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Interactive Free Energy Relationships for Nonadditive Multiple Substituent Effects. Cross-Interaction Constant in α-Methylstilbene Bromination

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The interactive free energy relationship (IFER) for multiple substituent effects (MSEs), $\log k/k_0 = \rho\sum\sigma_i + q\sum\sigma_i\sigma_j$, derived here from the LFER formalism, is applied to the treatment of nonadditive effects in α-methylstilbene bromination. An interaction term expresses the nonadditivity; q, the cross interaction constant, is directly related to the dependence of ρ on the substituents by the relationship $\rho^X = \rho^H + q\sigma_X$. The bromination of $XC_6H_4C(Me)=CHC_6H_4Y$ is a two-pathway reaction leading to tertiary and secondary carbocations. The parameters of the IFER for MSE of each pathway are determined: $\log k_T = -4.59\sigma_X^+ - 1.66\sigma_Y - 0.7\sigma_X^+\sigma_Y + 1.27$ and $\log k_S = -5.00\sigma_Y^+ - 2.14\sigma_X - 0.95\sigma_Y^+\sigma_X - 0.95$. The predictive capacity and the mechanistic significance of the FER are markedly improved when the interactive model rather than the additive one is used for the analysis of α-methylstilbene bromination rates. As a consequence of the ρ variation, the classical expression for the transmission coefficients must be corrected by factors taking into account the interaction constants. Damping factors of general validity can only be obtained from and used for reactions where interaction constants are negligible compared to reaction constants. In α-methylstilbene bromination and in any reaction where substituent effects are not additive, kinetic methyl effects are substituent dependent. This classical test for charge magnitude at the transition state is, therefore, limited to additive systems.

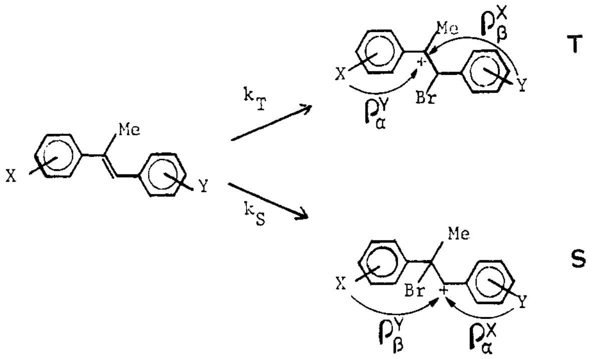
The nonadditivity of kinetic substituent effects is well-known in the literature.[1] However, owing to the lack of a general method for treating cumulative effects, the additive model of Jaffé[2] is usually applied, and the most outstanding deviations are assigned to some specific interaction.[3] This shortcoming is, in fact, a serious amputation of the predictive capacity and of the mechanistic significance of the free energy relationships.

Miller[4] and later Dubois et al.[5] have proposed an empirical free energy relationship where the nonadditivity is taken into account by adding an interaction term to the additive ones. However, this relationship has received few applications, perhaps because the mechanistic significance of the interaction term was not clearly established.

In this paper we show that the multiple substituent effects (MSEs) can be analyzed quantitatively in terms of interactive free energy relationships (IFERs) by extending the classical Hammett-Brown relationships established for one substituent. Such treatment (IFER for the MSE) of nonadditivity restores both the predictive capacity and the mechanistic significance of the usual LFER.

The bromination of polysubstituted α-methylstilbenes (Scheme I) has been chosen as an experimental basis for the development of this treatment for two reasons. First, bromination of aryl olefins $ArCR_1=CHR^2$ can be considered as a valuable model for reactions via carbocationic intermediates where substituent effects are not additive; in this reaction the ρ value for the ring substituent depends markedly on R_1 and R_2.[6,7] Second, in α-methylstilbene bromination, the effects of X and Y are not additive, as is shown by the dependence of ρ on the substituents.[8]

Scheme I



The theoretical expression of the IFER for the MSE will be established first. Then we shall determine the parameters of these empirical IFERs for the two pathways of α-methylstilbene bromination, and the results will be checked against experimental rate constants and regiochemistry. Finally, the consequences of the IFER for the MSE on empirical kinetic tests such as methyl effects and the transmission coefficient will be discussed.

Free Energy Relationships for the Cumulative Effects of Substituents. The additive model of Jaffé[2] states that the effect of two substituents is the product of the effect of each of them on the unsubstituted compound (eq 1).

$$\frac{k_{XY}}{k_{HH}} = \frac{k_{XH}}{k_{HH}}\frac{k_{YH}}{k_{HH}} \tag{1}$$

It is readily seen that such a decomposition is not correct. One should write

$$\frac{k_{XY}}{k_{HH}} = \frac{k_{XY}}{k_{XH}}\frac{k_{XH}}{k_{HH}} \tag{2a}$$

or

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[1] Exner, O. "Advances in Linear Free Energy Relationships"; Chapman, N. B., Shorter, J., Eds.; Plenum Press: London, 1972.

[2] Jaffé, H. H. *Chem. Rev.* **1953**, *53*, 191–261.

[3] Nishida, S. *J. Org. Chem.* **1967**, *32*, 2692–2701.

[4] Miller, S. I. *J. Am. Chem. Soc.* **1959**, *81*, 101–106.

[5] Dubois, J. E.; Aaron, J. J.; Alcais, P.; Doucet, J. P.; Rothenberg, F.; Uzan, R. *J. Am. Chem. Soc.* **1972**, *94*, 6823–6828.

