

Kinetic Isotope Effects in the Nucleophilic Substitution Reactions of Benzyl- and 1-Phenylethyl -benzenesulfonates with Deuterated Aniline Nucleophiles

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Primary and secondary α -deuterium kinetic isotope effects are determined with deuterated aniline nucleophiles in the nucleophilic substitution reactions of benzyl benzenesulfonates and 1-phenylethyl benzenesulfonates in acetonitrile at 30.0 °C. The k_H/k_D values support our previous conclusions regarding the transition state structures proposed for the two reactions based on the cross-interaction constants ρ_{ij} ; the former is a typical S_N2 reaction whereas in the latter the four-center transition state may be involved.

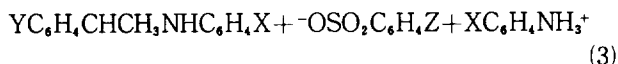
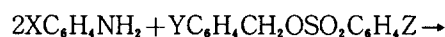
Introduction

Primary and secondary deuterium kinetic isotope effects (KIE) have been widely applied as a measure of the transition state (TS) structure in studies of substitution¹ and elimination reactions². In most of these studies, however, deuterium was incorporated in the substrate molecules.³ We report here a useful approach to the characterization of TS structures by deuterium KIE using deuterated nucleophiles.

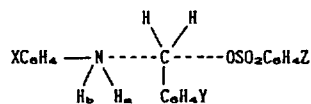
Recently in a series of work⁴ on the application of cross interaction constants, ρ_{ij} in eq. 1 where $i, j = X, Y$ or Z , as a measure of TS structure, we have shown that the reaction of benzyl benzenesulfonates with anilines, eq. 2, is a normal S_N2 type with TS structure (I).^{4a, 5} In contrast, the reaction of

$$\log(k_{i,j}/k_{H,H}) = \rho_i \sigma_i + \rho_j \sigma_j + \rho_{i,j} \sigma_i \sigma_j \quad (1)$$

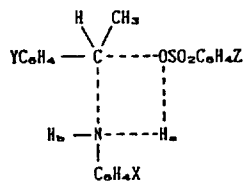
1-phenylethyl benzenesulfonates with anilines, eq. 3 proceeds by an intermolecular S_Ni mechanism^{4c,h} in which a hydrogen-bond bypass bridge is



formed in the TS, (II), providing another interaction route between substituents in the nucleophile (X) and the leaving group (Z). In both reactions 2 and 3, involvement of a second aniline molecule in the TS is precluded by the clean second-order kinetics obtained in all cases.^{4h,5} The cross interaction constants between X and Z, $|\rho_{XZ}|$, was exceptionally large (0.56 in methanol at 25.0 °C) in TS(II) reflecting a strong interaction through dual interaction routes.^{4h} That



(I)



(II)

the H-bond bridge formation is responsible for this is supported by the less than half $|\rho_{XZ}|$ value (0.23 in methanol at 25.0 °C) for the reaction with, N,N-dimethylanilines^{4l} in which no hydrogen is available for the H-bond bridge formation.

We have shown in this work that these TS structures, (I) and (II), predicted by the magnitudes of the cross interaction constants, ρ_{ij} , are indeed plausible based on the primary and secondary deuterium KIE observed using the deuterated aniline nucleophiles.

The ρ_{XY} values for reaction 2 were negative, and recently Jencks *et al.*⁶ questioned the validity of such negative ρ_{XY} (ρ_{XY}) values as a measure of the TS structure, since negative ρ_{XY} values may represent simple electrostatic effects between two polar substituents in the nucleophile (X) and in the substrate (Y) and do not necessarily require a change in the TS structure. The results of our KIE with deuterated aniline nucleophiles, however, clearly show that the ρ_{XY} values,^{4a,h,5} albeit negative, do represent structural changes involved in TS (I) by varying polar substituents in the nucleophile (X) and in the substrate (Y).

Results and Discussion

Replacement of both hydrogens, H_a and H_b on N, in the aniline nucleophiles should lead to inverse secondary KIE in TS(I), $k_H/k_D < 1.0$, since the two benzene rings on the nucleophile and substrate form *ca.* 150° (this is also true for $N-H_b$ in structure (II)) and the $N-H$ and $N-D$ bending vibrations are inhibited in the TS relative to the initial state.⁷ In contrast, primary KIE is expected for $N-H_a$ stretching while $N-H_b$ bending should lead to inverse secondary KIE in TS (II). These are indeed supported by the results of our observed KIE in Table 1 and 2.

