Theoretical and Experimental Evaluation of IFER for MSE (Interactive Free Energy Relationship for Multiple-Substituent Effects). Mechanistic Significance of the Reaction Constant and Cross-Interaction Constant[†]

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Abstract: Substituent–substituent interactions are quantitatively investigated by the interactive free energy relationship (IFER), $\log k_{XY}/k_{HH} = \rho_1{}^H\sigma_X + \rho_2{}^H\sigma_Y + q\sigma_X\sigma_Y$, which is theoretically derived on the reasonable assumption that the quadratic terms in $\sigma_X{}^2$ and $\sigma_Y{}^2$ are negligible compared to the cross term in $\sigma_X\sigma_Y$. The IFER equation is tested for different types of substituent effects on various classes of reactions involving one or two reagents and including all the possible behaviors with respect to RSP. This equation is applied to 35 data sets of multiple-substituent effects (MSE); the additive ($q = 0$) and nonadditive ($q \neq 0$) effects are accurately described provided that the elementary FER's, where only one substituent varies, are linear. With this condition, 32 values of the cross-interaction constant can be calculated, mainly from kinetic and thermodynamic data; q is found to vary markedly, from +1 to −8. As regards the kinetic effects, the IFER works regardless of the reactivity–selectivity dependence. The extensive survey of q values enables interactions to be compared in rates and equilibria: the interaction constant is systematically higher for kinetic than for thermodynamic data; ρ for rates is twice as sensitive to the structure as ρ for equilibria. This result, analyzed in terms of the thermodynamic and intrinsic kinetic contributions to the reactivity, suggests that the interaction constant q reflects at least in part a change in the transition-state position induced by the substituent. The constant q is a free energy relationship parameter, complementary to the reaction constant ρ for investigating the structure of the transition state.

According to the Hammond postulate[1] and to more recent theoretical developments[2,3] such as those of Marcus and Lewis–More O'Ferrall, free energy relationships (FER) should not be linear. This intriguing deduction is the subject of frequent debate since it casts doubt upon the very significance of the FER parameters usually considered as terms characteristic of the transition-state position. Experimental proofs of curvature in FER are not common. The situation is, moreover, quite different depending on whether Brønsted[4] rate–equilibrium relationships or Hammett[5] structure–reactivity relationships are concerned. While there is experimental[6] support for the theoretical prediction of curvature[7] in Brønsted relationships, very little has been done in connection with Hammett or Hammett–Brown equations.[8] More O'Ferrall has shown[9] from a study on rates and equilibria in five reactions that the Hammett ρ for one substituent could be a variable described by the following expression.

$$\rho = \rho_0 + 2m\sigma \qquad (1)$$

However the opposite theory, namely that structure–reactivity relationships are linear and that ρ is constant, has been upheld[10] on a pragmatic basis. This debate is of fundamental importance since the assumption of a constant ρ leads one to conclude, contrary to what is commonly agreed,[11] that ρ cannot be an index of the transition-state position. In fact linearity of reactivity–structure relationships means merely that the second derivative of the reactivity[12] is negligible compared to the first derivative ($m \ll \rho$).

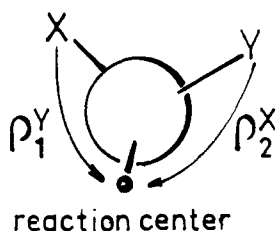$$(\partial \log k_X)/\partial\sigma_X = \rho \qquad (2)$$

$$(\partial^2 \log k_X)/\partial\sigma_X{}^2 = \partial\rho/\partial\sigma_X = m \qquad (3)$$

Several reasons, both experimental and theoretical,[13] can be invoked to explain the fact that no curvature has yet been detected

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(5) Hammett, L. P. *Chem. Rev.* **1935**, *17*, 126–136.

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(7) (a) Eigen, M. *Angew. Chem.* **1963**, *75*, 489–508. (b) Kresge, A. J. *Acc. Chem. Res.* **1975**, *8*, 354–360. (c) Crooks, J. E. "Proton Transfer Reactions"; Caldin, E. F., Gold, V., Eds.; Chapman and Hall: London, 1975; pp 153–199. (d) More O'Ferrall, R. A. In ref 7c, pp 201–261. (e) Murdoch, J. R.; Magnoli, D. E. *J. Am. Chem. Soc.* **1982**, *104*, 3792–3800.

(8) Brown, H. C.; Okamoto, Y. *J. Am. Chem. Soc.* **1957**, *79*, 1913–1917.

(9) O'Brien, M.; More O'Ferrall, R. A. *J. Chem. Soc., Perkin Trans. 2* **1978**, 1043–1045.

(10) (a) Johnson, C. D. *Chem. Rev.* **1975**, *75*, 755–765. (b) Johnson, C. D. *Tetrahedron* **1980**, *36*, 3461–3480. (c) Kemp, D. S.; Casey, M. L. *J. Am. Chem. Soc.* **1973**, *95*, 6670–6680. (d) Poh, B. L. *Aust J. Chem.* **1979**, *32*, 429–432.

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IFER for MSE

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Scheme I

reaction center

in the Hammett equation. It seems then that, to understand the inherent contradiction between the observed linearity of FER and the relationship between ρ and the transition-state position, the analysis of the effect of only one substituent is inadequate and that another approach must be adopted. We have decided to tackle this problem through a study of multiple-substituent effects. We can pragmatically assume that the second derivative of the reactivity relative to the effect of one substituent is zero, but the cross second derivative[14] for the effect of two substituents is not necessarily zero.

$$(\partial^2 \log k_{XY})/\partial\sigma_X\partial\sigma_Y = q \neq 0 \qquad (4)$$

Present data on the cross second derivatives in Hammett relationships are scarce and confused. We have already studied several systems (bromination of polysubstituted benzenes[15] and electrophilic addition of bromine on conjugated alkenes[16]) where the existence of a q value[14] different from zero was firmly established. However there are other examples[17] which might support the alternative statement that q is most often zero. In the Brønsted relationship this cross derivative, otherwise known as Cordes' coefficient,[18] is well established. Although the Cordes' coefficient does not depend only on the transition state, it has been used[12] with some reservations to estimate variation in the position of the latter.

