

Substituent Effects on Chemical Reactivity. Improved Evaluation of Field and Resonance Components

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Abstract: Logarithms of relative equilibrium or rate constants for 14 reaction series, 2 of which include 43 substituents and 6 of which define the Hammett substituent constants σ_m , σ_p , σ' , σ_m^+ , σ_p^+ , and σ_p^- , are fitted by $fF + rR + h$, where F (the nonresonance or "field" constant) and R (the resonance constant) depend on only the substituent, and f , r , and h depend on the reaction series but not at all on the substituent. All 128 ($=2 \times 43 + 3 \times 14$) constants are evaluated by nonlinear least squares using equal statistical weighting of 220 log data, the four trivial, scale-setting, subsidiary conditions $F = R = 0$ for H and $F = R = 1$ for NO_2 , and the two critical subsidiary conditions $r = 0$ for ionization of trans-4-substituted cyclohexanecarboxylic acids in water at 25 °C and $R = 0$ for the $(\text{CH}_3)_3\text{N}^+$ substituent. The precision (standard deviation) is tabulated for each of the 86 substituent constants, 42 reaction constants, and 75 typical predicted data. The overall correlation coefficient between input data and predictions is 0.9945, and none of the 14 reactions is below 0.984. The results confirm that one R is sufficient for each substituent and indicate that CH_3 and C_2H_5 substituents tend to donate electrons moderately strongly by resonance but have no other electronic (field or inductive) influence. The correlation coefficient between R and F constants is 0.09. Use of orthogonality between R and F , as an alternative critical condition, does not lower it. Use of zero covariance, which forces it to be zero, must be rejected because it gives R values in conflict with other chemical evidence. Another 32 reactions, more randomly chosen but including reactions in aprotic solvents, gas-phase ionizations, and enzymic reactions, exhibit a median correlation coefficient of 0.991 in ordinary multiple linear least-squares analyses using the same F and R values already determined by the 14 reactions, which were all in protic solvents.

A previous analysis¹ in 1968 attempted to separate resonance vs. other ("field") components of substituent effects by use of two defensible assumptions: that resonance between substituent and reaction center is negligible (1) if they are separated by three or more interposed saturated carbons or (2) if the substituent is the saturated $(\text{CH}_3)_3\text{N}^+$ substituent. However, that analysis of 797 data for 42 substituents and 43 reaction series suffers from two major deficiencies. First, the derived constants are based on only three reactions (only the 98 data comprising σ_m , σ_p , and σ' values); hence there is no averaging to mitigate possible damage to the accuracy of particular constants caused by occasional erroneous data in this minimum-size basis set. Second, and even more important, precisions of the constants were not calculated. They would have to be calculated by a valid method to a precision (relative standard deviation) of $\pm 20\%$ to be sure that differences between particular values are meaningful or at least significantly larger than differences attributable to random experimental noise.

The present analysis removes these deficiencies by basing the calculations on 220 data from 14 series of equilibria and rates (by adding 11 series including σ_m^+ , σ_p^+ , and σ_p^- to the former 3 and giving them all equal statistical weight) and by calculating the standard deviation of each derived constant with a precision of $\pm 5\%$ by an unbiased, reliable method.² Several of the substituent constants show changes in rank order compared to the earlier values, but in every case the new orders agree better with expectation and independent evidence. We conclude that there are in fact significant errors in some of the data on which σ_m , σ_p , and σ' are based, although we cannot pinpoint them exactly. As expected, this broadening of the data base markedly improves the overall correlation coefficient C , from 0.967 for the previous analysis to 0.9945 for this analysis. *The portion of the observed variations not accounted for by our treatment ($1 - C^2$) is thus reduced sixfold, from 6.5% to 1.1%.*

The same F and R values deduced from the present analysis of 14 reactions (220 data) were applied in ordinary multiple linear least-squares analyses of a more randomly selected and more heterogeneous assortment of 32 other reactions to evaluate their sensitivities to F and R and their correlation coefficients. The correlation coefficients have a median of 0.991 and are quite

satisfactory (above 0.981) even for reactions in much less polar media, free radical formation, and several biological reactions, i.e., for solvents and reaction types vastly different from any of the original 14.

Input Data and Procedure

Observed Data. The 220 data are free energies for reaction series 1-14 of the previous study.¹ Addition of $(\text{CH}_3)_3\text{N}$ increases the number of substituents from 42 to 43. For complete data, see footnote *e* of Table II and the section entitled Data Base.

Procedure and Subsidiary Conditions. We use the DOVE (Dual Obligate Vector Evaluation) nonlinear least-squares procedure, which is described elsewhere,³ to fit all of the parameters (a_i , b_i , c_i , x_j , y_j) of eq 1. Here F ($=x_j$ = the nonresonance or "field"

$$p_{ij} = a_i x_j + b_i y_j + c_i = fF + rR + h \quad (1)$$

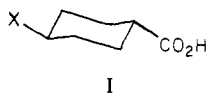
constant) and R ($=y_j$ = the resonance constant) depend on only the substituent j , while f ($=a_i$), r ($=b_i$), and h ($=c_i$) depend on the series i (particular reaction, solvent, temperature, etc.) but are entirely independent of substituent, and p_{ij} is the predicted datum for any possible combination of i and j . The DOVE procedure accomplishes this in two stages or phases. In phase 1, in an iterative calculation, it converges to a best fit between predicted p_{ij} and observed data but predicted values are not consistent with the valid (true) subsidiary conditions required for realistic values for the constants. In phase 2, to make the solution unique with the R constants correctly representing the tendency of substituents to accept (+) or donate (-) electrons by resonance only and the F constants their tendency to accept (+) or donate (-) electrons by nonresonance (field, inductive, solvation, and other modes of interaction), DOVE then transforms the practically meaningless hybrid constants obtained in phase 1 to incorporate the six desired, true, subsidiary conditions. Of these, the four trivial (arbitrary) conditions, which merely set scale zeros and scale ranges, are chosen as $F = R = 0$ for the hydrogen (H) substituent and $F = R = 1$ for the nitro (NO_2) substituent. The two critical (true) conditions are chosen as $r = 0$ (no resonance component) for $\log K_A/K_A^H$ values (σ'') of trans-4-substituted cyclohexanecarboxylic acids (structure I) in water at 25 °C⁴ and $R = 0$ (no resonance component) for the $(\text{CH}_3)_3\text{N}^+$ substituent. The new trivial

(1) Swain, C. G.; Lupton, E. C., Jr. *J. Am. Chem. Soc.* **1968**, *90*, 4328.

(2) Swain, C. G.; Swain, M. S.; Strong, P. F. *J. Chem. Inf. Comput. Sci.* **1980**, *20*, 51-55.

(3) Strong, P. F.; Swain, C. G.; Swain, M. S. *J. Chem. Inf. Comput. Sci.* **1979**, *19*, 13-18.

(4) Siegel, S.; Komarmy, J. M. *J. Am. Chem. Soc.* **1960**, *82*, 2549.



conditions setting scale ranges ($F = R = 1$ for NO_2) make F values slightly smaller and R values considerably larger than those in the previous study, and former irregularities caused by local inaccuracies in the data are now considerably reduced by the broader data base used. This was the first application of DOVE to a problem in which the answers were not known in advance.

These six subsidiary conditions set the six zero and unity values that are enclosed in parentheses in Tables I and II. The trivial assignments for H and NO_2 really need no justification because any similar assignment for any two substituents would be practically as satisfactory. Only the zero positions and unit sizes on the F and R scales would change. There would be no inversion or interchange of substituents in any order of increasing size of F or R . The location of zeros on the F and R scales is arbitrary, like the choice of the zero reference on an energy scale. However, the choices of $F = R = 0$ for H do have the fortuitous advantage that they agree with the commonly accepted conclusion from dipole moment and other evidence that the H substituent always has zero or only a very low electron attracting or releasing tendency when attached to carbon. The other trivial conditions, $F = R = 1$ for NO_2 , also have a fortuitous feature: they agree with Wheland's evidence on the acidity of phenols that only half of the effect of a p - NO_2 substituent can be sterically inhibited by o -methyls and is therefore attributable to resonance.⁵ This equal scaling of F and R is therefore appropriate and permits us to compare F with R values rather than only an F with other F 's or an R with other R 's.

On the other hand, the assignment of $R = 0$ for $(\text{CH}_3)_3\text{N}^+$ is a critical condition upon which the validity of the whole analysis depends. Theoretical and experimental justifications for this critical condition were given previously.⁶ Likewise the assumption of no resonance through three or more intervening saturated atoms must be correct for our analysis to be valid. The change in the particular reaction for which r is set equal to zero, from acidity of 4-substituted bicyclo[2.2.2]octanecarboxylic acids in 50% ethanol by weight to acidity of trans-4-substituted cyclohexanecarboxylic acids in water at 25 °C,⁴ by itself results in no significant change in the constants, but fewer synthetic steps would be required to add substituents not yet studied to this latter series in possible future work.

Unacceptability of Orthogonality or Zero Covariance Conditions.

As an alternative to the critical condition that $R = 0$ for $(\text{CH}_3)_3\text{N}^+$, we tried $\sum_j FR = 0$ (orthogonality).⁷ When assuming orthogonality, we also used $\sum_j F^2 = \sum_j R^2 = 43$ (normalization) instead of $F_{\text{NO}_2} = R_{\text{NO}_2} = 1$ for two of the trivial conditions. However, the choice of orthogonality as a critical condition leads to three difficulties.

First, the substituent constants and even the rank ordering of F and R values then depend sensitively on which j is chosen for reference. In the present problem, it is logical to choose $F = R = 0$ for H ($j = 19$), but it is troublesome that the choice of

reference ceases to be a trivial choice. With most other critical conditions, as with $r = 0$ for σ'' and $R = 0$ for $(\text{CH}_3)_3\text{N}^+$, an alternative choice of $F = R = 0$ for a different substituent than H is trivial (noncritical and equally acceptable) because it simply linearly shifts F and R values without any changes in rank order.