According to the mechanistic criteria based on the cross interaction constants, ρ_{ij} , the sign of ρ_{XZ} serves as an indication of the nature of a reaction series⁴ⁱ; if it is negative the reaction is intrinsic-controlled,^{4i,j} for which the quantum mechanical (QM) model for prediction of TS variation^{4g, 8, 9a} applies, *i.e.*, a stronger nucleophile (e.g. $X = p-OCH_3$) as well as a better leaving group (e.g. $Z = p-NO_2$) leads to a later TS so that the following relations hold.^{8a,b,9a,d}

$$\begin{aligned} \Delta r_{XY} &= a\sigma_Z & a < 0 \\ \Delta r_{YZ} &= a'\sigma_X & a' < 0 \end{aligned} \quad (4)$$

Table 1. Secondary α -Deuterium Isotope Effect for Reaction 2 in Acetonitrile at 30.0 °C

X	Y	Z	$k_H(\text{M}^{-1}\text{s}^{-1})$	$k_D(\text{M}^{-1}\text{s}^{-1})$	k_H/k_D
<i>p</i> -CH ₃ O	H	<i>p</i> -CH ₃	2.697×10^{-3}	2.810×10^{-3}	0.955 ± 0.007^b
			2.687	2.827	
			2.690	2.843	
<i>p</i> -CH ₃ O	H	<i>p</i> -NO ₂	2.696 ± 0.005^a	2.824 ± 0.021	0.898 ± 0.007
			65.83×10^{-3}	73.86×10^{-3}	
			66.78	74.01	
			66.38	73.79	
<i>m</i> -NO ₂	H	<i>p</i> -CH ₃	63.33 ± 0.477	73.89 ± 0.875	0.973 ± 0.005
			1.620×10^{-4}	1.654×10^{-4}	
			1.613	1.662	
			1.617	1.669	
<i>m</i> -NO ₂	H	<i>p</i> -NO ₂	1.617 ± 0.001	1.662 ± 0.001	0.951 ± 0.007
			8.491×10^{-4}	8.903×10^{-4}	
			8.507	9.020	
			8.551	8.945	
<i>p</i> -CH ₃ O	<i>p</i> -NO ₂	<i>p</i> -CH ₃	8.516 ± 0.003	8.956 ± 0.006	0.900 ± 0.008
			1.156×10^{-3}	1.293×10^{-3}	
			1.161	1.281	
			1.167	1.300	
<i>p</i> -CH ₃ O	H	H	1.163 ± 0.004	1.291 ± 0.010	0.946 ± 0.010
			5.454×10^{-3}	5.702×10^{-3}	
			5.477	5.815	
			5.457	5.800	
			5.463 ± 0.013	5.772 ± 0.061	

^aStandard deviation, ^bStandard error¹⁶ = $1/k_D[(\Delta k_H)^2 + (k_H/k_D)^2 \times (\Delta k_D)^2]^{1/2}$.

Table 2. Primary Kinetic Isotope Effect for Reaction 3 in Acetonitrile at 30.0 °C

X	Y	Z	$k_H(\text{M}^{-1}\text{s}^{-1})$	$k_D(\text{M}^{-1}\text{s}^{-1})$	k_H/k_D
<i>p</i> -CH ₃ O	H	<i>p</i> -CH ₃	13.94×10^{-2}	7.068×10^{-2}	1.964×0.022^b
			13.66	7.021	
			13.85	7.012	
<i>p</i> -CH ₃ O	H	<i>p</i> -NO ₂	13.82 ± 0.143^a	7.034 ± 0.030	1.703 ± 0.026
			104.4×10^{-2}	61.16×10^{-2}	
			104.8	62.68	
			105.7	61.17	
<i>m</i> -NO ₂	H	<i>p</i> -CH ₃	105.0 ± 0.065	61.67 ± 0.875	2.583 ± 0.013
			7.286×10^{-5}	2.812×10^{-5}	
			7.276	2.809	
			7.285	2.836	
<i>m</i> -NO ₂	H	<i>p</i> -NO ₂	7.282 ± 0.006	2.819 ± 0.015	2.348 ± 0.036
			34.78×10^{-5}	15.10×10^{-5}	
			35.83	15.00	
			35.30	15.00	
			35.30 ± 0.525	15.03 ± 0.058	

^aStandard deviation, ^bStandard error.

