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Characterization of Transition States for Reactions in Solution by Cross-interaction Constants

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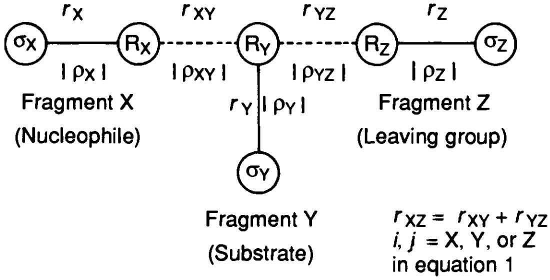
1 Introduction

The Hammett (ρ) and Brönsted coefficients (β) have long served as experimental measures of charge development, and bond orders for forming and cleaving bonds, in the transition state (TS) for various reactions in solution. However, it has often been pointed out that the efficiency of charge transmission between reaction centres R_i and R_j (i,j = X, Y, or Z in Scheme 1) in bond formation and cleavage may differ for different reaction series so that $|\rho_i|$ or $|\beta_i|$ can at most serve as a relative measure of bond length r_{ij} within a particular family of closely related reactions.[1] A more useful measure of the TS structure is provided by the cross-interaction constant ρ_{ij} or β_{ij}, defined by a Taylor expansion of log k_{ij} up to second order around $\sigma_i = \sigma_j = 0$ or $\Delta pK_i = \Delta pK_j = 0$ where $\Delta pK_i = \Delta pK_a^{(i)} - \Delta pK_a^{(H)}$ *etc.* and neglecting the pure second-order terms, ρ_{ii} or β_{ii}, in equations 1a and 1b.[2]



Scheme 1 *Typical* S_N2 *TS*

$$\log(k_{ij}/k_{HH}) = \rho_i\sigma_i + \rho_j\sigma_j + \rho_{ij}\sigma_i\sigma_j \qquad (1a)$$

$$= \beta_i\Delta pK_i + \beta_j\Delta pK_j + \beta_{ij}\Delta pK_i\Delta pK_j \qquad (1b)$$

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[1] (*a*) D. J. McLennan, *Tetrahedron*, 1978, **34**, 2331; (*b*) B.-L. Poh. *Can. J. Chem.*, 1979, **57**, 255; (*c*) I. Lee and H. K. Kang, *Tetrahedron Lett.*, 1987, **28**, 1183; (*d*) I. Lee, H. K. Kang, and H. W. Lee, *J. Am. Chem. Soc.*, 1987, **109**, 7472; (*e*) I. Lee, C. S. Shim, S. Y. Chung, H. Y. Kim, and H. W. Lee, *J. Chem. Soc., Perkin Trans. 2*, 1988, 1919.

[2] (*a*) I. Lee and S. C. Sohn, *J. Chem. Soc., Chem. Commun.*, 1986, 1055; (*b*) I. Lee, C. S. Shim, and H. W. Lee, *J. Chem. Soc., Perkin Trans. 2*, 1989, 1205.

$$= \rho_i\sigma_i + \beta_j\Delta pK_j + \lambda_{ij}^{(i)}\sigma_i\Delta pK_j \qquad (1c)$$

Similar expansion involving σ_i and ΔpK_j leads to a mixed type interaction constant λ_{ij}, equation 1c [2b] Obviously the following definitions hold.

$$\rho_{ij} = \frac{\partial^2 \log k_{ij}}{\partial\sigma_i\partial\sigma_j} = \frac{\partial\rho_j}{\partial\sigma_i} = \frac{\partial\rho_i}{\partial\sigma_j} \qquad (2a)$$

$$\beta_{ij} = \frac{\partial^2 \log k_{ij}}{\partial\Delta pK_i\partial\Delta pK_j} = \frac{\partial\beta_j}{\partial\Delta pK_i} = \frac{\partial\beta_i}{\partial\Delta pK_j} \qquad (2b)$$

$$\lambda_{ij}^{(i)} = \frac{\partial^2 \log k_{ij}}{\partial\sigma_i\partial\Delta pK_j} = \frac{\partial\beta_j}{\partial\sigma_i} = \frac{\partial\rho_i}{\partial\Delta pK_j} \qquad (2c)$$

The three parameters ρ_{ij}, β_{ij}, and λ_{ij} are related by

$$\rho_{ij} = \rho_{e^i}\rho_{e^j}\beta_{ij} = \lambda_{ij}^{(i)}\rho_{e^i} = \lambda_{ij}^{(j)}\rho_{e^j} \qquad (3)$$

$$\text{where} \quad \left.\begin{aligned} \Delta pK_i &= \rho_{e^i}\sigma_i \\ \Delta pK_j &= \rho_{e^j}\sigma_j \end{aligned}\right\} \qquad (4)$$

These parameters are variously referred to as *q*, *C*, or *p* by several workers,[3] and are known to reflect the intensity of interaction between the two reacting fragments comprising the TS (Scheme 1). The magnitude of the Hammett type constants $|\rho_{ij}|$ represents the intensity of *indirect interaction* between two substituents, $i(\sigma_i)$ and $j(\sigma_j)$ through the respective reaction centres, R_i and R_j, when the two fragments are involved in forming or breaking of a bond, r_{ij}, between the two reaction centres in the TS. Thus the $|\rho_{ij}|$ should be related inversely to the distance between the two substituents σ_i and σ_j, since it represents the intensity of interaction between them through reaction centres; in fact it has been shown that the distance r_{ij} is related to $|\rho_{ij}|$ by equation 5, where α and β are positive

$$r_{ij} = \alpha + \beta\log(|\rho_{ij}|)^{-1} \qquad (5)$$

constants, assuming the rigidity of the fragment's skeleton in the reaction.[4] According to equation 2a, the magnitude of ρ_{ij} is subject to fall-off by a factor of 2.4 ~ 2.8 when a nonconjugating group, like CH_2 (or CO), intervenes in one of the fragments (i) between the substituent, σ_i, and the reaction centre, R_i, since

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[3] (*a*) S I Miller, *J Am Chem Soc*, 1959, **81**, 101, (*b*) E H Cordes and W P Jencks, *J Am Chem Soc*, 1962, **84**, 4319, (*c*) D A Jencks and W P Jencks, *J Am Chem Soc*, 1977, **99**, 7948, (*d*) J-E Dubois, M-F Ruasse, and A Argile, *J Am Chem Soc*, 1984, **106**, 4840, (*e*) W P Jencks, *Chem Rev*, 1985, **85**, 511

[4] I Lee, *Bull Korean Chem Soc*, 1988, **9**, 179

normally each CH_2 group reduces the magnitude of ρ_i by such an amount in equation 2a.[5]

On the other hand, the magnitude of the Brönsted type constants, $|\beta_{ij}|$, represents the intensity of *direct interaction* between the two reaction centres, R_i and R_j, so that there will be no such complications involving fall-off of the intensity of interaction due to any intervening groups between a substituent (σ_i) and its reaction centre (R_i). Another advantage of using β_{ij} is that the value (of β_{ij}) can be determined for a reaction series in which structural variations in the fragments i and/or j do not involve substituent changes. In this respect $|\lambda_{ij}|$ will be useful when the structural variation in one of the reactants does not involve substituent changes. Since ρ_{e^i} or ρ_{e^j} is normally a negative constant for a particular fragment i or j, ρ_{ij} and β_{ij} should have the same sign while λ_{ij} will have an opposite sign. Moreover $|\beta_{ij}|$ and $|\lambda_{ij}|$ will have similar distance dependence as $|\rho_{ij}|$ with different set of constant values, α and β, in equation 5, since the ρ_{e^i} or ρ_{e^j} value is constant for a series of reactions.

