solvents are summarized in Van Wazer, J. R.; Dungan, C. H. *Compilation of Reported F^{19} NMR Chemical Shifts. 1951-Mid-1967*; Wiley-Interscience: New York, 1970; New York, pp 3889-4223. Positive values of $-\delta_H^{m-Y}$ and $-\delta_H^{p-Y}$ denote upfield shifts (shielding) in ppm for meta and para substituted fluorobenzenes, respectively, relative to internal fluorobenzene in 0.10 (or less) M solutions. Some additional references are as follows: (1) Eaton, D. R.; Sheppard, W. A. *J. Am. Chem. Soc.* 1963, 85, 1310. (2) Maciel, G. E. *J. Am. Chem. Soc.* 1964, 86, 1269. (3) Taft, R. W.; Carter, J. W. *J. Am. Chem. Soc.* 1964, 86, 4199. (4) Sheppard, W. A. *J. Am. Chem. Soc.* 1965, 87, 2410. (5) Taft, R. W.; McKeever, L. D. *J. Am. Chem. Soc.* 1965, 87, 2489. (6) Taft, R. W.; Klingensmith, G. B.; Ehrenson, S. *J. Am. Chem. Soc.* 1965, 87, 3620. (7) Fawcett, F. S.; Sheppard, W. A. *J. Am. Chem. Soc.* 1965, 87, 4341. (8) Taft, R. W.; Rakskys, J. W. *J. Am. Chem. Soc.* 1965, 87, 4387. (9) Ramsey, B. G.; Taft, R. W. *J. Am. Chem. Soc.* 1966, 88, 3058. (10) Pews, R. G.; Tsuno, Y.; Taft, R. W. *J. Am. Chem. Soc.* 1967, 89, 2391. (11) Giam, C. S.; Taft, R. W. *J. Am. Chem. Soc.* 1967, 89, 2397. (12) Cairncross, A.; Sheppard, W. A. *J. Am. Chem. Soc.* 1968, 90, 2168. (13) Rakskys, J. W.; Taft, R. W.; Sheppard, W. A. *J. Am. Chem. Soc.* 1968, 90, 5236. (14) Kitching, W.; Adcock, W.; Hegarty, B. F. *Aust. J. Chem.* 1968, 21, 2411. (15) Uschold, R. E.; Taft, R. W. *Org. Magn. Res.* 1969, 1, 375. (16) Timberlake, J. W.; Thompson, J. A.; Taft, R. W. *J. Am. Chem. Soc.* 1971, 93, 274. (17) Sheppard, W. A.; Taft, R. W. *J. Am. Chem. Soc.* 1972, 94, 1919. (18) Brownlee, R. T. C.; Dayal, S. K.; Lyle, J. L.; Taft, R. W. *J. Am. Chem. Soc.* 1972, 94, 7208.

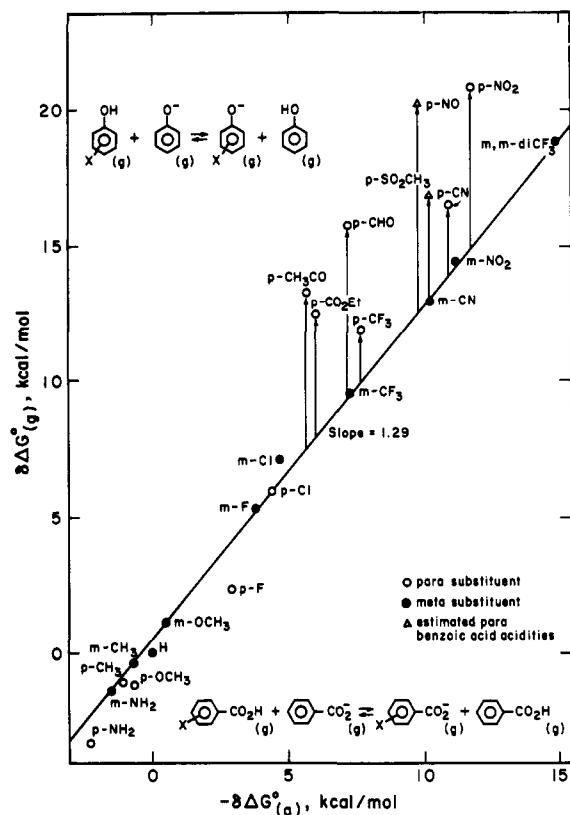


Figure 2. Enhanced resonance effects of para- π acceptor substituents in the gas phase acidities of phenols relative to benzoic acids.

benzoic acids.^{30,51} The closed circle points are for unconjugated meta- and para-substituents and these points give

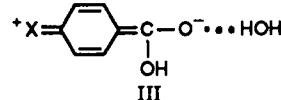
$$-\delta\Delta G^\circ_{(g)} = -0.03 + 11.1(-\delta\Delta G^\circ_{(aq)}) \quad (17)$$

$$n = 14, r = 0.974,$$

$$s = 1.0 \text{ kcal/mol (or } 0.09 \text{ in } \sigma_m \text{ or } \sigma_p\text{)}$$

The open circle points are for conjugated para π -electron donor substituents which all deviate in the direction of enhanced resonance effects in water. The enhancements are most notable for *p*-F, *p*-OMe, and *p*-NH₂, i.e., they tend to increase as π -donation in-

creases. Hydrogen bonding by water to the carbonyl oxygen of the un-ionized benzoic acids (in the high dielectric constant of water) accounts for the enhanced negative σ_p values probably through transquinoidal resonance of III. The high dielectric constant of water,



together with its ability to strongly solvate by hydrogen bonding the COO⁻ and OH centers of both the ionized and neutral forms of benzoic acids, contributes to the 11-fold reduction of substituent effects in water vs the gas-phase as indicated by eq 17.

Several additional kinds of evidence support these conclusions. Figure 2 shows the gas-phase relative acidities, $-\delta\Delta G^\circ_{(g)}$ of meta- and para-substituted phenols plotted against the corresponding gas-phase relative acidities of meta- and para-substituted benzoic acids. Para π -electron acceptor (+R) substituents show large, but variable, acidity enhancements in the phenol series (σ_p^- type behavior) compared to the approximately linear Hammett relationship followed satisfactorily by all of the other substituents. The failure of Figure 2 to display enhanced resonance effects for para π -electron donor (-R) substituents for the gas-phase benzoic acids indicates the absence of transquinoidal resonance when there is no aqueous medium present. This is also indicated by the relative acidities of meta- and para-substituted benzoic acids in ion-pair formation with 1,3-diphenylguanidine in very dilute benzene solution.⁵² A Hammett plot of this series gives a satisfactory linear relationship, except for the para -R substituents. These show significantly smaller acid weakening effects than expected from the aqueous σ_m and σ_p constants (cf. Table IX). Finally, the F NMR substituent chemical shifts of meta- and para-substituted fluorobenzenes show that $-\sigma_R$ values (Table IV) are significantly less than the corresponding (aqueous benzoic acid) $-R$ values (Table I) for the strong π -donor substituents.

A final point that corroborates the interpretation of Figure 1, is that the R values in Table I for -R para substituents are roughly correlated with the gas-phase

TABLE V. Resonance Parameters R^+ and R^-

substituent	σ_p^+	ref	σ_p^-	ref	F	R^+	R^-
1. BCl_2	0.86	267					
2. Br	0.15	194	0.25	206	0.45	-0.30	-0.20
3. SiBr_3	0.41	245					
4. Cl	0.11	194	0.19	251	0.42	-0.31	-0.23
5. $\text{P}(\text{O})\text{Cl}_2$	0.38	208			0.70	-0.32	
6. PCl_3	0.62	208			0.50	0.12	
7. $\text{P}(\text{S})\text{Cl}_2$	0.33	208			0.63	-0.30	
8. GeCl_3	0.57	249			0.65	-0.08	
9. SiCl_3	0.57	249			0.44	0.13	
10. F	-0.07	194	-0.03	198	0.45	-0.52	-0.48
11. SO_2F			1.54	109	0.72		0.82
12. SF_5			0.86	179	0.56		0.30
13. I	0.14	194	0.27	251	0.42	-0.28	-0.15
14. NO			1.63	197	0.49		1.14
15. NO_2	0.79	194	1.27	87	0.65	0.14	0.62
16. $\text{N}^+\equiv\text{N}$			3.43	182	1.58		1.85
17. N_3^-			0.11	130	0.48		-0.37
18. O^-	-2.30	218	-0.82	88	-0.26	-2.04	-0.56
19. SO_2^-			0.08	235	0.03		0.05
20. PO_3^-			-0.16	202			
21. SO_3^-			0.58	239	0.29		0.29
22. S ⁻	-2.62	269			0.03	-2.56	
23. H	0.00		0.00		0.00	0.00	0.00
24. AsO_3H^-			0.46	244	0.04		0.42
25. OH	-0.92	194	-0.37	251	0.33	-1.25	-0.70
26. SH	-0.03	269			0.30	-0.33	
27. $\text{As}(\text{O})(\text{OH})_2$			0.97	244	0.04		0.93
28. $\text{B}(\text{OH})_2$	0.38	267			-0.03	0.41	
29. NH_2^-	-1.30	194	-0.15	195	0.08	-1.38	-0.23
30. SO_2NH_2			0.94	196	0.49		0.45
31. PH_2	0.06	253			0.09	-0.03	
32. NH_3^+			-0.56	74	0.92		-1.48
33. SiH_3	0.14	237			0.06	0.08	
34. 5-chloro-1-tetrazolyl			0.70	165	0.58		0.12
35. COCl	0.79	236	1.24	250	0.46	0.33	0.78
36. CF_3^-	0.61	194	0.65	178	0.38	0.23	0.27
37. $\text{N}=\text{NCF}_3$	0.74	72			0.50	0.24	
38. OCF_3			0.27	145	0.39		-0.12
39. $\text{S}=\text{O}(\text{CF}_3)$			1.05	221	0.58		0.47
40. $\text{SO}_2(\text{CF}_3)$			1.63	221	0.74		0.89
41. OSO_2CF_3			0.49	221	0.56		-0.07
42. SCF_3			0.64	145	0.36		0.28
43. SeCF_3			0.53	221	0.43		0.10
44. CN	0.66	194	1.00	196	0.51	0.15	0.49
45. $\text{N}=\text{C}=\text{O}$	-0.19	236			0.31	-0.50	
46. $\text{N}=\text{C}=\text{S}$			0.34	238	0.51		-0.17
47. $\text{SC}\equiv\text{N}$			0.59	251	0.36		0.23
48. $\text{N}=\text{N}-\text{C}\equiv\text{N}$	1.03	72			0.56	0.47	
49. CO_2^-	-0.02	194	0.31	200	-0.10	0.08	0.41
50. COOR	0.48	194	0.64	87	0.34	0.14	0.30
51. OCHF_2			0.11	221	0.37		-0.26
52. SOCHF_2			0.93	221	0.51		0.42
53. SO_2CHF_2			1.44	221	0.67		0.77
54. 1-tetrazolyl			0.57	165	0.52		0.05
55. CHO	0.73	236	1.03	200	0.33	0.40	0.70
56. COOH	0.42	194	0.77	206	0.34	0.08	0.43
57. CH_2Br	0.02	243			0.14	-0.12	
58. CH_2Cl	-0.01	194			0.13	-0.14	
59. $\text{SO}_2\text{CH}_2\text{F}$			1.17	221			
60. CONH ₂			0.61	206	0.26		0.35
61. OCH_2O^-	-0.68	254			-0.11	-0.57	
62. CH_3^-	-0.31	194	-0.17	204	0.01	-0.32	-0.18
63. $\text{SiCl}_2(\text{CH}_3)$	0.08	245			0.29	-0.21	
64. $\text{SiF}_2(\text{CH}_3)$	0.23	245			0.32	-0.09	
65. OCH ₃	-0.78	194	-0.26	198	0.29	-1.07	-0.55
66. CH_2OH	-0.04	243	0.08	200	0.03	-0.07	0.05
67. $\text{S}=\text{O}(\text{CH}_3)$			0.73	222	0.52		0.21
68. $\text{S}=\text{O}(\text{OCH}_3)$			0.89	235	0.24		0.65
69. SO_2CH_3			1.13	278	0.53		0.60
70. OSO_2CH_3	0.16	241			0.40	-0.24	
71. SCH ₃	-0.60	194	0.06	214	0.23	-0.83	-0.17
72. NHCH ₃	-1.81	269			-0.03	-1.78	
73. $\text{NHC}(\text{NH}_2)=\text{NH}_2^+$			0.32	247			
74. $\text{C}=\text{O}(\text{CF}_3)$	0.85	236	1.09	266	0.54	0.31	0.55
75. CF_2CF_3			0.69	165	0.44		0.25
76. OCF_2CF_3			0.28	178	0.55		-0.27
77. $\text{N}(\text{CF}_3)_2$			0.53	145	0.35		0.18

