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SHORT COMMUNICATION

MULTIPLE STRUCTURE–REACTIVITY RELATIONSHIPS FOR NUCLEOPHILIC SUBSTITUTION REACTION

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Novel mechanistic criteria for S_N reactions were proposed on the relative magnitudes of ρ_Z and interaction terms, ρ_{ij} or P_{ij} values. The mechanistic change by the sign of the product of ρ_{ij}s or P_{ij}s was also proposed. These criteria were applied to the reaction between substituted phenyl benzoates and amines and indicated that the sign of ρ_Z is positive and the interaction term P_{XZ} is larger than P_{YZ}, hence these reactions proceed via an S_AN mechanism and a change in the substituent of the substrate leads to a change in the substituent of the substrate leads to a change in the transition state towards the Hammond effect.

The sizes of the Hammett and Brønsted coefficients, ρ and β, are commonly believed to give an indication of the extent of charge development at the reaction site which is directly involved in the bond-making and -breaking processes in the transition state (TS).[1,2] However, it has been suggested that the ρ and β values cannot be used as a measure of TS structure, since the efficiency of charge transmission for different reaction series may differ.[1,3]

In this work, we present such an example showing the failure of ρ and β values as a direct measure of the degree of bond forming and breaking in the TS; we propose instead the use of the absolute value of the interaction term ρ_{ij} as a semi-quantitative measure of tightness in the TS.

In a previous paper,[4] we showed that the magnitude of the interaction term ρ_{ij} between substituents i and j is expressed by

$$\log(k_{ij}/k_{00}) = \rho_i\sigma_i + \rho_j\sigma_j + \rho_{ij}\sigma_i\sigma_j \qquad (1)$$

Equation (1) can be applied to Brønsted-type interactions [equation (2)] and mixed Hammett–Brønsted-type interactions[5] [equation (3)]:

$$\log(k_{XY}/k_{00}) = \beta_X\Delta pK_X + \beta_Y\Delta pK_Y + \beta_X\Delta pK_X\Delta pK_Y \qquad (2)$$

where X and Y are substituents of the leaving moiety and nucleophile, respectively;

$$\log(k_{ij}/k_{00}) = \rho_i\sigma_i + \beta_j\,\Delta pK_j + P_{ij}\sigma_i\,\Delta pK_j \qquad (3)$$

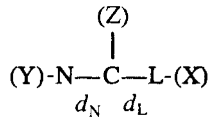
The ρ_i value is the reaction constant of the substrate with Z and β_j is the Brønsted coefficient of the nucleophile with Y or leaving moiety with X.

The interaction terms, ρ_{ij}, β_{XY} and P_{ij}, described by second derivatives, involve a change in the structure–reactivity (SR) parameter that applies to one reaction group when the structure of a different reaction group is changed.[6]

The TS for the S_N reaction can be represented as composed of three fragments, i.e. nucleophile with Y, substrate with Z and leaving moiety with X, attached to each reaction centre, as shown in Scheme 1.

$$\text{(Z)-}C_6H_4CO_2C_6H_4\text{-(X)} + \text{amine} \xrightarrow{25\ ^\circ\text{C, MeCN}} \qquad (4)$$

amine = piperidine, diethylamine, triethylamine



$$\begin{array}{c} \text{(Z)} \\ | \\ \text{(Y)-N—C—L-(X)} \\ d_N\ \ d_L \end{array}$$

Scheme 1

The interaction between substituents, being a second-order effect, will become significant as an interaction term ρ_{ij} or P_{ij} only when the mutual interaction is involved in an activation process with substantial changes in the distance between the two substants i and j, since the sensitivity of the reaction to the mutual substituent interaction will be manifested in changes in the distances between fragments and C, i.e., d_N and d_L in Scheme 1. This means that at least one of the two

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Table 1. Hammett, Brønsted and mixed Hammett–Brønsted-type coefficients for reaction (4)

Z	β_{lg}	β_{Nu}	Y	ρ_Z	P_{XZ}	X	ρ_Z	P_{YZ}
p-MeO	−1·95	4·64	Piperidine	0·79	0·71	*p*-MeO	2·92	−0·41
H	−1·52	4·60	Diethylamine	0·92	–	H	2·89	–
p-Cl	−1·41	4·51	Triethylamine	1·72	–	*p*-Cl	2·24	–
p-NO_2	−1·14	4·23	–	–	–	*m*-NO_2	1·18	–
–	–	–	–	–	–	*p*-NO_2	0·79	–

fragments with interacting substituents should be involved in a bond-forming 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 interaction will be inversely proportional to an appropriate distance,[7] d_N or d_L.

Determination of P_{ij} values for reaction (4) by multiple regression led to the partial list given in Table 1. Reference to Table 1 reveals that (i) the sign of ρ_Z is positive, hence the charge of the central atom is negative, (ii) the value of ρ_Z increases with decreases in the pK_a of amine hence the C–N bond becomes tighter, (iii) the magnitude of the absolute β_{Nu} value is twice as large as β_{lg} for each substituent of the substrates in Table 1, and the TS moves from * towards *′ when the substituent of the substrate changes from *p*-MeO to *p*-NO_2 (Figure 1), (iv) the magnitude of the interaction term P_{XZ} is larger than P_{YZ}, which means that reaction (4) proceeds by an addition–elimination pathway and (v) the sign of the product of P_{XZ} and P_{YZ} is negative, hence the TS moves towards the bottom right or top left (comparison between β_{lg}, β_{Nu} and substituent with Z and Figure 1), i.e. if $\rho_{XZ}\rho_{YZ} < 0$ (or $P_{XZ}P_{YZ} < 0$) then the TS changes by the Hammond effect, and if $\rho_{XZ}\rho_{YZ} > 0$ (or $P_{XZ}P_{YZ} > 0$) then the TS changes by the anti-Hammond effect.