2 Sign of the Cross-interaction Constants

Let us consider the significances of sign of the constants ρ_{ij} for nucleophilic substitution reactions. Charge development on R_i and the sign of ρ_i (or β_i) show a simple relationship in the bond-forming and -breaking steps;[6] a more negative (positive) charge development at R_Z (R_X) leads to a more positive ρ_Z (a more negative ρ_X). Thus a negative ρ_{XZ} in equation 6 indicates that a more electron-

$$\rho_{XZ} = \frac{\partial^2 \log k_{XZ}}{\partial\sigma_X \partial\sigma_Z} = \frac{\partial\rho_Z}{\partial\sigma_X} = \frac{\partial\rho_X}{\partial\sigma_Z} \tag{6}$$

donating substituent (EDS) in the nucleophile (*i.e.*, a stronger nucleophile), $d\sigma_X < 0$, leads to a greater positive ρ_Z, $d\rho_Z > 0$ (a greater degree of bond breaking), and a more electron-withdrawing substituent (EWS) in the leaving group (LG), $d\sigma_Z > 0$ (*i.e.*, a better LG), leads to a greater negative ρ_X, $d\rho_X < 0$ (a greater degree of bond formation). In effect the negative ρ_{XZ} value predicts a 'later' TS for a stronger nucleophile or a better LG. This prediction is precisely what we would expect from the quantum-mechanical (QM) model for predictions of TS variation[7] which has been shown to apply to the intrinsically controlled reaction series.[8] Of the two factors comprising the activation energy of a reaction ($\Delta G^{\neq}$), the intrinsic ($\Delta G_0^{\neq}$) and the thermodynamic (ΔG^0) barriers in the Marcus

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[5] (*a*) M. Charton, *Prog. Phys. Org. Chem.*, 1981, **13**, 119; (*b*) M. R. F. Siggel, A. Streitwiser, Jr., and T. D. Thomas, *J. Am. Chem. Soc.*, 1988, **110**, 8022.

[6] C. D. Johnson, 'The Hammett Equation,' Cambridge University Press, Cambridge, 1973, p. 7– 11.

[7] (*a*) A. Pross and S. S. Shaik, *J. Am. Chem. Soc.*, 1981, **103**, 3702; (*b*) I. Lee and C. H. Song, *Bull. Korean Chem. Soc.*, 1986, **7**, 186; (*c*) D. J. Mitchell, H. B. Schlegel, S. S. Shaik, and S. Wolfe, *Can. J. Chem.*, 1985, 63, 1642; (*d*) I. Lee, S. C. Sohn, C. H. Kang, and Y. J. Oh, *J. Chem. Soc., Perkin Trans. 2*, 1986, 1631; (*e*) I. Lee, C. S. Shim, S. Y. Chung, and H. W. Lee, *J. Chem. Soc., Perkin Trans. 2*, 1988, 975.

[8] (*a*) I. Lee, Y. H. Choi, H. W. Lee, and B. C. Lee, *J. Chem. Soc., Perkin Trans. 2*, 1988, 1537; (*b*) I. Lee, *J. Chem. Soc., Perkin Trans. 2*, 1989, 943.

equation,[8b,9] $\Delta G^{\ddagger} = \Delta G_0^{\ddagger} + \Delta G^0/2 + (\Delta G^0)^2/16\Delta G_0^{\ddagger}$, either can be dominant, and the TS variation in the intrinsic controlled reactions follows that predicted by the QM model.[7]

Conversely, if the ρ_{XZ} value is positive, a stronger nucleophile and a better LG lead to an 'earlier' TS with a lesser degree of bond-breaking/bond-making. In this case the TS variation can be predicted with the potential energy surface (PES) diagram,[10] Figure 1; an EWS in the LG will stabilize the upper corners, D and P, so that the TS will shift to F, which is obtained as a sum of the two vectors, OE and OG, in accord with the Hammond[10d,11] and anti-Hammond (or Thornton[10d,12]) rules. The bond-formation is predicted to decrease. On the other hand, a strong nucleophile will stabilize the right-hand corners, P and A, so that the TS is expected to shift to I, *i.e.*, towards less bond-breaking. These effects of substituents in the nucleophile and the LG on the TS variation are in complete agreement with what we would expect thermodynamically; a stronger nucleophile and a better LG will give thermodynamically more stable products so that the reaction will become more exothermic. An increase in exothermicity will lead to an earlier TS according to the Hammond postulate,[10d,11] which is also based on thermodynamic stabilities of reactants and products. Thus a reaction series becomes thermodynamically controlled when the TS variation follows that predicted by the PES model.[7e,13] These will apply to the sign of β_{ij} as well since the sign of β_{ij} is normally the same as that of ρ_{ij}; the reverse will be true, however, for λ_{ij}.

A later (earlier) TS with a stronger nucleophile, $d\sigma_X < 0$, and a better LG, $d\sigma_Z > 0$, in the intrinsic-controlled (thermodynamic-controlled) series should lead to the following relations:

$$\left.\begin{aligned} \Delta r_{XY} &= a\sigma_Z \\ \Delta r_{YZ} &= b\sigma_X \end{aligned}\right\} \qquad (7)$$

where a and b are both negative for the intrinsic controlled, whereas they are both positive for the thermodynamic reaction series. Thus $\rho_{XZ} < 0$, and $a,b < 0$ for intrinsic-controlled series, for which QM model applies; $\rho_{XZ} > 0$, and $a,b > 0$ for thermodynamic-controlled series for which PES model applies. The value of ρ_Y (or β_Y) for substituents on a central atom will depend on both bond-forming and -breaking processes so that no simple general interpretation of the sign is possible; the signs of ρ_{XY} and ρ_{YZ} should therefore be interpreted for the specific case involved.

