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We, then, tested the substrate concentration dependent RNase-like activity of the $Cu(DS)_2$ micellar solution. The activity increased linearly as the concentration of the substrate RNA was increased up to the concentration of 0.60 mg/ml tested (Figure 3).

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Correlation Between Cross-Interaction Constant and Transition-State Imbalance

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Cross-interaction constant and transition state imbalance are two important concepts in organic reaction mechanisms.

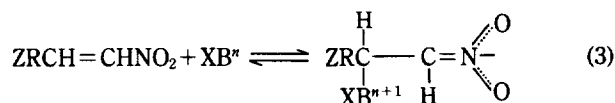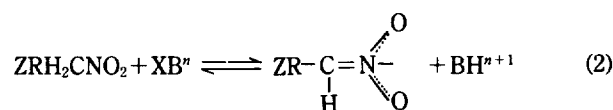Here we report a close relationship between the two.

Cross-interaction constants ρ_{XZ} or β_{XZ} (Eq. 1) defined by a Taylor expansion of log k_{XZ} up to second order around $\sigma_X = \sigma_Z = 0$ or $\Delta pK_X = \Delta pK_Z = 0$ where X and Z are substituents in the nucleophile, substrate or leaving group, and $\Delta pK_X = \Delta pK_a^X - \Delta pK_a^H$ etc., and neglecting the pure second-order terms, ρ_{XX}, β_{ZZ} etc., have proved to be a useful measure of transition state (TS) structure[1]. The magnitude of β_{XZ} represents the intensity of direct interaction

$$\log\ (k_{XZ}/k_{HH}) = \rho_X\sigma_X + \rho_Y\sigma_Y + \rho_{XY}\sigma_X\sigma_Y \tag{1a}$$

$$= \beta_X\Delta pK_X + \beta_Z\Delta pK_Z + \beta_{XZ}\Delta pK_X\Delta pK_Z \tag{1b}$$

between two reaction centers, R_X and R_Z, so that the $|\beta_{XZ}|$ is related inversely to the distance between the two reaction centers under a set reaction condition[1].

In proton transfers involving carbon acids (Eq. 2) or nucleophilic additions to olefins (Eq. 3) with a strong electron withdrawing substituent, *e.g.*, NO_2, that stabilizes the negative charge, structural and solvent reorganizations in forming resonance stabilized carbanion are often

$$ZRH_2CNO_2 + XB^n \rightleftharpoons ZR-\underset{\underset{H}{|}}{C} = N^-\overset{\nearrow O}{\underset{\searrow O}{}} + BH^{n+1} \tag{2}$$

$$ZRCH = CHNO_2 + XB^n \rightleftharpoons ZR\underset{\underset{XB^{n+1}}{|}}{C} \overset{\overset{H}{|}}{-} \underset{\underset{H}{|}}{C} = N^-\overset{\nearrow O}{\underset{\searrow O}{}} \tag{3}$$

found to lag behind the bond changes in the TS[2]. This phenomenon referred to as "imbalance", (I), manifests itself by an inequality between the Brönsted β_X (variation of base; denoted as β_B for proton transfer and β^n_{nuc} for nucleophilic addition[3]) and β_Z (variation of substrate; α_{CH} for proton transfer and α^n_{nuc} for nucleophilic addition[3]), $I = \beta_Z - \beta_X$. The inequality $\beta_Z \rangle \beta_X$ is known to arise from an exalted β_Z value relative to the "normal" β_X representing an approximate measure of the degree of proton transfer or progress of adduct formation in the TS.

The enhanced value of β_Z over β_X is observed because in the TS, **1** and **2**, the negative charge is mainly on carbon in contrast to the delocalized anion on the nitro group in the product ion (Eq. 2 and 3).

1   **2**
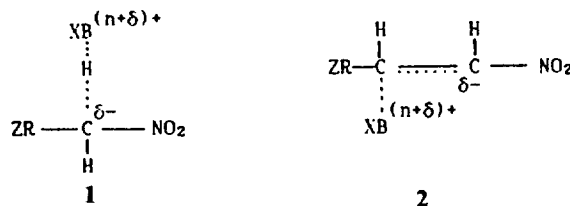
The lag in the delocalization of negative charge in the TS will result in the excess electron density on reaction center or the adjacent carbon over that would have if the resonance development were normal in the TS, and as a result the interaction between the two reaction centers will become enhanced *i.e.*, $|\beta_{XZ}|$ will become enhanced due to the imbalance. This enhanced $|\beta_{XZ}|$ induced by the imbalance, $|\beta_{XZ(imb)}|$, is thus expected to vary proportionally to the magnitude of the imbalance, $|I|$.