Since the cross-interaction constant is rarely calculated explicity in the literature,[19] we propose in this paper to establish its theoretical and experimental reality through an extensive analysis of the effect of multiple substituents on kinetic and thermodynamic properties. Comparing experimental values of q for rates and equilibria provides fundamental results on the contribution of the transition-state position to the FER parameters.

Theoretical Definition of the IFER and the Cross-Interaction Constant q

When the effect of a substituent is described by a single variable, the interactive free energy relationship (IFER) for the effect of two substituents (Scheme I) can be deduced from the Taylor

expansion of the reactivity[20] considered as a function of two variables, here σ_X and σ_Y. If the elementary Hammett equations for the effect of one substituent are assumed to be linear, second and higher derivatives of the reactivity with respect to one variable only are null and the Taylor expansion leads to the classical equation[24] (5) where the interactive term arises from the cross secondary derivative.

$$\log (k_{XY}/k_{HH}) = \rho_1^H\sigma_X + \rho_2^H\sigma_Y + q\sigma_X\sigma_Y \qquad (5)$$

If elementary Hammett equations are not linear, one must take into account supplementary terms in σ_X^2 and σ_Y^2 such as those introduced by More O'Ferrall and even in $\sigma_X^2\sigma_Y$ and $\sigma_X\sigma_Y^2$. A complete treatment is still possible, but there are usually not enough experimental data for all the parameters to be calculated significantly.

The IFER for multiple-substituent effect (MSE) (eq 5) can also be derived more directly from the expression for the reactivity of a disubstituted compound in terms of the more customary form of the Hammett equation. The cumulative effect of two substituents, X and Y, on the reactivity is equal to the sum of the effect of X (or Y) on the nonsubstituted system and of that of Y (or X) on the monosubstituted system.[25] Since there is no reason to assume a priori that the ρ value remains constant whatever X or Y, one denotes the reaction constant when X (or Y) is the fixed substituent by ρ_2^X (or ρ^Y).

$$\log (k_{XY}/k_{HH}) = \rho_2^X\sigma_Y + \rho_1^H\sigma_X = \rho_1^Y\sigma_X + \rho_1^H\sigma_Y \qquad (6)$$

From identity 6, it follows

$$\frac{\rho_2^X - \rho_2^H}{\sigma_X} = \frac{\rho_1^Y - \rho_1^H}{\sigma_Y} = q \qquad (7)$$

Equality 7 holds whatever X and Y. Therefore the ratios are constant. Considering eq 6 and 7 leads to the IFER for the cumulative effect of substituents X and Y on the reactivity (eq 5). This relationship shows that an interactive term must be considered as well as the additive ones. Additivity holds only if $q = 0$.

Application of the IFER for MSE to Experimental Systems

To obtain the cross-interaction constant for a given disubstituted system, the IFER for MSE (eq 5) in the simplified form of eq 8 derived from the identities of eq 7 is preferable.

$$\rho^Y = \rho^H + q\sigma_Y \qquad (8a)$$

$$\rho^X = \rho^H + q\sigma_X \qquad (8b)$$

This procedure has several advantages: it avoids artifical optimizations resulting from statistical treatments by multiple regression; it forces one to verify the criterion for applying the IFER, i.e., that the FER for the effect of one substituent alone is linear; it checks the identify of the q values obtained by the variation of one or the other substituent.

There are three experimental methods for obtaining q. The most significant (method A) uses eq 8. When only ρ_1^H and ρ_2^H are available, q can be calculated by plotting the deviations of disubstituted compounds from additivity against $\sigma_X\sigma_Y$ (method B). Finally, method C, based on multiple regression according to eq 5, can be used as a last resort. Agreement between the three methods should be checked when possible.

(13) Firstly the σ^+ scale[8] and those derived from it are based on rate data and therefore include the variation of the transition-state position in the reference reaction. The fact that the Hammett equation for a given reaction is usually linear means that the transition-state position varies proportionally in this and the reference reaction. Secondly, curvature can only be detected when the reactivity can be studied over a wide range. But an extension of the reactivity range generally changes at least the type of substituent effect (polar or resonance) if not the reaction mechanism. Moreover, the scales of substituent constants which express these different effects have been derived one from the other, the chief concern being to conserve the linearity of the $\rho\sigma$ equation. Alternatively, from a theoretical point of view, the curvature of a FER is related to the intrinsic barrier[2,3,7] of the reaction; it is likely that nonreversible reactions have barriers too high for the second derivative to be significant.

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(20) Taylor expansions of the free energy of a reaction were used by Leffler[21] Palm,[22] and Wold[23] to give a mathematical fundation to LFER. Here the LFER's are assumed to be true and log k or log K are expanded as a function of the substituent parameters considered as variables.

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(22) Palm, V. A.; Istomin, I. *Reakts. Sposobn. Organ. Soedin.* **1969**, *6*, 427.

(23) Wold, S. "Correlation Analysis in Chemistry"; Chapman, N. B., Shorter, J., Eds.; Plenum Press: London, 1978; pp. 1–54.

(24) The first expression of the IFER for MSE was deduced by Miller[14] using geometrical considerations. However, this relationship has not yet received many applications in multisubstituted systems.