[6] Ruasse, M. F.; Dubois, J. E. *J. Org. Chem.* **1972**, *37*, 1770–1778; **1973**, *38*, 493–499.

[7] Ruasse, M. F.; Argile, A.; Dubois, J. E. *J. Am. Chem. Soc.* **1978**, *100*, 7645–7652.

[8] Ruasse, M.-F.; Argile, A. *J. Org. Chem.*, preceding paper in this issue.

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$$\frac{k_{\mathrm{XY}}}{k_{\mathrm{HH}}} = \frac{k_{\mathrm{XY}}}{k_{\mathrm{HY}}}\,\frac{k_{\mathrm{HY}}}{k_{\mathrm{HH}}} \quad (2b)$$

In each ratio only one substituent changes while the other, X, Y, or H, remains constant; consequently, simple Hammett relationships hold. For the tertiary pathway of α-methylstilbene bromination (Scheme I) eq 3 is obtained,[9]

$$\log (k_{\mathrm{XY}}/k_{\mathrm{HH}}) = \rho_\beta{}^{\mathrm{X}}\sigma_{\mathrm{Y}} + \rho_\alpha{}^{\mathrm{H}}\sigma_{\mathrm{X}}{}^{\ddagger} = \rho_\alpha{}^{\mathrm{Y}}\sigma_{\mathrm{X}}{}^{\ddagger} + \rho_\beta{}^{\mathrm{H}}\sigma_{\mathrm{Y}} \quad (3)$$

where $\sigma_{\mathrm{X}}{}^{\ddagger}$ is $\sigma_{\mathrm{X}} + r^+\Delta\sigma_{\mathrm{X}}{}^+$; $\rho_\alpha{}^{\mathrm{H}}$ and $\rho_\alpha{}^{\mathrm{Y}}$ are, as described in Scheme I, the reaction constants for the substituent X on the ring α to the charged carbon when the other substituent (H or Y) is kept constant; $\rho_\beta{}^{\mathrm{H}}$ and $\rho_\beta{}^{\mathrm{X}}$ are the reaction constants for the Y substituent in the β position, the other (H or X) being constant. From eq 3 one obtains eq 4.

$$\frac{\rho_\beta{}^{\mathrm{X}} - \rho_\beta{}^{\mathrm{H}}}{\sigma_{\mathrm{X}}{}^{\ddagger}} = \frac{\rho_\alpha{}^{\mathrm{Y}} - \rho_\alpha{}^{\mathrm{H}}}{\sigma_{\mathrm{Y}}} = q \quad (4)$$

This equality must be true whatever X and Y are. Therefore, the ratios are equal to a constant we name q by analogy with earlier work.[8,9]

Equation 4 shows that the reaction constants ρ are not random variables. They are directly dependent upon the substituent constant of the invariable substituent (eq 5a,b).

$$\rho_\beta{}^{\mathrm{X}} = \rho_\beta{}^{\mathrm{H}} + q\sigma_{\mathrm{X}}{}^{\ddagger} \quad (5a)$$

$$\rho_\alpha{}^{\mathrm{Y}} = \rho_\alpha{}^{\mathrm{H}} + q\sigma_{\mathrm{Y}} \quad (5b)$$

The free energy relationship that expresses the cumulative effect of X and Y is readily obtained from eq 3 by setting $\rho_\alpha{}^{\mathrm{Y}}$ or $\rho_\beta{}^{\mathrm{X}}$ to their values from eq 5.

$$\log (k_{\mathrm{XY}}/k_{\mathrm{HH}}) = \rho_\alpha{}^{\mathrm{H}}\sigma_{\mathrm{X}}{}^{\ddagger} + \rho_\beta{}^{\mathrm{H}}\sigma_{\mathrm{Y}} + q\sigma_{\mathrm{X}}{}^{\ddagger}\sigma_{\mathrm{Y}} \quad (6)$$

Equation 6 has been established for the tertiary pathway of α-methylstilbene bromination. For the secondary pathway, where the effects of X and Y are transposed, eq 7 is obtained.

$$\log (k_{\mathrm{XY}}/k_{\mathrm{HH}}) = \rho_\alpha{}^{\mathrm{H}}\sigma_{\mathrm{Y}}{}^{\ddagger} + \rho_\beta{}^{\mathrm{H}}\sigma_{\mathrm{X}} + q\sigma_{\mathrm{Y}}{}^{\ddagger}\sigma_{\mathrm{X}} \quad (7)$$

Thus, the interaction between substituents which leads to the departures from additivity can be expressed quantitatively by the interaction term, equal to the product of a constant, q, the "cross-interaction constant", with the product of the substituent constants. *It follows that a polysubstituted reaction system is accurately defined only if one knows the reaction constant ρ and the cross-interaction constant q.* The value of q cannot be determined a priori, but only from experimental results. When q is zero, Jaffé's equation is obtained, and additivity holds. Thus the additive relationship is a particular case of the general relationship (eq 6).