Second, and probably more important, it is disturbing that acetoxy (OCOCH_3 , $j = 2$) and iodo (I , $j = 21$) acquire positive resonance constants as well as positive field constants. There is thus no possibility of ever predicting electron donation. Yet these substituents are known to be effective electron donors by resonance, because they are ortho,para directors in electrophilic aromatic substitution.⁸ Use of $R = 0$ for $(\text{CH}_3)_3\text{N}^+$ correctly yields negative resonance constants for acetoxy and iodo.

Third, and certainly most important, the only possible justification for orthogonality is the notion that it should eliminate any dependence of R on F . Unfortunately, this assumption of orthogonality does not imply or result in zero correlation between the derived R and F values but gives a positive correlation coefficient ($C = 0.22$) between them, whereas we were expecting it to be zero.

To test the assumption that the correlation between R and F should be zero, we can force it to be zero by assuming zero covariance, $(\sum_j FR - \sum_j F \sum_j R / 43) / 43 = 0$, instead of orthogonality as a critical condition. However, the R and F values then become even more absurd. E.g., $(\text{CH}_3)_3\text{N}^+$ becomes a moderately strong electron donor by resonance (-0.41) and COO^- becomes a stronger resonance acceptor than COOH in spite of its negative charge, conclusions that are obviously wrong. Since there is a small but real correlation coefficient between the true R and F values (0.09), assuming that it is zero imposes a serious error. Even if there were zero correlation for an infinitely large set of substituents, there would generally be a nonzero correlation for a small sample (such as 43); hence assuming zero correlation can introduce a significant error. Therefore one should avoid using any statistical statements as subsidiary conditions.

We investigated many other alternative choices for the two critical conditions, but they also lead to results refuted by other evidence. Furthermore, use of $\sum_j F^2 = \sum_j R^2 = 43$ (normalization) is undesirable for the range-setting trivial conditions because (1) they are more complicated to implement than $F = R = 1$ for NO_2 and (2) addition of new substituents or reactions causes larger revisions of F and R values. It is more convenient to have the H constants fixed at 0, the NO_2 constants fixed at 1, and the values for other substituents nearly constant, regardless of the particular data set used.

Standard Deviations. We shall tabulate or use nine kinds of standard deviations S . S_z is the simple standard deviation of observed data z_{ij} in one reaction series (i) from its own mean and therefore indicates the range of those data. Its square is expressed by eq 2. Here e_{ij} is unity if z_{ij} exists but zero for any ij com-

$$S_z^2 = \frac{\sum_j e_{ij}(z_{ij} - \sum_j e_{ij}z_{ij}/n_j)^2}{n_j - 1} \quad (2)$$

bination not observed, and n_j is the number of j (substituent) data in series i , i.e., $\sum_j e_{ij}$ for that i .

S_δ is the standard deviation of observed data z_{ij} from predicted data p_{ij} for one reaction series and is therefore a simple measure of goodness of fit. Its square is given by eq 3. Unfortunately,

$$S_\delta^2 = \frac{\sum_j e_{ij}(z_{ij} - p_{ij})^2}{n_j - 3} \quad (3)$$

$n_j - 3$ is not quite the correct number of degrees of freedom because F and R are being fitted as well as f , r , and h , but S_δ is nevertheless commonly reported or used by other workers. Better measures of goodness of fit (see Correlation Coefficients, next section) take the range of the data into account and make a better estimate of the number of degrees of freedom.

(5) Wheland, G. W. "Resonance in Organic Chemistry"; Wiley: New York, 1955; pp 367-368.

(6) Cf. last two paragraphs of p 4333 and ref 33 and 34 of ref 1. Ross, I. G.; Tonnet, N. L. *J. Chem. Soc.* **1959**, 2013. American Petroleum Institute Research Project 44, "Selected UV Spectral Data", Texas A&M University: College Station, TX, 1945-1970, serial numbers 1, 2, 114, 227, 775, 1082, 1083. Silverstein, R. M.; Bassler, G. C.; Morrill, T. C. "Spectrometric Identification of Organic Compounds", 3rd ed; Wiley: New York, 1974; pp 249-250.

(7) Unger, S. H. Ph.D. Thesis, M.I.T., 1970, pp 1-183. Rosenquist, N. R. Ph.D. Thesis, M.I.T., 1973; Part II, pp 109-276. We began this study of substituent effects in 1968 because of a notion that F and R and generally any two factors x and y determined by DOVE ought to be orthogonal. Hence "DOVE" was originally "dual orthogonal vector evaluation". We were forced by our application to a cylinder problem³ as well as by three difficulties in the substituent effect problem to abandon this hypothesis and to adopt different critical subsidiary conditions that make the vectors "optimal" instead of "orthogonal". The use of different subsidiary conditions by Unger and Rosenquist does not change or invalidate C_j values and predicted data for the many more reactions that they analyzed.

(8) Hoeflake, J. M. A. *Recl. Trav. Chim. Pays-Bas* **1916**, 36, 59, for phenyl acetate. Roberts, J. D.; Sanford, J. K.; Sixma, F. L. J.; Cerfontain, H.; Zagt, R. *J. Am. Chem. Soc.* **1954**, 76, 4525, for iodobenzene.

S_F , S_R , S_f , S_r , S_h , $S_{\%r}$, and S_p are standard deviations of field and resonance substituent constants, the three kinds of reaction constants, percent resonance, and predicted data, respectively. These last seven measures of precision were calculated for all 43 substituents, 14 reactions and 602 ($=43 \times 14$) predicted data by the simple, reliable, fast, UNCERT error analysis, which is described elsewhere.² Since 200 trials were averaged, the relative standard deviation of each of the 744 separate standard deviations determined by this Monte Carlo method is $\pm 5\%$.

Correlation Coefficients. Statistical weighting is used to correct for different ranges for the data in the different reaction series. The data in some reactions span a much wider range of values than those in others, e.g., 3.19 (\log_{10} units) in reaction 3 (σ_p^-) but only 0.49 in reaction 12 (σ_6). Without such weighting, reaction 3 would have much more influence than reaction 12 in the least-squares determination of F and R values. The DOVE program assigns a statistical weighting factor w_i to each reaction equal to the reciprocal of the variance of data for the reaction from its own mean (eq 4). This has nothing to do with precision or accuracy,

$$w_i = 1/S_z^2 \quad (4)$$

but it tends to give more nearly equal weight to all data in determining the constants. It lowers the overall correlation coefficient considerably compared to not weighting, but the lowered value is still impressively high (0.9945).

Unless otherwise noted, our correlation coefficients C are not Pearson coefficients but are corrected for sample size by inclusion of the proper number of degrees of freedom.³ C is the square root of $1 - E$. E (the "evil"³) for all the data is given by eq 5. It

$$E = 1 - C^2 = \frac{\sum_i \sum_j e_{ij} w_i (z_{ij} - p_{ij})^2}{d + 6 - 3u - 2v} \quad (5)$$

is the fraction of all the z_{ij} variations that is not explained by eq 1. Here the denominator is the number of degrees of freedom, d is number of data (220), u is number of reaction series (14), and v is the number of substituents (43).

E_i for an individual reaction series is given by eq 6 and is the

$$E_i = 1 - C_i^2 = \frac{w_i \sum_j e_{ij} (z_{ij} - p_{ij})^2}{(n_{j_i} - 3)(d + 6 - 3u - 2v)/(d - 3u)} \quad (6)$$

fraction of the variations within that series that is not explained by eq 1. Use of the $(d + 6 - 3u - 2v)/(d - 3u)$ ($=98/178$) multiplier of $n_{j_i} - 3$ results in nonintegral degrees of freedom for the individual series but has the virtue that the sum of the degrees of freedom for all the individual series is then the correct number ($d + 6 - 3u - 2v = 98$) for all the data.

Results and Discussion

A. Substituent Constants. Values of F and R . Table I lists the 43 substituents and their nonresonance or "field" (F) and resonance (R) substituent constants, each with its standard deviation (the \pm value). The order of F constants for 14 of the 43 substituents is $N_2^+ > N(CH_3)_3^+ > NO_2 > CN > Br \approx Cl \approx F \approx NHCOCH_3 > OH > NH_2 > C_6H_5 > H \approx CH_3 (0) > CO_2^-$. The order of R constants is $N_2^+ > NO_2 > CN > CO_2^- > H \approx N(CH_3)_3^+ (0) > Br \approx Cl > C_6H_5 \approx CH_3 > F > NHCOCH_3 > OH > NH_2$. The extreme F values of N_2^+ , $N(CH_3)_3^+$, and CO_2^- are due to their net charges, which are more influential than any of the dipoles. By resonance, CO_2^- attracts electrons in spite of its negative charge.

Figure 1 is a computer-generated plot of R vs. F . The correlation coefficient C between R and F is only 0.09. Figure 2 is the computer-generated plots of measured vs. predicted data for 6 of the 14 reactions. Arrows point out many of the substituents j .