(25) This expression is more exact than that of additivity where it is assumed that the effect of X and Y is equal to the sum of the effects of each on the nonsubstituted system.
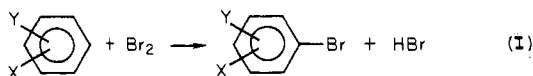
Table I. Calculation of the Cross-Interaction Constant q from IFER for MSE: Kinetic Data

no.	reaction	$\rho_H{}^o$	q^b	$\mathcal{D}_{expil}{}^f$
1	bromination of X,Y-disubstituted benzenes[15]	$-12.05\ (\sigma^+)$	-7.98 ± 0.43	15.1
2	hydrogen exchange in X,Y-disubstituted pyridines[g]	$-12.9\ (\sigma^+)$	-7.6 ± 1.2	7.0
3	hydrogen exchange in X,Y-disubstituted benzenes[g]	$-7.5\ (\sigma^+)$	-3.0 ± 0.34	11.9
4	ethanolysis of benzhydryl chlorides[h]	$-4.39\ (\sigma^+)$	-2.2 ± 0.3	7.1
5	reaction of X,Y-disubstituted N,N-dimethylanilines with alkyl bromides[i]	$-2.44\ (\sigma)$	-1.6 ± 0.3	1.45
6	bromination of 1,1-diarylethylenes[j]	$-3.57\ (\sigma^+)$	-1.55 ± 0.08	6.1
7	addition of arylsulfenyl chlorides to styrenes (X—C_6H_4—CH=CH$_2$ + Y—C_6H_4SCl)[30]	$-1.37\ (X,\sigma^+)$	-1.02 ± 0.11	3.2
		$-0.20\ (Y,\sigma^+)$	-1.01 ± 0.04	
8	bromination of α-methylstilbenes (X—C_6H_4—C(Me)=CH—C_6H_4—Y)[k]	$-4.59\ (X,\sigma^+)$	-0.71 ± 0.04	6.4
		$-1.66\ (Y,\sigma)$	-0.68 ± 0.01	
9	reaction of arylsulfonyl chlorides with anilines (X—C_6H_4—NH$_2$ + Y—C_6H_4—SO$_2$Cl)[28]	$-2.16\ (X,\sigma)$	-0.75 ± 0.03	3.0
		$+1.01\ (Y,\sigma)$	-0.75 ± 0.06	
10	E-2 elimination from (2-phenylethyl)arenesulfonates (X—C_6H_4—(CH$_2$)$_2$—OSO$_2$—C_6H_4—Y)[l]	$2.51\ (X,\sigma)$	-0.50 ± 0.09	2.5
		$1.08\ (Y,\sigma)$	-0.50 ± 0.04	
11	cycloaddition of 9-X-substituted acrizidinium ions with p-Y-substituted styrenes[m]	$1.71\ (X,\sigma)$	-0.36 ± 0.06	2.8
		$-0.57\ (Y,\sigma^+)$	-0.36 ± 0.04	
12	solvolysis of N-(2,2-dinitro-2-arylethyl)aryl amines (X—C_6H_4—NH—CH$_2$—C(NO$_2$)$_2$—C_6H_4—Y)[n]	$-2.75\ (X,\sigma)$	-0.32 ± 0.01	3.6
		$+1.97\ (Y,\sigma)$	-0.31 ± 0.01	
13	hydrolysis of X,Y-disubstituted ethyl cinnamates[o]	$1.18\ (\sigma)$	$+0.28^e \pm 0.07$	1.8
14	reaction of X-substituted diphenyldiazomethanes with Y-substituted benzoic acids[p]	$-1.69\ (X,\sigma)$	$-0.27^{d,e} \pm 0.02$	4.0
		$+2.22\ (Y,\sigma)$		
15	addition of X-substituted arylthiols to ethyl Y-substituted phenyl propionates[q]	$-0.94\ (X,\sigma^-)$	$-0.09^e \pm 0.01$	1.3
		$+2.50\ (Y,\sigma)$		
16	hydrolysis rates of carbohydrazones (X—C_6H_4—CO—NH—N=CH—C_6H_4Y)[r]	$0.14\ (X,\sigma)$	$+0.08 \pm 0.01$	1.2
		$-0.78\ (Y,\sigma)$	$+0.08 \pm 0.01$	
17	hydrolysis of substituted phenylbenzoates (X—C_6H_4—CO—O—C_6H_4—Y)[17]	$2.0\ (X,\sigma)$	0.0^s	4.5
		$1.28\ (Y,\sigma)$	0.0	

[a] Substituent constants used for the aromatic substituents: (X,σ_i) σ_i for the X substituent; (Y,σ_i') σ_i' for the Y substituent. [b] Calculated by method A, B, and/or C (see text); when $\rho^X \neq \rho^Y$ the two q values calculated from the variation of either ρ^X or ρ^Y are given whenever method A could be used (see footnote c). The q value is followed by its standard deviation when statistically significant according to the F test. The usual 95% confidence level has been adopted: Draper,, N. R.; Smith, H. "Applied Regression Analysis"; Wiley: New York, 1966. [c] Method A: variation of ρ, eq 8. [d] Method B: calculated from the deviations from additivity. [e] Method C: application of the general relationship of eq 5. [f] Experimental field. Amplitude of the experimental measurements in log unit. [g] Clementi, S.; Johnson, C. D.; Katritzky, A. R. *J. Chem. Soc., Perkin Trans. 2* **1974**, 1294–1298. [h] Nishida, S. *J. Org. Chem.* **1967**, *32*, 2692–2701. [i] Crocker, H. P.; Jones, B. *J. Chem. Soc.* **1959**, 1808–1816. [j] Hegarty, A. F.; Lomas, J. S.; Wright, W. V.; Bergmann, E. D.; Dubois, J. E. *J. Org. Chem.* **1972**, *37*, 2222–2228. [k] Argile, A.; Ruasse, M. F. *J. Org. Chem.* **1983**, *48*, 209–214. [l] Banger, J.; Cockerill, A. F.; Davies, G. L. O. *J. Chem. Soc. B* **1971**, 498–502. [m] Porter, N. A.; Westerman, I. J.; Wallis, T. G.; Bradsher, G. K. *J. Am. Chem. Soc.* **1974**, *96*, 5104–5107. [n] Ghidaspov, B. V.; Ivanov, P. A.; Selwanov, V. P.; Shscherbinin, M. B. *Org. React. (Tartu)* **1972**, *9*, 1061. [o] Jones, E.; Watkinson, J. G. *J. Chem. Soc.* **1958**, 4064–4069. [p] Hancock, C. K.; Foldvary, E. *J. Org. Chem.* **1965**, *30*, 1180–1184. [q] Krhishnamurthy, G. S.; Miller, S. I. *J. Am. Chem. Soc.* **1961**, *83*, 3961–3965. [r] Dekelbaum, A. B.; Passet, B. V.; Fiodorov, G. F. *Org. React (Tartu)* **1973**, *10*, 645. [s] Significance of a q value near 0 cannot be estimated by the F test.