Where a and a' are negative constants, and r_{XY} and r_{YZ} are lengths of bond being formed and broken in the TS respectively. Alternatively if ρ_{XZ} is positive the reaction is thermodynamic-controlled,^{4a,i} for which the potential energy surface (PES) model for prediction of TS variation^{8a,9} applies, *i.e.*, a stronger nucleophile as well as a better leaving group leads to an earlier TS so that the sign of a and a' in eqs. 4

reverses to positive.

Both reactions 2 and 3 had the negative ρ_{XZ} (and ρ_{XY}) values and the magnitudes of ρ_{ij} values were consistent with the TS variations predicted by eqs. 4.^{4g,i,8b,c}

The inverse secondary α -deuterium KIE in Table 1 are in full accord with the trends expected from the negative ρ_{XZ} values, and eqs. 4 are seen to apply to reaction 2; the inverse

KIE is greater, *i.e.*, k_H/k_D is smaller, for the reaction with a better leaving group ($Z=p-\text{NO}_2$) indicating a greater degree of bond formation ($\Delta r_{XY} < 0$ since $a < 0$ and $\sigma_Z > 0$). We note also that the degree of bond formation is greater, *i.e.*, k_H/k_D is smaller, with a stronger nucleophile ($X=p-\text{OCH}_3$). The k_H/k_D value is the smallest, *i.e.*, bond formation is the greatest for the reaction with the strongest nucleophile ($X=p-\text{OCH}_3$) and the best leaving group ($Z=p-\text{NO}_2$) studied in this work. We also note that k_f/k_D is smaller and hence bond formation is greater with an electron-withdrawing group in the structure ($Y=p-\text{NO}_2$). All these trends are in full accord with those predicted by the magnitudes of the cross interaction constants^{4,9a} even through ρ_{XY} as well as ρ_{XZ} was negative. Thus the ρ_{XY} (and ρ_{XZ}) values obtained for reaction 2 do not appear to represent simple electrostatic interactions⁶ between polar substituents in the nucleophile (X) and substrate (Y), even though they were negative, but they are seen to reflect correctly the variation of the TS structure, (I), with the substituents. Possibility of small electrostatic interactions affecting $|\rho_{XY}|$ may not, however, be ruled out entirely.^{4f}

The interpretation of the primary KIE in Table 2 is not so straightforward. The k_H/k_D values are in general small compared to the theoretical limiting value of 6~8.¹⁰ Several factors are contributing to such a small primary KIE: (i) The two pathways, rear-side attack (k_r) and front-side attack (k_f), may be competitive so that the contribution of TS(II) may be large but not an exclusive one. (ii) The distance between N and O is relatively great so that the KIE due to bond distention of $N-H_a$ caused by the H -bond formation may be small. (iii) The concomitant inverse secondary KIE may play a relatively greater role since both $N-H_a$ and $N-H_b$ vibrations in the TS for the rear-side attack path contribute to the inverse KIE in addition to the $N-H_b$ vibration in TS(II). (iv) The $N-H_a-O$ structure is bent^{3a,14} and unsymmetrical¹¹ so that the primary KIE due to the $N-H_a$ stretching should be small. (v) There is a heavy-atoms (N and O) contribution¹¹ to the reaction coordinate motion,^{7,12} which also reduces the primary KIE.

Since a stronger nucleophile ($X=p-\text{CH}_3\text{O}$) and a better leaving group ($Z=p-\text{NO}_2$) should lead to a greater degree of bond formation for a reaction series with the negative ρ_{XZ} values,^{4g,i,8b,c} the inverse secondary KIE ($k_H/k_D < 1.0$) in the k_r and k_f paths will be greater due to the greater steric hindrance reducing the overall KIE which is observed as a product of all contributing KIEs. In contrast a weaker nucleophile and nucleofuge will result in a lesser degree of bond formation *i.e.*, a lesser steric hindrance, causing lesser inverse secondary KIE so that the primary KIE will become relatively greater. The k_H/k_D values in Table 2 are consistent with the trends of TS variation required from the observed negative ρ_{XZ} values in accordance with eqs. 4, *i.e.*, the stronger the nucleophile ($\Delta\sigma < 0$), and the better the leaving group ($\Delta\sigma_Z > 0$), the later is the TS ($\Delta r_{XY} < 0$) or $\Delta r_{YZ} > 0$) since a and a' are negative, resulting in the smaller primary KIE ($\Delta(k_H/k_D) < 1.0$).

This means that, although the relatively large $|\rho_{XZ}|$ values and the primary KIE ($k_H/k_D > 1.0$) observed for reaction 3 suggest the involvement of TS(II), the reaction path (k_r) is not the exclusive one and may well be competing with the

back-side attacking path, k_f . In addition, the $k_H/k_D (> 1.0)$ values observed may provide a necessary condition but not a sufficient condition for the four-center TS, (II).