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[9] (*a*) R A Marcus, *Ann Rev Phys Chem*, 1964, **15**, 155, (*b*) E S Lewis and D D Hu, *J Am Chem Soc*, 1984, **106**, 3292, (*c*) J A Dodd and J I Brauman, *J Am Chem Soc*, 1984, **106**, 5356, (*d*) J R Murdock, *J Am Chem Soc*, 1983, **105**, 2660; (*e*) K Yates, *J Phys Org Chem*, 1989, **2**, 300

[10] (*a*) E R Thornton, *J Am Chem Soc*, 1967, **89**, 2915, (*b*) R A More O'Ferrall, *J Chem Soc*, (*B*), 1970, 274, (*c*) W P Jencks, *Chem Rev*, 1972, **72**, 705, (*d*) T H Lowry and K S Richardson, 'Mechanism and Theory in Organic Chemistry', 2nd ed, Harper and Row, New York, 1981, p 188 205

[11] G S Hammond, *J Am Chem Soc*, 1955, **77**, 334

[12] E R Thornton, *J Am Chem Soc*, 1967, **89**, 2915

[13] M J S Dewar and R C Dougherty, 'The PMO Theory of Organic Chemistry', Plenum, New York, 1975, p 212

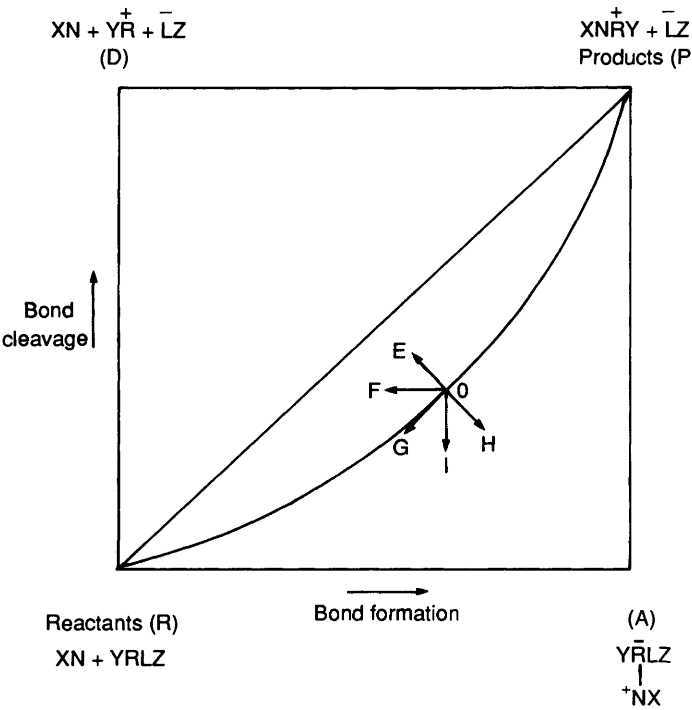


Figure 1 *Potential energy surface diagram for a typical associative* S_N2 *reaction*

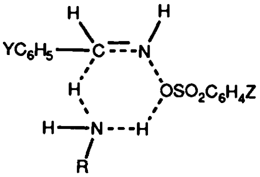
3 Magnitude of the Cross-Interaction Constants

A. No Interaction.—There will be two cases of no interaction. The first case occurs when the distance, r_{ij}, between the two reaction centres, R_i and R_j, is very large so that the intensity of interaction will be negligible, and hence $|\rho_{ij}| = 0$ (and $|\beta_{ij}| = |\lambda_{ij}| = 0$) in equation 5. In the second case, $|\rho_{ij}|$ or $|\beta_{ij}|$ will be zero if the two fragments, say with substituents σ_i and σ_j, are not involved in the direct mutual interaction through R_i and R_j so that a distance change, Δr_{ij}, does not occur in the rate-determining step. Thus there will be no interaction between R_Y and R_Z) (and hence between σ_Y and σ_Z) in the rate-determining bond formation step, since the bond length r_{YZ} remains intact in this step and $\rho_Z(\rho_Y)$ is independent of $\sigma_Y(\sigma_Z)$ leading to

$$\rho_{YZ} = \frac{\partial \rho_Z}{\partial \sigma_Y}\left(= \frac{\partial \rho_Y}{\partial \sigma_Z}\right) = 0.$$

Likewise in the rate-determining bond breaking step, the bond length r_{XY} should not vary leading to

$$\rho_{XY} = \frac{\partial \rho_Y}{\partial \sigma_X} = \frac{\partial \rho_X}{\partial \sigma_Y} = 0.$$



(1)

These two cases of no interaction can be applied to the characterization of S_N1 and S_AN mechanisms, in the S_N1 TS, no bond formation occurs but only bond cleavage takes place, so that $|\rho_{XY}| = |\rho_{XZ}| \cong 0$ with only non-zero cross-interaction between σ_Y and σ_Z, $|\rho_{YZ}| \neq 0$ Likewise in the addition–elimination mechanism (S_AN), $|\rho_{YZ}|$ will be zero if formation of the addition complex is rate determining, whereas $|\rho_{XY}|$ will be zero if elimination of the addition complex is rate limiting Two notable examples are found in the literature $OH + YC_6H_4CO_2C_6H_4\text{–}Z \longrightarrow \rho_{YZ} = 0$, rate-limiting addition,[14] $X\text{–}C_6H_4O^- + Y\text{–}C_6H_3(NO_2)Cl \longrightarrow \rho_{XY} = 0$, rate-limiting elimination [15] Similarly mechanistic criteria can be provided for the base-promoted alkene-forming β-elimination reactions For the eliminations in $YC_6H_4CH_2NHOSO_2C_6H_4Z$ promoted by benzylamine in methanol, a base-catalysed bridge structure, (1), has been considered by the original authors as a possible TS,[16] which can be readily ruled out as untenable based on the magnitude of cross-interaction constant ρ_{YZ} (= 0), since the TS structure (1) should require a large value of $|\rho_{YZ}|$, as will be shown below for reactions involving interactions between σ_Y and σ_Z through two routes (*vide infra*)

B. Manifold Interaction.—Substituents can, often, interact through multiple routes In such manifold interactions, the cross-interaction constants will be much greater than those for normal single route interactions There will be two types of manifold (twofold) interactions, as shown in Figure 2 In (A), two substituents, σ_i and σ_j, are both present in a single fragment so that both interact with the common reaction centre R_{ij} *via* the two common routes, whereas in (B) the two routes interconnecting the two reaction centres, R_i and R_j, are separate and the two substituents can interact through the two reaction centres simultaneously These types of interactions are rather common and some examples are shown in Table 1

We note that the $|\rho_{ij}|$ values are large for the twofold interaction pathways compared to those for the respective single path mechanism

C. Distance Dependence of the Cross-interaction Constants.—It has been shown that the distance r_{ij} between the two substituents σ_i and σ_j is a logarithmic inverse function of $|\rho_{ij}|$ [4] This means that