Before a more general overview, we shall discuss a few representative examples to illustrate the mechanistic implications of the IFER. The chosen reactions behave diversely with respect to the reactivity–selectivity principle (RSP);[26] for some of them, the substituent effect decreases as the reactivity increases (RSP(+)); for others, it increases (RSP(−)) or is independent[27] (RSP(0)). Nonetheless they can all be interpreted in terms of the IFER treatment.

(a) Interaction in a Reaction with RSP(+) Behavior: Bromination of Benzenes (No. 1, Table I). This reaction (eq I) is the first case where we used a multiparametric treatment for reactivity.[15] The tw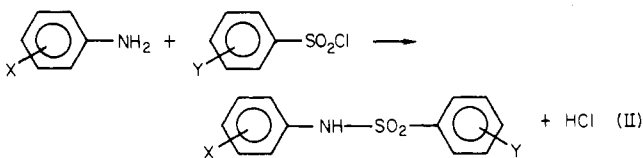o substituents and the reaction center are on the same ring. Table III shows the values of ρ^Y obtained for the effect of X when Y remains constant. In this case the effects of X and Y are symmetric, so eq 8a and 8b which express the effect of the fixed substituent on the reaction constant ρ are the same. From these relationships (method A) $q = -7.98$ with $\rho^H = -12.05$. Regression of the deviations from additivity against $\sigma_X^+\sigma_Y^+$ (method B) gives $q = -7.35$ ($R = 0.973$). Finally, the multiparametric regression of log k_{XY} against σ_X^+, σ_Y^+, and $\sigma_X^+\sigma_Y^+$ (method C) leads to $\rho^H = -11.0$ and $q = -5.4$. While methods

A and B give nearly identical values of q, smaller values of both ρ and q are obtained by method C. This is probably due to the fact that the variables used in the multiple regression are somewhat interdependent. Thus it is reasonable to adopt the q value obtained by the first two methods since method C does not give the experimental ρ^H value.

(b) Interaction between Substituents on Two Reactants in a RSP(−) Reaction: Reaction of Arylsulfonyl Chlorides with Anilines (No. 9, Table I). In this reaction (eq II) whose RSP(−) behavior is due to the nonsynchronous breaking and making of S–Cl and N–S bonds in the transition state,[28,29] both reactants carry sub-

stituents. The cross-interaction constant can be calculated independently from eq 8. Regression of ρ^Y (Table IV) against σ^Y gives $q = -0.75$ and of ρ^X against σ^X gives $q = -0.75$. The good agreement between these two values justifies the multiparametric treatment. From the departure from additivity (method B) a q value of −0.78 is obtained. The general relationship gives ρ values of −2.16 and 0.98 and $q = -0.75$. There is a quantitative agreement between the q values obtained by different methods.

(c) Interaction in a System with Substituent-Dependent RSP Behavior: Sulfenylation of Styrenes (No. 7, Table I). This reaction[30] (eq III) is a very unusual example where the sign of the

(26) Stock, L. M.; Brown, H. C. *Adv. Phys. Org. Chem.* **1963**, *1*, 44–154. Pross, A. *Ibid.* **1977**, *14*, 69–132. Giese, B. *Angew. Chem., Int. Ed. Engl.* **1977**, *16*, 125–136.
(27) Strictly speaking, when $q = 0$, the behavior of the system is in disagreement with the RSP since the selectivity remains constant whatever the reactivity. However, this behavior must be distinguished from an anti-RSP behavior where the variation of the selectivity parallels that of the reactivity.
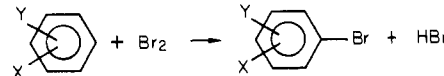
(28) Rogne, O. *J. Chem. Soc. B* **1971**, 1855–1858.
(29) Giese, B.; Heuck, K. *Chem. Ber.* **1978**, *111*, 1384–1394.

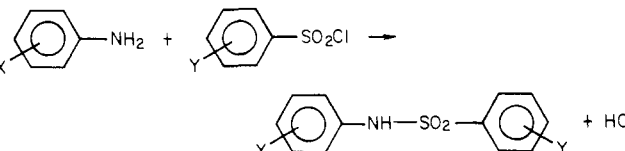**Table II.** Calculation of the Cross-Interaction Constant q from IFER for MSE: Thermodynamic Data

no.	ionization equilibria	$\rho_H{}^a$	q^b	$\mathcal{D}_{expH}{}^f$
1	2,7-X,Y-disubstituted fluorenes[g]	7.5 (σ)	[h]	9.6
2	conjugate acids of azoxybenzenes (X—C$_6$H$_4$—NO=N—C$_6$H$_4$—Y)[i]	1.73 (X,σ) 2.51 (Y,σ^-)	-1.6^e	4.6
3	stabilities of diphenylmethylcarbenium ions (X—C$_6$H$_4$—C$^+$H—C$_6$H$_4$—Y)[j]	-6.90 (σ^+)	$-1.57^c \pm 0.24$	27.1
4	addition of hydroxide ion to benzaldehydes (X,Y—C$_6$H$_3$—CHO)[k]	2.45 (σ)	$-1.34^e \pm 0.14$	3.1
5	stabilities of trityl cations[l]	-5.81 (σ^+)	$-1.30^{c,d,e} \pm 0.06$	22.8
6	tritylalcohols[j]	-5.25 (σ^+)	$-0.95^e \pm 0.13$	25.9
7	conjugate acids of azobenzenes (X—C$_6$H$_4$—N=N—C$_6$H$_4$—Y)[m]	2.18 (σ)	$0.61^{c,d,e} \pm 0.07$	6.0
8	conjugate acids of diphenylamines (X—C$_6$H$_4$—NH—C$_6$H$_4$—Y)[n]	$+3.09$ (σ)	$-0.46^{d,e} \pm 0.12$	7.6
9	conjugate acids of anilines (X,Y—C$_6$H$_3$—NH$_2$)[o]	$+2.89$ (σ^-)	$+0.44^e \pm 0.20$	5.1
10	benzoic acids (X,Y—C$_6$H$_3$—CO$_2$H)[p]	$+2.45$ (σ)	$-0.14^e \pm 0.06$	4.0
11	sulfonamides (X,Y—C$_6$H$_3$—SO$_2$NH$_2$)[q]	$+1.42$ (σ)	$-0.10^{c,d,e} \pm 0.08$	2.5
12	arylmethylphenacylsulfonium salts (X—C$_6$H$_4$—S$^+$(Me)—CH$_2$—CO—C$_2$H$_4$—Y,BF$_4^-$)[s]	$+1.23$ (X,σ) $+2.61$ (Y,σ)	$0^{e,r}$	2.5
13	phenols (X,Y—C$_6$H$_3$—OH)[t]	-3.08 (σ^-)	d,e,h	4.7
14	arylsulfonamides (X,Y—C$_6$H$_3$SO$_2$—NH—C$_6$H$_5$)[q]	$+1.57$ (σ)	$\simeq 0^{c,d,e,r}$	1.5