TABLE V (Continued)

substituent	σ_p^+	ref	σ_p^-	ref	F	R^+	R^-
78. C≡CH	0.18	171	0.53	223	0.22	-0.04	0.31
79. OCF ₂ CF ₂ H			0.21	178	0.38		-0.17
80. SCF ₂ CF ₂ H			0.61	178	0.35		0.26
81. CHCN	-4.67	271					
82. CH ₂ CF ₃			0.14	109	0.15		-0.01
83. CH ₂ CN	0.16	243	0.11	263	0.17	-0.01	-0.06
84. CH=CHNO _{2-t}			0.88	193	0.36		0.52
85. CH ₂ CO ₂ ⁻	-0.53	271	-0.16	88			
86. CH=CH ₂	-0.16	248			0.13	-0.29	
87. COCH ₃			0.84	200	0.33		0.51
88. SC=O(CH ₃)			0.46	195	0.37		0.09
89. OCOC ₂ H ₅	-0.19	265			0.42	-0.61	
90. COOCH ₃	0.49	194	0.75	74	0.34	0.15	0.41
91. CH ₂ COOH	-0.01	243	0.05	263			
92. NHCOCH ₃	-0.60	194	-0.46	251	0.31	-0.91	-0.77
93. CH ₂ CH ₃	-0.30	194	-0.19	251	0.00	-0.30	-0.19
94. OCH ₃ CH ₃	-0.81	256	-0.28	251	0.26	-1.07	-0.54
95. CH ₂ OCH ₃	-0.05	243			0.13	-0.18	
96. CH ₂ CH ₂ OH			-0.15	251			
97. SiCl(CH ₃) ₂	0.02	245			0.16	-0.14	
98. SiF(CH ₃) ₂	0.17	245			0.17	0.00	
99. N(CH ₃) ₂	-1.70	194	-0.12	195	0.15	-1.85	-0.27
100. SO ₂ N(CH ₃) ₂	0.86	275	0.99	215	0.44	0.42	0.55
101. N=NN(CH ₃) ₂	-0.46	72			-0.03	-0.43	
102. P(O)(CH ₃) ₂			0.74	258	0.40		0.34
103. P(CH ₃) ₂			0.22	224	0.05		0.17
104. P(S)(CH ₃) ₂			0.62	224			
105. S ⁺ (CH ₃) ₂			0.83	207	0.98		-0.15
106. SiH(CH ₃) ₂	-0.04	249			0.03	-0.07	
107. 1-(1,7-(BH) ₁₀ -C ₂ H)			0.32	242	0.23		0.09
108. 1-(1,2-(BH) ₁₀ -C ₂ H)			0.52	210	0.50		0.02
109. 2-(4,6-dichloro-s-triazinyl)			0.85	240			
110. CF=CFCF ₃			0.65	221	0.36		0.29
111. CF(CF ₃) ₂			0.68	172	0.31		0.37
112. SO ₂ (CF ₃) ₂ CF ₃			1.75	70	0.81		0.94
113. SO ₂ CF(CF ₃) ₂			1.76	70	0.80		0.96
114. S(CF ₃) ₂ CF ₃			0.65	70	0.43		0.22
115. SCF(CF ₃) ₂			0.69	70	0.46		0.23
116. COH(CF ₃) ₂			0.48	172	0.29		0.19
117. CH=CHCF _{3-t}			0.34	165	0.24		0.10
118. CH=CHCF _{3-c}			0.29	165	0.18		0.11
119. CH=CHSO ₂ CF ₃			0.83	221	0.22		0.61
120. CH=CHCOOH			0.62	188			
121. cyclopropyl	-0.41	209	-0.09	204	0.02	-0.43	-0.11
122. CH ₂ CH=CH ₂	-0.22	279	-0.18	201	-0.06	-0.16	-0.12
123. CH ₂ COCH ₃	0.03	243					
124. COOEt	0.48	194	0.75	251	0.34	0.14	0.41
125. CH ₂ COOCH ₃			0.07	88			
126. CH ₂ CH ₂ CH ₂ ⁻	-0.41	226					
127. CON(CH ₃) ₂			0.70	266			
128. CH(CH ₃) ₂	-0.28	194	-0.16	251	0.04	-0.32	-0.20
129. CH ₂ CH ₂ CH ₃	-0.29	225	-0.06	251	0.01	-0.30	-0.07
130. OCH(CH ₃) ₂	-0.85	254			0.34	-1.19	
131. OCH ₂ CH ₂ CH ₃	-0.83	256			0.26	-1.09	
132. N ^{+(CH₃)₃}	0.41	194	0.77	206	0.86	-0.45	-0.09
133. Si(CH ₃) ₂ OCH ₃	-0.02	245			0.09	-0.11	
134. SiCH ₃ (OCH ₃) ₂	0.01	245			0.05	-0.04	
135. Si(OCH ₃) ₃	0.13	245			0.10	0.03	
136. P ⁺ (CH ₃) ₃			0.95	258	0.36		0.59
137. Si(CH ₃) ₃	0.02	194			0.01	0.01	
138. Sn(CH ₃) ₃	-0.12	216			0.34	-0.46	
139. C(CF ₃) ₃			0.71	120	0.29		0.42
140. (CF ₃) ₃ CF ₃			0.73	172	0.44		0.29
141. SO ₂ C(CF ₃) ₃			1.81	70	0.84		0.97
142. SC(CF ₃) ₃			0.79	70	0.47		0.32
143. CH=C(CN) ₂	0.82	241	1.20	165	0.57	0.25	0.63
144. 2-furyl	-0.39	228	0.21	228	0.10	-0.49	0.11
145. 2-thienyl	-0.43	228	0.19	159	0.13	-0.56	0.06
146. 3-thienyl	-0.38	228	0.13	159	0.08	-0.46	0.05
147. 2-seleniyl			0.22	84	0.10		0.12
148. 2-tellurienyl			0.25	84	0.10		0.15
149. CH=CH—CH=CH-	-0.14	194	0.12	197	0.19	-0.33	-0.07
150. CH=CHCOCH ₃	0.39	261			0.31	0.08	
151. cyclobutyl	-0.29	127	-0.07	204	0.02	-0.31	-0.09
152. CH ₂ COOEt	-0.16	194					
153. CH ₂ CH ₂ CH ₂ CH ₂ ⁻	-0.41	226			-0.40	-0.01	
154. C(CH ₃) ₃	-0.26	194	-0.13	206	-0.09	-0.17	-0.04

TABLE VI. Selected Substituents Having Extreme Values of F and R

substituent	F	σ_F^* (F NMR)	substituent	R	σ_R^* (F NMR)
$N^+ \equiv N$	1.58		BCl_2		0.34
$I^-NSO_2CF_3$	1.20		$C(CN) \equiv C(CN)_2$	0.33	0.26
$I(OOCOF_3)_2$	1.18		$CH=CHSO_2CF_3$	0.33	0.22
$P(=NSO_2CF_3)(C_6F_5)_2$	1.11		$N^+ \equiv N$	0.33	
$SO(CF_3)=NSO_2CF_3$	1.09		$COCN$		0.31
$As^+(C_6H_5)_3$		1.05	SO_2CN	0.29	0.27
$P^+(CH_3)(C_6H_5)_2$	1.04	0.86	BF_2	0.26	0.28
ICl_2	1.03	1.15	$CH=C(CN)_2$	0.28	0.25
$NHNO_2$	0.99		$SO_2C_2F_5$	0.27	
IF_4	0.98		PF_4	0.26	0.28
S^+Me_2	0.98	1.10	$COCF_3$	0.22	0.27
SO_2CN	0.97	0.99	$CONHC_6H_5$	0.24	
$N(CN)_2$		0.94	4-pyridyl	0.23	
$P(Et)_3$	0.94		SO_2CF_3	0.22	0.26
$C(CN)_3$	0.92	0.95	$P^+(C_6H_5)_3$		0.20
$N^+(CH_3)_3$	0.86	9.99	SiF_3	0.22	0.21
$SO_2C(CF_3)_3$	0.84		SO_2F	0.19	0.22
IF_3	0.82		SO_2CH_3	0.19	
SO_2CF_3	0.74	0.83	$COCH_3$	0.17	0.16
OCN	0.69	0.86	PF_2	0.15	0.18
NO_2	0.65		CN	0.16	
$COCN$		0.62	SF_3	0.17	0.17
$B(OH)_3$	-0.42		NO_2	0.13	0.16
$t\text{-}Pt(PEt)_2Me$		-0.43	S^-	-1.24	
$Ni(C_6H_5)_3(\pi\text{-}C_6H_5)$		-0.35	$N(CH_3)_2$	-0.98	-0.56
NHC_4H_9	-0.21		$OCH(CH_3)_2$	-0.79	
$(CH_3)_3$	-0.20		NHC_6H_5	-0.78	-0.35
OCH_2O^-	-0.11		NH_2	-0.74	-0.48
CO_2^-	-0.10		$N=CHC_6H_5$	-0.69	
$N=P(C_6H_5)_3$	-0.10	-0.12	$N=P(C_6H_5)_3$	-0.67	-0.46
ferrocenyl	-0.09		$NHET$	-0.57	
1-adamantyl	-0.07		OCH_3	-0.56	-0.43
Me	0.01		$OCH_2CH=CH_2$	-0.50	
cyclopropyl	0.02		$NHOH$	-0.45	
$C^+(C_6H_5)_2$		0.74	$OCH=CH_2$	-0.43	-0.31
$N=NCN$	0.47		N_3	-0.40	
$C_3^+(C_6H_5)_2$		0.46	F	-0.39	-0.33
NO	0.42	0.25	$Fe(CO)_2(\pi\text{-}C_6H_5)$		0.29
$CH=NSO_2CF_3$	0.37				

SH , $NHCOCH_3$, $NHNH_2$, NHC_6H_5 , and NH_2 . Further, the σ_R^+ values for $N=P(C_6H_5)_3$, $OCH=CH_2$, $C(OCH_3)_3$, and C_6H_5 have been taken as equal to the σ_R^* values obtained from F NMR substituent chemical shifts of meta- and para-substituted fluorobenzenes (Table IV).

C. R^+ and R^- Values

One of the shortcomings of the Hammett constant σ_p , which was recognized early,⁶³ is that correlations obtained with it were poor when the substituents were conjugated with the reaction center. The first case where this problem arose was with phenols and anilinium ions where a lone pair of electrons on the O^- or NH_2 group could be delocalized into substituents such as $p\text{-}NO_2$ and $p\text{-}CN$. This problem was solved by defining a new constant σ_p^- obtained from the phenol or aniline data. Later H. C. Brown⁶⁴ and his colleagues developed σ_p^+ constants for substituents conjugated with a reaction center which could effectively delocalize a positive charge. The OCH_3 group in the nitration of anisole is a typical example. The σ_p^+ constants can be used in eq 2 to define R^- and R^+ which are regarded as resonance constants.⁴ In Table V we have assembled all of the σ_p^- and σ_p^+ values which we could find and, using the appropriate F values we have by eq 12 calculated R^+ and R^- . In a number of examples σ_p^+ and σ_p^- have been listed but no F values are yet available for calculating the R resonance constants. There are

113 R^+ and 143 R^- values in Table V. In their studies on factoring σ into F and R , Swain and Lupton argued that a single R value should suffice for all kinds of resonance effects. However, we have never accepted this point of view,⁴ nor have prominent workers in this field.

In Table V are considered the R^+ and R^- substituent parameters that are made available from the σ_p^+ and σ_p^- values, respectively, through eq 2. Compared to the corresponding values of R , (Table I) the R^+ values for π -electron donor substituents are significantly enhanced. The enhancements involve changes in electron demand that are produced by solvated π -electron deficient reaction centers, as well as by solvation of certain substituents. Nonetheless, a fairly reasonable correlation is found between corresponding R^+ and R values for the π -electron donor substituents.

$$\pi\text{-} \text{donors: } R^+ = 1.90 (\pm 0.26)R - 0.07 (\pm 0.11) \quad (19)$$

$$n = 29, r = 0.945, s = 0.170$$

In contrast, R^+ values for the π -electron acceptor substituents in these same reaction series remain nearly equal to their corresponding R values (eq 20).

$$\pi\text{-} \text{acceptors: } R^+ = 1.16 (\pm 0.45)R - 0.01 (\pm 0.07) \quad (20)$$

$$n = 16, r = 0.829, s = 0.060$$

TABLE VII. Values of σ_1 for Various Heterocycles Obtained from the pK_a of Guanidines⁴¹

substituent	σ_1
1. pyrimidin-2-yl	0.23
2. pyrimidin-4-yl	0.26
3. 1,2,4-triazin-6-yl	0.37
4. 2-furyl	0.17
5. 3-furyl	0.10
6. 2-thienyl	0.19
7. 3-thienyl	0.10
8. pyrrol-2-yl	0.17
9. indol-3-yl	0.01
10. 1-phenylpyrazol-3-yl	0.21
11. oxazol-2-yl	0.38
12. imidazol-2-yl	0.27
13. 1-methylimidazol-2-yl	0.26
14. imidazol-4(5)-yl	0.08
15. 1,2,4-oxadiazol-5-yl	0.49
16. 1,2,4-thiadiazol-5-yl	0.41
17. 2 <i>H</i> -1,2,3-triazol-2-yl	0.41
18. pyridin-2-yl	0.18
19. 6-methylpyridin-2-yl	0.17
20. quinolin-6-yl	0.17
21. pyrazin-2-yl	0.25
22. 6-methylpyrazin-2-yl	0.24
23. 5,6-dimethylpyrazin-2-yl	0.23
24. quinoxazin-2-yl	0.27
25. 4,6-dimethylpyrimidin-2-yl	0.21
26. 4-phenylpyrimidin-2-yl	0.21
27. 4-methylquinazolin-2-yl	0.22
28. 2-methylpyrimidin-4-yl	0.25
29. 2-phenylpyrimidin-4-yl	0.28
30. pyridazin-3-yl	0.26
31. 3-methyl-1,2,4-triazin-6-yl	0.36
32. 3-phenyl-1,2,4-triazin-6-yl	0.40
33. 4-methyloxazol-2-yl	0.37
34. 4,5-dimethyloxazol-2-yl	0.35
35. benzoxazol-2-yl	0.41
36. thiazol-2-yl	0.34
37. 4-methylthiazol-2-yl	0.32
38. 4,5-dimethylthiazol-2-yl	0.31
39. benzothiazol-2-yl	0.37
40. 4-methylimidazol-2-yl	0.26
41. 1-methylimidazol-2-yl	0.26
42. benzimidazol-2-yl	0.32
43. 1-phenylpyrazol-3-yl	0.21
44. 3-methyl-1,2,4-oxadiazol-5-yl	0.48
45. 3-methyl-1,2,4-thiadiazol-5-yl	0.40
46. 2 <i>H</i> -1,2,3-triazol-2-yl	0.41
47. tetrazol-5-yl	0.49
48. 3,4-dihydro-4-oxopyrimidin-2-yl	0.41
49. 3,4-dihydro-4-oxoquinazolin-2-yl	0.40
50. 1,6-dihydro-6-oxopyridazin-3-yl	0.27
51. 1,6-dihydro-1-methyl-6-oxopyridazin-3-yl	0.28
52. 4,5-dihydro-4-oxothiazol-2-yl	0.46