Major Changes from Previous Study. The values differ from the previous study¹ in several major respects. $(CH_3)_2S^+$, SO_3^- , $SOCH_3$, and SO_2CH_3 resonance constants formerly calculated as -0.04 , $+0.06$, $+0.007$, and $+0.22$ are now all found to be moderately large ($+0.52$, $+0.53$, $+0.45$, and $+0.85$), in accord with their known substantial tendencies to accept electrons by

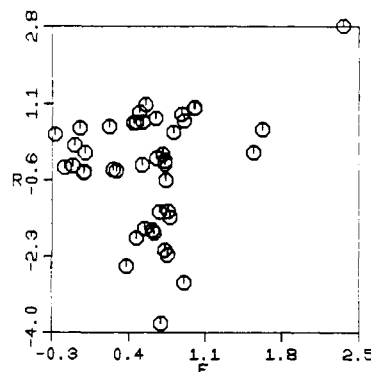


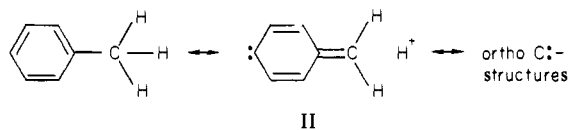
Figure 1. Computer-produced plot of resonance constant vs. field constant for 43 substituents.

resonance (in contrast to $(CH_3)_3N^+$).⁹ The $(CH_3)_3Si$ resonance constant, formerly slightly negative, is now positive (0.16), in accord with the well-known ability of silicon to expand its valence to 5 or 6. The CN resonance constant, formerly larger than that of NO_2 , is now gratifyingly smaller (0.71 ± 0.07), similar to $CO_2C_2H_5$ (0.67 ± 0.07) and lower than CF_3 (0.76), SO_2CH_3 (0.85), $COCH_3$ (0.90), NO_2 (1.00), and N_2^+ (2.81). Among field constants the largest change is that for NH_2 , formerly very small at 0.04 but now 0.38 ± 0.08 in accord with the considerably higher electronegativity of N than of C.

Most of the important conclusions of the previous study are reinforced by the present results. N_2^+ still has the largest field constant (2.36) and the largest resonance constant (2.81). Again, all the substituents known to be ortho,para-directing in electrophilic aromatic substitution have negative resonance constants ($AcNH$, AcO , R_2N , RO , R , F , Cl , Br , I , RS , C_6H_5). In resonance, F (-0.60) is still a markedly better donor than the other halogens (-0.12 to -0.24). CO_2^- is a field donor (-0.27) but resonance acceptor (0.40). SO_3^- anion has a negligible field effect but is a moderate resonance acceptor (0.53). CF_3 is a moderate field acceptor (0.64) but a strong resonance acceptor (0.76).

Alkyl Substituents. Alkyl groups appear to have negligible field effects but to be moderate resonance (hyperconjugative) donors. The field constants of CH_3 and C_2H_5 are both within a standard deviation (0.03) of zero, but their resonance constants are -0.41 ± 0.08 and -0.44 ± 0.10 . As resonance donors, they appear to be similar to phenyl (C_6H_5 , -0.37 ± 0.11) and stronger than Cl (-0.24 ± 0.08).

The measured effect of CH_3 ($j = 25$) is smaller than the random error noise level ($z_{ij} = -0.013 \pm 0.025$) when it is attached to a saturated carbon skeleton (σ_2' , $i = 5$, Figure 2d). However, its measured effects ($z_{ij} \pm S_j$) in σ_m , σ_p , σ_p^- , and σ_p^+ (Figure 2, a-c), where resonance is possible, are each substantial, i.e., -0.069 ± 0.012 , -0.170 ± 0.016 , -0.150 ± 0.036 , and -0.311 ± 0.031 , respectively. We see no reasonable alternative to hyperconjugation (II) to explain these resonance effects.



Resonance between substituents and an aromatic ring often persists even when charges or electronic demands at the reaction center might be expected to oppose it (as with CH_3 in σ_p^- , or with NO_2 as well as NH_2 in σ_p^+ , as noted in the Reaction Constants section). It seems fallacious to reinterpret it as a kind of inductive effect associated with sp^2 hybridized carbon instead of sp^3 attached to the substituent, because that would also be true for a hydrogen substituent and these z_{ij} 's are all differential effects relative to the hydrogen substituent.

(9) Doering, W. E.; Hoffmann, A. K. *J. Am. Chem. Soc.* **1955**, *77*, 521. Doering, W. E.; Schreiber, K. C. *Ibid.* **1955**, *77*, 514. Johnson, A. W. "Ylid Chemistry"; Academic Press: New York, 1966; Chapters 7 and 9.

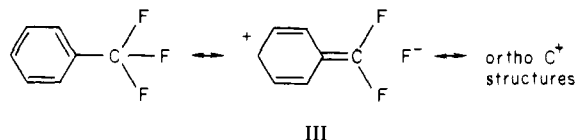
Table I. Substituent Constants

<i>j</i>	substituent	formula	<i>ni_j^a</i>	<i>F</i>	<i>R</i>	<i>C_j^b</i>
1	acetylamino	NHCOCH ₃	3	0.77 ± 0.07	-1.43 ± 0.17	0.9831
2	acetoxy	OCOCH ₃	2	0.70 ± 0.08	-0.04 ± 0.25	
3	acetyl	COCH ₃	4	0.50 ± 0.05	0.90 ± 0.12	0.9960
4	acetylthio	SCOCH ₃	2	0.53 ± 0.08	0.68 ± 0.24	
5	amino	NH ₂	6	0.38 ± 0.08	-2.52 ± 0.23	0.9945
6	bromo	Br	12	0.72 ± 0.03	-0.18 ± 0.07	0.9956
7	<i>n</i> -butoxy	O(CH ₂) ₃ CH ₃	2	0.72 ± 0.10	-2.16 ± 0.32	
8	tert-butyl	C(CH ₃) ₃	6	-0.11 ± 0.05	-0.29 ± 0.11	0.9962
9	carboxy	CO ₂ H	6	0.44 ± 0.03	0.66 ± 0.08	0.9920
10	carboxylate anion	CO ₂ ⁻	7	-0.27 ± 0.03	0.40 ± 0.08	0.9919
11	chloro	Cl	10	0.72 ± 0.03	-0.24 ± 0.08	0.9947
12	cyano	CN	13	0.90 ± 0.03	0.71 ± 0.07	0.9945
13	diazonium cation	N ₂ ⁺	3	2.36 ± 0.10	2.81 ± 0.27	0.9826
14	dimethyl S ⁺ cation	S(CH ₃) ₂ ⁺	3	1.62 ± 0.08	0.52 ± 0.13	0.9977
15	ethoxy	OC ₂ H ₅	2	0.61 ± 0.10	-1.72 ± 0.30	
16	ethoxycarbonyl	CO ₂ C ₂ H ₅	7	0.47 ± 0.02	0.67 ± 0.07	0.9973
17	ethyl	C ₂ H ₅	6	-0.02 ± 0.03	-0.44 ± 0.10	0.9988
18	fluoro	F	5	0.74 ± 0.06	-0.60 ± 0.12	0.9823
19	hydrogen	H	14	(0.00 ± 0.00) ^c	(0.00 ± 0.00) ^c	0.9965
20	hydroxy	OH	11	0.46 ± 0.04	-1.89 ± 0.17	0.9980
21	iodo	I	4	0.65 ± 0.06	-0.12 ± 0.11	0.9889
22	iodoxy	IO ₂	2	0.99 ± 0.08	0.99 ± 0.25	
23	mercapto	SH	2	0.52 ± 0.09	-0.26 ± 0.25	
24	methoxy	OCH ₃	11	0.54 ± 0.03	-1.68 ± 0.16	0.9964
25	methyl	CH ₃	11	-0.01 ± 0.03	-0.41 ± 0.08	0.9963
26	methylseleno	SeCH ₃	2	0.28 ± 0.08	-0.39 ± 0.26	
27	methylsulfinyl	SOCH ₃	3	0.80 ± 0.05	0.45 ± 0.11	0.9991
28	methylsulfonyl	SO ₂ CH ₃	3	0.88 ± 0.05	0.85 ± 0.12	0.9877
29	methylthio	SCH ₃	5	0.68 ± 0.07	-1.30 ± 0.16	0.9786
30	nitro	NO ₂	12	(1.00 ± 0.00) ^c	(1.00 ± 0.00) ^c	0.9968
31	<i>n</i> -pentoxy	O(CH ₂) ₄ CH ₃	2	0.75 ± 0.10	-2.27 ± 0.33	
32	phenoxy	OC ₆ H ₅	4	0.76 ± 0.07	-1.29 ± 0.15	0.9988
33	phenyl	C ₆ H ₅	5	0.25 ± 0.05	-0.37 ± 0.11	0.9986
34	phosphonate anion	PO ₃ H ⁻	2	0.22 ± 0.09	0.58 ± 0.27	
35	isopropoxy	OCH(CH ₃) ₂	2	0.90 ± 0.12	-2.88 ± 0.37	
36	<i>n</i> -propoxy	O(CH ₂) ₂ CH ₃	2	0.63 ± 0.10	-1.77 ± 0.30	
37	2-siliconeopentyl	CH ₂ Si(CH ₃) ₃	2	-0.19 ± 0.08	-0.32 ± 0.26	
38	sulfamoyl	SO ₂ NH ₂	2	0.55 ± 0.09	1.07 ± 0.27	
39	sulfonate anion	SO ₃ ⁻	3	-0.05 ± 0.06	0.53 ± 0.12	0.9973
40	trifluoromethyl	CF ₃	6	0.64 ± 0.03	0.76 ± 0.08	0.9869
41	trimethyl N ⁺ cation	N(CH ₃) ₃ ⁺	5	1.54 ± 0.05	(0.00 ± 0.00) ^c	0.9880
42	trimethylsilyl	Si(CH ₃) ₃	4	-0.10 ± 0.06	0.16 ± 0.11	0.9955
43	dimethylamino	N(CH ₃) ₂	2	0.69 ± 0.13	-3.81 ± 0.42	

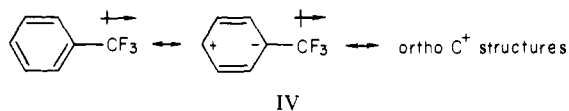
220^d

^a Number of reactions *i* out of the 14 for which experimental data *z_{ij}* for this substituent *j* exist. ^b *C_j* is the correlation coefficient for substituent *j*. In eq 6, omit *w_i* and sum over *i* and replace *ni_j - 3* by *ni_j - 2* and (*d - 3u*) by (*d - 2v*). ^c Values in parentheses are each forced to be zero or unity by one of the six subsidiary conditions. ^d For the 220 experimental data, see Table VI and footnote *e* of Table II.