^{a} Substituent constants used for the aromatic substituents: (X,σ_i) σ_i for the X-substituent; (Y,σ_i') σ_i' for the Y substituent. ^{b} Calculated by method A, B, and/or C (see text). When several methods have been applied, the value given here is the statistically most significant. The q value is followed by its standard deviation when it is statistically significant according to the F test. The usual 95% confidence level has been adopted: Draper, N. R.; Smith, H. "Applied Regression Analysis"; Wiley: New York, 1966. ^{c} Method A: variation of ρ, eq 8. ^{d} Method B: calculated from the deviations from additivity. ^{e} Method C: application of the general relationship eq 5. ^{f} Amplitude of the experimental measurements. ^{g} Bordwell, F. G.; McCollum, G. J. *J. Org. Chem.* **1976**, *41*, 2391-2395. $^h q$ and ρ^H values obtained by methods B and C are not identical. ^{i} Hahn, C. S.; Jaffé, H. H. *J. Am. Chem. soc.* **1962**, *84*, 949-953. ^{j} Freedman, H. H. "Carbonium Ions"; Olah, G. A., Schleyer, P. v. R., Eds.; Wiley: New York, 1973; Vol. 4, p 1532. ^{k} Greenzaid, P. *J. Org. Chem.* **1973**, *38*, 3164-3167. ^{l} McKinley, S. V.; Rakshys, J. W., Jr.; Young, A. E.; Freedman, H. H. *J. Am. Chem. Soc.* **1971**, *93*, 4715-4724. ^{m} Yeh, S. Y.; Jaffé, H. H. *J. Am. Chem. Soc.* **1959**, *81*, 3279-3283. ^{n} Dolman, D.; Stewart, R. *Can. J. Chem.* **1967**, *45*, 903-910. ^{o} de Courville, A. *C.R. Hebd. Seances Acad. Sci., Ser. C* **1966**, *296*, 1196-1199. ^{p} Kolthoff, J. M.; Chantoni, M. K., Jr. *J. Am. Chem. Soc.* **1971**, *93*, 3843-3849. ^{q} Dauphin, G.; Kergomard, A.; Veschambre, H. *Bull. Soc. Chim. Fr.* **1967**, 3395-3410. ^{r} The q value obtained is near 0; the F-test is therefore not significant. ^{s} Ratts, K. W. *J. Org. Chem.* **1972**, *37*, 848-851. ^{t} Ritchie, C. D.; Sager, W. F. *Prog. Phys. Org. Chem.* **1964**, *2*, 362.

Table III. Electrophilic Bromination of Multisubstituted Benzenes: $q = -7.98$


Y	H	2-Me	2-OMe	4-OMe	4-NMe$_2$
ρ^Y	-12.05	-10.60	-7.00	-6.60	-2.50
log k_{HY}	-5.57	-2.74	2.30	3.98	8.34

Table IV. Reaction of Arylsulfonyl Chlorides with Anilines: $q = -0.78$
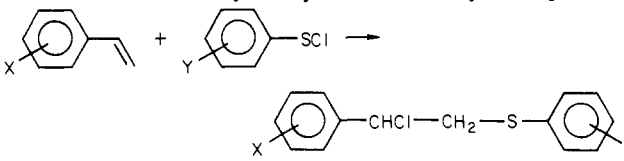
X	3,4-Me$_2$	4-Me	3-Me	H	4-Cl	3-Cl	3-NO$_2$
ρ^X	1.14	1.11	1.02	1.01	0.78	0.71	0.44
log k_{XH}	-0.60	-0.77	-0.97	-1.16	-1.56	-1.90	-2.69

Y	4-OMe	4-Me	H	4-I	3-NO$_2$	4-NO$_2$
ρ^Y	-1.88	-1.99	-2.15	-2.38	-2.77	-2.67
log k_{HY}	-1.56	-1.32	-1.16	-0.94	-0.41	-0.38

reaction constant ρ^X (Table V) for the Y substituent depends on X: $\rho^{3-NO_2} = -0.84$, $\rho^{4-MeO} = +0.69$. As the reaction passes
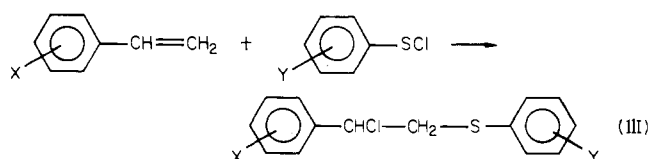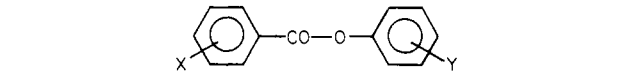

through the isokinetic point ($\rho^X = 0$), the RSP behavior of the system changes.[31]

Table V. Addition of Arylsulfenyl Chlorides on Styrenes: $q = -1.01$

X	3-NO$_2$	H	4-Me	4-OMe
ρ^X	-0.84	-0.20	-0.02	0.69
log k_{XH}	-0.12	1.01	1.36	1.88

Y	4-NO$_2$	H	4-Me
ρ^Y	-2.17	-1.38	-1.07
log k_{HY}	0.84	1.01	1.05

Table VI. Alkaline Hydrolysis of Aryl Benzoates: $q = 0$

Y	4-Me	H	3-NO$_2$	4-NO$_2$
ρ^Y	2.03	1.98	2.04	2.01
log k_{HY}	0.30	0.52	1.44	1.68

X	4-NMe$_2$	4-Me	H	4-NO$_2$
ρ^X	1.20	1.28	1.27	1.25
log k_{XH}	-1.14	0.14	0.52	2.07

The same value of q is obtained from regression of ρ^X and ρ^Y against σ_X^+ and σ_Y^+: -1.02 and -1.01, respectively. Moreover the value of q calculated from the departure from additivity is -1.03 ($R = 0.986$).