($\text{SO}_2\text{N}(\text{CH}_3)_2$ and CHO with deviations of 0.19 and 0.29, respectively, have been excluded). The results of eqs 19 and 20 show that a different resonance effect reaction constant is required for π -donors and π -acceptors. The poor precision of eq 20 reflects uncertainties in the reliability of R^+ values for π -electron acceptors in reaction series with π -electron deficient centers. In gas-phase proton-transfer equilibria that involve strongly π -electron deficient centers, resonance effects for π -acceptors are found to be very small (σ_{R}^+ for these substituents can reliably be taken as zero).³⁰

Comparing corresponding R^- and R values for π -electron acceptor substituents in reactions with π -electron-rich centers shows that there are generally significant enhancements only for the former. Equation 21 gives the relatively crude correlation of the R^- values with corresponding R values (Table I). A major cause

$$\pi\text{-donors: } R^- = 1.93 (\pm 0.59)R + 0.19 (\pm 0.11) \quad (21)$$

$$n = 34, r = 0.758, s = 0.173$$

for the poor precision of eq 21 is that new solvation sites are created for certain substituents (most important for oxy-anionic substituents) as the result of strong conjugation with electron-rich reaction centers (the SSAR effects).⁴⁶ This solvation effect is known to be even more important in the solvent dimethyl sulfoxide than in aqueous solvents.^{46d,e}

With π -electron donor substituents, no useful general correlation is found between R^- (Table V, reactions with π -electron-rich centers) and corresponding R values (Table I). For some, the expected π -electron saturation effects are observed $|R^-|$ values are significantly smaller than the corresponding $|R|$ values (this is true for $\text{N}(\text{CH}_3)_2$, NH_2 , I , $\text{c-C}_3\text{H}_5$, CH_3 , C_2H_5 , and SC_6H_5). For others, $|R^-| \approx |R|$ (as for OC_2H_5 , OCH_3 , OC_6H_5 , OH , SCH_3 , Cl , Br , C_6H_5 , and $i\text{-C}_3\text{H}_7$). Apparent anomalies are that $|R^-|$ values are significantly larger than corresponding $|R|$ values for NHCOCH_3 , F , $\text{CH}_2\text{Si}(\text{CH}_3)_3$, and $\text{CH}_2\text{C}_6\text{H}_5$. Again it appears that R^- values for π -donor substituents (just as for R^+ values for π -acceptor substituents) are questionable. These anomalies are probably largely artifacts resulting from the restrictions of the Hammett single parameter treatment.

D. Resonance Effect σ_R Values from NMR Chemical Shifts of Para-Substituted Fluorobenzenes Relative to Their Meta Isomers as Internal References

These chemical shifts (in parts/million) were shown to be very sensitive measures of para-substituent π -electron donor acceptor interactions.⁵⁵ Dilutions of 0.05 to a few tenths molar solutions of the two isomers in solvents, such as CCl_4 , FCCl_3 , cyclohexane, benzene, methanol, and others, have been obtained for an extensive number of substituents. Table IV presents a representative summary of F NMR shifts in the indicated solvent relative to internal fluorobenzene for both para ($-\delta_{\text{H}}^{p-\text{Y}}$) and meta ($-\delta_{\text{H}}^{m-\text{Y}}$) isomers. Positive values denote upfield shifts (increased shielding) relative to fluorobenzene. The difference, $-\delta_{\text{H}}^{p-\text{Y}} + \delta_{\text{H}}^{m-\text{Y}} = -\delta_{m-\text{Y}}$, permits a cancellation of the substituent field/inductive effects,⁵⁵ giving essentially the pure resonance effect. A correlation of values of $-\delta_{m-\text{Y}}$ with corresponding values of σ_{R}^- from Taft and Topsom³⁰ for the following 18 π -acceptor or inactive substituents, H , $\text{C}(\text{CF}_3)_3$, $\text{C}(\text{CN})_3$, $\text{C}(\text{Cl})_3$, $\text{Si}(\text{CH}_3)_3$, SF_5 , CF_3 , SCF_3 , SO_2CH_3 , $\text{SO}_2\text{C}_6\text{H}_5$, $\text{CO}_2\text{C}_6\text{H}_5$, SiCl_3 , COCH_3 , COC_6H_5 , NO_2 , NO , COCl , and COCF_3 , gives eq 22.

$$\sigma_{\text{R}}^- = -0.0280 (\pm 0.001) (-\delta_{m-\text{Y}}^{\text{p-Y}}) + 0.01 (\pm 0.01) \quad (22)$$

$$n = 18, r = 0.982, s = 0.02$$

For the following π -donor ($-\text{R}$) substituents eq 23 is obtained for H and $\text{N}(\text{CH}_3)_2$, NH_2 , OCH_3 , OH , OC_6H_5 , F , Cl , Br , CH_3 , CH_2NH_2 , CH_2OCH_3 , CH_2CF_3 , CH_2Cl , and CH_2F .

values ($c\sigma_m$ and $c\sigma_p$) given in Table IV are quite reasonable and suggest that this method can be used to obtain σ values for substituents unstable in aqueous solution or other solutions. For individual substituents, values of corresponding σ and $c\sigma$ may be compared by reference to both Tables I and IV. In the case of eq

$$c\sigma_m = 0.971 (\pm 0.05) \sigma_F (\text{F NMR}) + 0.473 (\pm 0.07) \sigma_R (\text{F NMR}) - 0.036 (\pm 0.02) \quad (26)$$

$$n = 135, r = 0.972, s = 0.064$$

$$c\sigma_p = 0.985 (\pm 0.03) \sigma_F (\text{F NMR}) + 1.058 (\pm 0.03) \sigma_R (\text{F NMR}) - 0.047 (\pm 0.01) \quad (27)$$

$$n = 130, r = 0.984, s = 0.066$$

26, four data points (SO_2Cl , $\text{CN}\cdot\text{BCl}_3$, HgMe , and SnMe_2) were badly fit and hence not used in its derivation. Nine poorly fit data points were excluded in the derivation of eq 27 (NO , $\text{CN}\cdot\text{BCl}_3$, OCOMe , $\text{S}(\text{Me})_2^+$, $\text{CH}=\text{CHCN}$, $\text{P}(\text{NMe}_2)_2$, NHC_6H_5).

The standard deviations for eqs 26 and 27 are surprisingly good considering that the σ_m and σ_p values have been obtained by a variety of means in a number of different laboratories. Clearly it is a satisfaction that σ constants obtained by the various methods discussed above are in such good general agreement.

In making the first large compilation of σ constants, it was noted that there was a high degree of collinearity between σ_m and σ_p .³⁴ By using the present much expanded set of substituents, the collinearity is even more evident as eq 28 shows.

$$\sigma_p = 1.19 (\pm 0.04) \sigma_m - 0.08 (\pm 0.02) \quad (28)$$

$$n = 530, r = 0.941, s = 0.137, F_{1,527} = 4095$$

The resonance and inductive parameters F and R , however, are not highly collinear and can be used as independent variables.

$$F = 0.41 (\pm 0.10) R + 0.34 (\pm 0.02) \quad (29)$$

$$n = 529, r = 0.336, s = 0.257, F_{1,527} = 66.9$$

The collinearity of eq 28 is a result of the large number of substituents which show very little resonance interaction. Of the 529 substituents in Table I, 287 have R values between +0.12 and -0.12. That is, they have very little resonance interaction so that σ_m and σ_p are almost identical.

By comparing only the 38 substituents upon which eq 8 rests, eq 30 is obtained.

$$\sigma_p = 1.46 (\pm 0.27) \sigma_m - 0.20 (\pm 0.08) \quad (30)$$

$$n = 38, r = 0.879, s = 0.176$$

Although the collinearity in eq 30 is much lower than that of eq 28, it is still high and brings out a shortcoming of the Hammett σ constant: one should draw no firm conclusions about the relative importance of resonance or inductive effects from unfactored σ constants.

II. Discussion

Table I, with over 500 substituents having both σ_m and σ_p values is impressive testimony to the enormous

effort which has contributed so much to our understanding of organic reaction mechanisms, both in simple physical organic chemical systems and in biological systems.

In the past two decades there have been increasing efforts to factor σ into its inductive and resonance components, a field which Charton has reviewed.²⁹ Of these factoring methods, the one proposed by Charton and that of Swain and Lupton offer large data sets for use in correlation analysis. Even though there has been criticism of the exactness of this method, we believe that for many purposes, and especially for biological structure-activity studies, these constants are valuable. This belief is reinforced by eqs 9–11 all of which show that the agreement between the Swain and Lupton's modified F and Charton's σ_I is good despite the fact that they are derived from completely different systems. The relationship between modified R and σ_D shown by eqs 10 and 11 gives us confidence that R will also be valuable in correlation analysis. However, one must be aware that not all of the values in Table I are of equal quality. One should check the original sources when working with unusual substituents.

One of the features of Table I is that it provides substituents with a wide range of electronic effects as illustrated in Table VI. The NO_2 group is usually thought of as having nearly maximal electron-withdrawing power, but there are many substituents with higher F values in Table I. Furthermore, there are substituents with R values 3–6 times the value of 0.13 for NO_2 . Many of these substituents with extreme electronic effects have received almost no attention in QSAR studies, but we believe some of them would be well worth the trouble to synthesize and investigate. Yagupol'skii in particular has designed a most interesting variety of new substituents with unusual electronic properties.⁵⁶

In Table VII, σ_I values for a wide variety of heterocyclic substituents obtained from guanidines by Taylor and Wait⁴¹ have been listed. In Table VIII, σ_I values for substituents not in Table I derived from substituted acetic acids by Charton are given. For many purposes, these could be used along with values from Tables I or IV.

In recent years, considerable interest has developed in the ionization of compounds in the gas phase. Comparison of the gas-phase ionization constants with those obtained in solution clearly brings out the effect of the solvent. Figure 1 compares the substituent effects on the ionization of benzoic acids in water and in the gas phase. Although the substituent effect is very much larger in the gas phase, the correlation between the two types of ionization constants is surprisingly good, except for the conjugated electron-releasing substituents, 4-NH₂, 4-OCH₃, 4-CH₃, and 4-F. Table X gives comparisons of σ_m and σ_p values from benzoic acids obtained in the gas phase and in benzene solution with the corresponding aqueous solution values of Table I.

A point which has generated heated discussions is the assumption of Swain and Lupton that R for $\text{N}^+(\text{CH}_3)_2$ could be assumed to be zero. It is noteworthy that in Table I where the calculations do not include this assumption, we find R for this group to be -0.04 which for most purposes could be called zero. The value of $\sigma_R (\text{F NMR})$ of Table IV is -0.08 and Charton has reported a σ_D value of -0.11.

It has been advocated by a number of workers in the field that Swain's original F and R parameters be dropped. We have delineated the principle basis for this criticism as being the inadequate treatment of π -electron-donor/-acceptor interactions. With proper consideration of this matter we have demonstrated that at a level of precision useful for present purposes, field/inductive substituent parameters, F , (as herein modified) are in general not significantly different from corresponding σ_I , σ_F , and σ_L values. For QSAR requiring greater precision, additional modifications of field/inductive parameters due to substituent solvation and solvent effects, such as for the fall-off factor of dipolar effects, need to be considered. Corresponding resonance (π -electron delocalization) effect parameters, R , and corresponding σ_R and σ_D may also not differ significantly if they are based upon similar electron demands for the rate or equilibrium processes. However, care must be taken that proper recognition be accorded to the conditions of both π -electron-donor/acceptor interactions and of substituent solvation effects.

