

## Application of a Quadratic Free Energy Relationship to Non-additive Substituent Effects

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A quadratic free energy relationship is formulated in which the reaction constant depends linearly upon substituent constant, *e.g.* in Hammett's formalism  $\rho = \rho_0 + 2m\sigma$ . The relationship is applied to dual substitution at equivalent positions (X and Y) in the form  $\log k_{XY}/k_{HH} = \rho_0(\sigma_X + \sigma_Y) + m(\sigma_X + \sigma_Y)^2$ , using data from the literature for the bromination of diphenylethylenes, solvolytic and equilibrium formation of diphenylmethyl carbonium ions, and the ionisation of 2,7-substituted fluorenes. Non-additivity of substituent effects is quantitatively described and quadratic coefficients  $2m/\rho_0^2$  can be derived without specifying substituent constants. Values of  $2m/\rho_0^2$  measure the sensitivity of  $\rho$  and the selectivity of the reaction to changes in reactivity. Relative magnitudes are interpreted in terms of variations in transition state structure, resonance saturation, and steric inhibition of resonance. The relationship is compared with Miller's equation,  $\log k_{XY}/k_{HH} = \rho_0(\sigma_X + \sigma_Y) + q\sigma_X\sigma_Y$ , with respect to effectiveness of correlations, chemical interpretation, desirability of preserving linear relationships for monosubstitution, and practical application to multiple substitution at non-equivalent positions.

SUBSTITUENT effects on reaction rates and equilibria commonly involve polar or resonance interactions of substituents with full or partial ionic changes.<sup>1-5</sup> Slopes of free energy relationships then reflect differences in charge, at a functional group or a reaction site, between reactants and products or reactants and transition state. Of special interest are the variations in charge arising from variations in transition state structure,<sup>4-12</sup> resonance saturation,<sup>13,14</sup> or other causes.<sup>12-14</sup> The usual linear approximation for free energy relationships fails to take account of these, and in this paper we formulate a quadratic relationship which does, and apply it to reactions showing non-additive substituent effects.<sup>15,16</sup>

The relationship may be expressed as an extension of the familiar Hammett equation.<sup>1</sup> The simplest variation of  $\rho$  that can be considered is the linear dependence of  $\rho$  upon  $\sigma$  of equation (1), in which  $\rho_0$  is the value of  $\rho$

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

for a reference substituent, usually hydrogen, and  $2m$  is the increase in  $\rho$  for unit increase in  $\sigma$ . Substituting

$$d \log k/d\sigma = \rho \quad (2)$$

$$\log k_X/k_H = \rho_0\sigma + m\sigma^2 \quad (3)$$

for  $\rho$  in equation (2) and integrating between the limits  $\sigma = 0$  and  $\sigma$  gives the quadratic relationship (3). Equ-

ation (3) implies that a linear relationship exists in the limit that variations in reactivity or  $\sigma$  are not too large.

Quadratic extensions of other free energy relationships are possible and it is useful to consider (3) as a general expression in which substituent and reaction constants are undefined. Choice of substituent constants is difficult. Ideally reference and sample reactions should be so related that chemical dispersion is minimised. Less dispersion is acceptable in a quadratic than linear relationship because two reaction parameters are determined instead of one, but this requirement may conflict with the additional requirement that wide ranges of reactivity need to be spanned. Ideally, also, the reference reaction should involve no dependence of reaction constant upon  $\sigma$ .

Quadratic relationships have most commonly been applied to correlations of reaction rates and equilibria, notably the Brønsted relationship for acid-base catalysis, a quadratic form of which is shown in equation (4).

$$\log k/k_0 = \alpha \log K_a + m (\log K_a)^2 \quad (4)$$

Here, substituent constants for the reaction studied kinetically are defined in terms of the corresponding equilibria. Curvature of Brønsted relationships has been interpreted by Marcus<sup>8</sup> and others<sup>9,17-20</sup> in terms

<sup>1</sup> L. P. Hammett, 'Physical Organic Chemistry,' McGraw-Hill, New York, 1970, 2nd edn., ch. 11.

<sup>2</sup> Y. Yukawa and Y. Tsuno, *Bull. Chem. Soc. Japan*, 1959, **32**, 971; Y. Tsuno, Y. Kusuyama, M. Sawada, T. Fujii, and Y. Yukawa, *ibid.*, 1975, **48**, 337.

<sup>3</sup> J. Hine, 'Structural Effects on Equilibria in Organic Chemistry,' Wiley, New York, 1975.

<sup>4</sup> J. E. Leffler and E. Grunwald, 'Rates and Equilibria of Organic Reactions,' Wiley, New York, 1963.

<sup>5</sup> A. Pross, *Adv. Phys. Org. Chem.*, 1977, **14**, 69.

<sup>6</sup> G. S. Hammond, *J. Amer. Chem. Soc.*, 1955, **77**, 334.

<sup>7</sup> J. E. Leffler, *Science*, 1953, **117**, 340; J. R. Murdoch, *J. Amer. Chem. Soc.*, 1972, **94**, 4410; M. H. Mok and J. C. Polanyi, *J. Chem. Phys.*, 1969, **51**, 1451.

<sup>8</sup> R. A. Marcus, *J. Phys. Chem.*, 1968, **72**, 891.

<sup>9</sup> A. J. Kresge, *Chem. Soc. Rev.*, 1973, **2**, 475; A. J. Kresge in 'Proton-Transfer Reactions,' eds. E. F. Caldin and V. Gold, Chapman and Hall, London, 1975, p. 179.

<sup>10</sup> J. F. Bunnett, *Angew. Chem. Internat. Edn.*, 1962, **1**, 225; R. A. Bartsch and J. F. Bunnett, *J. Amer. Chem. Soc.*, 1969, **91**, 1376.

<sup>11</sup> E. R. Thornton, *J. Amer. Chem. Soc.*, 1967, **89**, 2915; J. E. Critchlow, *J.C.S. Faraday I*, 1972, 1774; W. P. Jencks, *Chem. Rev.*, 1972, **72**, 705; R. A. More O'Ferrall, *J. Chem. Soc. (B)*, 1970, 274.

<sup>12</sup> D. A. Jencks and W. P. Jencks, *J. Amer. Chem. Soc.*, 1977, **99**, 7948.

<sup>13</sup> F. G. Bordwell and G. J. McCollum, *J. Org. Chem.*, 1976, **41**, 2391.

<sup>14</sup> A. F. Hegarty, J. S. Lomas, W. V. Wright, E. D. Bergmann, and J. E. Dubois, *J. Org. Chem.*, 1972, **37**, 2222.

<sup>15</sup> O. Exner, *Coll. Czech Chem. Comm.*, 1976, **41**, 1516.

<sup>16</sup> O. Exner in 'Advances in Linear Free Energy Relationships,' eds. N. B. Chapman and J. Shorter, Plenum Press, London, 1972, pp. 41ff and references cited.