Table 1. Transition State Imbalances (I) and Cross-Interaction Constants (β_{XZ}) for some Carbanion Forming Reactions

Entry	Substrate (Z)	Base or Nucleophile (X)	β_Z	β_X	I	β_{XZ}
A	$ZC_6H_4CH=C(COO)_2C(CH_3)_2$	XR_2NH	0.235	0.11	$0.125^{a,b}$	0.017
B	$ZC_6H_4CH_2CH(COCH_3)_2$	$XRCOO^-$	0.58	0.44	0.14^c	0.015
C	$ZC_6H_3(NO_2)\cdot CH_2CN$	XR_2NH	0.36	0.61	-0.25^d	0.035
D	$ZC_6H_4CH=CHNO_2$	XR_2NH	0.51	0.25	$0.26^{b,e}$	-0.034^k
E	$C_6H_5CH=C(C_6H_4Z)\cdot NO_2$	XR_2NH	0.67	0.37	$0.30^{b,f}$	0.039
F	$ZC_6H_4CH_2CH(COCH_3)CO_2C_2H_5$	$XRCOO^-$	0.76	0.44	0.32^g	0.042
G	$ZC_6H_4CH_2C_6H_3\text{-}2,4\text{-}(NO_2)_2$	XR_2NH	0.87	0.45	0.42^h	0.052
H	$C_6H_5CH=C(C_6H_4Z)\cdot NO_2$	$XC_6H_4S^-$	0.87	0.19	0.68^i	-0.12^k
I	$ZC_6H_4CH_2NO_2$	XR_2NH	1.29	0.55	0.74^j	-0.040^k

[a] Averages of values in H_2O and 50% DMSO are used; C. F. Bernasconi and M. Panda, *J. Org. Chem.*, **52**, 3042 (1987). [b] Corrected values for the electrostatic interaction effects are used. [c] Ref. 2e. [d] C. F. Bernasconi and S. A. Hibdon, *J. Am. Chem. Soc.*, **105**, 4343 (1983). [e] C. F. Bernasconi, R. A. Renfrow, and P. R. *J. Am. Chem. Soc.*, **108**, 4541 (1986). [f] C. F. Bernasconi and R. A. Benfrow, *J. Org. Chem.*, **52**, 3035 (1987). [g] R. P. Bell and S. J. Grainger, *J. Chem. Soc. Perkin Trans 2*, 1367 (1976). [h] F. Terrier, J. Lelievre, A. P. Chatrousse, and P. G. Farrell, *J. Chem. Soc. Perkin Trans 2*, 1479 (1985). [i] C. F. Bernasconi and R. B. Killion Jr., *J. Am. Chem. Soc.*, **110**, 7506 (1988). [j] F. G. Bordwell and W. J. Boyle Jr., *J. Am. Chem. Soc.*, **94**, 3907 (1972); **97**, 3447 (1975). [k] The β_{XZ} (and ρ_{XZ}) can be negative, but the intensity of interaction is related only to the magnitude (for details see ref. 1).
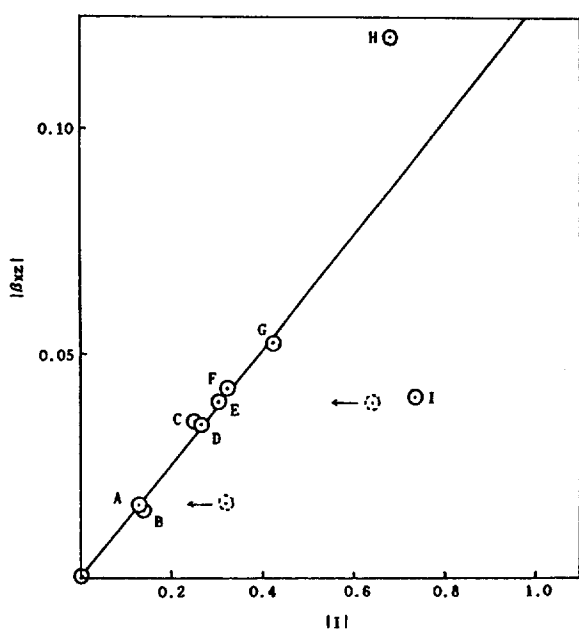

Figure 1. Plot of $|\beta_{XZ}|$ vs $|I|$. Points with dotted circles are uncorrected for electrostatic effects. For 8 points including the origin, $|\beta_{XZ}| = 0.13|I|$ with corr. coeff = 0.994. The labelings of points are the same as those in Table 1.

