Cross Interaction Constants as a Mechanistic Criterion for the Intermolecular S_Ni Mechanism

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Cross interaction constants are used to vindicate retentive displacements of 1-phenylethyl compounds *via* the intermolecular S_Ni mechanism.

In previous papers[1] we have reported the importance of cross interaction constants, ρ_{ij} in equation (1), as a mechanistic tool for the study of various types of reactions in solution. It has been shown that the intensity of interaction between substituents i and j, as exhibited by the magnitude of cross interaction constant, $|\rho_{ij}|$, varies inversely with the distance between the two substituents,[1a] and is strongly enhanced by the formation of a bypass bridge structure which provides an additional interaction route in the transition state (TS).[1b]

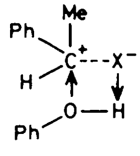
$$\log (k_{ij}/k_{\mathrm{HH}}) = \rho_i\sigma_i + \rho_j\sigma_j + \rho_{ij}\sigma_i\sigma_j \qquad (1)$$

Optically active 1-phenylethyl compounds are known to give rise to substitution products with retention of configuration.[2] Various mechanisms have been suggested in order to account for this; results of solvolyses are commonly interpreted in terms of an ion-pair mechanism in which nucleophilic solvent attack on the ion-pair plays a major role,[2a—d] while displacement by a nucleophile *e.g.* phenol, is best rationalized by a mechanism involving a four-centre TS, (I), which was termed an intermolecular S_Ni mechanism.[2e,3] In this work we have shown that nucelophilic substitution of 1-phenylethylbenzenesulphonates by anilines in methanol, reaction (2), affords such an example of retentive displacement in which the intermolecular S_Ni mechanism is operative, by

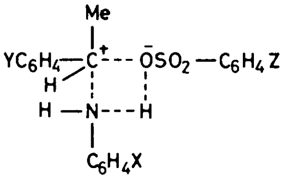
Table 1. Cross interaction constants for reaction (2) at 25 °C in MeOH (r = multiple correlation coefficient).[4]

ρ_{XY}	ρ_{YZ}	ρ_{XZ}	r^{a}
−0.23	0.10	−0.60	0.999

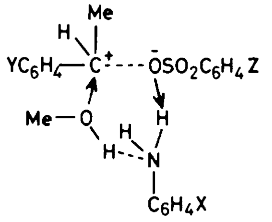
[a] All three ρ_{ij} values had $r = 0.999$



(I)



(II)



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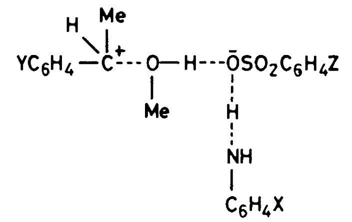

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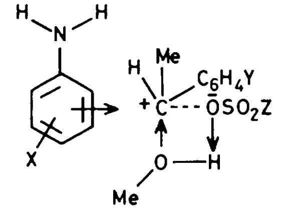

(V)

Table 2. Cross interaction constants for S_N2 reactions of substituted (X) anilines with various substrates (with substituents Y).

Substrate	Solvent (Temp./°C)	ρ_{XY}
$YC_6H_4CH_2SO_2Cl$	MeOH (35)	-0.69^a
$YC_6H_4SO_2Cl$	MeOH (35)	-0.70^b
$YC_6H_4CH_2Cl$	EtOH (50)	-0.77^c
$YC_6H_4CH_2OSO_2C_6H_4Z$	MeOH (35)	-0.62^d
$YC_6H_4CH_2SO_2F$	MeOH (45)	-1.24^e

[a] Ref. 5. [b] Ref. 6. [c] Ref. 7. [d] Ref. 1a. [e] Ref. 1c.

demonstrating an unusual enhancement of cross interaction between substituents X and Z in reaction (2).

$$\mathrm{YC_6H_4CHMeOSO_2C_6H_4Z} + 2\,\mathrm{XC_6H_4NH_2} \xrightarrow{\mathrm{MeOH}} \mathrm{YC_6H_4CHMeNHC_6H_4X} + \mathrm{XC_6H_4NH_3^+} + {}^-\mathrm{OSO_2C_6H_4Z} \qquad (2)$$

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

Rate constants k_{ij} (16 values each), where i, j = X, Y, or Z, obtained were subjected to multiple linear regression analysis[4] using equation (1). The cross interaction constants determined are summarized in Table 1, which reveals that in the TS bond formation has progressed somewhat but bond breaking is appreciable; the magnitude of ρ_{XY} values for S_N2 reactions involving aniline nucleophiles were found to range from 0.60 to 1.20 (Table 2) and hence $|\rho_{XY}| = 0.23$ in Table 1 is less than half that for the S_N2 reactions, indicating that the interaction between substituents X and Y is less pronounced, owing to much less bond formation in the S_Ni TS. Furthermore the small $|\rho_{YZ}|$ value is indicative of a dissociative nature of the TS for this reaction,[2] so that it closely resembles that expected for an S_N1 substitution mechanism. For a normal nucleophilic substitution reaction (S_N1 or S_N2), we should expect the $|\rho_{XZ}|$ value to be the smallest of the three cross interaction constants,† since the distance between a substituent (X) in the nucleophile and that (Z) in the leaving group should be greatest in the TS owing to bond making and/or bond breaking in progress.[1a] On the contrary, $|\rho_{XZ}|$ obtained for reaction (2) is the greatest of the three (Table 1).

This unusual enhancement of the cross interaction between X and Z can only be rationalized by a four-centre TS, (II), *i.e.*, by an intermolecular S_Ni mechanism.[2e,3] The two substituents X and Z in (II) can interact *via* two routes; an additional interaction route is provided by a bypass hydrogen bond bridge, so that the nucleophile, aniline, is restricted to a frontside approach leading to a product amine of retained configuration. Although one can envisage a similar interaction *via* a H-bond bypass bridge between Y and Z, it involves a long distance and may not be significant. Other mechanisms proposed by Okamoto *et al.*[2e] for the phenolyses can be readily ruled out as untenable based on the magnitude of cross interaction constants in Table 1; the six-membered cyclic model, (III), and solvent-separated ion-pair model, (IV), should require negligibly small $|\rho_{XY}|$ values, since the intervention of a solvent molecule between the substrate and the nucleophile should move the two substituents, X and Y, farther apart. The small but significant magnitudes of $|\rho_{XY}|$ and $|\rho_{YZ}|$ obtained (Table 1) constitute evidence against such a mechanism. On the other hand, the rearside shielding model, (V),[2e]‡ should give no clear-cut trends in $|\rho_{XY}|$ and $|\rho_{XZ}|$ values.

We conclude that cross interaction constants can be useful as a mechanistic tool, especially for a retentive substitution reaction of the intermolecular S_Ni mechanism.

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† For the dissociative S_N2 reaction $XC_6H_4NH_2 + YC_6H_4CH_2OSO_2C_6H_4Z \rightarrow$ (MeOH, 35 °C), the three cross interaction constants were ρ_{XY} −0.62, ρ_{YZ} 0.11, and ρ_{XZ} −0.10. S_N1 reactions should have negligible ρ_{XZ} values, $|\rho_{XZ}| \simeq 0$.[1a]

‡ Models involving two aniline molecules in the TS are untenable since experimentally the rate was found to be first order with respect to aniline concentration.