<sup>17</sup> A. I. Hassid, M. M. Kreevoy, and T.-M. Liang, *Faraday Symp. Chem. Soc.*, 1975, **10**, 69.

<sup>18</sup> W. J. Albery, A. N. Campbell-Crawford, and J. S. Curran, *J.C.S. Perkin II*, 1972, 2206.

<sup>19</sup> R. P. Bell, 'The Proton in Chemistry,' Chapman and Hall, London, 2nd edn., 1973.

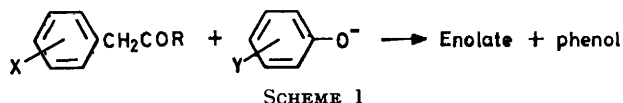
<sup>20</sup> E. S. Lewis, R. A. More O'Ferrall, and C. C. Shen, to be published.

of variations in transition state structure using specific reaction models.

The application we consider involves substituent effects at more than one molecular position. It may be introduced by considering the classic study of variation in Brønsted exponent with substrate reactivity made by Bell.<sup>21</sup> Bell measured rates of ionisation of a series of ketones of widely differing reactivity catalysed by a group of carboxylate bases. The variation in strength of the bases was small and for each ketone a linear Brønsted relationship was obtained. A plot of the exponents  $\beta$  against ketone reactivity showed  $\beta$  decreasing from 0.88 to 0.42 for a  $10^8$  fold increase in ketone reactivity.

Bell's example involves dual substitution, in the substrate and in the base. Linear free energy relationships were obtained because reactivity changes at one position were small and only at this position was a reaction constant determined.<sup>21-23</sup> More commonly large reactivity changes and variation of reaction constants occur at both sites of substitution.

The general case may be illustrated by Bell's example of ketone ionisation hypothetically modified as in Scheme



1 to fit a Hammett formalism. There are now two reaction constants, for substitution in the ketone and in the base, which are distinguished by superscripts,  $\rho^X$  and  $\rho^Y$ . They vary with  $\sigma$  as in equation (3) but now depend upon  $\sigma$  at either site of substitution, *i.e.* equations (5) and (6) where  $\rho_0^X$  and  $\rho_0^Y$  are values of  $\rho^X$  and  $\rho^Y$  when

$$\rho^X = \rho_0^X + 2m_X\sigma_X + 2m_{XY}\sigma_Y \quad (5)$$

$$\rho^Y = \rho_0^Y + 2m_Y\sigma_Y + 2m_{XY}\sigma_X \quad (6)$$

X and Y are hydrogens and  $m_X$ ,  $m_Y$ , and  $m_{XY}$  measure the increase in  $\rho^X$  and  $\rho^Y$  for unit increase in  $\sigma$  at a near or remote substitution site. The relationship between  $\log k$  and  $\sigma_X$  and  $\sigma_Y$  is straightforwardly obtained, as shown in the Appendix, by integration of equation (7) or,

$$\rho^X = d \log k / d\sigma_X; \quad \rho^Y = d \log k / d\sigma_Y \quad (7)$$

alternatively, as noted by Kemp,<sup>22</sup> by a Taylor expansion of  $\log k/k_H$  in terms of  $\sigma_X$  and  $\sigma_Y$ . The expression is shown in equation (8) in which the two subscripts for the rate constant  $k_{XY}$  indicate the substituents at X and Y.

$$\log k_{XY}/k_{HH} = \rho_0^X\sigma_X + \rho_0^Y\sigma_Y + m_X\sigma_X^2 + m_Y\sigma_Y^2 + 2m_{XY}\sigma_X\sigma_Y \quad (8)$$

Equation (8) is the parent quadratic expression for substitution at two molecular positions and is the counterpart of equation (3) for substitution at one. It is

<sup>21</sup> R. P. Bell, E. Gelles, and E. Möller, *Proc. Roy. Soc.*, 1949, **A198**, 308; R. P. Bell and O. M. Lidwell, *ibid.*, 1940, **A176**, 88; see also refs. 22 and 23.

<sup>22</sup> D. S. Kemp and M. L. Casey, *J. Amer. Chem. Soc.*, 1973, **95**, 6670.

a formidable relationship and its five linear and quadratic parameters ( $\rho_0$ s and  $m$ s) usually do not allow application without further simplification. However its interpretation is straightforward and without reference to it, simpler derived relationships are difficult to interpret. Moreover simplifications are possible. Bell's treatment is one, and the approximation  $m_X = m_Y = 0$ , leading to Miller's equation<sup>24</sup> considered below, is another.

The simplification we use occurs when the two positions of substitution are equivalent. Then  $\rho_0^X = \rho_0^Y$ ,  $m_X = m_Y = m$  and, provided that interactions between substituent and reaction site are dominant over interactions between substituents (see below),  $m_{XY} = m$ , and equation (8) reduces to (9).

$$\log k_{XY}/k_{HH} = \rho_0(\sigma_X + \sigma_Y) + m(\sigma_X + \sigma_Y)^2 \quad (9)$$

Equations (8) and (9) have the important advantage that they may be formulated and solved for quadratic coefficients without separating  $\rho_0$  and  $\sigma$  or, therefore, defining a set of substituent constants. It is assumed only that a common set of  $\sigma$ s applies to the family of multiply substituted reagents. This point has recently been made by Exner.<sup>15</sup> Transforming the quadratic variable to  $x = \rho_0\sigma$  and adopting Exner's notation, with substituents X and Y denoted i and j, equation (8) may be rewritten as (10), with  $y_{ij} = \log k_{XY}/k_{HH}$ ,

$$y_{ij} = x_i + x_j + a_i x_i^2 + a_j x_j^2 + a_{ij} x_i x_j \quad (10)$$

$x_i = \rho_0\sigma_X$ ,  $a_i = m_X/(\rho_0^X)^2$ , *etc.*, while equation (9) becomes (11). Solution of equation (11) for the quadratic

$$y_{ij} = x_i + x_j + a(x_i + x_j)^2 \quad (11)$$

coefficient  $a = m/\rho_0^2$  and the 'reactivity variables'  $x_i = \rho_0\sigma_X$ , and the significance of the derived values, is the subject of this paper.

A final point concerning equation (8) is the connection of dual substitution with reactivity-selectivity relationships. If the selectivity of a substrate, S, is written in logarithmic form (12),<sup>4,5</sup> it is seen that  $\rho_0 = S$  and  $\rho$  is a

$$S = \log k_X/k_H \quad (12)$$

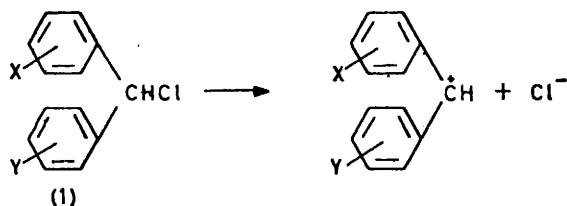
measure of selectivity, albeit relative to a reference reaction. Identification of the slope of a free energy relationship as a measure of selectivity is strictly correct only for a bimolecular reaction in which selectivity changes stem from substitution in the remote reactant, *i.e.* the substrate, but it is sometimes convenient to consider it as applying more widely, and this looser meaning is used here. Thus variation of selectivity with reactivity implies a dependence of  $\rho$  upon substitution in the substrate. Logically, in so far as the distinction between reagent and substrate is a formal one, it in general implies a dependence also upon substitution in the reagent.<sup>5</sup> In this sense equation (8) may be regarded as a generalised reactivity-selectivity relationship.