[14] J F Kirsch W Clewell and A Simon *J Org Chem* 1968 **33** 127

[15] J R Knowles R O C Norman and J H Prosser *Proc Chem Soc* 1961 341

[16] R V Hoffman and E L Belfoure *J Am Chem Soc* 1982 **104** 2183

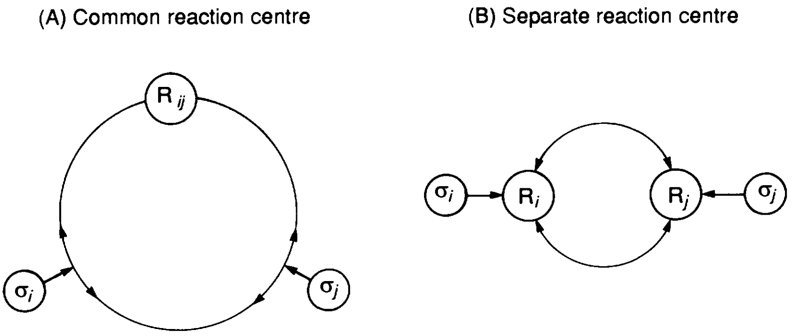


Figure 2 *Two-fold interaction pathways*

$$\left.\begin{array}{l}[(r_X + r_Y) + r_{XY}] \propto \log(|\rho_{XY}|)^{-1} \\ [(r_Y + r_Z) + r_{YZ}] \propto \log(|\rho_{YZ}|)^{-1}\end{array}\right\} \qquad (8)$$

However, the distances r_X, r_Y, and r_Z (Scheme 1) are normally constant and these do not vary during reactions unless there is a structural change involving strong resonance between the σ_i's and R_i's.[2a] This rigidity of skeletons will simplify the relationships of equation 8 into that of equation 5. Although r_i's are constant within a series during the reaction, an extra CH_2 group will lengthen r_i so that $|\rho_{ij}|$ will be reduced according to equation 8; this is reflected in the fall-off of $|\rho_{ij}|$ by a factor of 2.4 ~ 2.8 for each non-conjugating intervening CH_2 or CO group between σ_i and R_i.[5]

A comparison of equations 7 and 8 leads to another useful set of relationships, equation 9.

$$\left.\begin{array}{l}\Delta\log|\rho_{XY}| = a'\sigma_Z \\ \Delta\log|\rho_{YZ}| = b'\sigma_X\end{array}\right\} \qquad (9)$$

Constants a' and b' are now positive for the series under intrinsic control, whereas they are negative for the reaction series under thermodynamic control.

Similar relationships to those given in equations 5 and 9 are obtained using β_{ij} instead of ρ_{ij} with different set of constants (α, β, a', and b') based on equations 3 and 4.

Some applications of cross-interaction constants to characterization of TS structures for reactions in solution are given in the following sections.

4 A Measure of Bond-tightness in the TS

The ρ_{XY} values for some nucleophilic reactions are collected in Table 2.[1e] All except reaction G in class I involve anilines as nucleophiles and LG's of relatively good leaving ability, Cl^-, Br^-, and $C_6H_5O_2SO^-$.[17] A striking feature for the

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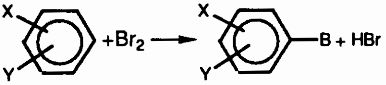
[17] Ref. 10(*d*), pp. 339 342.

Table 1 *Manifold interactions demonstrated by* $|\rho_{XY}|$

(i)

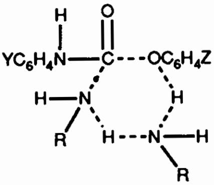


$|\rho_{XY}| = 7.98$

(ii) Hydrogen exchange in X,Y-disubstituted pyridines $|\rho_{XY}| = 7.60$
(iii) Hydrogen exchange in X,Y-disubstituted benzenes $|\rho_{XY}| = 3.00$

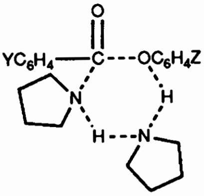
(B)[b] (iv) $YC_6H_4NHCOOC_6H_4Z + RNH_2 \xrightarrow[k_3]{k_2} YC_6H_4NHCONHR + HOC_6H_4Z$

k_2 path $|\rho_{YZ}| = 1.02$
k_3 path $|\rho_{YZ}| = 4.00$



(v) Pyrrolidine + $YC_6H_4COOC_6H_4Z \xrightarrow[k_3]{k_2} YC_6H_4CONC_4H_8 + HOC_6H_4Z$

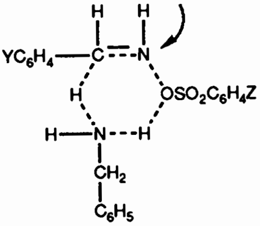
k_2 path $|\rho_{YZ}| = 1.76$
k_3 path $|\rho_{YZ}| = 9.33$



(vi) $YC_6H_4CH_2NHOSO_2C_6H_4Z + C_6H_5CH_2NH_2 \xrightarrow{MeOH}$

$YC_6H_4CH{=}NH + C_6H_5CH_2NH_3^+ \ {}^-OSO_2C_6H_4Z$

$|\rho_{YZ}| = 0$ no k_3 *path* possible (*E*1-like)



[a] Ref 3(*d*) [b] Ref 30

Table 2 *The ρ_{XY} values for some nucleophilic substitution reactions*[a]

Class		*Reactions*	ρ_X	ρ_Y	ρ_{XY}	*Correlation Coefficient*
I	A	$XC_6H_4NH_2 + YC_6H_4COCl \xrightarrow[35.0\ ^\circ C]{MeOH}$	-2.25	2.17	-0.68	0.999
	B	$XC_6H_4NH_2 + YC_6H_4CH_2Cl \xrightarrow[35.0\ ^\circ C]{MeOH}$	-0.98	-0.61	-0.77	0.974
	C	$XC_6H_4NH_2 + YC_6H_4SO_2Cl \xrightarrow[35.0\ ^\circ C]{MeOH}$	-2.14	0.96	-0.70	0.998
	D	$XC_6H_4NH_2 + YC_6H_4SO_2Cl \xrightarrow[25.0\ ^\circ C]{MeOH}$	-2.15	1.10	-0.75	0.997
	E	$XC_6H_4NH_2 + YC_6H_4CH_2OSO_2C_6H_4Z \xrightarrow[35.0\ ^\circ C]{MeOH}$	-0.92	-0.75	-0.62	0.999
	F	$XC_6H_4NH_2 + YC_6H_4CH_2Br \xrightarrow[35.0\ ^\circ C]{MeOH}$	-1.33	-0.67	-0.78	0.991
	G	$XC_6H_4S^- + YC_6H_4CH_2Cl \xrightarrow[20.0\ ^\circ C]{MeOH}$	-0.58	0.58	-0.62	0.982
II	H	$XC_6H_4NH_2 + YC_6H_4COF \xrightarrow[55.0\ ^\circ C]{MeOH}$	-3.14	1.72	-1.67	0.997
	I	$XC_6H_4NH_2 + YC_6H_4SO_2F \xrightarrow[45.0\ ^\circ C]{MeOH}$	-1.31	1.15	-1.07	0.999
III	J	$XC_6H_4CH_2NH_2 + YC_6H_4SO_2Cl \xrightarrow[35.0\ ^\circ C]{MeOH}$	-1.38	1.51	-0.39	0.999
	K	$XC_6H_4CH_2NH_2 + YC_6H_4CH_2Br \xrightarrow[45.0\ ^\circ C]{MeOH}$	-1.15	-0.46	-0.38	0.997
	L	$XC_6H_4CH_2NH_2 + YC_6H_4SO_2F \xrightarrow[45.0\ ^\circ C]{MeOH}$	-0.78	0.71	-0.66	0.999
	M[b]	$XC_6H_4CO_2^- + YC_6H_4SO_2Cl \xrightarrow[30.0\ ^\circ C]{MeOH}$	-0.37	0.69	-0.37	0.997
	N[b]	$XC_6H_4CHCHCO_2^- + YC_6H_4SO_2Cl \xrightarrow[30.0\ ^\circ C]{MeOH}$	-0.22	0.63	-0.22	0.998

