The Mechanistic Significance of Cross Interaction Constants, ρ_{ij}

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Novel mechanistic criteria for S_N reactions have been proposed based on the relative magnitudes of various ρ_{ij} values, which were found to vary inversely with the distance between the substituents *i* and *j*.

Recently interactions between substituents (cross interaction) have attracted much interest in the study of reaction mechanisms.[1,2] The concept of cross interaction has been derived from a multiple Hammett correlation, equation (1),[2] where we neglected terms in σ_i^2, $\sigma_i^2\sigma_j$,[1] and those higher than third order. The individual cross interaction constant ρ_{ij} can be obtained by varying substituents *i* and *j* only; thus ρ_{XY} for substituents X and Y can be determined from equation (2).

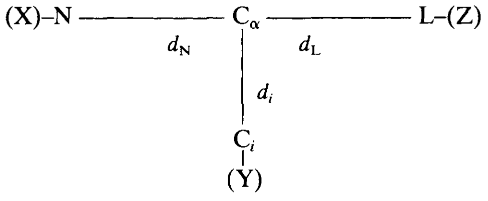
$$\log(k/k_H) = \sum_i \rho_i\sigma_i + \sum_{i \neq j} \rho_{ij}\sigma_i\sigma_j + \sum_{i \neq j \neq k} \rho_{ijk}\sigma_i\sigma_j\sigma_k \qquad (1)$$

$$\log(k_{XY}/k_{HH}) = \rho_X\sigma_X + \rho_Y\sigma_Y + \rho_{XY}\sigma_X\sigma_Y \qquad (2)$$

We have recently carried out extensive studies on the reaction of benzyl benzenesulphonates with anilines in MeOH–MeCN mixtures and accumulated enough kinetic data[3] to enable a comprehensive analysis of cross interaction constants for the first time, see reaction (3) where X = *p*-MeO, *p*-Me, H, *p*-Cl, *m*-NO$_2$, Y = *p*-Me, H, *p*-Cl, *p*-NO$_2$, and Z = *p*-Me, H, *p*-Cl, *m*-NO$_2$. In this paper, we examine the mechanistic significance of cross interaction constants for reaction (3) and propose semi-quantitative mechanistic criteria for S_N reactions based on the magnitude of various ρ_{ij} values.

Transition states (TS) for the S_N2 reaction (3) can be represented as composed of three fragments, *i.e.*, nucleophile with substituent X, substrate with Y, and leaving group with Z, attached to the reaction centre, C_α, as shown in Scheme 1. The C_α is the benzyl carbon and C_i is the *ipso* carbon atom of the substrate benzene ring. The interaction between substituents, being a second order effect,[2] will become significant as a cross interaction constant ρ_{ij} only when the mutual interaction is involved in an activation process with substantial

$$X{-}C_6H_4NH_2 + Y{-}C_6H_4CH_2OSO_2C_6H_4{-}Z \xrightarrow{\text{MeOH–MeCN}} X{-}C_6H_4\overset{+}{N}H_2CH_2C_6H_4{-}Y + {}^{-}O_3SC_6H_4{-}Z \qquad (3)$$



Scheme 1

Table 1. ρ_{ij} Values[a] for reaction (3) in MeOH.

ρ_{XY}				ρ_{XZ}			ρ_{YZ}				
Z = *p*-Me	H	*p*-Cl	*m*-NO$_2$	Y = H	*p*-Cl	*p*-NO$_2$	X = *p*-Me	*p*-Me	H	*p*-Cl	*m*-NO$_2$
−0.58 (0.997)[b]	−0.62 (0.998)	−0.65 (0.997)	−0.72 (0.994)	−0.10 (0.999)	−0.19 (0.998)	−0.25 (0.999)	0.35 (0.993)	0.20 (0.997)	0.11 (0.998)	0.13 (0.998)	0.14 (0.998)

[a] Hammett constants used for substituents in the substrate were σ^+ constants since it has been shown[3] that substantial positive charge development occurs at the benzylic carbon in the TS. For σ_X and σ_Z normal Hammett constants were used. [b] Values in parenthesis are the multiple correlation coefficients (J. Shorter, 'Correlation Analysis of Organic Reactivity,' Research Studies Press, Chichester, 1982, p. 20).

Table 2. Mechanistic criteria and examples for S_N reactions.

Type of reaction	Criteria	Example
S_N1	$\rho_{XY} = \rho_{XZ} \simeq 0, \rho_{XZ} \neq 0$	—
S_N1[a]	$\lvert\rho_{XY}\rvert \simeq \lvert\rho_{YZ}\rvert > \lvert\rho_{XZ}\rvert$	$X{-}C_6H_4S^- + Y{-}C_6H_4CH_2\overset{+}{N}Me_2C_6H_4{-}Z$,[c] $\rho_{XZ} = -0.53$
Associative	$\lvert\rho_{YZ}\rvert > \lvert\rho_{XY}\rvert > \lvert\rho_{XZ}\rvert$	$X{-}C_6H_4NH_2 + Y{-}C_6H_4SO_2Cl$,[d] $\rho_{XY} = -0.75$
Dissociative	$\lvert\rho_{XY}\rvert > \lvert\rho_{YZ}\rvert > \lvert\rho_{XZ}\rvert$	Present work, see Table 1
S_AN[b]		
Elimination	$\rho_{XY} \simeq 0, \lvert\rho_{XZ}\rvert \simeq \lvert\rho_{YZ}$	$X{-}C_6H_4O^- + Y{-}C_6H_3(NO_2)Cl$,[e] $\rho_{XY} = 0.00$ Pyridine + $Y{-}C_6H_4CO_2C_6H_4{-}Z$,[f] $\rho_{YZ} = -1.76$
Addition	$\rho_{YZ} \simeq 0, \lvert\rho_{XY}\rvert \simeq \lvert\rho_{XZ}\rvert$	$OH^- + Y{-}C_6H_4CO_2C_6H_4{-}Z$,[g] $\rho_{YZ} = 0.00$