<sup>23</sup> A. J. Kresge, H. L. Chen, Y. Chiang, E. Murrill, M. A. Payne, and D. Sagatys, *J. Amer. Chem. Soc.*, 1971, **93**, 413.

<sup>24</sup> S. I. Miller, *J. Amer. Chem. Soc.*, 1959, **81**, 101.

## RESULTS AND DISCUSSION

**Substituent Non-additivity and the Dependence of  $\rho$  upon  $\sigma$ .**—With dual substitution variation of reaction constants is most directly revealed by non-additivity



SCHEME 2

of substituent effects. If the  $\rho$  values for two substitution sites are independent of substituent the effect of two substituents acting simultaneously should be the sum of their effects acting independently, *i.e.* equation (13).

$$\log k_{XY}/k_{HH} = \log k_{XH}/k_{HH} + \log k_{HY}/k_{HH} \quad (13)$$

When the  $\rho$ s depend upon  $\sigma$ , as in equations (8) and (9), the effects are no longer additive, and equation (14) applies. Departure from additivity is indicated by

$$\log k_{XY}/k_{HH} = \log k_{XH}/k_{HH} + \log k_{HY}/k_{HH} + 2m_{XY}\sigma_X\sigma_Y \quad (14)$$

deviations from a line of unit slope in a plot of  $\log k_{XY}/k_{HH}$  versus  $\log k_{XH}/k_{HH} + \log k_{HY}/k_{HH}$ . An example is provided by Fox and Kohnstam's data for the

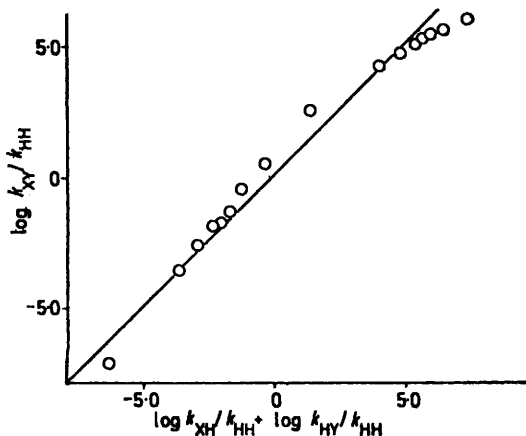


FIGURE 1 Plot of  $\log k_{XY}/k_{HH}$  versus  $\log k_{XH}/k_{HH} + \log k_{HY}/k_{HH}$  for the solvolysis of mono- and di-substituted diphenylmethyl chlorides (1). The straight line is of unit slope through the origin

ionisation of diphenylmethyl chlorides (1)<sup>25</sup> shown in Figure 1.

The non-additivity is revealed without specification of substituent constants. As implied by equation (11) a quadratic coefficient describing the variation of reaction constant may also be determined without specifying  $\sigma$  values. Rewriting equation (11) in the clumsier but more explicit Hammett notation of equation (15), in which the reaction variable is  $\rho_0\sigma$ , a trial value of the

<sup>25</sup> J. R. Fox and G. Kohnstam, *Proc. Chem. Soc.*, 1964, 115.

<sup>26</sup> J. Mindl and M. Vecera, *Coll. Czech. Chem. Comm.*, 1973, **38**, 3496.

quadratic coefficient  $m/\rho_0^2$  may be assigned and values of  $\rho_0\sigma_X + \rho_0\sigma_Y$  determined by solution of the quadratic.

$$\log \frac{k_{XY}}{k_{HH}} = (\rho_0\sigma_X + \rho_0\sigma_Y) + \frac{m}{\rho_0^2} (\rho_0\sigma_X + \rho_0\sigma_Y)^2 \quad (15)$$

Unlike  $\log k_{XY}/k_{HH}$ , values of  $\rho_0\sigma_X + \rho_0\sigma_Y$  should show additivity and a best value of  $m/\rho_0^2$  may be obtained by iteration until additivity is optimised.

For the solvolysis of diphenylmethyl chlorides  $2m/\rho_0^2$  is found to be  $-0.077$ . From this value and the corresponding set of  $\rho_0\sigma$ s, values of  $2m\sigma_X\sigma_Y$  may be calculated and a plot of  $\log k_{XY}/k_{HH}$  versus the right hand

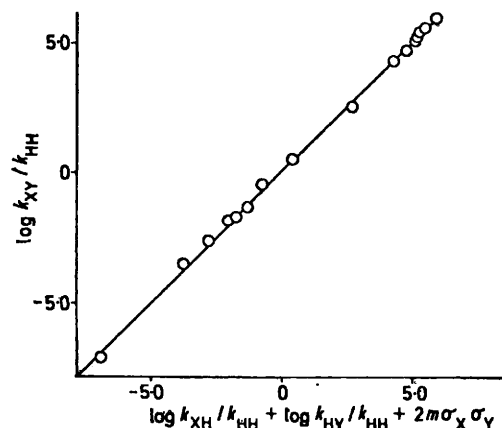
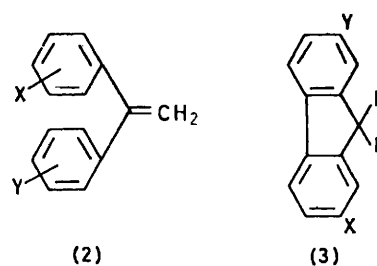


FIGURE 2 Plot of  $\log k_{XY}/k_{HH}$  versus  $\log k_{XH}/k_{HH} + \log k_{HY}/k_{HH} + 2m\sigma_X\sigma_Y$  for the solvolysis of mono- and di-substituted diphenylmethyl chlorides (1)

side of equation (14) constructed. As shown in Figure 2, in contrast to Figure 1, the results are now well correlated by a straight line of unit slope.

Values of  $2m/\rho_0^2$  and sets of  $\rho_0\sigma$  have been determined for a number of reactions for which suitable data exist. These include solvolyses of diphenylmethyl bromides in 80% aqueous acetone,<sup>26</sup> equilibrium ionisations of diphenylmethanols to diphenylmethyl carbonium ions in aqueous sulphuric acid,<sup>27</sup> bromination of diphenylethylenes (2) in methanol,<sup>14,28</sup> and equilibrium ionisations of 2,7-substituted fluorenes (3) to fluorenyl



carbanions in dimethyl sulphoxide.<sup>13</sup> Values of  $2m/\rho_0^2$  are listed in Table 1 and sets of  $\rho_0\sigma$  values in Table 2. Rate constants are given in the original references.