Relationships similar to eq 6 and 7 have been established also by Exner[10] from a statistical point of view and by Palm[11] and Jencks[12] from the Taylor expansion of the global effect on reactivity. In our presentation this relationship is derived directly from Hammett formalism. The only assumption needed is that the FERs for the variation of one substituent are linear.[13]

Table I. Comparison of the Predictive Capacity of the Additive and Interactive Models

no.[a]	X	Y	k_{exptl}[a]	Δ_{add}[b]	Δ_i[c]
19	3-Cl	4-NMe$_2$	1.54×10^5	0.43	−0.02
20	3-CF$_3$	4-NMe$_2$	1.02×10^5	0.51	−0.10
21	4-Me	4-OH	3.15×10^3	0.32	0.13
22	4-Cl	4-OH	4.45×10^2	0.32	0.13
23	4-CF$_3$	4-OH	2.0×10^2	0.78	0.24
24	4-Cl	4-OMe	6.27×10	0.12	−0.02
25	3-Cl	4-OMe	3.13×10	0.12	−0.09
26	3-CF$_3$	4-OMe	1.51×10	0.06	−0.23
27	4-Me	4-Me	5.24×10^2	−0.11	−0.08
28	4-Cl	4-Me	8.7	0.04	0.03
29	3-Cl	4-Me	0.6	0.07	0.02
30	4-Me	4-Cl	1.36×10^2	−0.04	−0.09
31	4-Me	3-CF$_3$	6.25×10	0.06	−0.04
32	4-OMe	3-Cl	1.0×10^4	0.22	0.04
33	4-OMe	3-CF$_3$	6.26×10^3	0.22	−0.02

[a] No. **1–18**, results are given in the preceding paper;[8] no. **19–26**, secondary pathway; no. **27** → **33** tertiary pathway. [b] $\Delta_{\mathrm{add}}{}^{\mathrm{T}} = \log k_{\mathrm{exptl}}{}^{\mathrm{T}} - \log k_{\mathrm{add}}{}^{\mathrm{T}}$, where $\log k_{\mathrm{add}}{}^{\mathrm{T}} = 4.59\sigma_{\mathrm{X}}{}^{\ddagger} - 1.66\sigma_{\mathrm{Y}} + 1.22$ (21). $\Delta_{\mathrm{add}}{}^{\mathrm{S}} = \log k_{\mathrm{exptl}}{}^{\mathrm{S}} - \log k_{\mathrm{add}}{}^{\mathrm{S}}$, where $\log k_{\mathrm{add}}{}^{\mathrm{S}} = -5.00\sigma_{\mathrm{Y}}{}^{\ddagger} - 2.14\sigma_{\mathrm{X}} - 0.95$ (22). [c] $\Delta_i = \log k_{\mathrm{exptl}} - \log k_{\mathrm{calcd}}$; $\log k_{\mathrm{calcd}}$ is obtained from 15 or 20.

In order to avoid the internal compensation of effects, which sometimes occur in statistical treatments of data, we choose to use our multisubstituent treatment in the form of eq 5a,b which express the variation of ρ when the other substituent changes, rather than as the general relationship (eq 6). To determine ρ values over a significant reactivity scale, one needs subpopulations where one substituent remains constant while the other varies. The rate constants for bromination of seven more α-methylstilbenes have been added (**27–33** in Table I) to those previously measured.[8]

Reaction Constants Variation and Cross Interaction Constants in α-Methylstilbene Bromination. Tertiary Pathway. The parameters of the tertiary pathway are the easier to determine since this pathway is followed by a great number of compounds (**1–10**, **14–18**, **27–33**). The $\rho_\beta{}^{\mathrm{X}}$ values when X is 4-OMe, 4-Me, and H, respectively, are obtained by linear correlation from compounds **2**, **32**, and **33** (eq 8), from **3**, **30**, and **31** (eq 9), and from **6** and **14–18** (eq 10).

$$\log k_{\mathrm{OMe,Y}} = -1.19\sigma_{\mathrm{Y}} + 4.41 \qquad R = 0.994 \quad s = 0.13 \quad (8)$$

$$\log k_{\mathrm{Me,Y}} = -1.46\sigma_{\mathrm{Y}} + 2.51 \qquad R = 0.993 \quad s = 0.12 \quad (9)$$

$$\log k_{\mathrm{H,Y}} = -1.66\sigma_{\mathrm{Y}} + 1.22 \qquad R = 0.994 \quad s = 0.09 \quad (10)$$

In order to calculate $\rho_\alpha{}^{\mathrm{Y}}$ values that measure the effect of X for a given Y, only meta X substituents free of resonance effects should be used. However, one can assume that the reduced resonance effect, shown by a smaller than unit value of the Yukawa–Tsuno coefficient[15] (0.83 for X-monosubstituted α-methylstilbenes), is essentially due to the nonplanarity of the molecule and remains constant

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(9) $\rho_\alpha{}^{\mathrm{Y}}$ is the reaction constant for the effect of variable X when Y remains constant. Similarly, $\rho_\beta{}^{\mathrm{X}}$ is the reaction constant for the effect of variable Y when X remains constant.

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

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

(12) Cordes, E. H.; Jencks, W. P. *J. Am. Chem. Soc.* **1962**, *84*, 4319–4328. Jencks, D. A.; Jencks, W. P. *Ibid.* **1977**, *99*, 7948–7960.

(13) Linearity is assumed on an empirical basis and is plausible for a limited reactivity change only. We acknowledge that the linearity of FER can be questioned, and recent work[14] has shown its limits. However, our approach pretends only to empirical efficiency, and linearity is not used here as a fundamental principle but as a convenient working hypothesis.

(14) O'Brien, M.; More-O'Ferrall, R. A. *J. Chem. Soc., Perkin Trans. 2* **1978**, 1045–1053.