Many practical problems limit the use of carboxylic acid acidities in establishing new electronic parameters: difficult synthesis of exotic structures and low sensitivity of substituent effects coupled with low solubility making pK_a measurements difficult. We have included in this review an analysis of the newer methods which can supplant this "classic" procedure for determination of these constants. It is shown that there is a remarkable consistency at several levels of precision between the results obtained with these methods using proper assumptions. The interested reader is directed also to the C^{13} NMR substituent chemical shift methods given in references.⁵⁷⁻⁵⁹

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N,N'-Disubstituted Indigos as Readily Available Red-Light Photoswitches with Tunable Thermal Half-Lives

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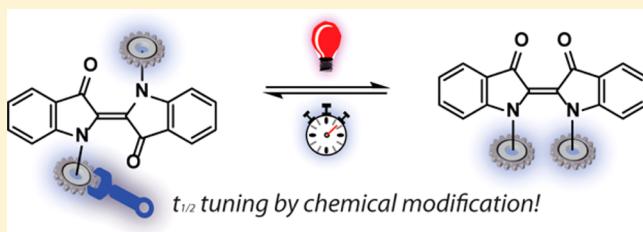
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Supporting Information

ABSTRACT: Some rare indigo derivatives have been known for a long time to be photochromic upon irradiation with red light, which should be advantageous for many applications. However, the absence of strategies to tune their thermal half-lives by modular molecular design as well as the lack of proper synthetic methods to prepare a variety of such molecules from the parent indigo dye have so far precluded their use. In this work, several synthetic protocols for *N*-functionalization have been developed, and a variety of *N*-alkyl and *N*-aryl indigo derivatives have been prepared. By installation of electron-withdrawing substituents on the *N*-aryl moieties, the thermal stability of the *Z*-isomers could be enhanced while maintaining the advantageous photoswitching properties upon irradiation with red light (660 nm LED). Both experimental data and computational results suggest that the ability to tune thermal stability without affecting the dyes' absorption maxima originates from the twisted geometry of the *N*-aryl groups. The new indigo photoswitches reported are expected to have a large impact on the development of optical methods and applications in both life and material sciences.



INTRODUCTION

In recent years the field of photochromism research has witnessed exciting developments, and photoswitchable molecules have been broadly applied in various disciplines of science. In particular in the context of biomedical applications, photoswitches have become a key tool to remotely and noninvasively regulate processes¹ *in vivo*, for example, associated with photopharmacology,² super-resolution fluorescence imaging,³ and optochemical genetics.⁴ To successfully implement photoswitches in biological systems, they have to meet three important criteria: First, the molecules should be able to undergo efficient photoisomerization upon irradiation with red or infrared light due to its superior ability to penetrate tissues ("biological window").⁵ Second, the two isomers should possess significantly different structures to maximize the light-induced activity modulation. Third, the thermal half-life of the metastable, ideally biologically active, isomer should be tunable to adjust its *in vivo* residence time according to circulation or other parameters of interest.

To date, azobenzenes have been the most promising candidates due to their significant structural changes as a result of the *E*–*Z* isomerization as well as their established photochemistry and the straightforward synthesis.⁶ Recent efforts by multiple groups have led to the development of novel azo compounds addressable by visible light,⁷ clearly improving their applicability. Despite the significant progress made, these

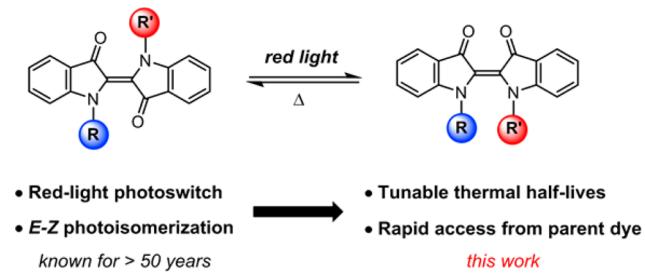
molecules are oftentimes not red-shifted enough for biological applications, even after delicate modifications of the azo framework. Thus, it is (still) desirable to develop even more red-shifted photoswitches. To our surprise, indigo, one of the most ancient dyes known in human history, has been left out in this recent wave of developments, although its photoisomerization under the influence of red light has been described more than half a century ago.⁸ This is presumably due to the fact that the parent, unsubstituted indigo does not undergo photo-induced *E*–*Z* isomerization because of its dominating and very efficient deactivation via excited state intramolecular proton transfer.⁹ In strong contrast, *N,N'*-disubstituted indigos, carrying no amide protons, are capable of undergoing efficient *E*–*Z* photoisomerization (Scheme 1).^{8,10–12}

Photoswitches based on indigos in principle offer several promising advantages. First and foremost, they could be prepared from highly abundant, low-cost materials. Due to their extended π -system and its inherent push–pull character, arising from coupling two charge-transfer halves in a so-called H-chromophore,¹³ indigos intrinsically absorb in the red region of the spectrum, even without specific donor/acceptor derivatization. Importantly, *E*–*Z* isomerization confers larger structural changes, in particular with regard to substituents projected from

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Scheme 1. Photoswitchable *N,N'*-Disubstituted Indigos

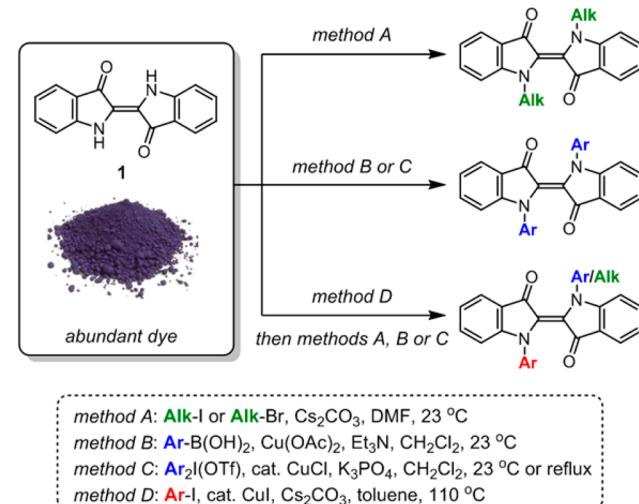
the indigo N-atoms as compared to the commonly exploited azobenzene *para*-positions, thus rendering indigos superior steric switches. In addition, indigo photoswitches should presumably exhibit reasonably low toxicity as evidenced by their extensive use for centuries. Last but not least, indigos display negative photochromism,¹⁴ providing a means to enhance penetration depth through the course of irradiation and therefore facilitating their application in pharmacology and bulk materials.

To date, symmetrical *N,N'*-diacyl,¹⁰ *N,N'*-dimethyl,¹¹ and *N,N'*-di(*tert*-butyloxycarbonyl)¹² indigos are among the only reported photoswitches in this family. Their absorption maxima (λ_{max}) range from 530 nm all the way to 670 nm, which is strongly red-shifted when compared to conventional *E*–*Z* photoswitches, such as stilbenes and azobenzenes.^{7a} However, these compounds suffer from either poor hydrolytic stability or lack of direct functionalization, and more importantly, molecular design rules allowing to rationally tune their thermal half-lives remain elusive. Herein, we report a series of symmetrical and nonsymmetrical *N*-alkyl- and *N*-aryl-substituted indigos, which allow for systematic modulation of their thermal half-lives by direct structural modification of the parent indigo while maintaining its advantageous red-shifted absorption (Scheme 1).

RESULTS AND DISCUSSION

The initial hurdle that we had to overcome was the lack of synthetic methods known to install *N*-substituents on the parent indigo. According to scattered reports in the literature, *N*-alkylation and *N*-arylation often require harsh conditions and result in complex mixtures and low yields. We tried to circumvent this problem by identifying appropriate functionalization reagents that would provide enhanced reactivity yet under milder conditions. To our delight, by using a weak base and activated electrophiles, such as benzyl bromide or α -bromoacetate, double *N*-alkylation of indigo can be achieved at room temperature (Scheme 2, method A). Furthermore, we developed two sets of complementary conditions that allow for double *N*-arylation¹⁵ of indigo under mild conditions. For installing electron-rich or electron-neutral aryl substituents, it was found that Chan-Lam coupling is the most suitable (Scheme 2, method B),¹⁶ while in the case of electron-deficient aryl groups, Cu-catalyzed cross-coupling reaction with aryliodonium salts was applied (Scheme 2, method C).¹⁷ Interestingly, both methods are extremely selective toward double *N,N'*-arylation, and only minor amounts of mono-*N*-arylated products were observed. However, to gain full synthetic flexibility for functionalizing indigos, the ability to prepare nonsymmetrical compounds is also critical. In this context, a Goldberg–Ullmann reaction proved useful as it reliably provides the mono-*N*-arylated indigos (Scheme 2,

Scheme 2. Approaches for Indigo Functionalization



method D),¹⁸ which subsequently can be alkylated or arylated using the previously described methods A–C to obtain indigos with two different *N,N'*-substituents. Although these reactions have not yet been fully optimized, they serve as rapid and straightforward entries into symmetrical and nonsymmetrical *N,N'*-disubstituted indigos from the abundant and inexpensive parent indigo dye. All of the prepared compounds were obtained as dark blue or green solids, and, unlike their parent indigo precursor, they are readily soluble in most organic solvents, simplifying purification, characterization, and further processing.

Our initial studies focused on compounds in series I, i.e., *N,N'*-dialkylindigos (Table 1). In accordance with the

Table 1. Photochemical Properties of Series I in CH_3CN

	series I: $\text{R}^1 =$		
	Me (2)	Bn (3)	$\text{CH}_2\text{CO}_2\text{tBu}$ (4)
$\lambda_{\text{max}, E}$ (nm)	641	648	623
$\lambda_{\text{max}, Z}$ (nm)	n.a. ^a	n.a. ^a	561
ϵ_E ($\text{M}^{-1} \text{cm}^{-1}$)	16700	10800	15700
$t_{1/2}$	<5 s	<5 s	2.8 min
Z-content PSS	n.a. ^a	n.a. ^a	77%
ϕ_{E-Z} (578 nm)	n.a. ^a	n.a. ^a	0.06 ^b
ϕ_{Z-E} (578 nm)	n.a. ^a	n.a. ^a	0.60 ^b

^aNot available due to extremely short lifetime of Z-isomer.
^bDetermined at 25°C .

literature,¹¹ *N,N'*-dimethylindigo 2 and *N,N'*-dibenzylindigo 3 are among the most red-shifted compounds examined in this study, whereas in the case of *N,N'*-di(benzyloxycarbonylmethyl)indigo 4 (Figure 1), the presence of electron-withdrawing ester groups causes a slight blue shift by 20 nm. Upon irradiation with a red LED (660 nm, 20 nm full width at half-maximum (fwhm)), the intensity of the long-wavelength absorption band decreased, and a shoulder below 600 nm started to rise. When the light was turned off, 2 and 3 returned

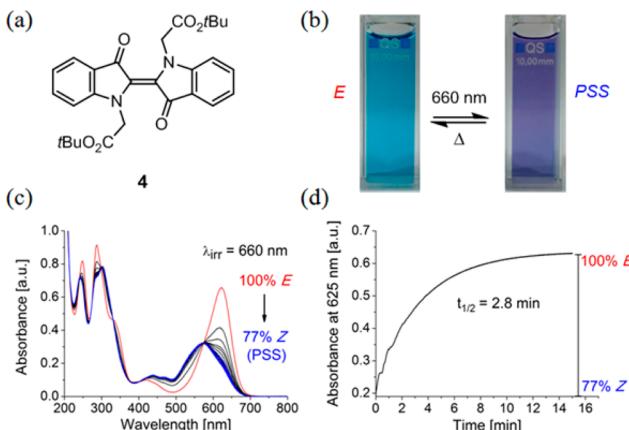
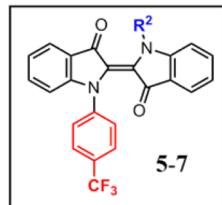


Figure 1. Photochromic and thermal behavior of indigo 4. (a) Chemical structure. (b) Photographs of *E*-4 and PSS-4 solutions in CH₃CN. (c) Evolution of the PSS upon irradiation with 660 nm LED with spectra taken every 30 s over 10 min at 25 °C (4.2 × 10⁻⁵ M in CH₃CN). (d) Thermal recovery at 25 °C monitored by absorbance at 625 nm in the dark.

to their initial state immediately, whereas **4** showed a slower recovery with a thermal half-life ($t_{1/2}$) of 2.8 min at room temperature (see Figure 1c, d for a representative photochemical forward and thermal back isomerization). The fact that these indigo photoswitches exhibit negative photochromism allowed us to obtain the composition of the photostationary state (PSS) and the absorption spectrum of the pure Z-isomer directly from the *E* and PSS spectra (see Section III of the Supporting Information). Applying this methodology, we found that the absorption maxima of *E*-4 and Z-4 are well separated ($\Delta\lambda_{\text{max}} = 62$ nm).