The magnitude of  $2m/\rho_0^2$  reflects the sensitivity of the reaction constant to changes in reactivity. It

<sup>27</sup> J. Mindl and M. Vecera, *Coll. Czech. Chem. Comm.*, 1972, **37**, 1143.

<sup>28</sup> J. E. Dubois, A. F. Hegarty, and E. D. Bergmann, *J. Org. Chem.*, 1972, **37**, 2218.

represents the fractional increase in  $\rho$  for unit increase in  $\rho_0\sigma$ , which, in the differential limit  $\sigma \rightarrow 0$  and  $\rho \rightarrow \rho_0$ , is the fractional increase in  $\rho$  for unit increase in  $\log k$ .

$$2a = \frac{2m}{\rho_0^2} = \frac{1}{\rho_0} \left( \frac{\partial \rho}{\partial \log k} \right)_{\sigma=0} \quad (16)$$

With the identification of  $\rho$  with selectivity of equation (12), it is in this limit also the fractional increase in

and these reactions have the largest values (0.077 and 0.140). For the ionisation of diphenylmethanols to diphenylmethyl carbonium ions, for which no variation in transition state structure is possible, a smaller value is found (0.063), and for the ionisation of substituted fluorenes in which resonance saturation alone can have effect, the smallest of all (0.036). The solvolysis of diphenylmethyl bromides (0.051) at first sight appears

TABLE 1  
Quadratic coefficients and Miller's parameter for dual substitution

	Equation (15)			Equation (21)		
	$2a = \frac{2m}{\rho_0^2}$	$2\epsilon_a^a$	$s^b$	$b = \frac{q}{\rho_0^2}$	$\epsilon_b^a$	$s^b$
1 Diphenylmethyl chloride solvolysis, 85% (v/v) aqueous acetone, 0 °C <sup>e</sup>	-0.077	0.0014	0.101	-0.092	0.0075	0.075
2 Diphenylmethyl bromide solvolysis, 80% aqueous acetone, 75 °C <sup>d</sup>	-0.051	0.0021	0.024	-0.049	0.0024	0.024
3 Ionisation of diphenylmethanols, aqueous H <sub>2</sub> SO <sub>4</sub> , 25 °C <sup>e</sup>	-0.063	0.0008	0.031	-0.083	0.0015	0.020
4 Bromination of diphenylethylenes, methanol, 25 °C <sup>f</sup>	-0.140	0.0046	0.060	-0.185	0.0111	0.086
5 Ionisation of fluorenes, DMSO <sup>g</sup>	-0.036	0.0013	0.044	-0.043	0.0015	0.038

<sup>a</sup> Estimated error of the mean. <sup>b</sup>  $s^2 = \Sigma[\log(k_{\text{obs}}/k_{\text{calc}})]^2/(N-2)$  where  $N$  is the number of substituents. <sup>c</sup> Ref. 25.  $\log k_{\text{HH}} = -6.090 \pm 0.0047$  (G. Kohnstam, personal communication). <sup>d</sup> Ref. 26. Some rate constants were extrapolated from measurements at other temperatures. <sup>e</sup> Ref. 27. <sup>f</sup> Refs. 14 and 28. <sup>g</sup> Ref. 13.

selectivity, at least in the wide sense of the term, with unit increase in reactivity ( $\log k$ ).

Table 1 illustrates the interpretation of experimental measurements of  $m/\rho_0^2$ . In all cases  $m/\rho_0^2$  is negative, indicating an inverse relationship between reactivity and selectivity. A factor that could be considered responsible is variation in transition state structure, especially as the observed behaviour is consistent with Hammond's postulate.<sup>6</sup> However, this cannot be the sole cause

out of line, but in this case only *meta*-substituents were used so there is no possibility of a contribution to non-additivity from resonance saturation.

The non-additivity of *meta*-substituents in the solvolysis of diphenylmethyl bromides points to the specific importance of transition state structure. Although the effect is small it contrasts with the close adherence to additivity of non-conjugating substituents in the equilibrium ionisation of fluorenes.<sup>13</sup> It is also noteworthy

TABLE 2  
Calculated reactivity parameters ( $\rho_0\sigma$ ) for reaction rates and equilibria<sup>a</sup>

Solvolysis of diphenylmethyl chlorides		Solvolysis of diphenylmethyl bromides		Ionisation of diphenylmethanols		Ionisation of fluorenes		Bromination of diphenylethylenes	
4-MeO	5.93	3-Me	0.22	4-MeO	4.20	2-MeO	-0.17	4-MeO	2.76
4-PhO	3.34	3-Br	-1.25	4-Me	1.21	2-PhS	2.23	4-Me	1.00
4-MeOC <sub>6</sub> H <sub>4</sub>	2.28	3-CF <sub>3</sub>	-1.62	3-Me	0.39	2-Br	2.59	3-Me	0.34
4-Me	1.69	3-NO <sub>2</sub>	-2.17	3-PhO	-0.29	2-Et <sub>2</sub> NSO <sub>2</sub>	4.12	3-MeO	-0.05
4-Bu <sup>t</sup>	1.25			4-Cl	-0.84	2-CN	4.86	4-F	-0.10
4-Ph	1.01							4-Cl	-0.52
4-F	0.32							4-Br	-0.59
4-Cl	-0.49							3-Cl	-1.21
4-NO <sub>2</sub>	-2.81							3-F	-1.19
								3-NO <sub>2</sub>	-2.08

<sup>a</sup> See Table 1 for sources for the reaction data.

because Table 1 includes equilibria as well as reaction rates, and the possibility of resonance saturation and, in diphenylmethyl carbonium ions, the inability of both rings simultaneously to achieve full conjugation have also been recognised as factors responsible for deviations from substituent additivity.<sup>13,14,26</sup>

A crude correlation may be noted between the magnitude of  $-2m/\rho_0^2$  and the number of factors capable of affecting selectivity in the reaction. For the solvolysis of diphenylmethyl chlorides and the bromination of diphenylethylenes all three factors can come into play,

that the sensitivity of  $\rho$  for rates of diphenylmethyl carbonium ion formation from diphenylmethyl chlorides is greater than in the equilibria for their formation from diphenylmethanols. Had resonance effects alone been responsible one might have expected a more strongly negative quadratic coefficient for the equilibrium, in which the carbonium ion centre is fully formed.

These arguments are illustrative rather than definitive. For data covering wide reactivity ranges a number of factors can affect apparent variations in reaction constants: changes in rate-determining step or mechanism

within the reaction series, differences in solvent, or specific substituent effects. In particular, curvature is dominated by substituents having the largest effect, and, for carbonium ions, especially the methoxy substituent. Although each reaction is characterised by a single curvature parameter the value should clearly be different for resonating *para*-substituents and non-resonating *meta*-substituents. The dominance of the methoxy substituent is illustrated for the solvolysis of diphenylmethyl chlorides by the sensitive plot of  $\log k_{XY}/k_{HH} - (\rho_0\sigma_X + \rho_0\sigma_Y)$  versus  $(\rho_0\sigma_X + \rho_0\sigma_Y)^2$ , with slope  $2m/\rho_0^2$ , which is shown in Figure 3 with methoxy substituents indicated by closed circles. Other limitations of the analysis are noted below.

