Kinetic Isotope Effects involving Deuteriated Aniline Nucleophiles

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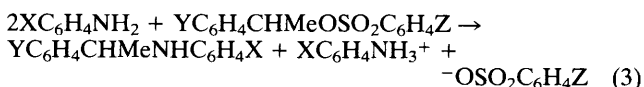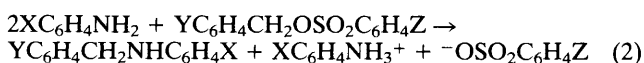*Department of Chemistry, Inha University, Inchon, 402-751, Korea*

Primary and secondary α-deuterium kinetic isotope effects are observed with deuteriated aniline nucleophiles in the S_N2 reactions of 1-phenylethyl and benzyl benzenesulphonates, providing evidence in support of the four centre transition state mechanism for the former reaction.

Deuterium kinetic isotope effects (KIE) are normally studied with deuteriated substrate molecules in organic reactions[1] such as nucleophilic substitution[2] and β-elimination.[3] We report here a novel approach to the characterization of transition state (TS) structures by deuterium KIE using deuteriated nucleophiles.

Recently in a series of reports[4] on the application of cross interaction constants, ρ_{ij} in equation (1) where i, j = X, Y, or Z (X = nucleophile, Z = leaving group), as a measure of the TS structure, we have shown that reaction (2) is a normal S_N2 type.[4a,j] In contrast, reaction (3) proceeds by the four centre TS mechanism[4c,h] in which a hydrogen bond bypass bridge is formed in the TS (I), providing another interaction path between substituents in the nucleophile and in the leaving group.

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

$$2XC_6H_4NH_2 + YC_6H_4CH_2OSO_2C_6H_4Z \rightarrow$$
$$YC_6H_4CH_2NHC_6H_4X + XC_6H_4NH_3^+ + {}^-OSO_2C_6H_4Z \qquad (2)$$

$$2XC_6H_4NH_2 + YC_6H_4CHMeOSO_2C_6H_4Z \rightarrow$$
$$YC_6H_4CHMeNHC_6H_4X + XC_6H_4NH_3^+ +$$
$${}^-OSO_2C_6H_4Z \qquad (3)$$

The cross interaction constant between X and Z, $|\rho_{xz}|$, was exceptionally large (0.56), reflecting strong interaction through dual interaction paths.[4h] That the H-bond bridge formation is responsible for this is supported by the less than half $|\rho_{xz}|$ value (0.23) for the reaction with N,N-dimethylaniline,[4l] and involvement of a second aniline molecule in the

TS is precluded by the clean second-order kinetics in both reactions.

Replacement of both hydrogens H_a and H_b with deuterium in (I) and (II), led to both the primary and secondary α-deuterium KIE as presented in Tables 1 and 2. In TS (I), $N-H_a$ stretching will give the primary KIE while $N-H_b$ bending will show the secondary KIE. In contrast in TS (II), bending vibrations of both $N-H_a$ and $N-H_b$ will give secondary KIE, which is of an inverse type, $k_H/k_D < 1.0$, since the two benzene rings on the nucleophile and substrate form an approximate angle of 150° [this is also true for $N-H_b$ in structure (I)] and the N–H and N–D bending vibrations are inhibited in the TS relative to the initial state.

The primary KIE in (I) is relatively small, since k_H/k_D is lowered (i) due to the nonlinear and unsymmetric structure[5] of N–H–O, (ii) by a concomitant inverse KIE of $N-H_b$, and (iii) by heavy-atom (N and O) contribution to the reaction-co-ordinate motion.[5,6] The size of KIE correctly reflects tightness of the TS structure. According to our results of $|\rho_{ij}|$, a stronger nucleophile (X = p-MeO) as well as a better leaving group (Z

(I)

(II)
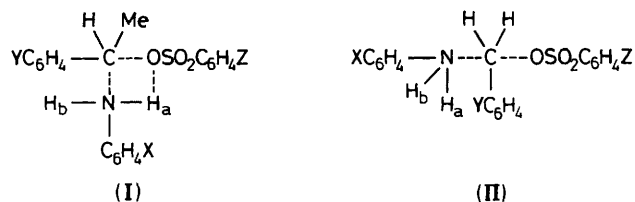
Table 1. Primary kinetic isotope effect for reaction (3) in acetonitrile at 30.0 °C.