[a] References given in Ref. 1(*e*). [b] I. Lee, H. J. Koh, and H. W. Lee, unpublished results.

class I reactions is that the ρ_{XY} values, which are negative, have a similar magnitude, $|\rho_{XY}| = 0.70 \pm 0.08$. Reactions in this class are considered to be good examples of the S_N2 type, and the similar size, therefore, provides evidence in support of a similar degree of bond formation, r_{XY}, in the TS.

Close examination of the ρ_X values, however, reveals that the magnitude varies widely, $|\rho_X| = 0.58 \sim 2.24$, in contrast to the relatively constant $|\rho_{XY}|$ values. This is a clear demonstration of variable charge transmission reflected in $|\rho_X|$ depending on the reaction centres R_X and R_Y, although in reality a similar degree of bond formation, *i.e.*, a similar value of r_{XY}, is involved in the TS of the reactions in this class, as the similar $|\rho_{XY}|$ values indicate.

The LG for reactions in class II is fluoride and, as for reactions in class I, ρ_X and ρ_{XY} are both negative. However, a notable difference between the reactions in the two classes is the size of ρ_{XY}, which is greater for the fluoride series by more than 1.5 times that of the corresponding series with chlorides LG in class I. It is well known that fluoride is a much worse LG than chloride owing to the weak electron-accepting ability of the C–F or S–F bond.[1c,18] The larger $|\rho_{XY}|$ values for class II reactions indicate that the poorer LG gives the greater degree of bond formation, which is consistent with the predictions of the TS variation by the PES model.

Comparison of reactions C and I indicates that $|\rho_X|$ is smaller for I despite the large $|\rho_{XY}|$ value, supporting the contention that the Hammett ρ_X values are unreliable as a measure of bond tightness because of the variable charge transmission.[1]

In class III, the nucleophile changes to benzylamine, benzoates, and cinnamates. Benzylamine is more basic than aniline, $\Delta pK_a \cong 5.0$,[19] and hence is a stronger nucleophile, but it has an extra intervening CH_2 group; we note that the magnitudes of ρ_{XY} for reactions J—L are slightly greater than half those for the corresponding reactions with anilines in classes I and II, but the signs of ρ_X, ρ_Y, and ρ_{XY} agree. Comparison of reactions J, K, and L again shows that $|\rho_{XY}|$ is greater for the fluoride series (reaction L) than for the chloride and bromide series (reaction J and K), although $|\rho_X|$ is smaller for the fluoride series. For reaction M, $|\rho_{XY}|$ $(= 0.37)$ is slightly greater than half of that for reaction D ($|\rho_{XY}| \cong 0.70$) suggesting a somewhat greater degree of bond formation, if the fall-off by a factor of 2.4—2.8 due to an extra intervening carbon in benzoate nucleophile is allowed for. Another intervening ethylene group (CH=CH) in the cinnamate (reaction N) seems to reduce $|\rho_{XY}|$ further (to $|\rho_{XY}| = 0.22$), but not so much as we would have expected,[20] indicating that for this case bond formation may be somewhat greater than that for the benzoate nucleophile.

Some mixed Hammett–Brönsted type cross-interaction constants λ_{ij} have been determined.[2] These parameters contain only one constant factor ($\rho_{e'}$) corresponding to the interaction between substituent (i) and reaction centre (R_i), so that the magnitudes are somewhat greater than the corresponding values of $|\beta_{ij}|$ but smaller than those of $|\rho_{ij}|$ with opposite sign, *e.g.*, $\lambda_{XY} > 0$, whereas $\rho_{XY} < 0$ and $\beta_{XY} < 0$. As expected, the magnitude of λ_{XY} (0.20—0.27), which is a measure of bond formation in the TS, does not show much variation for the typical S_N2 reactions with aniline nucleophiles; this is an indication of a nearly similar degree of bond formation, *i.e.*, $r_{XY} \cong$ constant, as concluded from the nearly constant values of $|\rho_{XY}|$ for the reactions. The size of λ_{XY} for the reaction of benzoyl fluoride is more than twice that for other reactions, indicating a much greater degree of bond formation in the TS of the nucleophilic substitution reaction of a carbonyl compound with a poorer LG, fluoride ion. Similarly, a comparison of reactions of benzenesulphoyl chloride ($\lambda_{XY} = 0.20$) and with fluoride ($\lambda_{XY} =$

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[18] S. S. Shaik and A. Pross, *J. Am. Chem. Soc.*, 1982, **104**, 2708.

[19] pK_a values in water at 25.0 °C are 9.35 and 4.60 for benzylamine and aniline respectively. J. A. Dean. 'Handbook of Organic Chemistry', McGraw-Hill, New York, 1987, Section 8.

[20] The ρ values for proton equilibria in water at 25.0 °C are 1.00 and 0.47 for benzoic and cinnamic acids, respectively. Ref. 6, p. 8.

0.39) also shows an increase in the degree of bond formation with fluoride LG. The increment of $|\lambda_{XY}|$ relative to the values for the reactions with anilines is seen to be inversely proportional to the nucleofugic power of the LG, *i.e.* the increase is in the order Br < Cl < F. This demonstrates an increase in bond formation in the TS with a weaker nucleofuge, the increase being greater for the compounds with worse LG's. This sort of fine quantitative analysis is difficult with $|\rho_{XY}|$, since $|\rho_{XY}|$ is also dependent on the intervening group between substituent and reaction centre, which reduces $|\rho_{XY}|$ to an uncertain degree, albeit approximately one such group is known to halve the magnitude of ρ_i or ρ_{ij} value in general.

The λ_{YZ} values for reactions of benzyl benzenesulphonates and 1-phenylethyl benzenesulphonates with anilines are 0.18 and 0.19 respectively with positive signs; the magnitude of λ_{YZ}, which is a measure of bond breaking, does not differ much from that of $|\lambda_{XY}|$, a measure of bond formation, for dissociative S_N2 reactions, indicating that similar bond distances, r_{XY} and r_{YZ}, are involved in the TS for the S_N2 type of reaction.