Next, we turned our attention to nonsymmetrical indigos substituted with one aryl and one alkyl group each. First, we compared series II, in which the aryl moiety (4-trifluoromethylphenyl) was kept constant and the alkyl group was varied (Table 2). Similar to what we observed in *N,N'*-dialkylindigos, the presence of the electron-withdrawing ester group in **6** causes a slight blue shift and an increased thermal half-life of

Table 2. Photochemical Properties of Series II in CH₃CN



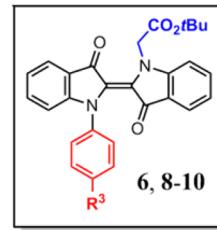
series II: R ² =		
Me (5)	CH ₂ CO ₂ tBu (6)	Boc (7)
$\lambda_{\text{max}, E}$ (nm)	635	622
$\lambda_{\text{max}, Z}$ (nm)	595	572
ϵ_E (M ⁻¹ cm ⁻¹)	13000	13200
$t_{1/2}$	57 s	3.5 min
Z-content PSS	38%	56%
ϕ_{E-Z}^{a}	0.04	0.03
ϕ_{Z-E}^{a}	0.04	0.03

^aDetermined at -5 °C and 578 nm (see Supporting Information for full details).

the Z-isomer. However, in compound **7**, where the *tert*-butyloxycarbonyl group is attached directly to the indigo N-atom, a much larger blue shift as well as a much longer thermal half-life was observed. These findings are in line with the behavior of *N,N'*-diacyl¹⁰ and *N,N'*-di(*tert*-butyloxy-carbonyl)¹² indigos, in which the electron-withdrawing carbonyl-based N-substituents result in thermally much more stable Z-isomers and yet inevitable significantly blue-shifted absorption spectra, rendering them no longer suitable for operation using red light. In order to overcome this problem, we subsequently decided to explore substituent effects on the N-aryl rings.

In series III we therefore fixed the CH₂CO₂tBu as the alkyl group and studied the electronic effect of *para*-substituents on the aryl ring (Table 3). We found that the nature of the

Table 3. Photochemical Properties of Series III in CH₃CN



series III: R ³ =			
OMe (8)	H (9)	CF ₃ (6)	CN (10)
$\lambda_{\text{max}, E}$ (nm)	633	629	622
$\lambda_{\text{max}, Z}$ (nm)	593	578	572
ϵ_E (M ⁻¹ cm ⁻¹)	13500	11900	13200
$t_{1/2}$	59 s	1.9 min	3.5 min
Z-content PSS	11%	62%	56%
ϕ_{E-Z}^{a}	0.05	0.01	0.03
ϕ_{Z-E}^{a}	0.04	0.10	0.03

^aDetermined at -5 °C and 578 nm (see Supporting Information for full details).

substituents does not have a large influence on the absorption maximum of the *E*-isomer, which for the entire series remains in the red domain (623 ≤ λ_{max} ≤ 633 nm). Introduction of electron-withdrawing substituent leads to an increased spectral separation of the absorption maxima of *E*- and Z-isomers. In addition, we observed a sixfold increase in thermal half-life when changing from an electron-donating methoxy (**8**) to an electron-withdrawing cyano group (**10**). Thus, in acceptor-substituted indigo **10**, both enhanced spectral separation and thermal lifetime lead to a much larger Z-content in the PSS as compared to indigo **8**. More importantly, this finding demonstrates that the thermal half-life of indigo photoswitches can indeed be tuned independently from their absorption spectra by proper structural modification and encouraged us to pursue *N,N'*-arylated indigo derivatives.

Utilizing the synthetic methods developed by us for indigo *N*-arylation, we finally prepared two series of symmetrically as well as nonsymmetrically substituted *N,N'*-diaryl indigos (series IV and V). To our surprise, NMR analysis for these compounds revealed that they all exist as a mixture of *E*- and Z-isomers. Typically, we observe an *E/Z* ratio between 2:1 and 3:1 in CD₂Cl₂ (see Section VIII of the Supporting Information). The existence of such mixtures in the dark state implies that the stability of both isomers is rather comparable and that the separating barrier allows for thermal isomerization (in both

directions) at room temperature. DFT-computed relative free energies of the two isomers (see Table S1 in the *Supporting Information*) confirm that the bis-arylated indigos exhibit negligible ground-state energy differences between the two isomers. Indeed, we determined free energy differences smaller than 1 kcal/mol between the *Z*- and *E*-isomers of **11–18**, a value which is within the typical DFT error bar, indicating nearly isoenergetic structures. A possible explanation involves attractive π – π interactions between the two aryl moieties in the *Z*-isomer on the one hand and repulsive interactions between the aryl moiety and the indigo carbonyl group in the *E*-isomer on the other hand. Both of these interactions are plausible by comparing the molecular structures (**Figure 2** for *E*-**12** vs *Z*-**12**), obtained by single-crystal X-ray diffraction and quantum chemical calculation (see Table S2 of the *Supporting Information*).

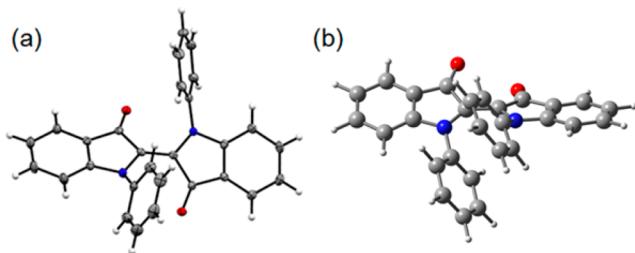


Figure 2. (a) X-ray structure of *E*-**12** (50% probability ellipsoids). (b) DFT-computed structure of *Z*-**12** (for details see Section XII of the *Supporting Information*).

Irradiating these *N,N'*-diaryl indigos with a red LED (660 nm, fwhm = 20 nm) led to a different *E/Z* ratio in the PSS. Based on ^{19}F -NMR spectroscopy, compound **14** went from a dark mixture containing 26% *Z*-isomer to a solution containing 81% *Z*-isomer in the PSS at room temperature, and when this sample was left in the dark, it returned to the initial *E/Z* mixture (**Figure 3** and *Supporting Information*). Initial cycling experiments with compound **12** indicated a robust switching process without noticeable fatigue (see Section XI in the *Supporting Information*).

Subsequently, we analyzed the kinetics of the thermal back reaction.¹⁹ To describe the time required for returning from the

PSS to the thermodynamic equilibrium in the dark, we introduce here the term “equilibration thermal half-life $t(\text{eq})_{1/2}$ ”. Following the recovery of absorbance at 620 nm, $t(\text{eq})_{1/2}$ was obtained for each compound (Table 4). A clear trend of how the substitution pattern influences $t(\text{eq})_{1/2}$ was observed as increasingly electron-withdrawing groups result in longer $t(\text{eq})_{1/2}$, spanning a range from 58 s for OMe (**11**) to 408 min for NO₂ (**16**). Importantly, this dramatic difference in the rate of thermal recovery is accompanied by negligible changes in the absorption maxima (λ_{max}) of the molecules, which remain red-shifted regardless of their substitution, and thus a red LED (660 nm, fwhm = 20 nm) was utilized in all cases to successfully induce the photoisomerization.

The observed correlation between the *N*-aryl substituents and thermal half-lives led us to further investigate the process of thermal relaxation. Comparing the compounds from series III through V, it appears that in general *N*-arylation seems to stabilize the *Z*-isomer relative to the *E*-isomer while at the same time the transition state (TS) does not seem to be affected, leading to a net increase of the thermal barrier. This is reflected by the analysis of our kinetic data that shows a linear correlation between the rate constants for thermal equilibration and Hammett's substituent parameters²⁰ for both series III and IV (**Figure 4** and Section VIII of the *Supporting Information*). In both cases the slope is clearly negative, indicating that electron-deficient aryl moieties, in particular when attached to both indigo *N*-atoms, slow down thermal return from the photostationary to the dark state.

We performed broken-symmetry density functional theory (BS-DFT) calculations aiming to determine and characterize the TS for all dyes of series IV and V (see Section XII of the *Supporting Information*). The obtained TS geometries exhibit a dihedral angle close to 90° between the two halves of the molecules, and the associated imaginary frequency is close to 50*i* cm⁻¹ (**Figure 5b**). Gratifyingly, the correlation found between our experimental and theoretical data is remarkable ($R^2 = 0.97$, **Figure 5a**), confirming the accuracy of our computational model and thus providing a solid foundation and encouraging prospect to design indigo derivatives with improved thermal stability. More detailed analysis of the TS (see Section XII of the *Supporting Information*) indicates that the largest spin density of the unpaired electron on each side is located on each of the neighboring bridging carbon atoms (ca. 0.5 e) whereas the spin density borne by the oxygen atoms is smaller (ca. 0.3 e). In addition, the Mulliken electronic charges borne by the oxygen atoms are only marginally larger in the TS (ca. -0.6 e) as compared to the *Z*- and *E*-isomers (ca. -0.5 e). These findings are in agreement with a predominant biradical character of the TS.^{10h}

We have also characterized the derivatives of series IV and V using time-dependent DFT. The theoretically predicted absorption maxima (see Table S3 of the *Supporting Information*) are well in line with the experimentally observed values for both *Z*- and *E*-isomers. As expected, the absorption maxima of all compounds and isomers are related to the lowest excited state, which can be assigned to a HOMO → LUMO transition. These frontier orbitals are centered on the H-chromophore of the indigo core (**Figure 5c, d**), and the aryl substituents contribute only little, explaining the relatively small variations of the absorption spectra (see Table 4). This decoupling of the aryl units is due to their almost perpendicular orientation relative to the plane of the indigo. Consequently, these groups can influence the central chromophore only via an

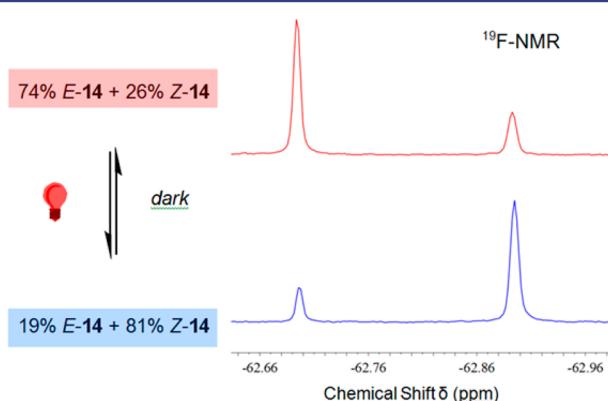


Figure 3. ^{19}F -NMR spectra of dark vs irradiated indigo **14**. Thermally equilibrated *E/Z* mixture of **14** (ca. 10⁻⁴ M in CD₃CN) in the dark (top) and after irradiation with 660 nm LED for 3 h at 25 °C (bottom). The initial spectrum (top) is recovered in the dark overnight (see *Supporting Information* for ^1H - and 2D NMR spectra).

Table 4. Photochemical Properties of Series IV and V in CH₃CN

	series IV: R ⁴ =						series V: R ⁵ =	
	OMe (11)	H (12)	F (13)	CF ₃ (14)	CN (15)	NO ₂ (16)	OMe (17)	F (18)
$\lambda_{\max, E}$ (nm)	645	635	630	621	619	620	632	624
$\lambda_{\max, Z}$ (nm)	599	594	584	577	568	577	590	582
Z-content dark	33%	24%	34%	27%	25%	12%	39%	33%
$t(\text{eq})_{1/2}$	58 s	3.1 min	7.9 min	81 min	187 min	408 min	13 min	19 min
Z-content PSS	52%	64%	71%	83%	80%	82%	67%	76%
ϕ_{E-Z}^{a}	n.d. ^b	n.d. ^b	0.13	0.06	0.06	0.07	0.36	0.15
ϕ_{Z-E}^{a}	n.d. ^b	n.d. ^b	0.08	0.04	0.03	0.04	0.08	0.08

^aDetermined at 25 °C and 578 nm (except for 17 at 546 nm; see Supporting Information for full details). ^bNot determined due to short lifetime of Z-isomer.

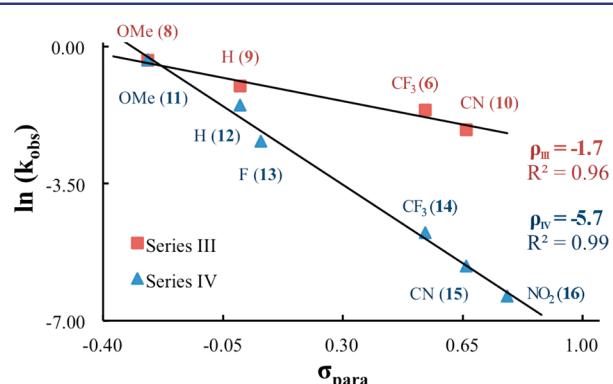


Figure 4. Hammett plots of the rate of thermal equilibration (from the PSS to the dark state) for indigo series III and IV.

inductive effect, in contrast to the carbonyl-based N-substituents, such as in 7, where resonance effects predominate, resulting in more stable Z-isomers yet significantly blue-shifted absorption spectra of the E-isomers.

An important merit of indigo photoswitches is their superior ability to change the distance between two functional motifs by light. A closer examination of both the DFT-optimized E- and Z-isomers of indigos 4, 6, and 12 revealed that during the course of photoisomerization a change of distance between the two substituents of 2.7, 3.8, and 3.5 Å, respectively, can be achieved (see Table S2 in the Supporting Information), which is, for the arylated indigos, slightly superior to the ca. 3 Å change that is generally exerted by azobenzenes. This finding demonstrates the potential of indigos to serve as superior steric switch. Furthermore, DFT calculations indicate that E-Z photoisomerization is able to induce significant changes in dipole moment of up to 7 D between the two isomers (see Table S1 in the Supporting Information).