The imbalances, I, and β_{XZ} values[4] determined by multiple linear regression of $\log k$ using Eq. (1b) are summarized in Table 1, which are presented graphically in Figure 1. We note that the linearity of the plot of $|\beta_{XZ}|$ versus $|I|$ is good, except the two cases with large I. The cross-interaction constant, β_{XZ}, being a second derivative parameter I, and the two are related by Eq. (4) with correlation coefficient of 0.994 for eight points. The straight line passes

$$|\beta_{XZ}| = 0.13|I| \qquad (4)$$

through the origin, where $I=0$ and $\beta_{XZ}=0$[5], suggesting that the distance effect on $|\beta_{XZ}|$ is insignificant or small for the reactions correlated by Eq. (4)[6].

Another remarkable aspect of the linear plot is that the $|I|$ values obtained using corrected β_Z $(=\alpha^n_{nuc,corr})$ for the electrostatic effect of positive charge in the TS (entries A, D, and E)[2,3] give the same correlation with those obtained by the β_Z (α_{CH}) of the proton transfer; the uncorrected $|I|$ values for the β_Z $(=\alpha^n_{nuc})$ in fact deviate strongly tending toward overestimation of the β_Z $(=\alpha^n_{nuc})$. The good correlation obtained with the corrected β_Z $(=\alpha^n_{nuc,corr})$ but not with the uncorrected values supports the contention that the cross-interaction constants, β_{XZ} (or ρ_{XZ}), are not contaminated by the electrostatic effect in the TS as we have already shown in other examples[7].

The two points deviating from the linear correlation (entries H and I) have large imbalances. In these two cases, we suspect involvement of distance effect on $|\beta_{XZ}|$[6]. In the thiophenoxide additions to olefins (entry H) the soft-soft interaction of the two reaction centers in the is seems to result in the interaction at a closer distance due to the diffuse nature of the reacting atoms. In contrast, in the proton abstraction from nitroalkanes (entry I) the TS would be very similar to a hydrogen bonded intermediate, as Cram[8] and Bordwell[9] have claimed, so that the distance between the two reacting atoms would become greater. These distance changes are, of course, reflected inversely to $|\beta_{XZ}|$, i.e., as an increased and a decreased $|\beta_{XZ}|$ respectively.

We conclude that the correlation between cross-interaction constant, β_{XZ}, and imbalance, I, Eq. (4), may be useful in the determination of I and a cross-check for the determined value.

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nasconi, *"Nucleophilicity"* *Adv. Chem. Ser.,* **215**, Ed., J. M. Harris and S. P. McManus, *Am. Chem. Soc.,* Washington D.C., p. 115 (1987).

3. The two parameters are defined by the original authors[2] using the rate constant k_1 for proton transfer or adduct formation as: $\beta^n{}_{nuc} = \beta_{nuc}/\beta_{eq}$ where $\beta_B = \beta_{nuc} = d \log k_1 / d p K_a{}^{R2NH2+}$ and $\beta_{eq} = d \log K_1 / d p K_a{}^{R2NH2+}$. $\alpha_{CH} = \alpha^n{}_{nuc} = d \log k_1 / d \log K_1$. $\alpha^n{}_{nuc,corr} = \alpha^n{}_{nuc}$ corrected for effect of positive charge in the adduct. Our definition of β_X is equal to β_B and β_{nuc} and β_Z is equal to α_{CH} and $\alpha^n{}_{nuc}$; $\alpha = d \log k_1 / d \log K_1 = -d \log k_1 / d p K_1 = -(-\beta_Z) = \beta_Z$.

4. In the calculations of β_{XZ} by multiple linear regression, the pK_a values are used as given in the original reports. However, when the reported pK_a values had great uncertainties ($\geq \pm 30\%$) the β_{XZ} calculation seemed meaning less so that such cases are omitted. *e.g.,* C. F. Bernasconi and R. B. Killion. Jr., *J. Org. Chem.,* **54**, 2878 (1989).

5. When $I = 0$, β_X is equal to β_Z, so that the definition of β_{XZ} requires $\beta_{XZ} = 0$.

$$\beta_{XZ} = \frac{\partial \beta_Z}{\partial \Delta p K_X} = \frac{\partial \beta_X}{\partial \Delta p K_X} = 0,$$

since $\beta_Z = \beta_X$ and a linear Brönsted plot is assumed; $\partial \beta_X / \partial \Delta p K_X$ corresponds to a pure second derivative term, β_{XX}, which was assumed to be zero in the derivation of equation 1b.

6. When I is zero, the β_{XZ} also becomes zero[4]. This is strictly true when $\beta_{XZ} = \beta_{XZ(imb)}$. But β_{XZ} also contains a part which is dependent on distance, *i.e.,* $\beta_{XZ} = \beta_{XZ(dist)} + \beta_{XZ(imb)}$, so that $\beta_{XZ} = 0$ implies that both components are negligible.

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