(d) Noninteractive Substituent Effects: Hydrolysis of Phenyl Benzoates (No. 17, Table I). This well-known reaction[17] (eq IV) is an example of the limiting case of a zero cross-interaction constant. The effects of the two ring substituents are independent and additive as shown in Table VI; ρ^Y and ρ^X are constant

(30) Bodrikov, I. V.; Borisov, A. V.; Chumakov, L. V.; Zefirov, N. S.; Smit, W. A. *Tetrahedron Lett.* **1980**, 115-118.

(31) This reaction is an electrophilic addition on the olefin, but it can be also be considered as a nucleophilic substitution at sulfur. The imbalance between C–S bond making and S–Cl bond breaking is well described by a More O'Ferrall–Jencks diagram.[32,12]
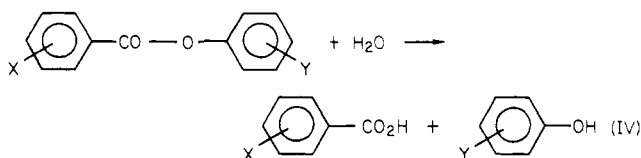
whatever X and Y. This reaction can be considered as a specific case of the interactive relationship when $q = 0$. The RSP(0) behavior may, in fact, result from compensation of the effects parallel and perpendicular to the reaction coordinate in the transition state.[11]

(e) General Survey. In the literature, 31 sets of data on multiple-substituent effects meet the criteria for applying the interactive treatment. The results are shown in Table I and II for rates and equilibria, respectively. For all but 5 of 31 data sets a significant non-zero value of q is obtained. When q can be calculated by several methods (methods A, B, or C), similar results are obtained. When the ρ values for each of the substituents are not identical, i.e., $\rho^X \neq \rho^Y$, the same value of q is obtained by varying either substituent as required by the identity of relationship 8. The IFER applies to rate data as well as to equilibrium data. Further, as regards the kinetic effects, the IFER applies whatever the behavior of the reaction with respect to the RSP. In conclusion, the IFER works and the existence of the cross interaction constant q is experimentally established.

Inspection of Tables I and II shows that high q values are observed for systems with high ρ values; conversely when ρ is small, q is low. Consequently, it is all the more necessary to use the IFER treatment when ρ values are high. Furthermore, q is generally smaller for thermodynamic than for kinetic data. For the two series q varies less than ρ: for the kinetic data, q goes from -8 to 0.3 while ρ ranges from -12 to $+2$.

The IFER can be extended to any multiple effects on properties other than kinetic or thermodynamic. For example, we have pinpointed two sets of spectroscopic data where $\rho\sigma$ relationships apply. The UV frequency shifts[33] of the s-cis ν_{CO} vibration of the disubstituted chalcones X—C$_6$H$_4$—CH=CH—CO—C$_6$H$_4$—Y give a statistically nonsignificant q value. For amine proton chemical shift of secondary amines,[34] a significant q value (-15) is found by methods A and C; ρ^H is 72.2.

The IFER can also be employed in the case of cumulative effects of temperature and solvent. Thus if the solvent effect is described by a Winstein–Grunwald equation, the FER is the following:

$$\log k = \log k_0 + mY + (\beta 10^3/T) + (qY10^3/T) \quad (9)$$

Two sets of data where such cumulative effects have been found are described by relationship 9: solvolysis of N-(2,2-dinitropropyl)-4-sulfamoylphenylamines and N-(2,2-dinitropropyl)-4-cyanophenylamines.[35] For the first substrate, m_{20} is 1.19, β_{H_2O} is -5.4, and q is 1.27. For the 4-cyano substrate, m_{20} is 1.04, β_{H_2O} is -5.2, and q is 1.27.

The treatment is therefore very versatile. The foremost requirement is the existence of elementary linear FER's and of constants describing the perturbation of the property. It should be possible moreover to circumvent this limitation by using relationships based on internal references,[36] such as the property of the monosubstituted compound, rather than relationships with external references such as substituent constants. Homogeneous sets of data could thus be correlated.

Rate-Equilibrium Comparison. Contribution of an Intrinsic Kinetic Term to the q^k Constant for Rates

From the general overview of Tables I and II we have established that the cross–interaction constant exists for kinetic substituent effects. Consequently, the initial assumptions expressed by the relationships 3 and 4 ($q^k \neq 0$ although $m \simeq 0$) are empirically verified. Now the question is whether q^k arises principally from thermodynamic factors, due to a minimization or a compensation of the kinetic factors, or if q^k reflects, at least in part, the transition state.