*Dependence of Quadratic Coefficients upon Transition State Structure.*—When changes in transition state structure are important a further factor affecting the sensitivity of the reaction constant to changes in reactivity can be recognised from consideration of correlations of rates and equilibrium constants derived from reaction models, such as the hyperbolic dependence of  $\log k$  upon  $\log K$  considered by Lewis and his co-workers,<sup>20</sup> or the comparable dependence based on BEBO potential energy surfaces derived by Marcus,<sup>8</sup> shown in equation (17), in which  $k$  and  $K$  are rate and equilibrium con-

$$\ln k/k_{lim} = \frac{\ln K}{2} - c - \frac{c}{\ln 2} \cosh\left(\frac{-\ln K \cdot \ln 2}{2c}\right) \quad (17)$$

stants,  $k_{lim}$  is the limiting rate constant for a highly exothermic reaction ( $kT/h$  in the absolute reaction rate approximation), and  $c$  is  $\ln k/k_{lim}$  when  $K = 1$ .\*

Marcus' and Lewis' expressions represent quantitative formulations of Hammond's postulate. Their

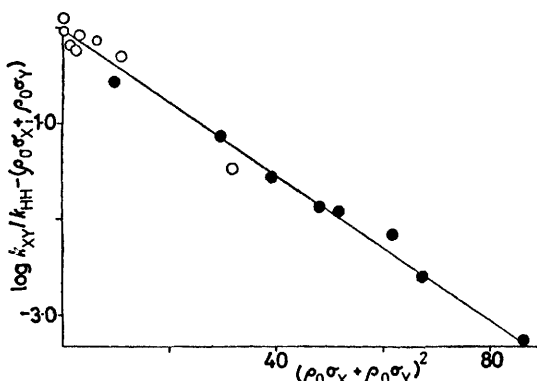


FIGURE 3 Plot of  $\log k_{XY}/k_{HH} - \rho_0\sigma_X - \rho_0\sigma_Y$  versus  $(\rho_0\sigma_X + \rho_0\sigma_Y)^2$ : closed circles denote *p*-methoxy substituents

essential feature is that  $k$  varies smoothly with  $K$  between the limits  $k_{lim}$  when  $K$  is large and  $K/k_{lim}$  when  $K$  is small and a limiting rate is achieved in the reverse direction.

A corresponding relationship between  $\log k$  and  $\sigma$  is shown graphically in Figure 4. At large values of  $\sigma$  the limit of high reactivity and low selectivity is approached,

\* Diffusion steps have not been included in equation (17) or its representation in Figure 4. In practice they prevent direct observation of any close approach to  $k_{lim}$ .<sup>8,20</sup>

i.e.  $k \rightarrow k_{lim}^*$  and  $\rho \rightarrow 0$ , while at large negative values of  $\sigma$ ,  $\rho \rightarrow \rho_{lim}$ , its low reactivity limit equal to  $\rho$  for the reaction equilibrium. When variation of  $\rho$  stems solely from changes in transition state structure  $\rho$  for the equilibrium is independent of  $\sigma$  and, following Lewis,<sup>20</sup> Figure 4 can be based quantitatively upon equation (17) by replacing  $\log K$  by  $\rho_{lim}\sigma$ .

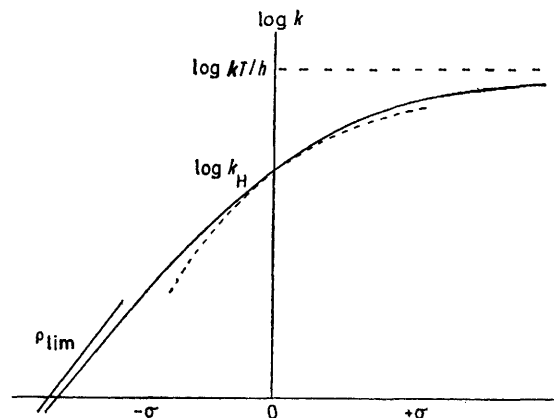


FIGURE 4 An ideal plot of  $\log k$  versus  $\sigma$ .  $\rho_{lim}$  is the limiting slope for highly endothermic reactions. The dashed curve represents a quadratic fit around  $\sigma = 0$

Our own analysis uses a quadratic relationship (represented by the dotted line in Figure 4) to determine curvature of the  $\log k$  versus  $\sigma$  plot at an arbitrary point determined by the reactivity of the unsubstituted substrate. It is plain from Figure 4 that the curvature of our relationship and its quadratic coefficient should depend on the reactivity of the unsubstituted substrate. For very high or very low reactivities the curvature will be small while in intermediate cases it will be large, ideally becoming maximised when  $K = 1$ . This may be expressed quantitatively in terms of equation (17) if we replace  $\log K$  by  $\rho_{lim}\sigma$  and recognise that the quadratic expression of equation (3) may be written as (18).

$$\log k/k_H = \left(\frac{\partial \log k}{\partial \sigma}\right)_{\sigma=0} \sigma + \left(\frac{\partial^2 \log k}{\partial \sigma^2}\right)_{\sigma=0} \sigma^2 \quad (18)$$

$$\log k/k_H = \rho_0 \sigma + \frac{\ln 2 (1-z)}{c} \frac{1}{z} \rho_0^2 \sigma^2 \quad (19)$$

Evaluating the differentials from equation (17) gives (19) where  $z = \rho_0/\rho_{lim}$ . The quadratic coefficient  $m$  is now seen to be given by equation (20) and it is apparent that

$$m = \frac{\ln 2 (1-z)}{c} \frac{1}{z} \rho_0^2 \quad (20)$$

$m \rightarrow 0$  in the limits of high and low reactivity, when  $\rho_0 \rightarrow 0$  or  $\rho_{lim}$  and has a maximum value when  $\rho_0 = \rho_{lim}/2$  at  $K = 0$ . The coefficient  $m/\rho_0^2$  measures curvature in a quadratic approximation to a plot of  $\log k$  versus  $\rho_0\sigma$ . In the low reactivity limit  $m/\rho_0^2 = 0$  also, but at high reactivity, at which  $\rho_0 \rightarrow 0$ ,  $m/\rho_0^2 \rightarrow \infty$ .

Of course, equation (17) will often not hold even qualitatively. Anti-Hammond substituent effects are commonplace<sup>5,10-12</sup> and  $\rho$  for the equilibrium will

commonly vary with  $\sigma$ . Nevertheless equation (19) demonstrates the possibility of relating experimentally measured quadratic coefficients to predictions of the sensitivity of transition-state structure to substituent effects based on reaction models.