CONCLUSION

In conclusion, we have revisited the classical indigo chromophore motif and developed a strategy to tune the

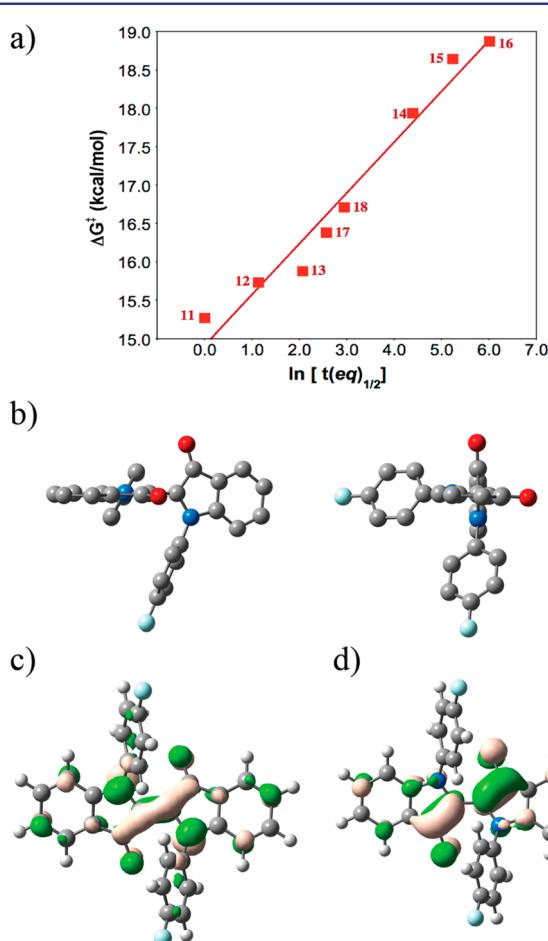


Figure 5. (a) Correlation between the experimentally determined $\ln(t(\text{eq})_{1/2})$ given in Table 4 and the PCM-(BS-)PBE0-D3^{BJ}/6-31G(d) computed free energy of the TS with respect to the Z-isomer (ΔG^\ddagger). (b) Two views of the TS obtained for 13 (H-atoms omitted for clarity). (c) HOMO of E-13. (d) LUMO of E-13 (contour threshold: 0.04 au).

thermal stability of the Z-isomers independently from the advantageous optical spectra. The introduction of electron-withdrawing N-aryl substituents has proven key to achieve sufficiently long thermal half-lives of the Z-isomers, which are attractive for biomedical applications, while maintaining the compounds' absorption in the red and hence photoisomerization ability with 660 nm light. In contrast to previously reported amide-containing indigos,^{10,12} the new indigo derivatives display excellent hydrolytic stability in aqueous solutions containing acetonitrile to facilitate solubility. Using a combined experimental and theoretical approach, we have gained general insight into the factors determining the thermal stability of the indigo isomers and their electronic and geometrical structure, encoding both their optical properties and activity differences. The latter are expected to be significant due to large geometry changes during photoisomerization and promise that indigos might indeed perform as superior steric photoswitches. Thus, our work introduces an exciting new generation of indigo derivatives, which are readily derived from one of the cheapest and most abundant dyes on the planet and which should greatly expand the tool box available to researchers, pursuing to exploit photoswitches in future life and material science applications.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: [10.1021/jacs.7b08726](https://doi.org/10.1021/jacs.7b08726).

Experimental details including synthetic procedures, compound characterization data, and photochemical and kinetic experiments, computational details ([PDF](#))
Crystallographic data ([CIF](#))

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Notes

The authors declare no competing financial interest.

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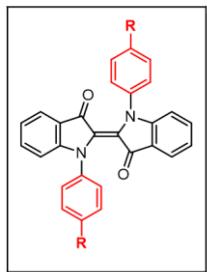
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1. Read the molecular structures and identify the varying moieties

The molecules shown below are indigo compounds with aryl groups attached to N (nitrogen) atoms. These compounds are photoswitches that can undergo photoisomerization between E- and Z-configuration. The structures of N-substituents can influence the rate of thermal back-reaction (from Z- to E-isomers). In particular, compounds in this series only differ by the group attached at the para-position of N-aryl substituents. The identity of these para-groups will influence the electronic properties of N-aryl groups and thus the rate of thermal back-reactions.



2. Go to the Hammett table and extract the relevant σ -values

The influence of para-groups on the electronic properties of N-aryl substituents can be quantitatively represented by the σ_p values in linear free energy analysis, or Hammett plot analysis. The σ values have been tabulated in a comprehensive review (Table 1, <https://pubs.acs.org/doi/10.1021/cr00002a004>).

TABLE I (Continued)

	substituent	σ_m	σ_p
78.	SO_2CF_3	0.83	0.96
79.	SeO_2CF_3	1.08	1.21
80.	OSO_2CF_3	0.56	0.53
81.	SCF_3	0.40	0.50
82.	SeCF_3	0.44	0.45
83.	HgCN	0.28	0.34
84.	CN	0.56	0.66
85.	NC	0.48	0.49
86.	$\text{CN}(\text{BBr}_3)$	0.61	0.48
87.	$\text{CN}(\text{BCl}_3)$	0.95	0.86
88.	$\text{CN}(\text{BF}_3)$	0.72	0.66
89.	$\text{N}=\text{C}=\text{O}$	0.27	0.19
90.	OCN	0.67	0.54
91.	SO_2CN	1.10	1.26
92.	$\text{N}=\text{C}=\text{S}$	0.48	0.38
93.	SCN	0.51	0.52
94.	SeCN	0.61	0.66
95.	$\text{N}=\text{NCN}$	0.71	1.03
96.	$\text{N}(\text{O})=\text{NCN}$	0.78	0.89
97.	$\text{C}(\text{NO}_2)_3$	0.72	0.82
98.	5-azido-1-tetrazolyl	0.54	0.54
99.	CO_2^-	-0.10	0.00
100.	CHBr_2	0.31	0.32
101.	CHCl_2	0.31	0.32
102.	OCHCl_2	0.38	0.26
103.	CHF_2	0.29	0.32

3. Understand the table containing properties of interest

The below table shows the properties of these indigo compounds. Specifically, we are interested in the rate of thermal back-reaction, as represented by the thermal half-life, $t(\text{eq})_{1/2}$. The rate constant of this reaction, k (or k_{obs}), can be used to calculate the thermal half-life, where $t(\text{eq})_{1/2} = (\ln 2)/k$.

Table 4. Photochemical Properties of Series IV and V in CH_3CN

	series IV: $\text{R}^4 =$						series V: $\text{R}^5 =$	
	OMe (11)	H (12)	F (13)	CF_3 (14)	CN (15)	NO_2 (16)	OMe (17)	F (18)
$\lambda_{\text{max}, E}$ (nm)	645	635	630	621	619	620	632	624
$\lambda_{\text{max}, Z}$ (nm)	599	594	584	577	568	577	590	582
Z-content dark	33%	24%	34%	27%	25%	12%	39%	33%
$t(\text{eq})_{1/2}$	58 s	3.1 min	7.9 min	81 min	187 min	408 min	13 min	19 min
Z-content PSS	52%	64%	71%	83%	80%	82%	67%	76%
ϕ_{E-Z}^a	n.d. ^b	n.d. ^b	0.13	0.06	0.06	0.07	0.36	0.15
ϕ_{Z-E}^a	n.d. ^b	n.d. ^b	0.08	0.04	0.03	0.04	0.08	0.08

^aDetermined at 25 °C and 578 nm (except for 17 at 546 nm; see Supporting Information for full details). ^bNot determined due to short lifetime of Z-isomer.

4. Understand the Hammett plot

We can then make connection between the electronic properties of N-aryl groups to the rate of thermal back-reactions. For example, compound 15, where a cyano group (CN) is attached at the para position, has a half-life of 187 min (Table 4). From the table of σ values, we can find the σ_p (or σ_{para}) for CN is 0.66. This analysis can be carried out for the entire series of compounds, and the relationship between σ_{para} and $\ln(k_{\text{obs}})$ can be plotted. As can be seen from the figure below, there is a linear correlation between these two parameters, where larger σ_{para} results in smaller $\ln(k_{\text{obs}})$, which means slower thermal back-reaction.

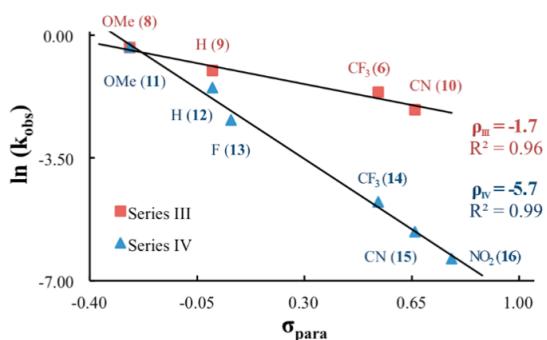
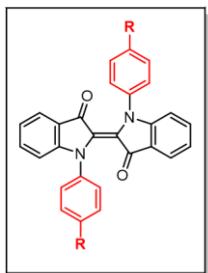


Figure 4. Hammett plots of the rate of thermal equilibration (from the PSS to the dark state) for indigo series III and IV.

5. Use the Hammett plot and σ -values to predict the properties of new molecules

Finally, based on the above linear relationship, we can predict the thermal back-reaction rates for new compounds. First, the structure of indigo compound is analyzed, and the para-group of the N-substituent is identified. Then the σ -value of this particular group is fetched from the table. Plugging this number into the linear regression model will yield the predicted $\ln(k_{\text{obs}})$, which can be used to calculate the corresponding predicted $t(\text{eq})_{1/2}$.





Hammett equation

In organic chemistry, the **Hammett equation** describes a linear free-energy relationship relating reaction rates and equilibrium constants for many reactions involving benzoic acid derivatives with meta- and para-substituents to each other with just two parameters: a substituent constant and a reaction constant.^{[1][2]} This equation was developed and published by Louis Plack Hammett in 1937^[3] as a follow-up to qualitative observations in his 1935 publication.^[4]

The basic idea is that for any two reactions with two aromatic reactants only differing in the type of substituent, the change in free energy of activation is proportional to the change in Gibbs free energy.^[5] This notion does not follow from elemental thermochemistry or chemical kinetics and was introduced by Hammett intuitively.^[a]

The basic equation is:

$$\log \frac{K}{K_0} = \sigma \rho$$

where

K_0 = Reference constant

σ = Substituent constant

ρ = Reaction rate constant

relating the equilibrium constant, K , for a given equilibrium reaction with substituent R and the **reference constant** K_0 when R is a hydrogen atom to the **substituent constant** σ which depends only on the specific substituent R and the **reaction rate constant** ρ which depends only on the type of reaction but not on the substituent used.^{[4][3]}

The equation also holds for reaction rates k of a series of reactions with substituted benzene derivatives:

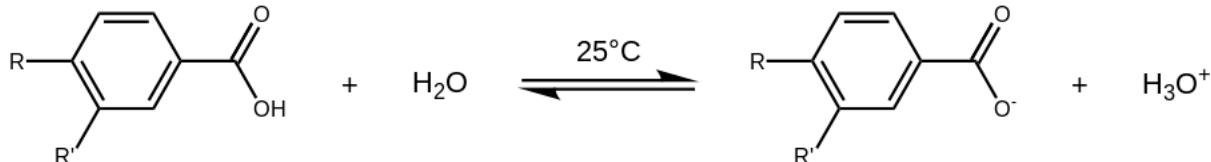
$$\log \frac{k}{k_0} = \sigma \rho$$

In this equation k_0 is the reference reaction rate of the unsubstituted reactant, and k that of a substituted reactant.

A plot of $\log \frac{K}{K_0}$ for a given equilibrium versus $\log \frac{k}{k_0}$ for a given reaction rate with many differently substituted reactants will give a straight line.

Substituent constants

The starting point for the collection of the substituent constants is a chemical equilibrium for which the substituent constant is arbitrarily set to 0 and the reaction constant is set to 1: the deprotonation of benzoic acid or benzene carboxylic acid (R and R' both H) in water at 25 °C.



Substituent constants: *para* and *meta* substituted benzene rings.^{[3][6]}

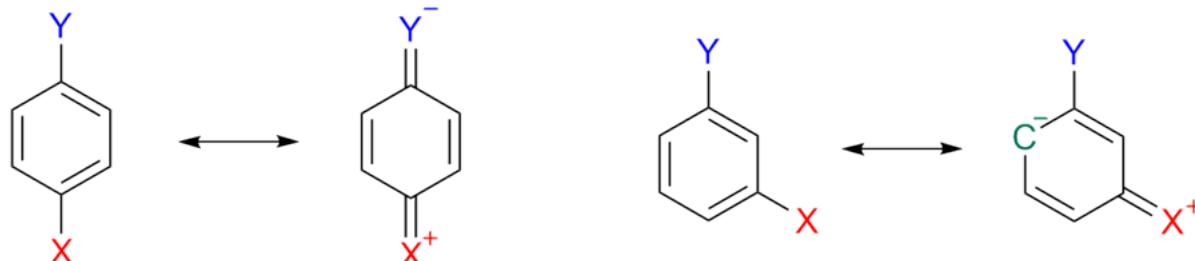
Having obtained a value for K_o , a series of equilibrium constants (K) are now determined based on the same process, but now with variation of the *para* substituent—for instance, p-hydroxybenzoic acid ($R=OH$, $R'=H$) or p-aminobenzoic acid ($R=NH_2$, $R'=H$). These values, combined in the Hammett equation with K_o and remembering that $\rho = 1$, give the ***para* substituent constants** compiled in table 1 for amine, methoxy, ethoxy, dimethylamino, methyl, fluorine, bromine, chlorine, iodine, nitro and cyano substituents. Repeating the process with *meta*-substituents afford the ***meta* substituent constants**. This treatment does not include ortho-substituents, which would introduce steric effects.