Trifluoromethyl Substituent. CF₃ (*R* = 0.76, *j* = 40 in Figure 2, a-d) is of particular interest because *R/F* is larger (resonance effects relatively greater) for it (1.19) than those for SOCH₃ (0.56), CN (0.79), SO₂CH₃ (0.97), or even NO₂ (1.00, defined by the scale-setting conditions), all substituents that certainly have considerable conjugative power. Fluoride hyperconjugation (III)



has generally been invoked to explain this resonance contribution in the past, and our constants support this view. However, the validity of this interpretation has been questioned. A suggested¹⁰ alternative rationalization is the π inductive effect (IV). Un-



fortunately, this is insufficient to explain our results. Such an effect should be nearly proportional to the magnitude of substituent dipoles and thus proportional to the *F* constants. Our treatment should exclude such an effect from the resonance term but generate an enhanced sensitivity factor *f* in the field term for environments with such polarized or polarizable π systems. In fact, *f*'s for the saturated substrates of reactions 5 and 6 are slightly larger than those for comparable aromatic systems. This can be attributed to the slightly lower effective dielectric constant in reactions 5 and 6 due to the larger carbon skeletons. The only other common rationalization for these effects is $p-\pi$ interaction,¹¹ which has a number of difficulties.¹⁰ We are thus forced to return to hyperconjugation to explain these constants.

Charged Substituents have reasonable constants. Field constants for N(CH₃)₃⁺ (1.54 ± 0.05) and S(CH₃)₂⁺ (1.62 ± 0.08) are practically equal, as might be expected for two saturated groups bearing a unit positive charge centered one bond length from the carbon skeleton. The larger *F* of the N₂⁺ group (2.36 ± 0.10) may be due to a somewhat greater bond moment when an *sp* orbital is involved in the bond to carbon instead of the *sp*³ orbital of the analogous bonds for N(CH₃)₃⁺ and S(CH₃)₂⁺. The small

(10) Streitwieser, A. Jr.; Marchand, A. P.; Pudjaatmaka, A. H. *J. Am. Chem. Soc.* **1967**, *89*, 693. Holtz, D. *Chem. Rev.* **1971**, *71*, 139. Stock, L. M.; Wasielewski, M. R. *Prog. Phys. Org. Chem.* **1981**, *13*, 253-313.

(11) Sheppard, W. A. *J. Am. Chem. Soc.* **1965**, *87*, 2410. Sheppard, W. A.; Sharts, C. M. "Organic Fluorine Chemistry"; Benjamin: New York, 1969; Chapter 3.

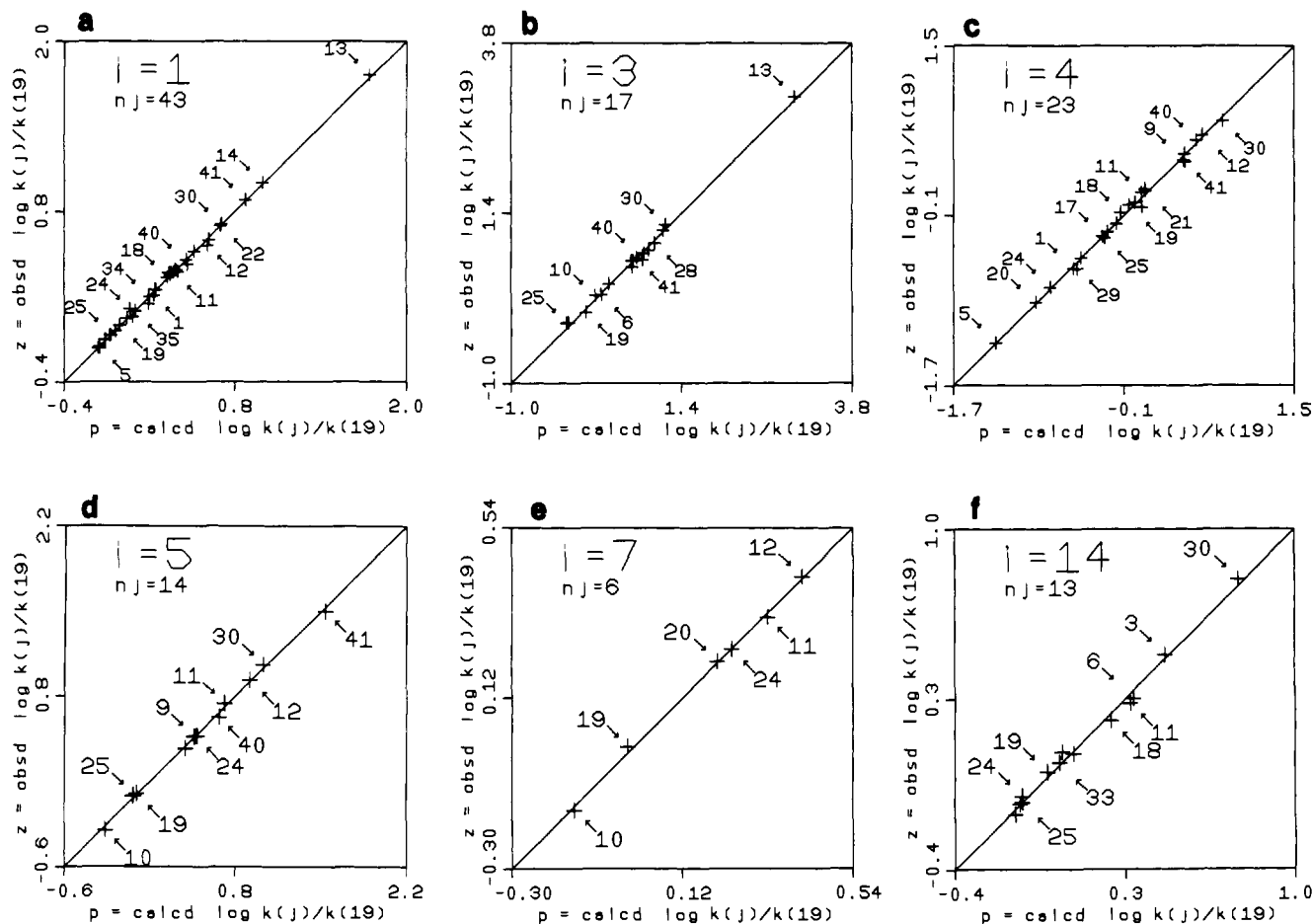


Figure 2. Computer-produced plots of observed vs. calculated data for 6 of the 14 reactions *i*. The number of points is n_j . Each arrow is labeled with a substituent *j*. See Table I for substituents *j*, Table II for reactions *i*.

CO_2^- and SO_3^- field constants (-0.27 ± 0.03 and -0.05 ± 0.06) reflect the low charge densities on C and S due to resonance delocalization of the negative charge over two or three oxygen atoms and further diffusion of the charge from the oxygens to the solvent through hydrogen bonding.

R is 2.81 ± 0.27 for N_2^+ (exceeded in magnitude by only -3.81 ± 0.42 for $\text{N}(\text{CH}_3)_2$). The large difference between this and that for CN (0.71), with which it is isoelectronic, arises because of its charge; whereas resonance with CN involves charge generation, resonance with N_2^+ involves charge dispersal.

Significant resonance electron attracting ability of $\text{S}(\text{CH}_3)_2^+$ ($R = 0.52 \pm 0.13$) was earlier proposed¹² to explain the data from which our constants are calculated. Ultraviolet studies (no shift from $\lambda_{\text{max}} = 254$ nm of benzene on $\text{N}(\text{CH}_3)_3^+$ substitution, but an 11-nm shift on $\text{S}(\text{CH}_3)_2^+$ substitution) corroborate this interpretation.

Other *F* Constants. The appended precisions (standard deviations) indicate that differences between some of the constants are less than the random experimental noise and are therefore of no significance. For example, the field constants of F, Cl, Br, and I, 0.74 ± 0.06 , 0.72 ± 0.03 , 0.72 ± 0.03 , and 0.65 ± 0.06 , indicate no detectable differences between F, Cl, and Br. However, the probability that the field constant of Cl (0.72 , $n_j = 10$) is greater than that of I (0.65 , $n_j = 4$) exceeds 95%. The *t* test of statistics can be used to estimate such probabilities for any combination of means, standard deviations, and numbers of data.

A recurring feature is increasingly positive *F* values for OR, SR, or NR_2 when *R* is increased from H to CH_3 to larger alkyl

groups. These differences are less certain because many are based on only two reactions ($n_i = 2$). However, they may be real inductive (localized) differences due to decreasing inductive electron supply to such electronegative atoms (O, S, N) from the alternative source, namely, their other attached atoms, as the electronegativity of these attached atoms increases over the range from H to C-H to C-C.

B. Reaction Constants. Values *f* and *r*. Table II lists the 14 reaction series and the sensitivities (r_i) of each to resonance (*R*) vs. other (*F*) influences, each with its standard deviation, the predicted datum for no substituent (*h*), the average relative importance of resonance (% *r*), the ordinary standard deviation S_i , and the correlation coefficient C_i .

Percent Resonance is defined by eq 7. It is a one-number

$$\% r = 100r/(f + r) \quad (7)$$

measure of the relative sensitivity of a reaction to resonance influences of substituents. It is a property of the reaction (*i*) and the same for all substituents. Since it is relative to $f + r$, differences in sizes of reaction constants associated with differences in units from one reaction to another are automatically compensated.