Some β_{XZ} values for S_N2 type reactions calculated by multiple linear regression using equation 1b are presented in Table 3.[2] As expected, the signs of β_{XZ} and ρ_{XZ} agree, and the magnitude of β_{XZ} is proportional to, but smaller than, that of ρ_{XZ}. For the phenacyl series (reactions D and F), however, $|\beta_{XZ}|$ is nearly constant, indicating that a similar bond distance r_{XZ} ($r_{XY} + r_{YZ}$ in Scheme 1) is involved in the TS. This is in contrast with the difference in $|\rho_{XZ}|$ of a factor of *ca.* two for the two phenacyl series—the result of a non-conjugating CH_2 group intervening between the benzene ring and the reaction centre, N, in the benzylamine nucleophiles, despite the fact that there is no significant change in the bond distance r_{XZ} in reality. This demonstrates that the Brönsted-type cross-interaction parameter is a more direct measure of the TS structure, while the Hammett-type parameters are mixed with constant factors ($\rho_{e'}$ and $\rho_{e'}$) corresponding to the interactions between substituents and reaction centres, which, for most practical purposes, can be considered to remain intact during the activation process.

The dissociative S_N2 reaction A has the smallest $|\beta_{XZ}|$ of 0.06, whereas the S_N reaction with twofold interaction pathways between the nucleophile and the LG in the TS (reaction B and E) (*vide infra*) give considerably greater $|\beta_{XZ}|$ values (0.32), as has been shown to be the case with $|\rho_{XZ}|$ values. For the associative S_N2 reactions (D and F) (*vide infra*), the magnitude of β_{XZ} (0.17—0.19) is greater by more than three times the value for the dissociative S_N2 reaction A, in addition to a change in the sign from negative to positive.

There are some mixed series of aliphatic and aromatic amines in the literature for which ρ_{XZ} values cannot be determined but β_{XZ} values are obtainable. Two examples, in which group transfers (PO_3^- and SO_3^-) are involved between aliphatic amines (Nuc) and pyridines (Nuc*), give $\beta_{XZ} = 0.023$ for PO_3^- transfer[21] and $\beta_{XZ} = 0.029$ for SO_3^- transfer.[22] These values are very small. The

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[21] (*a*) M. T. Skoog and W. P. Jencks, *J. Am. Chem. Soc.*, 1984, **106**, 7597; (*b*) N. Bourne and A Williams, *J. Am. Chem. Soc.*, 1984, **106**, 7591.

[22] A. Hopkins, R. A. Day, and A. Williams, *J. Am. Chem. Soc.*, 1983, **105**, 6062.

Table 3 *The Bronsted type cross-interaction constants,* β_{XZ} *for nucleophilic substitution reactions in methanol*[f]

Reaction[a]	β_X	β_Z	β_{XZ}	ρ_{XZ}	*Correlation coefficient*[b]	*N*[c]
A $XC_6H_4NH_2$ + $YC_6H_4CH_2OSO_2C_6H_4Z \xrightarrow{35.0\,°C}$	0.28	−2.24	−0.06	−0.10	0.996	20
B $XC_6H_4NH_2$ + $YC_6H_4CH(Me)OSO_2C_6H_4Z \xrightarrow{25.0\,°C}$	0.72	−1.60	−0.32	−0.56	0.998	16
C $XC_6H_4N(Me)_2$[d] + $YC_6H_4CH(Me)OSO_2C_6H_4Z \xrightarrow{35.0\,°C}$	0.50	−2.00	−0.11	−0.24	0.989	15
D $XC_6H_4NH_2$ + $YC_6H_4COCH_2OSO_2C_6H_4Z \xrightarrow{45.0\,°C}$	0.73	−2.14	0.19	0.31	0.995	16
E $XC_6H_4NH_2$ + $YC_6H_4CH_2CH_2OSO_2C_6H_4Z \xrightarrow{65.0\,°C}$	0.44	−1.79	−0.28	−0.45	0.995	16
F $XC_6H_4CH_2NH_2$[e] + $YC_6H_4COCH_2OSO_2C_6H_4Z \xrightarrow{45.0\,°C}$	0.73	−1.49	0.17	0.12	0.995	12

[a] pK_a values for benzenesulphonic acids were taken from ref 6 [b] 99% confidence level [c] Number of data points [d] The pK_a values are taken from W C Davies and H W Addis, *J Chem Soc*, 1937, 1622, and G Thompson, *J Chem Soc*, 1946, 1113 [e] The pK_a values are taken from L F Blackwell, A Fischer, I J Miller, R D Topsom, and J Vaughan, *J Chem Soc*, 1964, 3588 *p*-Methoxybenzylamine had a peculiar pK_a value so that it was excluded from the correlation [f] References are given in Ref 2*b*

TS had little change in effective charge on the nucleophile (Nuc) and a large change in departing leaving group (Nuc*) relative to the reactant state, indicating weak bonding between R and entering atoms corresponding to an 'open' (or 'exploded') TS or a pre-association stepwise process.

Another example is the β_{XZ} value of 0.052 obtained for tosyl transfer between imidazoles and primary aliphatic amines;[23] in this series none of five nucleophiles and three leaving groups contain substituents that can be represented by the Hammett substituent constant σ. The magnitude of β_{XZ} (0.052) is greater by a factor of *ca.* two than that for the PO_3^- and SO_3^- transfers cited above, and hence suggests that the TS's are less 'exploded' than those proposed for the PO_3^- and SO_3^- transfers, as the authors have concluded.

5 Dissociative S_N2 Reactions

The cross-interaction constants, ρ_{ij}, are determined for the reactions of benzyl benzenesulphonates (BBS) with anilines in methanol at 35.0 °C, which are summarized in Table 4.[2a,7a,24] The sign of ρ_{XZ} is negative so that the reaction should be under intrinsic control; in agreement with the predictions by equation 9, $|\rho_{XY}|$ increases with the more positive σ_Z and $|\rho_{YZ}|$ with the more positive σ_X

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[23] P Monjoint and M-F Ruasse, *Bull Soc Chim Fr*, 1988, 356

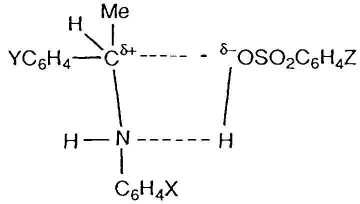
[24] (*a*) I Lee, H W Lee, S C Sohn, and C S Kim, *Tetrahedron*, 1985, **41**, 2635, (*b*) I Lee, S C Sohn, Y J Oh, and B C Lee, *Tetrahedron*, 1986, **42**, 4713