(15) Yukawa, Y.; Tsuno, Y.; Sawada, M. *Bull. Soc. Chim. Jpn.* **1966**, *39*, 2274–2286.

no matter what Y is. This assumption is justified by the very good linearity of the C/C relationships[16] (eq 11 and 12) which compare the effects of X when Y is 4-Me and

$$\log k_{\mathrm{X,Me}} = 0.985 \log k_{\mathrm{XH}} + 0.27 \qquad R = 0.999 \qquad s = 0.02 \tag{11}$$

$$\log k_{\mathrm{X,CF_3}} = 1.084 \log k_{\mathrm{XH}} - 1.12 \qquad R = 0.999 \qquad s = 0.008 \tag{12}$$

3-CF_3 with those when Y is a hydrogen. A change in the resonance effect from one subpopulation to the other would induce a curvature for conjugatively electron-donating substituents.

Accurate $\rho_\alpha{}^{\mathrm{Y}}$ values are determined from the slopes of these C/C relationships and $\rho_\alpha{}^{\mathrm{H}}$. The $\rho_\alpha{}^{\mathrm{Y}}$ values are −4.52, −4.59, and −4.98 when Y is 4-Me, H, and 3-CF_3, respectively.

The cross interaction constant, q, can now be obtained from two regressions, either of $\rho_\beta{}^{\mathrm{X}}$ on $\sigma_{\mathrm{X}}{}^{\ddagger}$ ($=\sigma_{\mathrm{X}} + 0.83\Delta\sigma_{\mathrm{X}}{}^{+}$) or of $\rho_\alpha{}^{\mathrm{Y}}$ on σ_{Y} (eq 13 and 14).

$$\rho_\beta{}^{\mathrm{X}} = -0.68(\sigma_{\mathrm{X}} + 0.83\Delta\sigma_{\mathrm{X}}{}^{+}) - 1.66 \qquad R = 0.999 \qquad s = 0.01 \tag{13}$$

$$\rho_\alpha{}^{\mathrm{Y}} = -0.71\sigma_{\mathrm{Y}} - 4.62 \qquad R = 0.994 \qquad s = 0.04 \tag{14}$$

As required by eq 5 the slopes of the two correlations are the same: the sensitivity of the reaction constants $\rho_\alpha{}^{\mathrm{Y}}$ and $\rho_\beta{}^{\mathrm{X}}$ to the effects of X and Y is the same. For the tertiary pathway of α-methylstilbene bromination the general relationship for the cumulative effects of X and Y is therefore given by eq 15.[17]

$$\log k_{\mathrm{XY}} = -4.59(\sigma_{\mathrm{X}} + 0.83\ \Delta\sigma_{\mathrm{X}}{}^{+}) - 1.66\sigma_{\mathrm{Y}} - 0.7(\sigma_{\mathrm{X}} + 0.83\Delta\sigma_{\mathrm{X}}{}^{+})\sigma_{\mathrm{Y}} + 1.27 \tag{15}$$

Despite the uncertainties on the $\rho_\beta{}^{\mathrm{X}}$ values due to the small number of compounds used in eq 8–10, some confidence can be placed in the parameters of eq 15 because of the similarity of the q values obtained from eq 13 and 14 and also because these parameters are in an acceptable range, as we shall see in the next paragraph.

Secondary Pathway. The parameters for the secondary pathway cannot be derived in the same way since few compounds react through the secondary ion only. The α effect, of Y in particular, can be measured for three substituents only, 4-OMe, 4-OH, and 4-NMe_2, which are all conjugatively electron-donating groups. Moreover, the Y-substituted ring is further from the plane of the double bond (45°[18] or 55°[19]) than the X-substituted ring. Since this deviation must strongly attenuate the resonance capacity of Y, a Yukawa–Tsuno coefficient smaller than unity is expected. In the absence of sufficient data from which to calculate conventionally the parameters of the secondary pathway, we estimate them in the following way.

First, the β effect of substituent X is determined for three subgroups where Y remains constant: 4-OMe, 4-OH, and 4-NMe_2. The secondary rate constants of these compounds, obtained by subtracting from the experimental rate constant the tertiary rate constant calculated by relationship 15, are correlated with σ_{X}. The $\rho_\beta{}^{\mathrm{Y}}$ are obtained by the correlations given in eq 16 (compounds **11**, **19**, and **20**), 17 (compounds **12** and **21**–**23**), and 18 (compounds **13** and **24**–**26**).

Table II. Parameters of the IFER for MSE of the Tertiary and Secondary Pathways in α-Methylstilbene Bromination

parameter	tertiary pathway	secondary pathway
ρ_α	−4.59	−5.0
$r_{\mathrm{YT}}{}^{+}$	0.83	0.70
ρ_β	−1.66	−2.14
q	−0.70	−0.95
$\log k_{\mathrm{HH}}$	1.22	−0.95

$$\log k_{\mathrm{X,NMe_2}} = -0.89\sigma_{\mathrm{X}} + 5.46 \qquad R = 0.998 \qquad s = 0.06 \tag{16}$$

$$\log k_{\mathrm{X,OH}} = -1.43\sigma_{\mathrm{X}} + 3.04 \qquad R = 0.998 \qquad s = 0.16 \tag{17}$$

$$\log k_{\mathrm{X,OMe}} = -1.53\sigma_{\mathrm{X}} + 1.99 \qquad R = 0.980 \qquad s = 0.20 \tag{18}$$