The magnitudes of ρ_{ij} values for reaction 3 were found to be consistent with the TS variation expected from eqs. 4,⁹ albeit ρ_{XY} and ρ_{XZ} were negative, so that here again for reaction 3 the ρ_{ij} values seem to provide a useful measure of the TS structure. Possibilities of other TS structures considered for the intermolecular S_Ni mechanism by Okamoto *et al.*,¹³ *i.e.* the six-membered cyclic model, the solvent-separated ion-pair model and the rear-side shielding model, can be ruled out as untenable since the primary KIE in Table 2 are not consistent with any of these structures.

We conclude that the inverse secondary α -deuterium KIE in reaction 2 and the primary KIE in reaction 3 are in full accord with the TS structures, (I) and (II) respectively, proposed on the magnitudes of cross interaction constants, ρ_{ij} ; this gives supports to the use of $|\rho_{ij}|$ values as a measure of TS structure. The method of KIE with the deuterated nucleophiles for characterizing the TS structure can be very useful, especially for the type of reactions studied in this work.

Experimental

Materials. Acetonitrile (Baker, GR) was dried over KOH and then fractionally distilled from P_2O_5 three times. (b.p: 81.6°C). Substituted benzyl benzenesulfonates and 1-phenylethyl benzenesulfonates were prepared as described previously.^{4h,5b}

Benzyl *p*-Nitrobenzenesulfonate.^{4h} m.p. 62-63°C, IR(KBr) 3100, 1985, 1930, 1670, 1310~1350, 785 cm^{-1} ; ¹H NMR δ 5.0(2H), 7.10~7.90(9H). Anal. Calcd for $C_{13}H_{11}O_5NS$: C, 86.31; H, 6.12; N, 7.51. Found: C, 86.19; H, 6.07; N, 7.74.

Preparation of Deuterated Anilines. Aniline was dissolved in dry ethyl acetate and HCl gas from H_2SO_4 and HCl was passed through the solution to form anilinium chloride salt. Completion of the salt formation was confirmed by Volhard Method.¹⁵ Approximately 0.015 mole of the salt was dissolved in 1.50 mole (30g) of D_2O under nitrogen atmosphere and left over 24 hours at 25.0°C. The solution was neutralized with 0.008 mole (1.04g) of K_2CO_3 . The deuterated aniline was extracted with dry ethyl ether and dried again over $MgSO_4$. After expulsion of solvent, a small amount (5%) of deuterated anilinium chloride salt was added and then recrystallized twice from D_2O . The analysis (NMR) of dried deuterated aniline had more than 99% deuterium content.

Rate Constants. Rates were measured conductometrically in acetonitrile and pseudo-first-order rate constants k_1^{obsd} were determined by the method of Guggenheim with a large excess of the aniline ($[\text{Substrate}] \cong 5 \times 10^{-4}$ M and $[\text{Aniline}] \cong 0.05 \sim 0.10$ M). Second-order rate constants k_2 were obtained from the slope of a plot of k_1^{obsd} vs. $[\text{aniline}]$ where k_1 is the rate constant of solvolysis which was negligible in all cases. Four or more different aniline concentrations were used in the plot. Triplicate kinetic runs showed the standard deviation of less than 1% for all the k_2 values determined.

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A Lattice Statistical Thermodynamic Study of Bilayer Amphiphile Molecules

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In order to elucidate conformational properties of bilayer semiflexible amphiphile molecules, we derive a expression of free energy separation with respect to bilayer width, and segment density profiles on the basis of cubic lattice model. Our result shows that at the moderate surface coverage region (*i.e.*, $\sigma < 0.35$), bilayer system tends to have thermodynamically favorable bilayer width corresponding to free energy minimum condition resulting from the major contribution of attractive interaction between chain segments. However such a favorable bilayer width do not occur in the region of high surface coverage (*i.e.*, $\sigma > 0.4$) where repulsive interaction between chain segments is considered to be dominant.

Introduction

In aqueous environment, bilayer can be formed by amphiphile chain molecules due to their hydrophobic and hydrophilic natures. It plays an important role in biological sys-

tems such as membranes and vesicles. Because of the flexibility of hydrocarbon chain of the amphiphiles, the amphiphiles can have various conformational states, which result in fluidity of inner layer region. Recently, by making use of Self-Consistent Field theory based on Dolan and Edwards'