Table 4 ρ_{ij} *Values for reactions of benzyl benzenesulphonates with anilines in methanol at* 35.0 °C[2a,7d,24]

$2XC_6H_4NH_2 + YC_6H_4CH_2OSO_2C_6H_4Z \longrightarrow XC_6H_4NHCH_2C_6H_4Y + XC_6H_4NH_3^+ + {}^-OSO_2C_6H_4Z$
X = *p*-MeO, *p*-Me, H, *p*-Cl, *m*-NO$_2$
Y = *p*-Me, H, *p*-Cl, *p*-NO$_2$
Z = *p*-Me, H, *p*-Cl, *m*-NO$_2$

ρ_{XY}				ρ_{YZ}					ρ_{XZ}		
Z = *p*-Me	H	*p*-Cl	*m*-NO$_2$	X = *p*-MeO	*p*-Me	H	*p*-Cl	*m*-NO$_2$	Y = H	*p*-Cl	*p*-NO$_2$
−0.58	−0.62	−0.65	−0.72	0.35	0.20	0.11	0.13	0.14	−0.10	−0.19	−0.25
R ≧ 0.994				*R* ≧ 0.993					*R* ≧ 0.998		

Table 5 ρ_{ij} *Values for reactions of* 1-*phenylethyl benzenesulphonates with anilines in methanol at* 25 0 °C[25]



(2)

$$2XC_6H_4NH_2 + YC_6H_4CH(Me)OSO_2C_6H_4Z \longrightarrow YC_6H_4CH(Me)NHC_6H_4X + XC_6H_4NH_3^+ + \ OSO_2C_6H_4Z$$

X = *p*-Me, H, *p*-Cl, *m*-NO$_2$
Y = *p*-OMe, *p*-Me, H, *p*-Cl
Z = *p*-Me, H, *p*-Cl, *p*-NO$_2$

Z	ρ_X	ρ_Y	ρ_{XY}	X	ρ_Y	ρ_Z	ρ_{YZ}	Y	ρ_X	ρ_Z	ρ_{XZ}
p-Me	−2 07	−0 39	−0 22	*p*-Me	−0 30	1 04	0 10	*p*-OMe	−2 11	0 91	−0 55
H	−2 20	−0 37	−0 21	H	−0 39	0 97	0 11	*p*-Me	−2 13	0 91	−0 55
p-Cl	−2 27	−0 34	−0 23	*p*-Cl	−0 45	0 78	0 13	H	−2 17	0 95	−0 56
p-NO$_2$	−2 61	−0 25	−0 25	*m*-NO$_2$	−0 50	0 56	0 14	*p*-Cl	−2 22	0 98	−0 56
		$R \geqq 0\ 999$				$R \geqq 0\ 990$				$R \geqq 0\ 999$	

There are anomalies for the electron-donating substituents in the nucleophile (X = *p*-MeO and *p*-Me), for which strong resonance between the reaction centre (R_Y) and the substrate ring has been reported to occur so that the distance r_Y is compressed in the TS giving smaller values for $|\rho_{YZ}|$ The size of ρ_{ij} is in the order $|\rho_{XY}| > |\rho_{YZ}| > |\rho_{XZ}|$ as expected from the dissociative S_N2 TS of somewhat advanced bond cleavage[2a]

Nucleophilic substitution reactions of 1-phenylethyl benzenesulphonates (1-PEB) with anilines in methanol are investigated at 25 °C[25] The cross-interaction constants, ρ_{ij}, are collected in Table 5 The sign of ρ_{XZ} is again negative so that the reaction is under intrinsic control, and indeed equations 9 are found to apply as required In the S_N type reactions, we should expect the $|\rho_{XZ}|$ value to be the smallest, as found in the reactions of BBS with anilines,[24] since $r_{XZ} = r_{XY} + r_{YZ}$ is normally longer than r_{XY} or r_{YZ} In contrast, however, the $|\rho_{XZ}|$ in Table 5 is the greatest of the three This unusual enhancement of the cross interaction between X and Z can only be rationalized by a four-centre TS, (2), *i e*, of an intermolecular S_Ni mechanism[26] The substituents X and Z in (2) can interact by two routes, the additional interaction route is provided by a bypass hydrogen-bond bridge, so that the approach of the nucleophile aniline is restricted to the front side, leading to retention of configuration in the amine product

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[25] (*a*) I Lee, H Y Kim, and H K Kang, *J Chem Soc*, *Chem Commun*, 1987 1216 (*b*) I Lee H Y Kim, H K Kang, and H W Lee, *J Org Chem* 1988, **53** 2678

[26] K Okamoto, K Takeuchi, and T Inoue *J Chem Soc Perkin Trans 2* 1980 842

One way of confirming that the TS is four-centred is to compare the $|\rho_{XZ}|$ values for a reaction with a nucleophile having no hydrogen atoms for bridge formation, *e.g.* *N*,*N*-dimethylanilines (DMA), with those in Table 5. Kinetic studies with DMA's conducted under the same conditions gave markedly smaller values of $|\rho_{XZ}|$, 0.23—0.25, about half that for aniline.[27] The impossibility of hydrogen-bond bridge formation should be the main cause of the smaller $|\rho_{XZ}|$.

Reactions between 2-phenylethyl benzenesulphonates (2-PES) and anilines in methanol at 65 °C have been investigated and the three cross-interaction constants determined.[8a] The reaction can proceed through two possible pathways, aryl-assisted (k_A)[28] and direct nucleophilic substitution (k_N) paths. A negative sign of ρ_{XZ} indicates that this reaction belongs to an intrinsic-controlled series and the relationship of equations 9 is found to hold. The values of $|\rho_{XY}|$ (0.10—0.17) were relatively small, in general slightly greater than half of the values for the 1-PEB reactions ($|\rho_{XY}| = 0.20$—0.25) under similar reaction conditions. These unusually small $|\rho_{XY}|$ values can be attributed to an extra CH_2 group in the substrate, which will reduce the intensity of interaction between σ_Y and R_Y, and hence the $|\rho_{XY}|$ values, by a factor of 2.4—2.8. Another reason for the small $|\rho_{XY}|$ values could be due to the participation of the aryl-assisted pathway,[8a,28] since the TS in this path, TS_A, does not include the nucleophile and constitutes an example of no interaction. The decrease in $|\rho_{YZ}|$ with a more EWS in the nucleophile ($d\sigma_X > 0$) indicated that the fraction of the phenonium-ion captured by the nucleophile, aniline, leading to the products increases with a stronger nucleophile. The ρ_{XZ} values were anomalously large, and similar to those for the reactions of 1-PEB. Thus it is likely that the two reactions proceed by the same mechanism, *i.e.*, a four-centre TS in an intermolecular S_Ni mechanism similar to (2).