A change in $\rho_\beta{}^{\mathrm{Y}}$ with Y is observed, but the substituent constant of Y with which $\rho_\beta{}^{\mathrm{Y}}$ has to be correlated in order to determine the cross-interaction constant, q, is not known. On the assumption that relationships 5a,b between ρ and a substituent constant hold, q can be estimated by determining the value of r^+ for which the best correlation between $\rho_\beta{}^{\mathrm{Y}}$ and $\sigma_{\mathrm{Y}} + r^+\Delta\sigma_{\mathrm{Y}}{}^{+}$ is obtained. This proved to be 0.7 (eq 19), smaller than the r^+ of the tertiary pathway.

$$\rho_\beta{}^{\mathrm{Y}} = -0.95(\sigma_{\mathrm{Y}} + 0.7\Delta\sigma_{\mathrm{Y}}{}^{+}) - 2.14 \qquad R = 0.9999 \tag{19}$$

The q value (−0.95) is of the same order of magnitude as that for the tertiary pathway.

In the general relationship for the secondary pathway, only $\rho_\alpha{}^{\mathrm{H}}$ and $\log k_{\mathrm{HH}}$ remain to be determined. They are obtained by correlating $\log k_{\mathrm{XY}} - \rho_\beta{}^{\mathrm{H}}\sigma_{\mathrm{X}} - q\sigma_{\mathrm{Y}}{}^{\ddagger}\sigma_{\mathrm{X}}$ with $\sigma_{\mathrm{Y}}{}^{\ddagger} = \sigma_{\mathrm{Y}} + 0.7\ \Delta\sigma_{\mathrm{Y}}{}^{+}$ for all the compounds where the secondary rate constants are known. The IFER for the MSE for the secondary pathway is given in eq 20.

$$\log k_{\mathrm{XY}}{}^{\mathrm{S}} = -5.0(\sigma_{\mathrm{Y}} + 0.7\Delta\sigma_{\mathrm{Y}}{}^{+}) - 2.14\sigma_{\mathrm{X}} - 0.95\sigma_{\mathrm{X}}(\sigma_{\mathrm{Y}} + 0.7\Delta\sigma_{\mathrm{Y}}{}^{+}) - 0.95 \tag{20}$$

The value of $\rho_\alpha{}^{\mathrm{H}}$ is plausible since it is similar to that determined in stilbene bromination[6] (−5.05), where the intermediate is also a secondary carbenium ion. All the ρ, r^+, and q values for both pathways are shown in Table II.

As we have already pointed out, the differences between the ρ_α for the two pathways are coherent with the structural differences of ions T and S: $|\rho|$ values are generally higher for the formation of secondary carbocations than for that of the homologous tertiary carbocations. The increase in r^+ on passing from the secondary to the tertiary pathway is in agreement with the geometrical requirements of the ring on which the conjugation depends. The fact that the $|\rho_\beta|$ value is higher in the secondary pathway than in the tertiary could result from the difference between the electron demand of the two intermediates: in the tertiary pathway the carbocation is stabilized both by the methyl and by the conjugated aromatic ring; the electron demand on the nonconjugated ring is then less than in the secondary pathway where there is no methyl group attached on the electron-deficient carbon. The $|q|$ value for the secondary pathway is slightly higher than that for the tertiary pathway. This is to be related to the higher $|\rho_\alpha|$ and $|\rho_\beta|$ value found for the secondary pathway. However,

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(16) Dubois, J. E.; Bienvenüe, A.; Barbier, G.; Tavernier, H. *C. R. Hebd. Seances Acad. Sci., Ser. C* **1968**, *266*, 997–1000.

(17) This equation contains four constants $\rho_\alpha{}^{\mathrm{H}}$, $\rho_\beta{}^{\mathrm{H}}$, r^+, and q and three variables σ_{X}, $\sigma_{\mathrm{X}}{}^{+}$, and σ_{Y}, but each constant has been determined when the corresponding substituent effect was isolated: determination of ρ from meta-substituted compounds only, of r^+ from the deviations of the para-substituted ones, and of q from the substituent effect on the reaction constants. These constants have a more precise mechanistic significance than if they were obtained from multiple regression analysis where different effects can cancel out.

(18) Bromberg, A.; Muszkat, K. A. *Tetrahedron* **1972**, *28*, 1265–1274.

(19) Favini, G.; Simonetta, M. *Theor. Chim. Acta* **1963**, *1*, 294–301.

Table III. Comparison of the Percentage of the Tertiary Pathway and of the Estimated Relative Stability of Ions S and T Calculated by the Interactive and Additive Models

X	Y	% T_{add}[a]	% T_{int}[b]	$\Delta\Delta G^{\ddagger}_{add}$[c]	$\Delta\Delta G^{\ddagger}_{int}$[d]
3-Cl	4-NMe_2	0	0	−5.40	−5.72
3-CF_3	4-OH	0	0	−3.20	−3.51
4-CF_3	4-OH	0	0	−3.35	−3.62
4-Cl	4-OMe	21	15	−0.84	−1.01
3-CF_3	4-OMe	0	0	−2.46	−2.74
4-CF_3	4-OMe	0	0	−2.70	−2.99
4-Me	4-Cl	100	100	4.80	4.85
4-OMe	3-Cl	100	100	8.37	8.50
4-OMe	3-CF_3	100	100	8.92	9.09

[a] Percent $T_{add} = 100(\log k_{add}^{T}/(\log k_{add}^{T} + \log k_{add}^{S}))$, where $\log k_{add}^{T}$ and $\log k_{add}^{S}$ are calculated from eq 21 and 22, respectively, in Table I. [b] Percent $T_{int} = 100(\log k_{int}^{T}/(\log k_{int}^{T} + \log k_{int}^{S}))$, where $\log k_{int}^{T}$ and $\log k_{int}^{S}$ are calculated from eq 15 and 20. [c] $\Delta\Delta G_{add}^{\ddagger} = 2.303RT(\log k_{add}^{T} - \log k_{add}^{S})$. [d] $\Delta\Delta G_{int}^{\ddagger} = 2.303RT(\log k_{int}^{T} - \log k_{int}^{S})$.