The σ values displayed in the Table above reveal certain substituent effects. With $\rho = 1$, the group of substituents with increasing positive values—notably cyano and nitro—cause the equilibrium constant to increase compared to the hydrogen reference, meaning that the acidity of the carboxylic acid (depicted on the left of the equation) has increased. These substituents stabilize the negative charge on the carboxylate oxygen atom by an electron-withdrawing inductive effect (-I) and also by a negative mesomeric effect (-M).

Substituent	<i>para</i> - effect	<i>meta</i> - effect
Dimethylamino	-0.83	-0.211
Amino	-0.66	-0.161
Butylamino	-0.51	-0.34
Hydroxy	-0.37	+0.12
Methoxy	-0.268	+0.115
Ethoxy	-0.25	+0.015
Methyl	-0.170	-0.069
Trimethylsilyl	-0.07	-0.04
None	0.000	0.000
Fluoro	+0.062	+0.337
Chloro	+0.227	+0.373
Bromo	+0.232	+0.393
Iodo	+0.276	+0.353
Ethoxycarbonyl	+0.45	+0.37
Trifluoromethyl	+0.54	+0.43
Cyano	+0.66	+0.56
Nitro	+0.778	+0.710

The next set of substituents are the halogens, for which the substituent effect is still positive but much more modest. The reason for this is that while the inductive effect is still negative, the mesomeric effect is positive, causing partial cancellation. The data also show that for these substituents, the *meta* effect is much larger than the *para* effect, due to the fact that the mesomeric effect is greatly reduced in a *meta* substituent. With *meta* substituents a carbon atom bearing the negative charge is further away from the carboxylic acid group (structure 2b).

This effect is depicted in *scheme 3*, where, in a *para* substituted arene **1a**, one resonance structure **1b** is a quinoid with positive charge on the X substituent, releasing electrons and thus destabilizing the Y substituent. This destabilizing effect is not possible when X has a *meta* orientation.



Other substituents, like methoxy and ethoxy, can even have opposite signs for the substituent constant as a result of opposing inductive and mesomeric effect. Only alkyl and aryl substituents like methyl are electron-releasing in both respects.

Of course, when the sign for the reaction constant is negative (next section), only substituents with a likewise negative substituent constant will increase equilibrium constants.

The σ_p^- and σ_p^+ constants

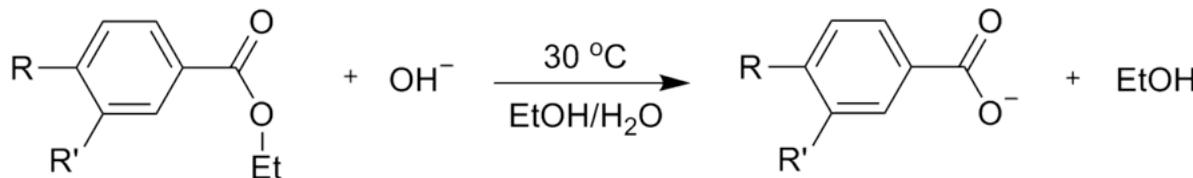
Because the carbonyl group is unable to serve a source of electrons for $-M$ groups (in contrast to lone pair donors like OH), for reactions involving phenol and aniline starting materials, the σ_p values for electron-withdrawing groups will appear too small. For reactions where resonance effects are expected to have a major impact, a modified parameter, and a modified set of σ_p^- constants may give a better fit. This parameter is defined using the ionization constants of *para* substituted phenols, via a scaling factor to match up the values of σ_p^- with those of σ_p for "non-anomalous" substituents, so as to maintain comparable ρ values: for $\text{ArOH} \rightleftharpoons \text{ArO}^- + \text{H}^+$, we define $\sigma_p^- = \frac{1}{2.11} \log_{10} \left(\frac{K_x}{K_H} \right)$.

Likewise, the carbonyl carbon of a benzoic acid is at a nodal position and unable to serve as a sink for $+M$ groups (in contrast to a carbocation at the benzylic position). Thus for reactions involving carbocations at the α -position, the σ_p values for electron-donating groups will appear insufficiently negative. Based on similar considerations, a set of σ_p^+ constants give better fit for reactions involving electron-donating groups at the *para* position and the formation of a carbocation at the benzylic site. The σ_p^+ are based on the rate constants of the S_N1 reaction of cumyl chlorides in 90% acetone/water: for $\text{ArCMe}_2\text{Cl} + \text{H}_2\text{O} \rightarrow \text{ArCMe}_2\text{OH} + \text{HCl}$, we define $\sigma_p^+ = -\frac{1}{4.54} \log_{10} \left(\frac{k_x}{k_H} \right)$.

Note that the scaling factor is negative, since an electron-donating group speeds up the reaction. For a reaction whose Hammett plot is being constructed, these alternative Hammett constants may need to be tested to see if a better linearity could be obtained.

Rho value

With knowledge of substituent constants it is now possible to obtain reaction constants for a wide range of organic reactions. The archetypal reaction is the alkaline hydrolysis of ethyl benzoate ($\text{R}=\text{R}'=\text{H}$) in a water/ethanol mixture at 30°C . Measurement of the reaction rate k_0 combined with that of many substituted ethyl benzoates ultimately result in a reaction constant of $+2.498$.^[3]



Reaction constants are known for many other reactions and equilibria. Here is a selection of those provided by Hammett himself (with their values in parentheses):

- the hydrolysis of substituted cinnamic acid ester in ethanol/water ($+1.267$)
- the ionization of substituted phenols in water ($+2.008$)
- the acid catalyzed esterification of substituted benzoic esters in ethanol (-0.085)

- the acid catalyzed bromination of substituted acetophenones (Ketone halogenation) in an acetic acid/water/hydrochloric acid (+0.417)
- the hydrolysis of substituted benzyl chlorides in acetone-water at 69.8 °C (-1.875).

The reaction constant, or sensitivity constant, ρ , describes the susceptibility of the reaction to substituents, compared to the ionization of benzoic acid. It is equivalent to the slope of the Hammett plot. Information on the reaction and the associated mechanism can be obtained based on the value obtained for ρ . If the value of:

1. $\rho > 1$, the reaction is more sensitive to substituents than benzoic acid and negative charge is built during the reaction (or positive charge is lost).
2. $0 < \rho < 1$, the reaction is less sensitive to substituents than benzoic acid and negative charge is built (or positive charge is lost).
3. $\rho = 0$, no sensitivity to substituents, and no charge is built or lost.
4. $\rho < 0$, the reaction builds positive charge (or loses negative charge).

These relations can be exploited to elucidate the mechanism of a reaction. As the value of ρ is related to the charge during the rate determining step, mechanisms can be devised based on this information. If the mechanism for the reaction of an aromatic compound is thought to occur through one of two mechanisms, the compound can be modified with substituents with different σ values and kinetic measurements taken. Once these measurements have been made, a Hammett plot can be constructed to determine the value of ρ . If one of these mechanisms involves the formation of charge, this can be verified based on the ρ value. Conversely, if the Hammett plot shows that no charge is developed, i.e. a zero slope, the mechanism involving the building of charge can be discarded.

Hammett plots may not always be perfectly linear. For instance, a curve may show a sudden change in slope, or ρ value. In such a case, it is likely that the mechanism of the reaction changes upon adding a different substituent. Other deviations from linearity may be due to a change in the position of the transition state. In such a situation, certain substituents may cause the transition state to appear earlier (or later) in the reaction mechanism.^[7]

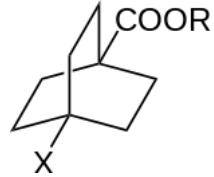
Dominating electronic effects

3 kinds of ground state or *static* electrical influences predominate:

- Resonance (mesomeric) effect
- Inductive effect: electrical influence of a group which is transmitted primarily by polarization of the bonding electrons from one atom to the next
- Direct electrostatic (field) effect: electrical influence of a polar or dipolar substituent which is transmitted primarily to the reactive group through space (including solvent, if any) according to the laws of classical electrostatics

The latter two influences are often treated together as a composite effect, but are treated here separately. Westheimer demonstrated that the electrical effects of π -substituted dipolar groups on the acidities of benzoic and phenylacetic acids can be quantitatively correlated, by assuming only direct electrostatic action of the substituent on the ionizable proton of the carboxyl group. Westheimer's treatment worked well except for those acids with substituents that have unshared electron pairs such as $-\text{OH}$ and $-\text{OCH}_3$, as these substituents interact strongly with the benzene ring.^{[8][9]}

Roberts and Moreland studied the reactivities of 4-substituted bicyclo[2.2.2]octane-1-carboxylic acids and esters. In such a molecule, transmission of electrical effects of substituents through the ring by resonance is not possible. Hence, this hints on the role of the π -electrons in the transmission of substituent effects through aromatic systems.^[10]



Reactivity of 4-substituted bicyclo[2.2.2]octane-1-carboxylic acids and esters were measured in 3 different processes, each of which had been previously used with the benzoic acid derivatives. A plot of $\log(k)$ against $\log(K_A)$ showed a linear relationship. Such linear relationships correspond to linear free energy relationships, which strongly imply that the effect of the substituents are exerted through changes of potential energy and that the steric and entropy terms remain almost constant through the series. The linear relationship fit well in the Hammett Equation. For the 4-substituted bicyclo[2.2.2]octane-1-carboxylic acid derivatives, the substituent and reaction constants are designated σ' and ρ' .

Comparison of ρ and ρ'

Reactivity data indicate that the effects of substituent groups in determining the reactivities of substituted benzoic and bicyclo[2.2.2]-octane-1-carboxylic acids are comparable. This implies that the aromatic π -electrons do not play a dominant role in the transmission of electrical effects of dipolar groups to the ionizable carboxyl group. Difference between ρ and ρ' for the reactions of the acids with diphenylazomethane is probably due to an inverse relation to the solvent dielectric constant D^e .

Reaction	ρ'	ρ	D^e
Ionization of acids	1.464	1.464	54
Alkaline hydrolysis of ethyl esters	2.24	2.494	28
Acids with diphenylazomethane	0.698	0.937	24

Comparison of σ and σ'

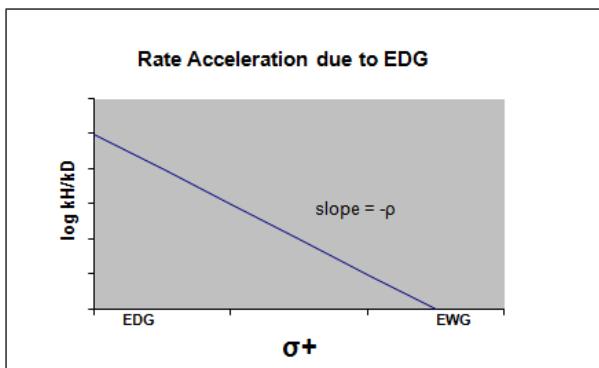
Substituent	σ'	σ_{para}^c	σ_{meta}^c	$\sigma_{\text{para}} - \sigma'$	$\sigma_{\text{meta}} - \sigma'$
H	0	0	0	0	0
OH	0.283	-0.341	0.014	-0.624	-0.269
$\text{CO}_2\text{C}_2\text{H}_5$	0.297	0.402	0.334	0.105	0.037
Br	0.454	0.232	0.391	-0.222	-0.063
CN	0.579	0.656	0.608	0.077	0.029

For meta-directing groups (electron withdrawing group or EWG), σ_{meta} and σ_{para} are more positive than σ' . (The superscript, c, in table denotes data from Hammett, 1940.^[11]) For ortho-para directing groups (electron donating group or EDG), σ' more positive than σ_{meta} and σ_{para} . The difference between σ_{para} and σ' ($\sigma_{\text{para}} - \sigma'$) is greater than that between σ_{meta} and σ' ($\sigma_{\text{meta}} - \sigma'$). This is expected as electron resonance effects are felt more strongly at the p-positions. The $(\sigma - \sigma')$ values can be taken as a reasonable measurement of the resonance effects.