*Departures from Quadratic Behaviour.*—It is true in general that while a linear relationship underestimates curvature a quadratic correction, over a sufficiently large reactivity range, overestimates it, as is apparent in Figure 4. For the solvolysis of diphenylmethyl chlorides (Figures 1 and 2) the very reactive *p,p'*-dimethoxy derivative is not correlated, and in the equilibrium ionisation of mono-, di-, and tri-*p*-methoxy substituted triphenylmethanols studied by Deno<sup>29</sup> the third methoxy substituent deviates from a quadratic representation. In both cases the degree of saturation of the substituent effect is less than calculated, as expected.

Other deviations must be of a different origin. In the bromination of diphenylethylenes the *m*-nitro-*p'*-methoxy substituent combination correlates poorly, as noted by Hegarty,<sup>14</sup> although no comparable deviation is found in the solvolysis of diphenylmethyl chlorides; conceivably this is due to interaction of the nitro substituted carbonium ion with the neighbouring bromine. For the diphenylmethyl chlorides Nishida has noted that two *m*-chloro substituents have less than twice the rate retarding effect of one,<sup>30</sup> which is the opposite of the expected saturation effect. The behaviour appears to be characteristic of halogen substituents<sup>14, 26, 28</sup> and perhaps reflects their opposed  $\sigma$  and  $\pi$  substituent components. Reversal of the normal saturation effect also occurs in other cases: in diphenylmethyl systems when the second substituent is placed in the same ring,<sup>27, 30</sup> and for electrophilic aromatic substitution in rings containing more than two substituents.<sup>31</sup> Probably these effects are steric in origin.

*Reactivity Parameters  $\rho_0\sigma$ .*—In addition to  $m/\rho_0^2$  the analysis yields a set of selectivity corrected reactivity parameters  $\rho_0\sigma$  [ $x$  in Exner's notation of equation (10)] which in contrast to  $\log k$  are additive with respect to multiple substitution.

Values of  $\rho_0\sigma$  for the reactions of Table 1 are listed in Table 2. They may be used to determine a reaction constant  $\rho_0$  if a suitable set of substituent constants free of selectivity changes in their defining reaction is available. Practically speaking the inductive constants  $\sigma^0$  provide such a set. They are free of resonance effects and are defined principally in terms of equilibria and for reactions covering a narrow range of equilibrium constants.<sup>32, 33</sup>

<sup>29</sup> N. C. Deno and A. Schreisheim, *J. Amer. Chem. Soc.*, 1955, **77**, 3051; N. C. Deno, H. E. Berkheimer, W. L. Evans, and H. J. Peterson, *ibid.*, 1959, **81**, 2344.

<sup>30</sup> S. Nishida, *J. Org. Chem.*, 1967, **32**, 2697; E. Berliner and M. Q. Malter, *ibid.*, 1968, **33**, 2595.

<sup>31</sup> J. E. Dubois, J. J. Aaron, P. Alcais, J. P. Doncet, F. Rothenburg, and R. Uzan, *J. Amer. Chem. Soc.*, 1972, **94**, 6823.

<sup>32</sup> R. W. Taft, jun., S. Ehrenson, I. C. Lewis, and R. E. Glick, *J. Amer. Chem. Soc.*, 1959, **81**, 5352.

<sup>33</sup> A. J. Hoefnagel and B. M. Webster, *J. Amer. Chem. Soc.*, 1973, **95**, 5357.

Use of  $\sigma^0$  is confined to reactions for which *meta*-substituents have been studied (Table 1, reactions 2—4). However, it has been noted already that where curvature of the free energy plot is dominated by strongly resonating substituents, as in the ionisation of diphenylmethanols or bromination of diphenylethylenes, the value of  $-2m/\rho_0^2$  is too large for *meta*-substituents. In these cases determining  $\rho$  from values of  $x = \rho_0\sigma$  has little advantage over direct determination from  $\log k$ , particularly if the *meta*-substituents span only a limited range of reactivity, as is often the case. Thus for the solvolysis of diphenylmethyl bromides, for which  $2m/\rho_0^2$  is based on *meta*-substituents, values of  $\rho$  from  $\rho_0\sigma$  and  $\log k$  respectively are  $-3.18$  and  $-3.37$ .

On the other hand use of the Yukawa-Tsuno treatment<sup>2, 33</sup> and values of  $\sigma^+$  lead to much larger estimates of the importance of resonance when based on values of  $\rho_0\sigma$  than when based on  $\log k$ . This is because the treatment makes no attempt to separate resonance effects from resonance saturation or variations in transition state structure. The estimate based on  $\rho_0\sigma$  is not a superior one because the effects are also not separated in the defining reaction.<sup>34</sup> This does not imply a limitation in the Yukawa-Tsuno treatment but emphasises that the derived resonance parameter has a more complex significance than a simple measure of resonance.

*Other Correlations of Dual Substitution.*—Substitution at two molecular positions has previously been dealt with by correlations<sup>14, 26, 27, 31, 35, 36</sup> based on Miller's

$$\log k_{XY}/k_{HH} = \rho_0^X \sigma_X + \rho_0^Y \sigma_Y + q \sigma_X \sigma_Y \quad (21)$$

$$y_{ij} = x_i + x_j + bx_i x_j \quad (22)$$

equation (21)<sup>24</sup> which in Exner's notation becomes (22) where  $x_i = \rho_0^X \sigma_X$  and  $b = q/\rho_0^X \rho_0^Y$ .

The quality of correlations achieved with equation (22) and equations (11) or (15) are compared in Table 1. The estimated errors in  $b$  of equation (22) are greater than in  $a$  of equation (15) but the variance of calculated from observed rate constants in the two cases differs insignificantly and even slightly favours (22). Satisfactory correlations of numerous examples of multiple substitution were also obtained by Exner using equation (23).

$$y_{ij} = x_i x_j + c \quad (23)$$

It appears that provided there is a sufficiency of parameters different correlations are not easily distinguished experimentally. The choice of which to use then must rest on other considerations, most obviously: (i) simplicity, (ii) the desirability of preserving linear

<sup>34</sup> H. C. Brown and Y. Okamoto, *J. Amer. Chem. Soc.*, 1958, **80**, 4979.

<sup>35</sup> E. H. Cordes and W. P. Jencks, *J. Amer. Chem. Soc.*, 1962, **84**, 4319.

<sup>36</sup> C. D. Ritchie, J. D. Saltiel, and E. S. Lewis, *J. Amer. Chem. Soc.*, 1961, **83**, 4601; S. A. Khan and A. J. Kirby, *J. Chem. Soc. (B)*, 1970, 1172; N. A. Porter, I. J. Westerman, T. G. Wallis, and C. K. Bradsher, *J. Amer. Chem. Soc.*, 1974, **96**, 5104; N. Gravitza and W. P. Jencks, *ibid.*, p. 507; J. M. Sayer and W. P. Jencks, *ibid.*, 1977, **99**, 464; H. F. Gilbert and W. P. Jencks, *ibid.*, p. 7931.

relationships for substitution at a single position, and (iii) the reasonableness of the chemical model implied.