[a] The magnitude of ρ_{ij} should be greater for associative S_N2 reactions. [b] The magnitude of nonzero ρ_{ij} should be normally much greater than that for S_N1 and S_N2 reactions. [c] K. C. Westaway and S. F. Ali, *Can. J. Chem.*, 1979, **57**, 1354. [d] O. Rogne, *J. Chem. Soc. B*, 1971, 1855. [e] J. R. Knowles, R. O. C. Norman, and J. H. Prosser, *Proc. Chem. Soc.*, 1961, 341. [f] F. M. Menger and J. H. Smith, *J. Am. Chem. Soc.*, 1972, **94**, 3824. [g] J. F. Kirsch, W. Clewell, and A. Simon, *J. Org. Chem.*, 1968, **33**, 127.

changes in the distance between the two substituents i and j, since the sensitivity of the reaction to the mutual substituent interaction will be manifested in changes in the amount of charge on C_α which in turn is a function of distances between fragments and C_α, *i.e.*, d_N, d_L, and d_i in Scheme 1. This means that at least one member of the two fragments with interacting substituents should be involved in a bond-making and/or bond-breaking process in the TS. Since the polar and resonance effects of the substituents are transmitted through the reaction centre, the magnitude of cross interaction will be inversely proportional to an appropriate sum of two out of the three distances, d_i, d_N, and d_L;† lengths of carbon chains connecting substituents to N, L, and C_i, may be considered to remain constant in the activation process for all practical purposes.[4]

Determination of ρ_{ij} values for the reaction (3) by multiple regression led us to the partial list given in Table 1. Correlations between observed and calculated values were excellent in all cases (r >0.995). Reference to Table 1 reveals that: (i) the magnitude decreases in the order, $|\rho_{XY}| > |\rho_{YZ}| > |\rho_{XZ}|$; (ii) the magnitude of ρ_{XY} increases with a more electron withdrawing substituent (EWS) in the leaving group (Z = m-NO_2); (iii) the magnitude of ρ_{XZ} increases with a more EWS in the substrate (Y = p-NO_2); (iv) the magnitude of ρ_{YZ} increases with a more electron donating substituent (EDS) (X = p-MeO) as well as with a more EWS in the nucleophile (X = m-NO_2). These trends are consistent with our contention of the inverse proportionality of $|\rho_{ij}|$ to the sum of two distances involved. (i) The reaction (3) is known to proceed by a dissociative S_N2 mechanism,[3] and hence $d_L > d_N > d_i$. The sum will increase therefore in the order $(d_N + d_i) < (d_L + d_i) < (d_L + d_N)$ which is exactly the reverse of the order for $|\rho_{ij}|$. (ii) A better leaving group with a more EWS (Z = m-NO_2) has been shown to give a more product-like TS.[3] Thus d_N will decrease with a more EWS which in turn will result in a greater $|\rho_{XY}|$. (iii) Our results[3] showed that a more EWS in the substrate (Y = p-NO_2) gave a more product-like TS, but bond-making is enhanced more than bond-breaking. The decrease in d_N will be greater than the increase in d_L so that the sum $d_N + d_L$ will decrease, which in turn means an increase in $|\rho_{XZ}|$. (iv) Since a more EDS in the nucleophile has a more product-like TS,[3] d_L will decrease with a more EWS in the nucleophile (X = m-NO_2) leading to an increase in $|\rho_{YZ}|$. On the other hand analysis of dual substituent parameter equations indicated that the resonance to polar component ratio is the greatest for X = p-MeO decreasing down to a minimum for X = m-NO_2.[5] Since the resonance contribution of Y tends to decrease[5] while the polar component tends to increase[4,6] d_i, the sum $d_i + d_L$ will be the smallest and hence $|\rho_{YZ}|$ will be the greatest for X = p-MeO.

Similar reasoning will lead to mechanistic criteria for other S_N types of mechanisms. Table 2 lists the criteria with some examples. The list can easily be extended to include other types of mechanisms such as S_E1, S_E2, $E1$, $E2$, $E1CB$ etc.

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References

1 J-E. Dubois, M-F. Ruasse, and A. Argile, *J. Am. Chem. Soc.*, 1984, **106**, 4840.

2 For a recent review, see, W. P. Jencks, *Chem. Rev.*, 1985, **85**, 511.

3 I. Lee, W. H. Lee, S. C. Sohn, and C. S. Kim, *Tetrahedron*, 1985, **41**, 2635; I. Lee, S. C. Sohn, C. H. Kang, and Y. J. Oh, *J. Chem. Soc., Perkin Trans. 2*, in the press; I. Lee, S. C. Sohn, Y. J. Oh, and B. C. Lee, *Tetrahedron*, submitted for publication.

4 K. C. Westaway and Z. Waszczylo, *Can. J. Chem.*, 1982, **60**, 2500.

5 I. Lee and S. C. Sohn, *Bull. Korean Chem. Soc.*, submitted for publication.

6 C. G. Swain, J. E. Sheats, and K. G. Harbison, *J. Am. Chem. Soc.*, 1975, **97**, 783. The electron-deficient phenyl cation of the type iv, noted as responsible for the polar effect in this paper, is stabilized and hence d_i is increased by the polar effect in the TS.

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† The direct electrostatic effect is normally small[2] and especially in this case it is opposite in direction so as to reduce the $|\rho_{ij}|$ values if any existed, since the reaction centre, C_α, is positively charged ($\rho^{+}_{y} < 0$).