Although % *r* ranges only from 0% to 62% for these 14 reactions, we can deduce that it must be greater for isomer distributions of electrophilic aromatic substitutions by the following argument. The relative difference in predicted data p_{ij} with any substituent X compared to no substituent (or substituent H) can be calculated as a function of % *r* by eq 8. Table III lists these relative

$$\frac{p_{iX} - p_{iH}}{f_i} = F_X + \frac{(\% r)R_X}{100 - \% r} \quad (8)$$

differences for four substituents (X = NH_2 , C_6H_5 , CO_2^- , and Cl⁻) in reactions with six selected % *r* values ranging from 0% to 80%. Note that resonance dominates (causing the sign to change) for NH_2 in reactions with % *r* above 17%, but for C_6H_5 or CO_2^- only

(12) Bordwell, F. G.; Boutan, P. J. *J. Am. Chem. Soc.* **1956**, *78*, 87; *Ibid.* **1957**, *79*, 717.

(13) Howard, J. C.; Lewis, J. P. *J. Org. Chem.* **1966**, *31*, 2005.

(14) McDaniel, D. H.; Brown, H. C. *J. Org. Chem.* **1958**, *23*, 425. Johnston, J. *Proc. R. Soc. London Ser. A* **1906**, *78*, 82.

(15) Jaffé, H. H. *Chem. Rev.* **1953**, *53*, 222.

Table II. Reaction Constants

<i>i</i>	reaction ^a	<i>n</i> _{<i>i</i>} ^b	<i>f</i>	<i>r</i>	<i>h</i>	% <i>r</i> ^d	<i>S</i> _δ ^d	<i>C</i> _{<i>i</i>} ^d
1	σ _{<i>m</i>}	43	0.57 ± 0.02	0.14 ± 0.01	-0.01 ± 0.01	20 ± 2	0.018	0.9977
2	σ _{<i>p</i>}	43	0.49 ± 0.03	0.30 ± 0.02	-0.02 ± 0.02	38 ± 3	0.040	0.9941
3	σ _{<i>p</i>} ⁻	17	0.46 ± 0.04	0.66 ± 0.06	0.05 ± 0.03	59 ± 4	0.057	0.9945
4	σ _{<i>p</i>} ⁺	23	0.34 ± 0.04	0.54 ± 0.04	-0.05 ± 0.03	62 ± 4	0.043	0.9940
5	σ ₂ ⁺	14	1.00 ± 0.04	0.04 ± 0.01	0.00 ± 0.02	4 ± 1	0.026	0.9974
6	σ ₂ [']	5	0.64 ± 0.03	0.01 ± 0.01	0.00 ± 0.00	1 ± 1	0.003	0.9998
7	σ ₂ ^{''}	6	0.48 ± 0.02	(0.00 ± 0.00) ^c	-0.01 ± 0.01	(0 ± 0) ^c	0.013	0.9969
8	σ _{<i>m</i>} ⁺	19	0.52 ± 0.03	0.15 ± 0.02	0.03 ± 0.01	23 ± 2	0.027	0.9893
9	σ ₃	5	0.53 ± 0.05	0.10 ± 0.02	0.00 ± 0.04	16 ± 4	0.037	0.9845
10	σ ₄	9	0.50 ± 0.05	0.38 ± 0.03	0.01 ± 0.03	43 ± 4	0.038	0.9956
11	σ ₅	9	0.38 ± 0.03	0.13 ± 0.02	0.03 ± 0.02	26 ± 3	0.028	0.9885
12	σ ₆	8	0.28 ± 0.01	0.12 ± 0.01	0.00 ± 0.01	30 ± 3	0.010	0.9977
13	σ ₇	6	0.26 ± 0.02	0.12 ± 0.01	-0.01 ± 0.01	32 ± 3	0.013	0.9964
14	σ ₀	13	0.55 ± 0.03	0.24 ± 0.02	-0.02 ± 0.02	30 ± 3	0.028	0.9906
		220 ^e						

^a Same as first 14 reactions in Table II of previous paper,¹ where references are listed. Except where noted here or in footnote *e*, data are *σ* values taken from tables in these references (because reported *k*'s are often more rounded) but were calculated in these references from $(1/\rho) \log(k/k^H)$ at 25 °C, where $\rho = 1.00$, *k* = acid dissociation constant *K*_A in water: 1 and 2 are for 3- and 4-XC₆H₅COOH (original Hammett substituent constants); 3 is for 4-XC₆H₅OH, $\rho = 2.23$; 4 and 8 are for *k* = first-order rate constant for solvolysis of 4- and 3-XC₆H₅C(CH₃)₂Cl in 90% acetone-10% water by volume, $\rho = -4.54$; 5 and 6 are for 4-XC₈H₁₂COOH (bicyclo[2.2.2]octane-1-carboxylic acids, VI) in 50% ethanol by weight, $\rho = 1.65$, or in 50% ethanol by volume, $\rho = 1.46$; 7 is for 4-XC₆H₁₀COOH (*trans*-cyclohexanecarboxylic acids, I);⁴ 9-13 are for 3-, 4-, 5-, 6-, and 7-XC₁₀H₈COOH (1-naphthoic acids in 50% ethanol by volume, $\rho = 1.52$); 14 is for *k* = second-order rate constant for HO⁻ + 4-XC₆H₄CH₂COOC₂H₅ in 60% acetone by volume. ^b Number of substituents *j* out of the 43 for which experimental data^e *z*_{*ij*} for this reaction *i* exist. ^c Value forced to be zero by one of the six subsidiary conditions. ^d See eq 3, 6, and 7 for definitions of standard deviation *S*_δ, correlation coefficient *C*_{*i*}, and percent resonance (% *r*). ^e The 220 data used are given in Table VI. These are the same as the 220 in series 1-14 of Table II of ref 1 and its footnote *u* (reaction index *i*, substituent index *j*, *z*_{*ij*}), except for the three added data (1, 43, -0.150¹³; 2, 43, -0.830¹⁴; 7, 10, -0.1559⁴), six data replaced by better data (1, 20, -0.002¹⁵; 2, 32, -0.028¹⁵; 7, 11, 0.3196; 7, 12, 0.4195; 7, 20, 0.2093; 7, 24, 0.2401), and three dubious data deleted (3, 24; 8, 41; 13, 6). Although there is a value reported for 7, 9 (COOH), we did not include it because it makes the fit significantly poorer (*C* = 0.9941, *C*₇ = 0.9865) and Professor Siegel has kindly informed us that this one *K*_A was unfortunately miscalculated in the paper⁴ and thesis.

Table III. Relative Differences in Predicted Data (Eq 8) for Substituted vs. Unsubstituted Reactant with Various Values for % *r*

% <i>r</i>	NH ₂	C ₆ H ₅	CO ₂ ⁻	Cl
0	0.38	0.25	-0.27	0.72
17	-0.12	0.15	-0.19	0.67
38	-1.13	0.03	-0.03	0.58
41	-1.38	-0.01	0.01	0.55
67	-4.66	-0.49	0.53	0.24
80	-9.70	-1.23	1.33	-0.24

if % *r* exceeds 40%, and for Cl only if % *r* exceeds 70%. The facts that diphenyl is more reactive¹⁶ but that chlorobenzene is less reactive than benzene in electrophilic aromatic substitutions therefore means that their log rates (determined by free energy difference between transition state and ground state) have % *r* between 40% and 70%. However, the fact that chlorobenzene directs para more than half as often as meta means that the logs of the product ratios (determined by difference between meta and para transition states) have % *r* greater than 70%, i.e., higher than that of any of the 14 reactions in Table II.

It is not correct to use relative *f* values as measures of relative sensitivity to field influences (or relative *r* values as measures of relative sensitivity to resonance influences), because most of such differences were removed before calculating the constants by our use of data (*z*_{*ij*}) of the form $(1/\rho) \log(K/K^H)$ when this was the form tabulated by the original investigators. Therefore all reaction constants must be multiplied by ρ whenever a ρ different from unity was employed (e.g., by $\rho = -4.54$ for ρ_p^+ , 2.23 for ρ_p^- , 1.65 for ρ_2^+). We have done this for the comparisons in the next two paragraphs.

Arranged in order of decreasing sensitivity to field effects (*ρf*), five of the reactions are ρ_2^+ (1.65), ρ_p^+ (1.54), ρ_p^- (1.03), ρ_m (0.57), ρ_p (0.49), and ρ'' (0.48). The higher value for ρ_m than for ρ_p is due to the closer distance of meta substituents. The highest value for ρ_2^+ (bicyclooctanecarboxylic acids) is due partly to a less polar solvent (50% C₂H₅OH) and partly to the effectively lower internal dielectric constant provided by the saturated bicyclic skeleton.

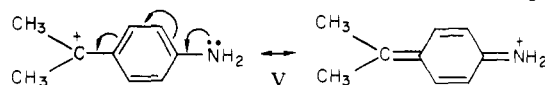
The higher values for ρ_p^+ and ρ_p^- than for ρ_p arise from the location of the charge in the reaction center, directly on the ring in cumyl ions and phenoxides instead of one atom removed as in carboxylates. The difference between ρ_p^+ and ρ_p^- is due to the less polar solvent (90% acetone) used for ρ_p^+ . The slightly lower internal dielectric constant in ρ'' (cyclohexanecarboxylic acids) than in ρ_p is just balanced by the slightly closer distance of substituents in ρ_p than in ρ'' .

The order of decreasing sensitivity to resonance effects (*ρr*) for the same six reactions is also reasonable: ρ_p^+ (2.5), ρ_p^- (1.47), ρ_p (0.30), ρ_m (0.14), and ρ'' (0.00).