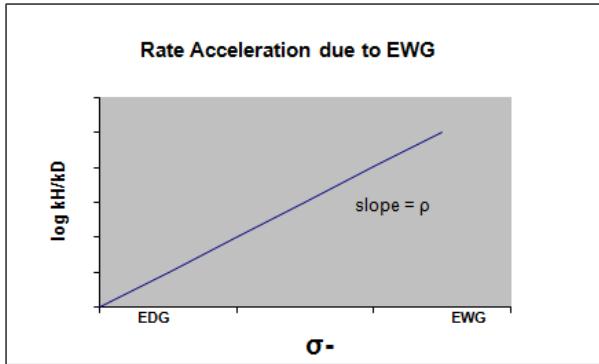
Nonlinearity

The plot of the Hammett equation is typically seen as being linear, with either a positive or negative slope correlating to the value of rho. However, nonlinearity emerges in the Hammett plot when a substituent affects the rate of reaction or changes the rate-determining step or reaction

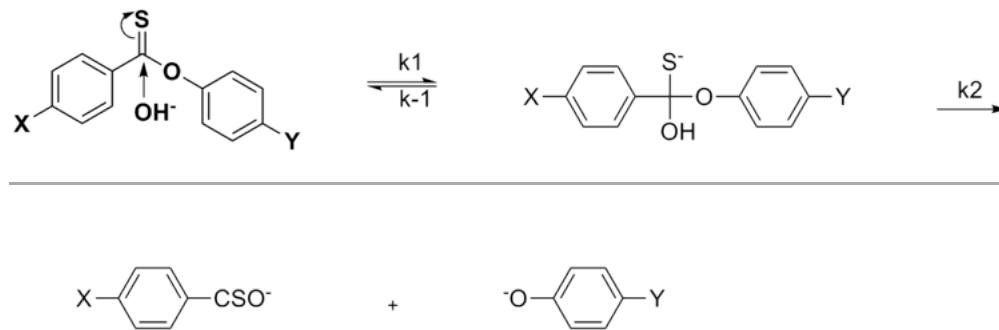
mechanism of the reaction. For the reason of the former case, new sigma constants have been introduced to accommodate the deviation from linearity otherwise seen resulting from the effect of the substituent. σ_+ takes into account positive charge buildup occurring in the transition state of the reaction. Therefore, an electron donating group (EDG) will accelerate the rate of the reaction by resonance stabilization and will give the following sigma plot with a negative rho value.^[12]



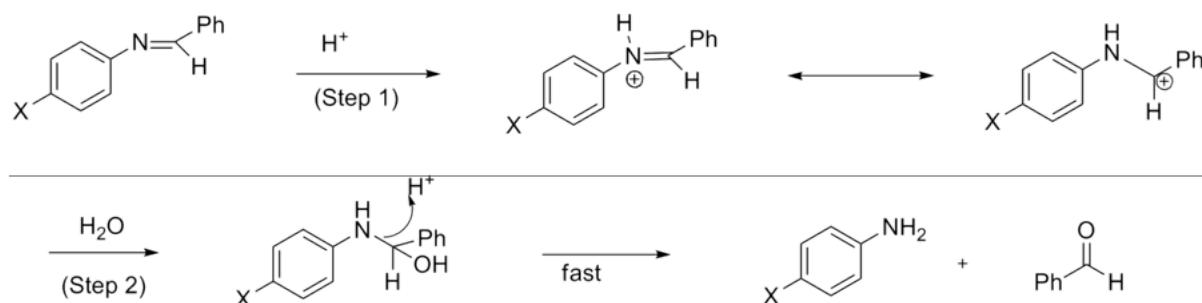
σ_- is designated in the case where negative charge buildup in the transition state occurs, and the rate of the reaction is consequently accelerated by electron withdrawing groups (EWG). The EWG withdraws electron density by resonance and effectively stabilizes the negative charge that is generated. The corresponding plot will show a positive rho value.



In the case of a nucleophilic acyl substitution the effect of the substituent, X, of the non-leaving group can in fact accelerate the rate of the nucleophilic addition reaction when X is an EWG. This is attributed to the resonance contribution of the EWG to withdraw electron density thereby increasing the susceptibility for nucleophilic attack on the carbonyl carbon. A change in rate occurs when X is EDG, as is evidenced when comparing the rates between X = Me and X = OMe, and nonlinearity is observed in the Hammett plot.^[13]



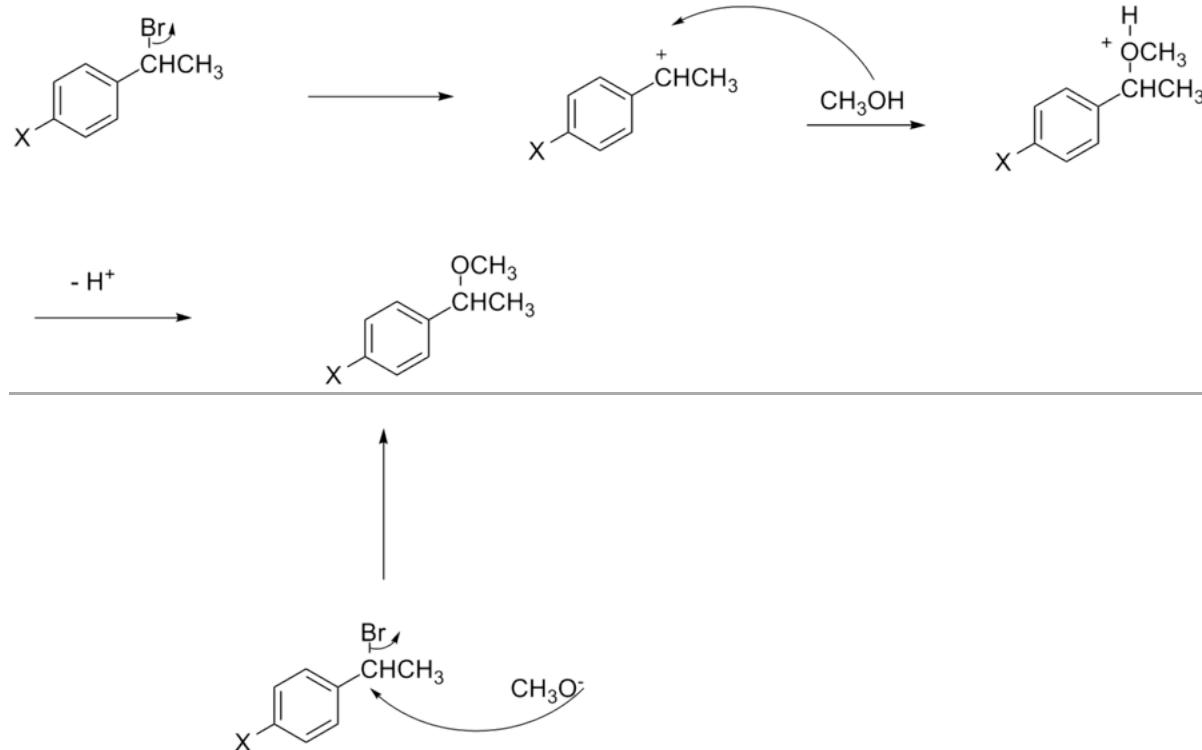
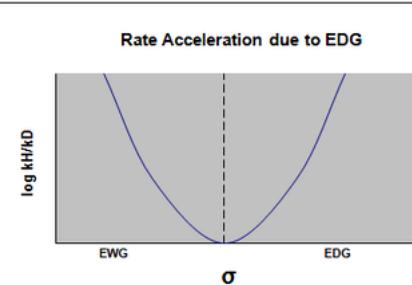
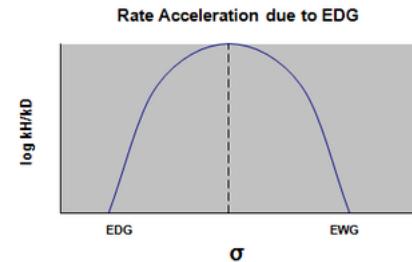
The effect of the substituent may change the rate-determining step (rds) in the mechanism of the reaction. A certain electronic effect may accelerate a certain step so that it is no longer the rds.^[14]



A change in the mechanism of a reaction also results in nonlinearity in the Hammett plot. Typically, the model used for measuring the changes in rate in this instance is that of the SN₂ reaction.^[15] However, it has been observed that in some cases of an SN₂ reaction that an EWG

does not accelerate the reaction as would be expected^[16] and that the rate varies with the substituent. In fact, the sign of the charge and degree to which it develops will be affected by the substituent in the case of the benzylic system.^[15]

For example, the substituent may determine the mechanism to be an S_N1 type reaction over a S_N2 type reaction, in which case the resulting Hammett plot will indicate a rate acceleration due to an EDG, thus elucidating the mechanism of the reaction.



Another deviation from the regular Hammett equation is explained by the charge of nucleophile.^[15] Despite nonlinearity in benzylic S_N2 reactions, electron withdrawing groups could either accelerate or retard the reaction. If the nucleophile is negatively charged (e.g. cyanide) the electron withdrawing group will increase the rate due to stabilization of the extra charge which is put on the carbon in the transition state. On the other hand, if the nucleophile is not charged (e.g. triphenylphosphine), electron withdrawing group is going to slow down the reaction by decreasing the electron density in the anti bonding orbital of leaving group in the transition state.

Hammett modifications

Other equations now exist that refine the original Hammett equation: the Swain–Lupton equation, the Taft equation, the Grunwald–Winstein equation, and the Yukawa–Tsuno equation. An equation that addresses stereochemistry in aliphatic systems has also been developed.^[17]

Estimation of Hammett sigma constants

Core-electron binding energy (CEBE) shifts correlate linearly with the Hammett substituent constants (σ) in substituted benzene derivatives.^[18]

$$\Delta\text{CEBE} \approx \kappa\sigma_p$$

Consider para-disubstituted benzene p-F-C₆H₄-Z, where Z is a substituent such as NH₂, NO₂, etc. The fluorine atom is para with respect to the substituent Z in the benzene ring. The image on the right shows four distinguished ring carbon atoms, C₁(ipso), C₂(ortho), C₃(meta), C₄(para) in p-F-C₆H₄-Z molecule. The carbon with Z is defined as C₁(ipso) and fluorinated carbon as C₄(para). This definition is followed even for Z = H. The left-hand side of (1) is called CEBE shift or ΔCEBE , and is defined as the difference between the CEBE of the fluorinated carbon atom in p-F-C₆H₄-Z and that of the fluorinated carbon in the reference molecule FC₆H₅.

$$\Delta\text{CEBE} \equiv \text{CEBE}(\text{C4 in } \text{p-F-C}_6\text{H}_4\text{-Z}) - \text{CEBE}(\text{C4 in } \text{p-F-C}_6\text{H}_5) \quad (2)$$

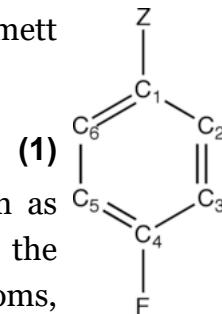
The right-hand side of Eq. 1 is a product of a parameter κ and a Hammett substituent constant at the para position, σ_p . The parameter κ is defined by eq. 3:

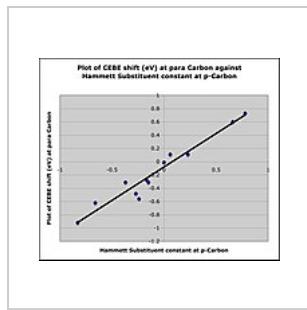
$$\kappa = 2.3kT(\rho - \rho^*) \quad (3)$$

where ρ and ρ^* are the Hammett reaction constants for the reaction of the neutral molecule and core ionized molecule, respectively. ΔCEBEs of ring carbons in p-F-C₆H₄-Z were calculated with density functional theory to see how they correlate with Hammett σ -constants. Linear plots were obtained when the calculated CEBE shifts at the ortho, meta and para carbon were plotted against Hammett σ_o , σ_m and σ_p constants respectively.

- κ value calculated ≈ 1 .

Hence the approximate agreement in numerical value and in sign between the CEBE shifts and their corresponding Hammett σ constant.^[19]

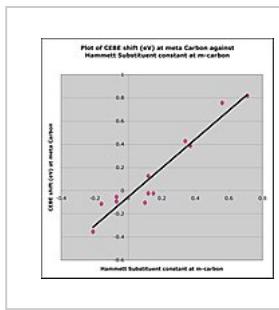




Plot of calculated CEBE shift (eV) against sigma-para

Substituent	σ_p	Calculated Δ CEBE (eV)
$\text{N}(\text{CH}_3)_2$	-0.83	-0.92
NH_2	-0.66	-0.62
OH	-0.37	-0.31
OCH_3	-0.27	-0.48
OCH_2CH_3	-0.24	-0.56
CH_3	-0.17	-0.27
C_6H_5	-0.15	-0.31
SCH_3	0	-0.01
F	0.06	0.11
Cl	0.23	0.11
CN	0.66	0.6
NO_2	0.78	0.73

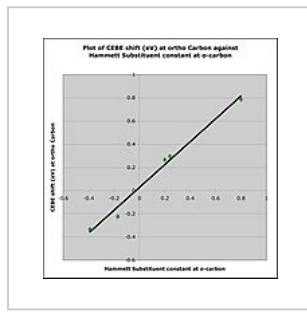
Table of CEBE shifts (eV) and sigma-para



Plot of calculated CEBE shift (eV) against sigma-meta

Substituent	σ_m	Calculated Δ CEBE (eV)
$\text{N}(\text{CH}_3)_2$	-0.21	-0.35
NH_2	-0.16	-0.11
OH	0.12	0.13
OCH_3	0.12	-0.02
OCH_2CH_3	0.1	-0.1
CH_3	-0.07	-0.05
C_6H_5	-0.07	-0.09
SCH_3	0.15	-0.02
F	0.34	0.43
Cl	0.37	0.39
CN	0.56	0.76
NO_2	0.71	0.82

Table of CEBE shifts (eV) and sigma-meta



Plot of calculated CEBE shift (eV) against sigma-o

Substituent	σ_o	Calculated Δ CEBE (eV)
OCH_3	-0.39	-0.33
CH_3	-0.17	-0.22
F	0.24	0.3
Cl	0.2	0.27
NO_2	0.8	0.79

Table of CEBE shifts (eV) and sigma-ortho

See also

- [Bell–Evans–Polanyi principle](#)
- [Craig plot](#)
- [Free-energy relationship](#)
- [pK_a](#)
- [Quantitative structure–activity relationship](#)

Notes

- a. The opening line in his 1935 publication reads: "The idea that there is some sort of relationship between the rate of a reaction and the equilibrium constant is one of the most persistently held and at the same time most emphatically denied concepts in chemical theory".^[4]

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