X	Y	Z	k_H /mol^{-1} dm^3 s^{-1}	k_D /mol^{-1} dm^3 s^{-1}	k_H/k_D
p-MeO	H	p-Me	13.94×10^{-2}	7.068×10^{-2}	$1.96_4 \pm 0.022^b$
			13.66	7.021	
			13.85	7.012	
			$13.82 \pm 0.14_3^a$	$7.034 \pm 0.03_0$	
p-MeO	H	p-NO$_2$	104.4×10^{-2}	61.16×10^{-2}	$1.70_3 \pm 0.026$
			104.8	62.68	
			105.7	61.17	
			$105.0 \pm 0.06_5$	$61.67 \pm 0.87_5$	
m-NO$_2$	H	p-Me	7.286×10^{-5}	2.812×10^{-5}	$2.58_3 \pm 0.013$
			7.276	2.809	
			7.285	2.836	
			$7.282 \pm 0.00_6$	$2.819 \pm 0.01_5$	
m-NO$_2$	H	p-NO$_2$	34.78×10^{-5}	15.10×10^{-5}	$2.34_8 \pm 0.036$
			35.83	15.00	
			35.30	15.00	
			$35.30 \pm 0.52_5$	$15.03 \pm 0.05_8$	

^{a} Standard deviation. ^{b} Standard error $= 1/k_D [(\Delta k_H)^2 + (k_H/k_D)^2 \times (\Delta k_D)^2]^{1/2}$.

Table 2. Secondary α-deuterium isotope effect for reaction (2) in acetonitrile at 30.0 °C.

X	Y	Z	k_H /mol^{-1} dm^3 s^{-1}	k_D /mol^{-1} dm^3 s^{-1}	k_H/k_D
p-MeO	H	p-Me	2.697×10^{-3}	2.801×10^{-3}	$0.95_5 \pm 0.007^b$
			2.687	2.827	
			2.690	2.843	
			$2.696 \pm 0.00_5^a$	$2.824 \pm 0.02_1$	
p-MeO	H	p-NO$_2$	65.83×10^{-3}	73.86×10^{-3}	$0.89_8 \pm 0.007$
			66.78	74.01	
			66.38	73.79	
			$66.33 \pm 0.47_7$	$73.89 \pm 0.11_2$	
m-NO$_2$	H	p-Me	1.620×10^{-4}	1.654×10^{-4}	$0.97_3 \pm 0.005$
			1.613	1.662	
			1.617	1.669	
			$1.617 \pm 0.00_0$	$1.662 \pm 0.00_0$	
m-NO$_2$	H	p-NO$_2$	8.491×10^{-4}	8.903×10^{-4}	$0.95_1 \pm 0.007$
			8.507	9.020	
			8.551	8.945	
			$8.516 \pm 0.00_3$	$8.956 \pm 0.00_6$	

^{a} Standard deviation. ^{b} Standard error.

= p-NO_2) in reactions (2) and (3) leads to a later TS, *i.e.*, a greater degree of bond formation and bond cleavage.[4h,7] Thus the reaction with X = p-MeO and Z = p-NO_2 has the least k_H/k_D value, *i.e.*, the greatest inverse secondary KIE, since bond formation is the greatest, whereas that with X = m-NO_2 and Z = p-Me has the least inverse secondary KIE since bond formation is the least.

In contrast, however, the primary KIE is the least with X = p-MeO and Z = p-NO_2 for which the TS is expected to be the latest, *i.e.*, bond-formation and -breaking are the greatest, and it is the greatest with X = m-NO_2 and Z = p-Me for which the TS will be the earliest, *i.e.*, bond-formation and -breaking are the least. A simple explanation of the smaller primary KIE for a later TS is that a strong electron-donating group on the nucleophile, X = p-MeO, and electron-withdrawing group on the leaving group, Z = p-NO_2, tend to reduce developing positive charge on N and negative charge on O, as bond-formation and -breaking proceed, by direct conjugation through the benzene ring, so that hydrogen bond $H_a \cdots O$ is weakened and N–H_a bond breaking becomes smaller. This effect will be the greatest in the latest TS (X = p-MeO and Z = p-NO_2) and hence k_H/k_D is the smallest, while it will be the smallest in the earliest TS (X = m-NO_2 and Z = p-Me) so that the primary KIE becomes the largest (Table 1). Alternatively, coupling of heavy-atom motion (N–C contraction and C–O stretching) with the proton transfer in the reaction co-ordinate[5,6] may be the cause of the decrease in the primary KIE in a later TS, since the greater the coupling of heavy-atom motion with the proton transfer in a later TS the smaller the primary KIE will become. We do not expect any significant contribution of a tunnelling effect, since the three atom system, $N \cdots H \cdots O$, is bent and unsymmetrical.[5]

We conclude that the KIE involving deuteriated nucleophiles can provide a very useful probe for unravelling the TS structure for nucleophilic substitution reactions.

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