Adequacy of a Single Set of Substituent Resonance Constants R. The high overall correlation coefficient of 0.9945 for the 14 reactions in Table II confirms that, for these data, there are only two significant modes of interaction. It implies that $(0.9945)^2 = 98.9\%$ of all the observed variations are attributable to variations in *F* and *R* and that only 1.1% are due to experimental errors or theoretical factors not properly allowed for by eq 1.

The most surprising result of this application of DOVE to substituent effects is the success of the approximation of a single constant set of *R* values. Although *C* would surely drop below 0.98 if DOVE were improperly extended to reactions with significant variations in steric hindrance or other factors than field and resonance influences, a single set of field constants and a single set of resonance constants do account remarkably well for all of our 126 ρ_m , ρ_p , ρ_p^+ , and ρ_p^- data (and the 94 other data), where such additional factors are evidently absent.

In ρ_p^+ (series 4, Figure 2c, based on rates of ionization of 4-substituted α,α -dimethylbenzyl chlorides to carbonium ions), for example, effects due to NH₂, OH, and OCH₃ are not abnormally large compared to effects of CH₃, H, CF₃, CN, NO₂, or other substituents, although one might have expected that special or enhanced *R* values would be required to allow for the favorable, direct conjugation possible with the first three or four of these substituents, as shown in structure V. Yet for NH₂, OH,



OCH₃, CH₃, H, CF₃, CN, and NO₂, respectively, the measured

(16) Streitwieser, A., Jr. "Molecular Orbital Theory"; Wiley: New York, 1961; p 324.

Table IV. Standard Deviations S_p of Predicted Data p_{ij} for 15 of the Substituents j and 5 of the Reaction Series i

j	formula	S_p of p_{ij} for $i =$				
		1	2	3	4	5
5	NH ₂	0.019	0.026	(0.126)	0.038	(0.061)
6	Br	0.010	0.014	0.039	0.025	0.017
10	CO ₂ ⁻	0.014	0.022	0.044	0.032	0.022
11	Cl	0.010	0.016	(0.047)	0.027	0.021
12	CN	0.012	0.017	0.038	0.030	0.021
13	N ₂ ⁺	0.018	0.030	0.057	(0.100)	(0.087)
18	F	0.019	0.019	(0.070)	0.041	(0.049)
19	H	0.011	0.018	0.035	0.030	0.021
20	OH	0.014	0.022	(0.098)	0.031	0.020
24	OCH ₃	0.014	0.019	(0.092)	0.033	0.021
25	CH ₃	0.012	0.016	0.036	0.031	0.025
30	NO ₂	0.013	0.018	0.042	0.029	0.025
33	C ₆ H ₅	0.018	0.017	(0.060)	0.040	(0.048)
40	CF ₃	0.014	0.019	0.036	0.033	0.025
41	N(CH ₃) ₃ ⁺	0.016	0.024	0.051	0.038	0.023

effects (z_{ij}) are -1.3, -0.92, -0.78, -0.31, 0.00, 0.61, 0.66, and 0.79 vs. predicted effects (p_{ij}) of -1.3, -0.93, -0.79, -0.28, -0.05, 0.58, 0.64, and 0.83. The deviations ($z_{ij} - p_{ij}$) are small (0.00, 0.01, 0.01, -0.03, 0.05, 0.03, 0.02, -0.04), similar to the standard deviation (0.03) for all 23 substituents studied and *not* dependent on whether the substituent is electron donating or electron attracting. If anything, deviations are larger for CH₃ (-0.03), H (+0.05), CN (+0.02), and NO₂ (-0.04) than for NH₂ (0.00), OH (0.01), and OCH₃ (0.01), but we consider these as random noise because CH₃ and NO₂ deviate in the opposite direction from H and CN. Certainly there is nothing abnormal about the effect of NH₂, OH, or OCH₃ on these carbonium ions, because deviations for these substituents are quite negligible (≤ 0.01). The resonance contribution (rR) is the dominant term for NH₂, OH, OCH₃, CH₃, CN, and NO₂, but a minor term for many other substituents (Br, Cl, I, N(CH₃)₃⁺). The correlation coefficient for σ_p^+ (series 4) is 0.9940, almost equal to the average for all 14 series (0.9945).

In σ_p^- (series 3, Figure 2b, based on acidities of 4-substituted phenols), the deviations of observed from predicted data for CN and NO₂ substituents are similar to the standard deviation for all 17 substituents (0.06), and the error is not even in the same direction for CN (-0.05) as for NO₂ (+0.07). Evidently these substituents are not exceptional in any way. Yet the average relative importance of resonance (% r) is practically as great in series 3 ($59 \pm 4\%$) as in series 4 ($62 \pm 4\%$). Therefore there is no evidence for two different, unrelated kinds of resonance operating in σ_p^- and σ_p^+ . Again the single set of resonance constants seems adequate because it gives a quite satisfactory fit. The correlation coefficient for series 3 is 0.9945, exactly equal to the average for the 14 series.

Evidently *the apparently enhanced* or abnormally important resonance, formerly thought to operate with NH₂ or OH in the σ_p^+ reaction or with CN or NO₂ in the σ_p^- reaction, *was only an artifact or illusion* resulting from the use of a one-vector model over a range of reactions (from σ_p to σ_p^+ or from σ_p to σ_p^-) where two substituent vectors (F and R) are really involved and their blend (% r) changes significantly (from 38% to about 60%).

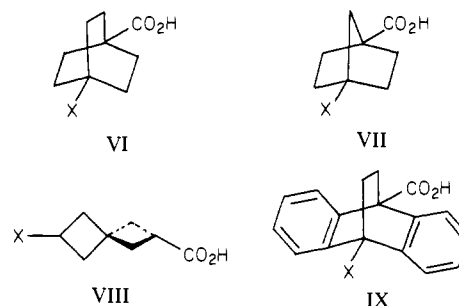
C. Precisions of Predicted Data. Table IV lists the precisions (standard deviations, S_p) of 75 of the 602 (14×43) predicted data (p_{ij}) values. All 602 were calculated by UNCERT,² but it would take much more space to list them all, and these 75 are typical and representative. S_p tends to be smaller for combinations measured than for combinations not measured (those enclosed in parentheses), e.g., in σ_p^+ (series 4, $S_8 = 0.043$) S_p is 0.030 for CN (measured) but 0.100 for N₂⁺ (missing). S_p is of course also less for series having a smaller range of values, e.g., never over 0.025 for σ_6 (series 12 where S_8 is only 0.010).

It may seem surprising that these data can be predicted so closely in view of the relatively large standard deviations of the component constants (F , R , f , r , and h in eq 1) that are listed in Tables I and II. For example, if one assumed that these constants were not interdependent, one could easily erroneously calculate

by conventional propagation-of-error analysis (by eq 6 of ref 2) that S_p for series 4 (σ_p^+) for NH₂ would be 0.127 rather than the 0.038 listed in Table IV. However, a 0.127 value would be wrong because its calculation would neglect some important covariances. For example, positive errors in f tend to be associated with, but compensated by, negative errors in F . Thus, although $\delta F \times \delta R$ covariances are small, $\delta f \times \delta F$ and $\delta r \times \delta R$ covariances are each very large and negative and serve to reduce markedly the predicted errors in p . Although our Monte Carlo error analysis UNCERT² ingeniously circumvents the detailed summation of all the many covariance terms and is simple and fast, it effectively encompasses the effect of more than a dozen first- and second-order covariance terms and gives the most realistic random error (S) values for all the calculated constants and for all the data that are available by any method. The uncertainties (relative standard deviations) of all these S values themselves have been reduced to $\pm 5\%$ (because they are all based on 200 trials).

D. Extension to Other Reactions. A wide variety of reactions can now be more easily analyzed by standard multiple linear least squares by using eq 1, 6, and 7 and the F and R constants already evaluated to calculate reaction constants (f , r , h), relative importance of resonance (% r), and correlation coefficients (C_i) for these other reactions. The results can be used to check the validity and generality of F and R and to test current chemical theories and reaction mechanisms. The substituents and data for 32 other reactions are listed in the section entitled Data Base.

For the simple, rigid, saturated systems in Table V (reactions 7, 5-6, 15, and 16 of structures I, VI-VIII), C_i always exceeds



0.990 and % r varies from 0% to 4%.^{17,18} Since all of these systems should be as free from resonance interactions as the standard series (7, I), we doubt that this small variation is due to anything other than small experimental errors. However, reaction 17 involves a carbon skeleton (IX) with interposed double bonds but in positions not conjugated with either reaction center or substituent.¹⁹ Its % r value of 10 is enough greater than any exhibited by the saturated aliphatic systems to suggest resonance involvement less than but approaching that in meta-substituted benzoic acids (% $r = 20$).

Naphthalene derivatives afford an opportunity for variation of distance and relative orientation between substituent and reaction center. Reactions 18-25 are dissociations of 2-naphthoic acids^{20,21} and anilinium²² and pyridinium²² cations. C_i is perceptibly poorer for 4- and 8-substituted than for 5-, 6-, 7-substituted 2-naphthoic acids but remarkably good (above 0.975) for all, considering the varying field effect that one might have expected from such a large variation in substituent dipole angle relative to the reaction center.

Aprotic media are included to test the generality of our substituent constants, since F and R were based entirely on reactions in aqueous solvents. Data on acid dissociations in dipolar aprotic solvents using benzoic acids²³ and picolinium cations²⁴ are useful

(17) Wilcox, C. F.; Leung, C. *J. Am. Chem. Soc.* **1968**, *90*, 339.(18) Liotta, C. L.; Fisher, W. F.; Greene, G. H., Jr.; Joyner, B. L. *J. Am. Chem. Soc.* **1972**, *94*, 4893.(19) Baker, F. W.; Parish, R. C.; Stock, L. M. *J. Am. Chem. Soc.* **1967**, *89*, 5678.(20) Wells, P. R.; Adcock, W. *Aust. J. Chem.* **1965**, *18*, 1368.(21) Dewar, M. J. S.; Golden, R.; Harris, J. M. *J. Am. Chem. Soc.* **1971**, *93*, 4187.(22) Wells, P. R.; Ehrenson, S.; Taft, R. W. *Prog. Phys. Org. Chem.* **1968**, *6*, 188.