Table IV. Transmission Factor for the Methylene Group

reaction	ϵ_G[a]
pK_a ArGCOOH[d]	0.562
pK_a $ArCH_2GCOOH$[d]	0.42
pK_a $ArGNH_3^+$[d]	0.36
$ArGCO_2Et + OH^-$[d]	0.40
$ArGCO_2H + Ph_2CN_2$[d]	0.40
$ArGC(Me)_2Cl$[e]	0.24
$ArC(Me){=}CHAr' + Br_2$	0.36[b]
$ArC(Me){=}CHAr' + Br_2$	0.43[c]
$ArCH_2CHOHAr' + H^+$[f]	0.27

[a] Transmission factor for a methylene group ($G = CH_2$) unless otherwise noted. [b] Tertiary pathway: $\epsilon_{CHBr} = \rho_{\beta}^{H}/\rho_{\alpha}^{H}$. [c] Secondary pathway: $\epsilon_{C(Me)Br} = \rho_{\beta}^{H}/\rho_{\alpha}^{H}$. [d] Reference 1. [e] Okamoto, Y.; Inukai, T.; Brown, H. C. *J. Am. Chem. Soc.* **1958**, *80*, 4972-4976. Landis, A.; Vanderwerf, C. A. *Ibid.* **1958**, *80*, 5277-5280. [f] Noyce, D. S.; Hartter, D.; Miles, F. B. *Ibid.* **1968**, *90*, 3794-3796.

both q values are in the expected range for an interaction between α and β substituent effects.[5]

The estimated rate constant of the unsubstituted compound (X = Y = H) for the secondary pathway is in fair agreement with that obtained for stilbene[6] where $\log k_{HH}$ is −1.1. A difference in reactivity of about 2 logarithm units is observed between the two pathways. Consequently, α-methylstilbene reacts only via the tertiary pathway. This difference gives an estimate of the kinetic methyl effect in aryl olefin bromination: $k_{\alpha\text{-Me}}/k_H = 150$ which is attributable to the accelerating inductive effect of the methyl group reduced by the decelerating secondary steric effect on the resonance of the aromatic ring. Consequently, comparisons with similar effects[20] in solvolysis where k_{Me}/k_H can be as high as 10^8 are not reliable.

Predictive Capacity and Mechanistic Significance of the IFER for the MSE. In Table I are shown the differences between experimental rate constants and the rate constants calculated either by the interactive or the additive models. One can see that in both the tertiary and the secondary pathways, the rate constants estimated by the additive relationship are correct only if the substituents are not strong electron donors. For strong resonant electron donors the deviations are large, and, without a general model, they would have been interpreted in terms of specific interactions between resonant groups.[21] Such an interpretation is not needed since the deviations are reduced and the rate constants correctly predicted when the IFERs for the MSEs are used. These relationships where substituent interactions are taken into account systematically are an important and convenient extension of LFERs for the treatment of cumulative substituent effects.

Moreover, it must be noted that the interactive treatment reveals a variation of the reaction constant, ρ, which would be neglected by the additive treatment. This aspect is very important in the discussion of the mechanistic significance of the reaction constant. Using the additive model, one would obtain a mean ρ value from mono- and disubstituted compounds. But these average values can be quite different from the true values of ρ. They have no precise mechanistic significance and cannot be meaningfully interpreted.

The application of the interactive model rather than the additive one does not change drastically the predicted competition between secondary and tertiary pathways as shown in Table III. The similarity of the prediction by the two models results from the similar magnitude of the interaction terms in eq 15 and 20. This is not surprising since both relationships describe the reactivity of two closely related systems: the same reactant, bromine, attacks two different positions of the same substrate so that reactivity-determining factors measured by the constant q are almost the same for both pathways.

Since the relative rates calculated for the two pathways are similar whichever model is used, the regiochemistry evaluation is not changed by going from additive to interactive FERs. This explains why in the previous paper we were able to find fair agreement between product regiochemistry and rates calculated without taking into account the substituent interactions. But this agreement is valid only in the particular case of bromination and cannot be transposed to any other reaction where the interactions in the two pathways are not so closely similar.

The general IFERs (eq 15 and 20) can also be used to estimate the energy differences between the secondary (S) and tertiary (T) carbocations although these relationships are strictly related to transition-state energies and not to that of the intermediates. The extrapolation to the carbocations is possible for several reasons. Arnett[22] showed that there is a very good relationship between the heats of formation of carbocations and the rate constants for their formation by solvolysis, confirming elegantly the classical hypothesis that structural effects on the solvolysis transition state are nearly identical with those on the intermediate ions. Since the solvent effects in bromination and solvolysis are similar,[23] typical of a late transition state, one can transpose Arnett's results to bromination and assume that structural effects on the rate-determining

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[20] Gassmann, P. G.; Pascone, J. M. *J. Am. Chem. Soc.* **1973**, *95*, 7801–7813.