Table 2. Mechanistic criteria and examples of S_N reactions of neutral substances

No.	Reaction example	Result ρ_Z	 β_{Nu}	 β_{lg}	 ρ_{YZ} (P_{YZ})	 ρ_{XZ} (P_{XZ})	Mechanism	Criteria[b]	Ref.
1	(Z)$C_6H_4CH_2OSO_2C_6H_4$(X) + (Y)$C_6H_4N(CH_3)_2$, 35 °C, MeCN	−0·85	−0·50	−0·73	Z = *p*-Me~H 0 Z = H~*p*-NO_2 −0·5	−0·06 −0·06	Z = *p*-Me~H S_N1 Z = H~*p*-NO_2 diss-S_N2	$\rho_Z<0$, $\rho_{YZ}\approx 0$, $\rho_{XZ}\neq 0$ $\rho_Z<0$, $\rho_{YZ}>\rho_{XZ}$	4
2	(Z)$C_6H_4CH_2OSO_2C_6H_4$(X) + (Y)$C_6H_4NH_2$, 35 °C, MeOH	−0·84	0·28	0·43	−0·62	0·11	Diss-S_N2	$\rho_Z<0$, $\rho_{YZ}>\rho_{XZ}$	7
3	(Z)$C_6H_4CH_2CH_2OSO_2C_6H_4$(X) + (Y)$C_6H_4NH_2$, 65 °C, MeOH	−0·15	0·44	−0·35	−0·12	0·07	Concert-S_N2	$\lvert\rho_Z\rvert < \sim 0.3$, $\rho_{YZ}\approx\rho_{XZ}$	8
4	(Z)$C_6H_4CH_2CH_2OSO_2C_6H_4$(X) + (Y)$C_6H_4N$, 60 °C, MeCN	−0·15	0·26	–	−0·26	–	Concert-S_N2	$\lvert\rho_Z\rvert < \sim 0.3$, $\rho_{YZ}\approx\rho_{XZ}$	9
5	(Z)$C_6H_4COCH_2OSO_2C_6H_4$(X) + (Y)$C_6H_4NH_2$, 45 °C, MeOH	0·66	0·72	−0·41	0·11 (−0·076)	−0·66 (0·33)	Ass-S_N2	$\rho_Z>0$, $\rho_{YZ}<\rho_{XZ}$ $\rho_{XZ}<1$	10
6	(Z)$C_6H_4CO_2CH_2C_6H_4$(X) + OH^- 34 °C, 80% (v/v) aq. acetone	2·25	–	−0·68	–	−0·22 (0·16)	Ass-S_N2	$\rho_Z>0$, $\rho_{YZ}<\rho_{XZ}$ $\rho_{XZ}<1$	11
7	(Z)$C_6H_4CO_2C_6H_4$(X) + amine, 25 °C, MeCN	(Y = pip., X = *p*-NO_2) 0·79	4·6	−1·5	(−0·41)	−1·57 (0·70)	S_AN	$\rho_Z>0$, $\rho_{YZ}\neq 0$, $\rho_{XZ}>1$	This work

[a] The ρ_{ij}s are magnitudes of absolute values of the interaction term and the values in parentheses are mixed Hammett–Brønsted-type interaction terms, P_{ij}.

[b] The same comparisons apply for the corresponding P_{ij} except Ass-S_N2, $P_{XZ}<0.5$, and S_AN, $P_{XZ}>0.5$.

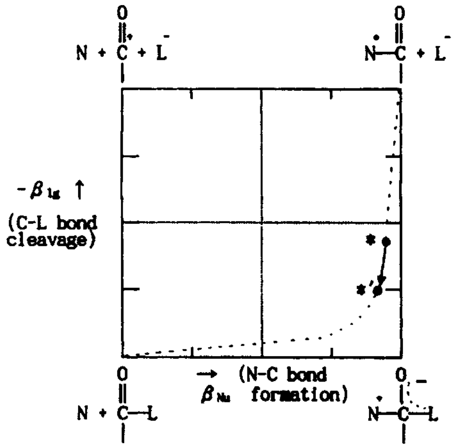

Figure 1. Energy diagram based on SR coefficient for reaction (4). The energy contours are not shown. The transition state * moves towards *' with lowering of the energy of the intermediate when the substituent of the substrate changes from p-MeO to p-NO_2

These results show that reaction (4) proceeds via an S_AN mechanism and a change in the substituent of the substrate leads to a change in the TS towards the Hammond effect.

Similar reasoning will lead to mechanistic criteria for other S_N types of mechanism. Table 2 lists the criteria with some examples.

Full details of this work will be reported elsewhere.

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