The kinetic barrier of a reaction, $\Delta G^\ddagger$, results from a thermodynamic contribution related to its free energy ΔG° and from an intrinsic kinetic contribution related to its transition-state energy. The kinetic effect of a substituent, $\partial \Delta G^\ddagger/\partial \sigma_X = \rho^k$, is usually[3,21] related to its effect on the reaction free energy, $\partial \Delta G^\circ/\partial \sigma_X = \rho^t$, by relationship 10, where α characterizes the transition-state position. An expression for q^k of a reaction with

$$\rho^k = \alpha\rho^t \quad (10)$$

a two-dimensional energy profile[38] can be obtained by differentiating eq 10 with respect to either σ_X or σ_Y.

$$q^k = \frac{\partial^2 \Delta G_{XY}^\ddagger}{\partial \sigma_X \partial \sigma_Y} = \alpha_{XY}\frac{\partial^2 \Delta G_{XY}^\circ}{\delta \sigma_X \partial \sigma_Y} + \frac{\partial \Delta G_{XY}^\circ}{\partial \sigma_X}\frac{\partial \alpha_{XY}}{\partial \sigma_Y} \quad (11)$$

$$q^k = \frac{\partial^2 \Delta G_{XY}^\ddagger}{\partial \sigma_Y \partial \sigma_X} = \alpha_{XY}\frac{\partial^2 \Delta G_{XY}^\circ}{\partial \sigma_Y \partial \sigma_X} + \frac{\partial \Delta G_{XY}^\circ}{\partial \sigma_Y}\frac{\partial \alpha_{XY}}{\partial \sigma_X} \quad (12)$$

The identity of the q^k values obtained for the variation of either substituent implies the identity of eq 11 and 12. It follows that the constancy of q^k for rates requires that eq 13, which can be converted into eq 14 for unsymmetrically placed substituents, is satisfied.

$$\frac{\partial \Delta G_{XY}^\circ}{\partial \sigma_X}\frac{\partial \alpha_{XY}}{\partial \sigma_Y} = \frac{\partial \Delta G_{XY}^\circ}{\partial \sigma_Y}\frac{\partial_{XY}}{\partial \sigma_X} \quad (13)$$

$$\frac{\partial \alpha_{XY}}{\partial \sigma_X} \bigg/ \frac{\partial \alpha_{XY}}{\partial \sigma_Y} = \rho_1^Y/\rho_2^X \quad (14)$$

Equation 14 means merely that the substituent effects on the transition state are proportional to their effects on the free energy of the reaction. When expressions such as those of Marcus,[2] Murdoch,[39] Lewis–More O'Ferrall,[3] or others[40] are taken to account for α, it can be shown that eq 13 is satisfied in the usual case where the intrinsic barrier is independent of the substituents;[2,3,41] if the height of this barrier varies with the substituents,[42] the constancy of q imposes severe and unlikely restrictions on its variation.[43]

(32) More O'Ferrall, R. A. *J. Chem. Soc. B* **1970**, 274–277.

(33) Silver, N. L.; Boyhrin, D. W., Jr. *J. Org. Chem.* **1970**, *35*, 759–764.

(34) Lynd, B. H.; McDonald, B. C.; Webb, J. G. K. *Tetrahedron* **1968**, *24*, 3595–3605.

(35) Pivovarov, S. A.; Perepletchikova, G. V.; Selivanov, V. F.; Gidaspov, B. V. *Org. React. (Tartu)* **1977**, *14*, 211–225, 226–234.

(36) Exner[37] used also internal variables in his treatment of non-additivity of substituent effects. However, the objective was to test mathematical models statistically not to explain the variation of ρ or of selectivity parameters from a mechanistic point of view.

(37) Exner, O. *Collect. Czech. Chem. Commun.* **1976**, *41*, 1516–1540.

(38) For a three-dimensional reaction coordinate profile, response of $\Delta G^\ddagger$ to ΔG° depends on the variable substituent, and eq 11 and 12 must be rewritten with specific α values. When the same procedure is used it follows that q is constant only if eq 14' is satisfied.

$$(\partial \alpha_Y/\partial \sigma_Y)\rho_1^Y + q^i\alpha_Y = C^{si} \quad (14a')$$

$$(\partial \alpha_X/\partial \sigma_X)\rho_2^X + q^i\alpha_X = C^{si} \quad (14b')$$

(39) Magnoli, D. E.; Murdoch, J. R. *J. Am. Chem. Soc.* **1981**, *103*, 7465–7467.

(40) Agmon, N. *J. Chem. Soc., Faraday Trans. 2* **1978**, *74*, 388–404.

(41) Levine, R. D. *J. Phys. Chem.* **1979**, *83*, 159–170.

(42) (a) Marcus, R. A. *J. Am. Chem. Soc.* **1969**, *91*, 7224–7225. (b) Bell, R. P. *J. Chem. Soc., Faraday Trans 1*, **1982**, *78*, 2593–2598. (c) Roberts, R. M. G.; Ostovic, D.; Kreevoy, M. M. *Faraday Discuss. Chem. Soc.* **1982**, *74*, 257–265.

(43) The Marcus expression for α is $\alpha_{XY} = 1/2 + \Delta G_{XY}^\circ/8\lambda$, where λ is the intrinsic kinetic barrier of the reaction. When λ is independent of the substituents, derivatives of α with respect to σ_X and σ_Y obviously satisfy eq 13. If the intrinsic barrier is not independent of substituents, its variation must obey the following equation:

$$\frac{\partial \lambda}{\partial \sigma_X} \bigg/ \frac{\partial \lambda}{\partial \sigma_Y} = \rho_1^X/\rho_2^Y$$

IFER for MSE

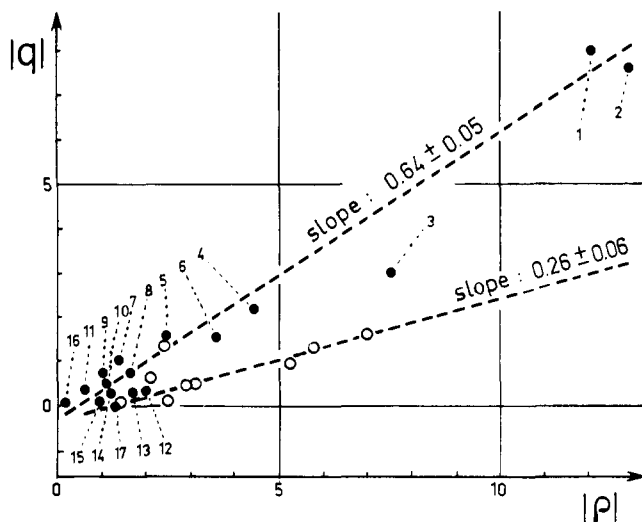*J. Am. Chem. Soc., Vol. 106, No. 17, 1984* 4845

Figure 1. Comparison of interaction constants for rates (●) and for equilibria (○). An extrafactor, probably the variation in charge magnitude, enhances the sensitivity of ρ to structure effects for kinetic data.