In practice multiple correlations used hitherto have preserved linearity for substitution at a single position,<sup>15,24,37</sup> *i.e.* they have included cross terms  $x_i x_j$  but not terms in  $x_i^2$  and  $x_j^2$ . One approach has emphasised more formal aspects of the correlations<sup>15,24,38</sup> and variables other than reactivity, such as temperature<sup>39</sup> or spectroscopic properties,<sup>15</sup> have been considered. In correlations of reactivity however the emphasis has more often been upon chemical interpretation<sup>12,14,26,31,35,36,40</sup> and Miller's equation and its elaborations have implicitly been treated as approximations to a quadratic equation, equation (8) for example with the constants  $m_X$  and  $m_Y$  taken as zero.\*

The practical advantage of Miller's equation over equation (8) is that substituent non-additivity is described by one parameter rather than three, which permits its application to substitution at non-equivalent positions. However, if this represents an approximation there are good reasons why it should be recognised.

In the first place the approximation can break down. There are cases of monosubstitution, notably extended Brønsted relationships,<sup>8,9,17-20</sup> where curvature of free energy plots not ascribable to a cross term are found. There are also cases where multiple substitution is not described by a single parameter,<sup>41</sup> and where substitution involves equivalent positions the approximation becomes unnecessary because the three parameters of equation (8) reduce to one. Although equation (21) gives as good or better correlation than (15) inspection of Table 1 shows that the cross term  $q/\rho_0^2$  derived from the analysis corresponds only crudely to  $2m/\rho_0^2$  from (15).

Secondly, analysis of the data can be carried out so as to minimise the approximation. When dealing with a bimolecular reaction in which changes in reactivity at one position are small and at the other are large, as in Bell's example of the reaction of ketones with carboxylate bases<sup>21</sup> considered above, changes in the 'small' substituent, X say, while the other, Y, is kept constant are represented by a linear free energy relationship (24)

$$\log k_{XY}/k_{HY} = \rho\sigma_X \quad (24)$$

with slope  $\rho = \rho_0^X + q\sigma_Y$ . A plot of  $\rho$  for each value of Y against  $\sigma_Y$  then gives a straight line of slope  $q$ , accurately equal to  $m_{XY}$  for  $\sigma_Y = 0$  and the middle of the substituent range spanned by  $\sigma_X$ . This indeed is the method normally used to evaluate  $q$ . Where X substituents span a larger reactivity range equation (24) effectively represents a tangent at an appropriate value of  $\sigma_X$ .

On the other hand the implication of equation (21)

\* Formally Miller's equation is the counterpart for multiple substitution of the linear equation (1) for monosubstitution. Strictly speaking, equation (8) is itself an approximation to the corresponding quadratic expression (see Appendix).

<sup>37</sup> B. Gutbezahl and E. Grunwald, *J. Amer. Chem. Soc.*, 1953, **75**, 559.

<sup>38</sup> S. Wold, *Chemical Scripta*, 1974, **5**, 97; B. I. Istomin, S. A. Pivarov, V. F. Selivanov, B. V. Eidasov, and S. N. Istomina, *Org. Reactivity*, 1975, **12**, 287.

that a plot of  $\rho = \rho_0^X + q\sigma_Y$  versus  $\log k_{HY}$  should give a straight line of slope  $q/\rho_0^X$  determinable without specifying  $\sigma_Y$  is clearly not correct for large substituent effects at Y: as expected, for Bell's data (for which ' $\rho$ ' is the Brønsted exponent  $\beta$ ), such a plot gives a curve. Nor, strictly speaking, should the method used in this paper yield  $b$  ( $q/\rho_0^X \rho_0^Y$ ) in agreement with  $2a$  ( $2m_{XY}/\rho_0^X \rho_0^Y$ ), and indeed it is a disadvantage of treating (21) and (22) as approximations that the convenient solution not requiring definition of substituent constants is no longer applicable. However, if  $b$  is determined in this way it is clear from Table 1 that it is roughly equal to  $2a$ , to within 30% or better. Expressing  $b$  in terms of the parameters of equation (11),  $b = 2a/(1 - ax_i)(1 - ax_j)$  and it can be seen that the approximation will be a fair one when  $a$  is small, or, for unsymmetrical substitution, when the coefficients of the direct terms  $a_i$  and  $a_j$  of equation (10) are small.

Finally, recognising the approximation makes a literal interpretation of Miller's equation unnecessary. In terms of charge distribution at the reaction site the expression implies the existence of two reaction sites, one associated with substitution in the substrate, at which the charge distribution is sensitive to substituents in the reagent but not in the substrate, the other associated with substitution in the reagent, at which the charge distribution is sensitive to substitution in the substrate but not in the reagent. It has been pointed out before that chemically this makes little sense.<sup>5,40</sup> Moreover if (21) is an approximation neither need one accept the necessary existence of an isokinetic point.<sup>42</sup>

Miller's equation can be given a direct interpretation, as noted by Mindl and Vecera,<sup>26</sup> but in terms of interaction between substituents, presumably by inductive or field effects, not affecting the reaction site. It is hard to know how important such an effect might be but it has been given little previous consideration compared with factors affecting  $\rho$ . The greater curvature in the correlation of rates than equilibria in the ionisation of diphenylmethyl halides and alcohols and the absence of curvature for non-conjugating substituents in equilibrium ionisations of fluorenes suggest that it is of minor importance, at least in systems where the substituents are well separated. In so far as it is significant the simplification of equation (8) to (15) for equivalent substitution sites itself becomes an approximation and the values of  $2m/\rho_0^2$  in Table 1 overestimate the substituent sensitivities of the reaction constants.

In so far as Miller's expression is consistent with the strict, and most limited, definition of a reactivity-selectivity relationship<sup>5</sup> the advantages and shortcomings noted apply to this relationship also.

*Linear Free Energy Relationships.*—The formulation of a quadratic free energy relationship does not of course

<sup>39</sup> Ruey-Long Lii and S. I. Miller, *J. Amer. Chem. Soc.*, 1973, **95**, 1602; G. S. Krishnamurthy and S. I. Miller, *ibid.*, 1961, **83**, 3961.

<sup>40</sup> J. S. Lomas and J. E. Dubois, *J. Org. Chem.*, 1975, **40**, 3303.

<sup>41</sup> A. Dondoni and G. Barbaro, *J.C.S. Perkin II*, 1973, 1769.

<sup>42</sup> C. D. Johnson, *Chem. Rev.*, 1975, **75**, 756.

imply a practical limitation on linear relationships. On the contrary, examples of measurable departures from linearity are sufficiently rare that even their existence has occasionally been questioned.<sup>23,42</sup>

Reasons for the wide applicability of the linear approximation have been summarised elsewhere.<sup>5,20</sup> Prominent among them is the low intrinsic curvature expected of slow reactions.<sup>8,9</sup> Some further points have been noted in this paper. Detection of curvature normally requires a wide range of reactivity and a small dispersion of experimental points. Families of reactants that meet both these requirements, particularly where they must apply both to sample and reference reactions, are comparatively rare. Where large reactivity changes do occur curvature may be absorbed by a parameter introduced for other reasons, as in the Yukawa-Tsuno relationship. And, in special cases, chemical reasons for extended linearity exist<sup>12</sup> or may be suspected.<sup>43</sup>

Dual substitution probably offers the most general and effective means of detecting variations in reaction constants<sup>12</sup> and for this reason merits detailed examination. Qualitative applications, in which the effect of a structural change in substrate, reagent, or leaving group on  $\rho$  or a Brönsted exponent is measured, are of course far more common than quantitative studies, and are governed by the same considerations.