[21] In benzhydryl chloride solvolysis[3] this interpretation was used to explain the marked deviation from additivity of disubstituted compounds where a methoxy group was substituted on the ring.

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Table V. Transmission Coefficients for the CHBr (Tertiary Pathway) and C(Me)Br Groups (Secondary Pathway) in α-Methylstilbene Bromination

	Y					
	3-CF_3		H		4-NMe_2	
X	ϵ_{CHBr}	$\epsilon_{C(Me)Br}$	ϵ_{CHBr}	$\epsilon_{C(Me)Br}$	ϵ_{CHBr}	$\epsilon_{C(Me)Br}$
3-CF_3	0.41	0.48	0.44	0.39	0.50	0.16
H	0.34	0.52	0.36	0.43	0.41	0.18
4-NMe_2	0.14	0.62	0.15	0.51	0.17	0.21

[a] ϵ_{CHBr} is evaluated from the tertiary pathway reaction constants ρ_α^Y and ρ_β^X; it increases when X becomes more electron electron attracting. [b] $\epsilon_{C(Me)Br}$ is evaluated from the secondary pathway reaction constants ρ_β^Y and ρ_α^X; it increases when Y becomes more electron attracting.

transition state are a good estimate of those on the intermediate. The extrapolation should even be more accurate in bromination since the two ions are formed from the same olefin, thus eliminating errors due to different ground-state stabilities. Some energy differences between substituted secondary (S) and tertiary (T) cations calculated from kinetic data are given in Table III. The differences between the calculations with and without interaction are negligible.

The interest of equations such as eq 15 and 20 lies in their ability to predict both the rates and the regiochemistry of electrophilic additions: the results in α-methylstilbene bromination can be transposed to other electrophilic additions and even to some polar cycloadditions, the regiochemistry of which has been explained by an electrophilic model. For instance, the regiospecificity of the addition of styrene to acrizidinium ion[24] depends upon the substituents to the double bond, in full agreement with the rule predicting the orientation of electrophilic addition.

Variation of Damping Factors for the Transmission of Ring-Substituent Effects. The ability of a group G to transmit substituent effects can be determined by the ratio of the reaction constants measured when the group is or is not inserted between the reaction center and the substituents.

$$\epsilon_G = \rho_{GZ}/\rho_Z$$

The capacity of different aromatic rings, atoms, or bonds to transmit the polar effect of substituents has been determined and compared on the basis of NMR spectroscopy or reactivity data.[1] As noted by Exner[1] "in order to obtain results of general validity ϵ_G must be independent of the reaction center". This independence has been assumed in the estimation of substituent constants.[25] More recently, McLennan[26] used a transmission coefficient to compare ρ values determined for structurally different side chains. Here again the method assumes that ε is constant for a given group.

In Table IV are shown some values of the damping factor of a methylene group taken from the literature and those of CHBr and CMeBr groups calculated from our results on α-methylstilbene bromination. The effects of substituents X and Y on the transmission coefficient of the CHBr group are given in Table V. It is readily seen from these tables that significant variations of the transmission coefficient are observed for the same group both when they are calculated on the same structure and on the same reaction as in bromination (Table V) and when they are obtained from two different structures for different reactions (Table IV).

In bromination the transmission coefficient given by the ratio of ρ_β^X and ρ_α^Y varies because the relative sensitivies of the reaction constants to substituent effects are different. In the tertiary pathway, ρ_α^Y for substituent X depends upon the overall charge on C_α in the transition state. On the other hand, ρ_β^X for Y depends upon the transition-state position but also on the charge delocalization by the X-substituted ring. Thus, in spite of the symmetry of eq 5 which expressed the sensitivity of ρ to substituent effects, ρ_β^X is more dependent on this effect than ρ_α^Y. This is quantitatively expressed by the following relationships where the correction term is greater for ρ_β^X than for ρ_α^Y.

$$\epsilon_{CHBr}^{XY} = \frac{\rho_\beta^X}{\rho_\alpha^Y} = \frac{\rho_\beta^H(1 + q\sigma_X^+/\rho_\beta^H)}{\rho_\alpha^H(1 + q\sigma_Y/\rho_\alpha^H)} = \epsilon_{CHBr}^{HH}\,\frac{(1 + 0.42\sigma_X^+)}{(1 + 0.15\sigma_Y)}$$

ε is substituent independent only if the factorized terms are close to unity. This is the case if *q* is negligible compared to ρ, i.e., if the effects of substituents are additive. More generally, the condition expressed by Exner concerning the validity of transmission coefficients calculated from kinetic data requires that the two ρ values which are compared must concern two reactions where the factors influencing the reactivity are the same and have equal relative contributions. The condition is not fulfilled, in particular, when the effects of substituents are not additive. This observation seriously restricts the applicability of these transmission coefficients.

Similar dependence on substituents is observed as regards the kinetic methyl effects classically used to estimate the charge on a carbon atom. In α-methylstilbene bromination, the methyl effect varies over more than a power of ten, depending on ring substituents. Interaction between substituents induces a variation in the charge delocalization to which the methyl effect is sensitive. Consequently, this effect is not an unequivocal criterion for measuring the charge magnitude.