6 Associative S_N2 Reactions

The nucleophilic substitution reactions of phenacyl benzenesulphonates (PAB) with anilines in methanol have been investigated at 45 °C and the cross-interaction constants determined are presented in Table 6.[7e] The sign of ρ_{XZ} is positive for this reaction series implying it is under thermodynamic control with negative a' and b' in equations 9. The relationship holds for the $|\rho_{XY}|$ values but not for $|\rho_{YZ}|$, which will be discussed below. We note that the magnitude of ρ_{YZ} is relatively large as compared with those for methanolysis ($\rho_{YZ} = -0.07$ at 45 °C)[29] and *E*1cB-like *E*2 elimination ($\rho_{YZ} = -0.57$ at 40 °C) of the alkyl analogues, 2-PEB.[30] This indicates that bond breaking has progressed very little in the TS of the reaction. The size of ρ_{XZ} is also relatively large, implying again a small degree of bond cleavage.

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[27] I. Lee, H. Y. Kim, H. W. Lee, and I. C. Kim, *J. Phys. Org. Chem.*, 1989, **2**, 35.

[28] (*a*) F. L. Schadt and P. v. R. Schleyer, *J. Am. Chem. Soc.*, 1973, **95**, 7860; (*b*) H. C. Brown, C. J. Kim, C. J. Lancelot, and P. v. R. Schleyer, *J. Am. Chem. Soc.*, 1970, **92**, 5244.

[29] G. L. Han, J. H. Park, and I. Lee, *Bull. Korean Chem. Soc.*, 1987, **8**, 393.

[30] (*a*) I. Lee, *Bull. Korean Chem. Soc.*, 1987, **8**, 426; (*b*) J. Banger, A. F. Cockerill, and G. L. O. Davies, *J. Chem. Soc.*, (*B*), 1971, 498.

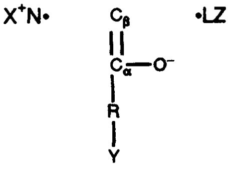
Table 6 ρ_{ij} *Values for reactions of phenacyl benzenesulphonates with anilines in methanol at* 65.0 °C[7e]

$$2XC_6H_4NH_2 + YC_6H_4COCH_2OSO_2C_6H_4Z \longrightarrow YC_6H_4COCH_2NHC_6H_4X + XC_6H_4NH_3^+ + {}^-OSO_2C_6H_4Z$$

X = *p*-OMe, *p*-Me, H, *p*-Cl
Y = H, *p*-Cl, *p*-NO_2
Z = *p*-Me, H, *p*-Cl, *m*-NO_2

Z	ρ_X	ρ_Y	ρ_{XY}	X	ρ_Y	ρ_Z	ρ_{YZ}	Y	ρ_X	ρ_Z	ρ_{XZ}
p-Me	−2.06	0.71	0.14	*p*-OMe	0.60	1.14	−0.63	H	−2.01	1.24	0.32
H	−1.97	0.61	0.11	*p*-Me	0.64	1.17	−0.65	*p*-Cl	−1.96	1.09	0.31
p-Cl	−1.92	0.47	0.10	H	0.66	1.23	−0.66	*p*-NO_2	−1.85	0.48	0.23
m-NO_2	−1.77	0.18	0.07	*p*-Cl	0.67	1.30	−0.67				
	$R \geqq 0.999$				$R \geqq 0.997$				$R \geqq 0.999$		

Two anomalies are recognizable in the size of ρ_{ij} in Table 6: (a) $|\rho_{XY}|$ is unusually small, and (b) $|\rho_{YZ}|$ increases in parallel with ρ_Y and ρ_Z. The magnitude of ρ_{XY} for other S_N2 reactions under normal conditions with LG's comparable to benzenesulphonates were found to range 0.62—0.78 in Table 2, and hence the ρ_{XY} values of 0.05—0.14 in Table 6 are abnormally small even after allowing for the fall-off factor of 2.4—2.8 for an intervening group, CO, in the substrate. This can be rationalized in terms of a 'shunt' or 'leak' provided by the α-CO group in the resonance between the reaction centre, C_β, and the substituent Y, as in (3), where substituents X, Y, and Z are, as usual, in the nucleophile (N), substrate (R), and leaving group (L). Since charge transfer to the reaction centre from the nucleophile is greater than that from the reaction centre to the LG, the reaction centre is negatively charged in the TS as positive ρ_Y values in Table 6 indicate. Thus delocalization of negative charge into the α-carbonyl group, as in (3), decreases the electron supply to the Y-substituted benzene ring (R) so that the interaction between substituents X and Y, and hence $|\rho_{XY}|$, is decreased. Although bond formation proceeds substantially, as the relatively large ρ_{XZ} value indicates, the interaction between X and Y is weakened markedly, not because of the large distance involved, but as a result of a 'shunt' or a 'leak' in the resonance provided by the α-CO group. This interpretation is



(3)

supported by the second anomaly already noted; the parallel increase in the $|\rho_{YZ}|$ value with ρ_Y and ρ_Z as the substituent X becomes more electron-withdrawing, *e.g.* X = *p*-Cl. The increase in the ρ_Z value within a series of reactions is normally taken as the increase in bond cleavage, which should result in a decrease, in contrast to the increase observed in the $|\rho_{YZ}|$ values. This can be rationalized in terms of the enhanced contribution of the resonance 'shunt' by the α-CO group as charge transfer increases; this has a shortening effect on the C_α–C_β bond due to the double bond character in structure (3); the greater degree of charge transfer (the larger ρ_Y) will result in a greater contribution from the resonance shunt, which in turn will give a shorter C_α–C_β bond, and hence a larger $|\rho_{YZ}|$ value as observed.

The reactions of methyl (MBS) and ethyl benzenesulphonates (EBS) with anilines and benzylamines (BA) in methanol and acetonitrile at 65.0 °C are investigated.[31] The signs and magnitudes of both ρ_{XZ} and β_{XZ} (0.33 and 0.19 for EBS and 0.30 and 0.18 for MBS, with anilines in methanol) are strikingly similar to those for the PAB reaction series under similar reaction conditions. These similarities support the similar nature of the reaction, *i.e.*, an associative S_N2 which is under thermodynamic control, for the two series.

The steric crowding due to an extra methyl group in the TS for EBS raises the activation energy and the rate is retarded, but a larger $|\rho_{XZ}|$ and $|\beta_{XZ}|$, *i.e.* a tighter TS, is obtained, *i.e.*, $r_{XZ}(\text{EBS}) < r_{XZ}(\text{MBS})$.[31]

7 Conclusions

The cross interaction constants, ρ_{ij}, β_{ij}, and λ_{ij}, are useful in the characterization of TS's for reactions in solution:

(i) The signs provide criteria for the nature of reactions, *i.e.* whether a reaction series is under intrinsic or thermodynamic control can be determined.
(ii) The magnitudes can be useful in characterizing the TS structure.

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[31] I. Lee, Y. H. Choi, K. W. Rhyu, and C. S. Shim, *J. Chem. Soc., Perkin Trans. 2*, 1989, 1881.