Table V. Linear Least-Squares Analyses of Other Reactions with Predetermined F and R Constants

i	reaction ^a	nj_i	f	r	h	% r	S_δ	C_i^b
15	VII	7	0.71	0.03	0.03	4	0.041	0.9954
16	VIII	7	0.48	0.02	-6.30	3	0.025	0.9926
17	IX	7	0.73	0.09	0.01	10	0.018	0.9984
18	4-X- β naph	10	0.73	0.18	-0.03	20	0.079	0.9790
19	5-X- β naph	6	0.47	0.15	0.00	24	0.035	0.9931
20	6-X- β naph	10	0.44	0.20	-0.01	32	0.044	0.9911
21	7-X- β naph	12	0.46	0.14	-0.02	24	0.033	0.9925
22	8-X- β naph	10	0.25	0.19	-0.02	42	0.043	0.9799
23	3-XPhNH ₃ ⁺	15	1.67	0.28	0.00	15	0.129	0.9806
24	3-XpyrH ⁺	15	3.36	0.81	-0.06	19	0.300	0.9790
25	4-XpyrH ⁺	15	2.56	1.59	-0.28	38	0.309	0.9912
26	(CH ₃) ₂ SO	6	1.37	0.82	-11.00	37	0.140	0.9946
27	CH ₃ OH	6	1.39	0.25	-6.01	15	0.070	0.9931
28	CH ₃ CN	6	1.70	0.31	-13.54	16	0.090	0.9925
29	HCON(CH ₃) ₂	6	1.35	0.03	-4.83	2	0.077	0.9882
30	gas phase	5	10.23	7.54	-0.95	42	0.960	0.9959
31	ip, 3-Xacet	6	0.10	0.47	9.33	83	0.124	0.9811
32	ip, 4-Xacet	6	0.30	0.48	9.33	62	0.100	0.9894
33	CH ₃ O ⁻ + ArCl	13	2.63	2.43	-5.71	48	0.312	0.9895
34	2-XpyrH ⁺	9	6.65	0.60	-5.34	8	0.673	0.9648
35	NADH	5	0.87	1.27	0.10	60	0.114	0.9910
36	NADD (X)	5	0.98	1.29	-0.01	57	0.041	0.9989
37	racemase (XI)	4	0.97	0.78	0.00	44	0.012	0.9998
38	3-XPhF	15	3.78	0.39	-0.47	9	0.518	0.9245
39	4-XPhF	16	4.13	5.42	-2.23	57	2.602	0.9436
40	3'-X-PhPhF	7	1.72	0.32	0.01	16	0.144	0.9868
41	4'-X-PhPhF	6	1.38	1.37	0.03	50	0.096	0.9963
42	4'-X-PhCH ₂ PhF	7	0.63	0.27	0.00	30	0.072	0.9838
43	4'-X-stil-F	8	1.27	0.73	-0.04	36	0.188	0.9888
44	4'-X-PhCOPhF	8	1.16	0.81	-0.07	41	0.090	0.9977
45	4'-X-PhC ⁺ PhF	6	6.39	12.93	-0.85	67	1.22	0.9933
46	4'-X-PhC ⁻ PhF	7	4.05	2.13	-0.25	35	1.72	0.8618

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^a VII-IX refer to structures in the text. Except where noted below, data are $(\log k)/\rho$ or $(1/\rho) \log(k/k^H)$ values with $\rho = 1.00$, $k =$ acid dissociation constant K in water at 25 °C: 16 and 17 in 50% ethanol by weight;^{18,19} 18-22 are 2-naphthoic acids in 50% ethanol by volume ($\rho = 1.52$);²⁰ 23 is 3-anilinium ions (water, 25 °C);^{20,21} Pyridinium ions are in water (24, 25, 34)^{22,32} or gas phase (30);²⁵ 26 is 4-X-benzoic acids in Me₂SO; 27-29 are 4-X picolinium ions in methanol (25 °C), acetonitrile (25 °C), and DMF (35 °C);²⁴ 30 is relative free energy of association;²⁵ 31 and 32 are gas-phase ionization potentials of acetophenones;^{26,27} 33 is $\log k_2$ for nucleophilic substitution on 4-X-1-Cl-2-NO₂-benzenes in methanol at 50 °C, but datum for SCH₃ deleted;³¹ 35 is $\log k$ for dehydrogenase-catalyzed reductions and 36 is corresponding data using deuterated NADH (X), all in a pH 8.5 glycine buffer in 80% water-20% glycerol at 25 °C;³³ 37 is $\log k$ for enzymic racemizations in water at 25 °C;³⁴ 38-46 are NMR data for F chemical shifts of 3- and 4-substituted fluorobenzenes in dilute CCl₄ at 27 °C,³⁵ of 4-F-biphenyls in benzene at 36 °C,³⁶ of 4-F-diphenylmethanes in CH₂Cl₂ at 25 °C,³⁷ of 4-F-stilbenes in benzene at 25 °C, of 4-F-benzo-phenones in CH₂Cl₂ at 25 °C,³⁷ of 4-F-benzylhydriyl cations in FSO₃H at -60 °C,³⁷ and of α -phenyl-4-F-benzhydryl anions in Me₂SO at 25 °C.³⁷ ^b Since F and R are predetermined, the number of degrees of freedom (denominator of eq 6) is now simply $nj_i - 3$ (for the three constants, f_i , r_i , and h_i being determined), without the extra multiplier in the denominator. Comparable correlation coefficients C_i of reactions 1-14 would have been slightly higher if they had been (improperly) evaluated without this multiplier, e.g., 0.9967 instead of 0.9941 for reaction 2. ^c See Table VII and Data Base for the 271 data.

for this purpose (series 26-29). Similar comparisons can be made between aqueous and gas-phase acidities of pyridinium cations by using ion cyclotron resonance data (series 25 and 30).^{22,25} The high correlation coefficients (0.988-0.996) indicate that F and R constants are also applicable to processes occurring in non-aqueous media.

Substituents less likely to be well correlated in aprotic environments are those that interact by hydrogen bonding with an aqueous solvent, thereby altering their overall polarity. For reactions 26-29, the only substituent of this type appearing in all data sets is OH. For this substituent, only in series 26 is the difference $z_{ij} - p_{ij}$ (0.10) nearly as large as the standard deviation of the reaction (0.14). For series 26, the NH₂ substituent was also studied, and $z_{ij} - p_{ij}$ is -0.16 for it. Thus, for OH, our F and R constants determined in aqueous solutions may slightly overestimate the actual substituent effect in aprotic solvents, while for NH₂ our constants may slightly underestimate the effect. This is about what one could expect from hydrogen bonding, which

makes OH slightly more like O⁻ and makes NH₂ slightly more like NH₃⁺ in protic solvents.

The percent resonance derived for these media generally agree closely with corresponding reactions in protic solvents. The relevant comparisons are between series 27 (CH₃OH, 15% r) and 28 (CH₃CN, 16% r), between 2 (H₂O, 38% r) and 26 ((CH₃)₂SO, 37% r), and between 25 (H₂O, 38% r) and 30 (gas phase, 42% r).

Ionization potentials provide another test of the limits of applicability of our F and R constants. Reactions 31 and 32 represent ionization potential data of acetophenones determined by mass spectrometry.^{26,27} From the correlation coefficients (0.981-0.989), it is apparent that our substituent constants are, in general, applicable to these processes. Closer examination reveals that the experimental values for OH and NH₂ deviate from prediction more than for other substituents and in a manner consistent with their behavior in aprotic solvents. Specifically, $z_{ij} - p_{ij}$ for OH in series 31 and 32 are small but positive, 0.18 and 0.13, respectively. For NH₂, the deviations as expected are small and negative, -0.10 and -0.07.

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Attempts were made to analyze ionization potential data on substituted benzenes. However, adiabatic ionization potentials from photoionization studies,²⁷ vertical ionization potentials from photoelectron spectroscopy,²⁸ and the substituent constant series σ_{ip} ²⁹ all gave poor results, the C_i values being 0.86, 0.71, and 0.89, respectively. We suspected that these studies included substituents from which electrons are ejected with ionization energies of magnitudes that allow these processes to be confused with ring-electron ejections, because I, SH, and COCH₃ are the substituents that deviate most in these correlations. As a test of this hypothesis, we reanalyzed the substituted benzenes using only the eight other substituents, which are less likely to interfere. The correlation coefficients improved to the range 0.968–0.983.

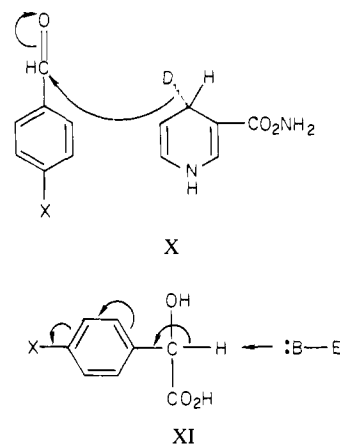
Aromatic substitution reactions offer an opportunity to test our constants in an environment in which resonance effects are expected to be especially important but where the aromatic π system is not retained intact throughout the reaction. Electrophilic substitutions have already been shown³⁰ to correlate well with σ_p^+ , used in defining our constants, and so must correlate well with F and R . A further test is provided by data on nucleophilic substitution. For the reaction of 1-Cl-2-NO₂-4-substituted-benzenes with methoxide, the correlation is good ($C_{33} = 0.990$).³¹

Proximity effects can be expected to prevent good correlations vs. F and R for systems in which the substituents can be closer to the reacting center than meta substituents in a benzoic acid (e.g., 2-substituted benzoic acids, α -substituted acetic acids, or γ -substituted butyric acids).³² Proximity effects can include steric hindrance, steric acceleration, intramolecular hydrogen bonding, or other types of neighboring-group participation, depending on the particular system. For 2-substituted pyridinium ions, the deviations may be due to the intrusion of inductive effects, which do not parallel the magnitude of field effects when the charge center is only two bond lengths removed from the substituent. In comparison to analogous 4-substituents (series 2, 3, 4, and 25), resonance effects for 2-substituents are rather small ($r = 8$ for series 34). Steric interactions with a reaction center often prevent 2-substituents from achieving the coplanarity with a ring needed for optimal resonance interaction.