#### DETAILS OF CALCULATIONS

Solution of the equivalent equations (11) and (15) for the quadratic coefficient  $a = m/\rho_0^2$  and a set of reactivity parameters  $x_i = \rho_0\sigma_X$  is conveniently considered in terms of a slightly modified form (25) of equation (11) where  $y_{ij} =$

$$y_{ij} = x_{ij} + ax_{ij}^2 \quad (25)$$

$\log k_{XY}/k_{HH}$ . Assignment of an initial value of  $a$  allows calculation of a first set of  $x_{ij}$  from solution of (25). Writing the identities (26), with  $\sigma$  denoting H,  $a$  may be iterated to minimise the sum of the squares of the residuals,  $\Sigma \epsilon_{ij}^2$ , from the difference of observed from calculated  $y_{ij}$ . The

$$x_i = x_{i0}; \quad x_j = x_{0j} \quad (26)$$

$$\epsilon_{ij} = y_{ij} - (x_i + x_j) - a(x_i + x_j)^2 \quad (27)$$

iteration was carried out on an IBM 360-50 computer, but values of good accuracy could be quickly obtained with a hand calculator by the alternative of optimising additivity in  $x$  using  $\Sigma \epsilon'_{ij}^2$  from equation (28).

$$\epsilon'_{ij} = x_{ij} - x_i - x_j \quad (28)$$

The values of  $a$  and  $x_i$  from (26) and (27) can be improved because equations (26) imply that errors are confined to disubstituted reactants. A more even distribution of errors was achieved by calculating averaged values of  $x_i$  from equation (29) in which  $n_i$  is the number of reactions

$$x_i = \sum_j (x_{ij} - x_{0j})/n_i \quad (29)$$

involving an  $i$  substituent. The revised values of  $x_i$  were used to calculate a new value of  $a$  from equation (27) using

<sup>43</sup> C. D. Ritchie, D. J. Wright, Der-Shing Huang, and A. A. Kamego, *J. Amer. Chem. Soc.*, 1975, **97**, 1163; C. D. Ritchie, *ibid.*, p. 1170 and references cited.

the least squares expression (30). The process was repeated iteratively and it was found that  $\Sigma \epsilon_{ij}^2$  at first decreased and

$$a = \frac{\Sigma[(x_i + x_j)^2(y_{ij} - x_i - x_j)]}{\Sigma(x_i + x_j)^4} \quad (30)$$

then slowly increased. Values of  $a$  and  $x$  reported in Tables 1 and 2 correspond to the minimum value of  $\Sigma \epsilon_{ij}^2$ ; they differ from the initially calculated values by no more than a few percent.

Test data generated by assuming a hyperbolic dependence of  $y$  upon  $x$  showed that the initial iteration converged correctly. An attempt to iterate  $\log k_{HH}$  and thus to treat the experimental value on a par with other data leads to consistently low values, a consequence of compensation for improved fit of extreme values of  $k_{XY}$  for which the quadratic relationship overestimates curvature. Mental adjustment of the dotted line in Figure 4 indicates how this occurs. Values of  $y_{ij}$  calculated from the experimental  $k_{HH}$  therefore were used.

Values of  $b = q/\rho_0^2$  for Miller's expression [equations (21) and (22)] listed in Table 1 were calculated in a manner analogous to that for values of  $a$ .

#### APPENDIX

Equation (8) may be derived as follows. For substituents at position X, rearrangement of (31) and substitution for

$$\rho^X = \left( \frac{\partial \log k_{XY}}{\partial \sigma_X} \right)_{\sigma_Y} \quad (31)$$

$\rho^X$  from equation (5) gives (32), on setting integration limits,

$$\int_{k_{HY}}^{k_{XY}} d \log k_{XY} = \int_0^{\sigma_X} (\rho_0^X + 2m_X\sigma_X + 2m_{XY}\sigma_Y) d\sigma_X \quad (32)$$

which on integration yields (33). Similarly, for sub-

$$\log k_{XY}/k_{HY} = \rho_0^X\sigma_X + m_X\sigma_X^2 + 2m_{XY}\sigma_X\sigma_Y \quad (33)$$

stituents at position Y, from equation (6) we obtain (34).

$$\log k_{XY}/k_{XH} = \rho_0^Y\sigma_Y + m_Y\sigma_Y^2 + 2m_{XY}\sigma_X\sigma_Y \quad (34)$$

Putting  $\sigma_Y = 0$  and  $\sigma_X = 0$  into equations (33) and (34) respectively, gives (35) and (36) and substitution for  $\log k_{HY}$

$$\log k_{XH}/k_{HH} = \rho_0^X\sigma_X + m_X\sigma_X^2 \quad (35)$$

$$\log k_{HY}/k_{HH} = \rho_0^Y\sigma_Y + m_Y\sigma_Y^2 \quad (36)$$

in (33) from (36) or for  $\log k_{XH}$  in (34) from (35) gives equation (8). The equivalent derivations from equations (5) and (6) demonstrate what has been assumed, that  $m_{XY}$  in (5) and (6) are the same. This indeed is a consequence of the fact that substituent effects on  $\log k$  commute, *i.e.* equation (37) applies.

$$\left( \frac{\partial \log(k_{XY}/k_{HH})}{\partial \sigma_X \partial \sigma_Y} \right) = \left( \frac{\partial \log(k_{XY}/k_{HH})}{\partial \sigma_X \partial \sigma_Y} \right) = m_{XY} \quad (37)$$

It should be noted that the above derivation assumes  $m_X$  to be independent of  $\sigma_Y$  and  $m_Y$  of  $\sigma_X$ , as well as that  $\sigma_X$  and  $\sigma_Y$  are mutually independent. Such assumptions are

$$y_{i0} = x_i + a_i x_i^2; \quad y_{0j} = x_j + a_j x_j^2 \quad (38)$$

permissible but they are not implicit in the quadratic equations for monosubstitution. In Exner's notation the equations for monosubstitution are (38) and the fullest



expression for dual substitution with which they are compatible is (39), in which  $a$  and  $c$  are constants.\* Equation (22), used by Miller, is the corresponding counterpart of *linear* equations for monosubstitution.<sup>24</sup>

$$y_{ij} = x_i + x_j + a_i x_i^2 + a_j x_j^2 + a_{ij} x_i x_j + c_i x_j x_i^2 + c_j x_i x_j^2 + c_{ij} x_i^2 x_j^2 \quad (39)$$

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\* We thank S. Wold and S. I. Miller for pointing this out.