Evidence for the contribution of an intrinsic kinetic factor to the q^k value is found in eq 15, which is derived from eq 11 and 12.

$$\frac{q^k}{\rho^k} = \frac{q^t}{\rho^t} + \frac{1}{\alpha}\frac{\partial\alpha}{\partial\sigma} \tag{15}$$

In the absence of any kinetic contribution, the ratio q/ρ for rate should be identical with that measured from substituent effects on equilibrium. Unfortunately, eq 15 cannot be checked directly with the results of Tables I and II since thermodynamic or kinetic data, from which it is possible to calculate an interaction constant, are not related to the same reactions. To overcome this deficiency, a general rate–equilibrium comparison is carried out in Figure 1, where $|q|$ values from Tables I and II are plotted against the corresponding $|\rho|$ values.[44] Strikingly, the points related to thermodynamic and kinetic data do not merge but, for the same $|\rho^H|$, $|q|$ values are systematically greater for rates than for equilibria. A regression line can be drawn for each set of data, corresponding to eqs 16 and 17, respectively.[45]

$$|q^k| = 0.64|\rho^k| - 0.30 \tag{16}$$

$$|q^t| = 0.26|\rho^t| - 0.25 \tag{17}$$

Since q expresses the sensitivity of ρ to substituent effects, it follows from eq 16 and 17 that ρ is twice as sensitive to substituents for rates as for equilibria. Consequently, the contribution of the kinetic term, $\alpha^{-1}(\partial\alpha/\partial\sigma)$ in eq 15 which represents the dependence of the transition-state position on the substituents, is important

and generally positive, since $|q^k/\rho^k|$ is generally higher than $|q^t/\rho^t|$. The positive contribution of $\alpha^{-1}(\partial\alpha/\partial\sigma)$ is expected only when the kinetic substituent effect is in agreement with the RSP[46] (RSP(+) system). For a RSP(−) system, the negative contribution of $\alpha^{-1}(\partial\alpha/\partial\sigma)$ should lead to $|q^k/\rho^k|$ ratios smaller than $|q^t/\rho^t|$; but these systems do not show any different behavior in Figure 1. However, it should be noted that for RSP(−) systems where q^k is accessible (no. 9, 11–15) ρ and q values are always small so that they are located in an area of Figure 1 where no really significant information can be deduced.

In conclusion, the variation in the transition-state position induced by a substituent change is poorly reflected in the ρ^k value but can be detected in q^k where the intrinsic kinetic contribution, proportional to $\alpha^{-1}(\partial\alpha/\partial\sigma)$, is more important. Consequently the paradox of linear FER despite variable transition states may be overcome by considering the magnitude of the cross-interaction constant rather than the curvatures in $\rho\sigma$ relationships.

Concluding Remarks

Although the nonadditivity of multiple-substituent effects has long been recognized,[19] there has been no comprehensive treatment of this phenomenon. Our analysis establishes that the IFER is a general expression for multiple-substituent effects; additivity must be considered as a particular case where q is null. Moreover, since we have shown that ρ^H and q are related, we can roughly predict the magnitude of the cross-interaction constant from the ρ^H value: the greater the sensitivity of the reaction to substituent effects, the more the interaction terms are important and the more the IFER is necessary. A consequence of this new approach is that previous interpretations based on the assumption of additivity must be revised. Approximate ρ values have often been calculated without distinction between mono- and polysubstituted compounds, although such statistically averaged values have no mechanistic significance. It is essential, therefore, both for predicting rates correctly and for obtaining reliable ρ values, to use IFER for MSE.

From a mechanistic point of view, the interaction constant is an overall expression of all the substituent–substituent interactions in the charged species involved in the process studied; it is, therefore, a composite value. The thermodynamic and intrinsic kinetic factors which contribute to the q value can be formally separated by differentiation of the classical rate–equilibrium relationship. The differences between rate and equilibrium results show that the kinetic factor is not negligible and that the q constant for rates is related in part to the variation of the transition-state position. Consequently, we would suggest that q and ρ are complementary FER parameters: the reaction constant ρ is a rough index of the charge at the transition state whose substituent-induced variation is expressed by the interaction constant q. But for an extension of this interpretation the structural factors controlling the ρ and q values must be defined on a single reaction system. This complementary work has been done through an extensive study of the variation of ρ in arylolefin bromination.[47]

(44) The lower $|\rho^H|$ value has been used in eq 16 and 17 for unsymmetrical disubstituted systems since this is the more dependent on the interaction.

(45) Data for reactions 3 and 17 (Table I), which are furthest from the kinetic data plot in Figure 1, have not been included in eq 6. If reaction 17 is included, the slope and regression coefficient are not significantly modified: 0.64 and 0.987, respectively. With reaction 3, the regression coefficient is smaller, 0.977, but the slope remains about the same, 0.61. For the same reason, reaction 4 of Table II has not been used in eq 17.

(46) $|q^k/\rho^k|$ is greater than $|q^t/\rho^t|$ if q^t/ρ^t and $\alpha^{-1}\partial\alpha/\partial\sigma$ have the same sign. For a RSP(+) system q^t and q^k are negative. Two cases follow depending on the sign of ρ. If $\rho < 0$ the reactivity increases when σ increases; $\partial\alpha/\partial\sigma$ is therefore greater than zero as well as are the ratios q^t/ρ^t and q^k/ρ^k. Alternatively $\partial\alpha/\partial\sigma < 0$ when ρ is positive. But again q^t/ρ^t and $\partial\alpha/\partial\sigma$ are of the same sign. Consequently whatever the sign of ρ, $|q^k/\rho^k|$ is greater than $|q^t/\rho^t|$ for RSP(+) systems.

(47) Ruasse, M. F.; Argile, A.; Dubois, J. E. *J. Am. Chem. Soc.*, following paper in this issue.