Biological effects might be expected to correlate poorly with F and R because the size and shape of a substituent may influence substrate–enzyme or substrate–antibody complexing. Since the complexing or adsorption on the substrate may involve fitting most or all of the substrate structure into the binding site of a protein, a substituent may still be too close to be free from steric effects in many biological systems even when it is para. Ease of penetration through skin or a membrane may also be involved, and this substituent influence may parallel fat solubility (lipophilicity or hydrophobicity).

Nevertheless, some enzymic reactions are correlated remarkably well by F and R . Yeast alcohol dehydrogenase catalyzed reductions of five 4-substituted benzaldehydes (Br, Cl, H, CH₃, OCH₃) by hydride transfer from NADH (reduced nicotinamide adenine dinucleotide, log k_H values³³) correlate well ($C_{35} = 0.991$) with the same blend of F and R as σ_p^- (60% r). Five analogous reductions involving deuteride transfer from NADD (reduced nicotinamide adenine dinucleotide with ²H in the 4 α position, structure X, log k_D data) fit even better ($C_{36} = 0.9989$).³³

Mandelic acid racemase racemizations of five 4-substituted mandelic acids correlate poorly ($C_i = 0.83$), but deletion of the OH datum gives $C_{37} = 0.9998$ and 44% r for the remaining substituents (Br, Cl, H, OCH₃), consistent with incipient formation of a carbanion intermediate (XI)³⁴ but suggesting some special catalysis by the phenolic OH.



NMR data on fluorine chemical shifts due to substituents are analyzed in Table V for nine aromatic skeletons (series 38–46).^{35–37} These correlations are often unsatisfactory. C_i is only 0.924–0.944 for 3- and 4-substituted fluorobenzenes. Substituted 1- and 2-fluoronaphthalenes also correlate poorly, although series 40–45 are acceptable. Evidently the substituent can introduce a magnetic influence or some other factor not correlated with either F or R that often has considerable importance. For fluorine bound to a bicyclooctane system,³⁸ fluorine chemical shifts are large and opposite in sign from the usual predictions, and correlation coefficients are below 0.80. We have no satisfactory interpretation for these data but do have a suggestion (under Handling a Third Vector) for a possible way to identify and evaluate the third factor.

Relation to σ_I and σ_R Values. Among other pairs of substituent constants much used in the past are Taft's σ_I and σ_R values. They have undergone frequent revision, but Charton reviewed them critically in 1981 and listed those that he considered most reliable.³⁹ He listed both σ_I and σ_R for 34 of our 43 substituents. Correlation coefficients for most of our 46 reactions are acceptable if one uses these σ_I and σ_R instead of F and R . However, significant failures include C_3 (C_i for $i = 3$, σ_p^- , phenoxide anions) = 0.913 instead of 0.994 and C_4 (σ_p^+ , benzyl cations) = 0.961 instead of 0.994. If σ_R is replaced by σ_R^- for the 17 substituents for which σ_R^- is listed, C_3 rises from 0.913 to 0.979 but C_2 (σ_m), C_4 (σ_p^+), and C_{10} collapse to 0.922, 0.892, and 0.942. If, instead, σ_R is replaced by σ_R^+ for the 18 substituents for which σ_R^+ is listed, C_4 (σ_p^+) rises from 0.961 to 0.988 but C_3 (σ_p^-) and C_{14} (σ^0) are unacceptable at 0.918 and 0.958. In contrast, F and R constants are constant, i.e., fit all 14 + 28 reactions without being varied (cf. Tables II and V, where C_1 – C_{21} , C_{25} – C_{30} , C_{32} – C_{33} , and C_{35} – C_{37} are all above 0.984).

Even if σ_I and σ_R had fitted all of these reactions just as well as F and R , which they do not, that would provide no evidence that they have properly separated nonresonance (localized) and resonance (delocalized) influences. Any two arbitrary mixtures or linear combinations of F and R such as $G_j = 0.9F_j + 0.1R_j + 0.1$ and $S_j = -0.7F_j + 0.8R_j$ reproduce all of the data exactly as well as F and R and much better than σ_I and σ_R , but G and S values certainly lack the obvious and simple physical significance of F and R values. Therefore we have also scrutinized the σ_I and σ_R values separately to see if they have credible signs and rank orders for constants intended to represent nonresonance and resonance influences respectively. The following two paragraphs cite some of the sign and order paradoxes that make us conclude that they do not.

The σ_I values are roughly 0.6 F for most substituents. Since σ_I for CH₃ and C₂H₅ are negligible (–0.01) compared to σ_R (–0.14

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index i is given only once, initially or after a backslash, followed by pairs of solvent j and z values, with leading and trailing zeros omitted to save space, in these computer-generated and computer-readable tables.

See Experimental Section of the following paper⁴⁰ for details

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of hardware and software used.

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Solvent Effects on Chemical Reactivity. Evaluation of Anion and Cation Solvation Components

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Abstract: Free energy changes due to solvent are fitted for 61 solvents and 77 reactions by $aA + bB + c$, where A (anion-solvating tendency) and B (cation-solvating tendency) depend on only the solvent and a , b , and c depend on solely the reaction. The input data are based on rate constants, product ratios, equilibrium constants, and electronic, IR, ESR, and NMR spectra. All 353 ($= (2 \times 61) + (3 \times 77)$) A , B , a , b , and c constants are evaluated by nonlinear least squares by using equal statistical weighting of 1080 data, the four trivial scale-setting subsidiary conditions $A = B = 0$ for *n*-heptane and $A = B = 1$ for water, and the two critical subsidiary conditions $A = 0$ for hexamethylphosphoric triamide and $B = 0$ for trifluoroacetic acid. There is no correlation between A and B values. The precision (standard deviation) is listed for each of the 353 constants and also the correlation coefficient for each solvent and for each reaction. The overall correlation coefficient between input data and predictions is 0.991; no individual solvent is below 0.970 and no reaction below 0.975. Benzene has $A = 0.15$, $B = 0.59$, which makes it more polar than CCl_4 but less polar than acetone. Solvolysis of *tert*-butyl chloride has $a = 7.4$, $b = 5.6$, but solvolysis of triphenylmethyl fluoride is more sensitive to the solvent's ability to solvate anions ($a = 14.9$, $b = 1.8$), while $\text{EtI} + \text{Et}_3\text{N}$ favors cation solvators relatively more ($a = 0.9$, $b = 4.4$). The reaction correlation coefficient is below 0.975 for many other reactions owing to a change in the mechanism or process under observation at some point within the range of solvents studied, with this point often becoming evident upon scrutiny of the individual deviations for each solvent.

Attempted Solvent Effect Predictions Based on One Constant per Solvent

Solvent effect equations have usually involved only a single solvent vector A , i.e., only a single string of solvent constants A_j , one for each solvent j , in a simple linear free energy relationship (eq 1) for predicted solvent effects p_{ij} . Here any lower case a_i

$$p_{ij} = a_i A_j + c_i \quad (1)$$

represents the sensitivity of reaction i to solvent change and c_i is the predicted value for the reference solvent j_0 (for which $A_j = 0$).

In 1948, Grunwald and Winstein² evaluated A_j values, which they called Y or "solvent ionizing power", for various solvents and solvent mixtures from logarithms of first-order rate constants for solvolysis of *tert*-butyl chloride at 25 °C ($Y = \log k_1(j) - \log k_1(80\% \text{ ethanol})$). Numerous alternative A sets appeared subsequently, e.g., Kosower's Z and Dimroth's E_T derived from spectral absorption frequencies and Berson's Ω from a product ratio.³⁻⁵ Each investigator plotted energy changes in other re-

actions vs. his A values. These plots are roughly linear, more nearly linear the closer the mechanism or nature of the reaction plotted is to that of the defining reaction. These different A sets also correlate moderately well with one another. In Reichardt's superb review⁶ of work on solvent effects through 1977, all pre-1978 equations and parameters for predicting solvent effects are clearly presented and critically assessed in his final chapter⁷ and all pertinent references are cited.

Use of eq 1 presupposes that only one solvent property significantly affects reactivity, or, if two independent properties are influential (as assumed in eq 2), that a_i/b_i (the ratio of sensitivities to the two properties or vectors) is nearly constant for reactions to which eq 1 applies. Evidently the blend or mix of a and b is comparable for the A sets mentioned above. In the light of the present study, it now appears that a_i/b_i is 1.3 for Y , 5.4 for Z , 6.8 for E_T , and 3.9 for Ω . This variation is minor compared to the range from -240 to +67 that we find for other reactions among the 77 listed in Tables I and II.

Tables I and II list 77 reactions and 1080 data suitable for testing various procedures.⁸⁻⁵⁹ The 77 reactions comprise 32 series

(1) (a) Chose the six subsidiary conditions. (b) Developed and executed computer programs. (c) Office of Naval Research from 1947 to 1979. Guest of M.I.T. Searched literature for accurate data. (d) Present address: Istituto di Chimica Organica, Università di Perugia. Measured reactions 45-47.

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