Conclusion

The additivity of substituent effects cannot be considered as a basic rule. The general expression of the multiple kinetic substituent effects, the IFER for the MSEs, involves, in addition to the additive terms, an interaction term proportional to the product of substituent constants and a cross-interaction constant, *q*. In α-methylstilbene bromination, this IFER for the MSEs accurately describes the substituent effects on the reactivity and the regiochemistry. Thus, the general expression not only restores the predictive power of the FERs but also their mechanistic interest. The existence of the interaction term has several consequences. First, additivity must be considered only as a borderline case where the interaction constant

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q is null or negligible. Second, deviations from additivity are not random nor due to specific interactions but are explained by a substituent dependence of the reaction constant ρ, which is proportional to q. Finally, making the additivity assumption leads to average reaction constants which optimize the deviations and which, in this way, lose a large part of their mechanistic significance. A reaction system is therefore perfectly described only if the reaction constants *and* the cross-interaction constants q are known. Moreover, q, which measures the ρ sensitivity to structural effects, can be a valuable source of information regarding the factors which causes ρ to vary. For this reason, more work is in progress to determine the generality of the IFER for the MSEs and the significance of the cross-interaction constant.

Experimental Section

α-Methylstilbenes were prepared by dehydration of the corresponding tertiary alcohols by *p*-toluenesulfonic acid in benzene.

$$XC_6H_4C(OH)MeCH_2C_6H_4Y \rightarrow XC_6H_4CMe{=}CHC_6H_4Y$$

The alcohols were prepared by condensation of Y-substituted benzylmagnesium chlorides with X-substituted acetophenones. α-Methylstilbenes were purified by preparative column chromatography on Al_2O_3 or preparative GLC and were identified by their NMR spectra.

Experimental rate constants were measured by potentiometry[27] and, for the methoxy derivatives, by couloamperometry[28] as described elsewhere.

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Registry No. (*E*)-**19**, 83816-17-5; (*E*)-**20**, 83830-92-6; (*E*)-**21**, 83816-18-6; (*E*)-**22**, 83816-19-7; (*E*)-**23**, 83816-20-0; (*E*)-**24**, 83816-21-1; (*E*)-**25**, 83816-22-2; (*E*)-**26**, 83816-23-3; (*E*)-**27**, 57058-24-9; (*E*)-**28**, 83816-24-4; (*E*)-**29**, 83816-25-5; (*E*)-**30**, 83816-26-6; (*E*)-**31**, 83816-27-7; (*E*)-**32**, 83816-28-8; (*E*)-**33**, 83816-29-9.

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Photochemical Oxidation of Thioketones: Steric and Electronic Aspects

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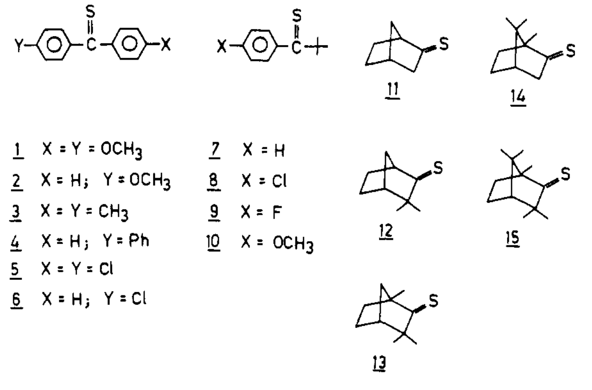
Oxidation of diaryl, aryl alkyl, and dialkyl thioketones by singlet oxygen generated via self-sensitization and other independent methods yielded the corresponding ketone and sulfine in varying amounts. A zwitterionic/diradical intermediate arising out of the primary interaction of singlet oxygen with the thiocarbonyl chromophore is believed to be the common intermediate for the ketone and sulfine. While closure of the zwitterion/diradical to give 1,2,3-dioxathietane would lead to the ketone, competing oxygen elimination is believed to lead to the sulfine. This partitioning is governed by steric and electronic factors operating on the zwitterionic/diradical intermediate.

Of known photochemical reactions oxidation has certainly been one of the most intensively investigated. However, most studies have been centered around the olefinic chromophore.[1] Oxidation of thiocarbonyl chromophores is of great concern to those interested in exploring their chemical behavior as oxidation contributes toward their instability. Since the initial report by Gattermann and Schulze,[2] the stability of several thioketones toward oxygen in the presence or absence of light has been investigated by several groups of workers. The reaction between thiobenzophenone and oxygen, in the dark, has been reported to yield the corresponding ketone and sulfine.[3] In contrast to this, oxidations in the presence of light of several dialkyl thioketones,[4] diaryl thioketones,[5] and *O*-alkyl thioesters[6] were reported to afford the corresponding carbonyl compounds in high yields together with elemental sulfur and sulfur dioxide. However, recently we[7] and Tamagaki and co-workers[8] noted that di-*tert*-butyl thioketone is an exception to this general behavior and yields the corresponding sulfine as the major product upon light-induced oxidation. Singlet oxygen generated by self-sensitization is believed to be the active species in all these cases. In spite of these scattered reports, no general picture has emerged on the oxidation of thiocarbonyls. Therefore, we have carried out a systematic investigation on the light-induced oxidation of a series of carefully chosen thioketones (Chart I), and the results are presented below.[9] The present study resulted from the surprising

Chart I. List of Thioketones Investigated



1 X = Y = OCH$_3$
2 X = H; Y = OCH$_3$
3 X = Y = CH$_3$
4 X = H; Y = Ph
5 X = Y = Cl
6 X = H; Y = Cl

7 X = H
8 X = Cl
9 X = F
10 X = OCH$_3$

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