Kinetic Isotope Effects Involving Deuterated Benzylamine Nucleophiles

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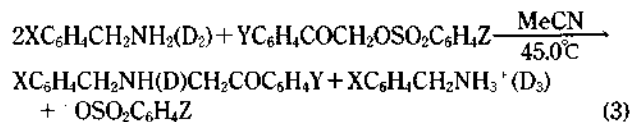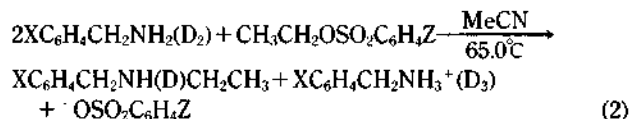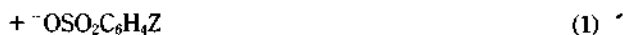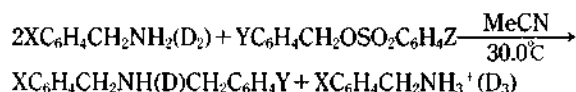## Ikchoon Lee*, Han Joong Koh, Dong Sook Sohn⁺, and Byung Choon Lee⁺

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The kinetic isotope effects (KIE) are determined for the reactions of benzyl benzenesulfonates (BBS), ethyl benzenesulfonates (EBS) and phenacyl benzensulfonates (PAB) with deuterated benzylamine nucleophiles. The inverse secondary α-deuterium KIE observed were somewhat smaller than those for the corresponding reactions with aniline nucleophiles. The primary KIE$_s$ obtained with PAB were slightly greater than those for the corresponding reactions with anilines, which suggested that the inverse secondary KIE is decreased due to a relatively earlier transition state for bond-making with little change in the hydrogen bonding strength to the carbonyl oxygen.

Introduction

Primary and secondary deuterium kinetic isotope effects (KIE) have been widely used in characterizing the transition state (TS) structure in studies of substitution[1] and elimination[2] reactions. Normally, however, deuterium is incorporated into the substrate molecules.[3] In the studies of secondary α-deuterium KIE in an S_N2 process, however, there are some ambiguities as to which of the two concurrent changes of bond-making and -breaking is reflected mainly in the observed secondary KIE. This type of ambiguities can, however, be prevented by incorporating deuterium into the nucleophile or into the leaving group (LG) so that the secondary KIE reflects only a change in the degree of bond-making or-breaking. We have carried out such KIE studies with deuterated aniline nucleophiles[4] in the S_N2 reactions and successfully applied to determine the TS structure and how the TS$_s$ vary with the substituents in the nucleophile (X) or in the LG (Z). In this work, we have extended our KIE studies to reactions 1-3, with deuterated benzylamine nucleophiles.

$$2XC_6H_4CH_2NH_2(D_2) + YC_6H_4CH_2OSO_2C_6H_4Z \xrightarrow[30.0°C]{MeCN}$$
$$XC_6H_4CH_2NH(D)CH_2C_6H_4Y + XC_6H_4CH_2NH_3{}^+(D_3)$$
$$+ {}^-OSO_2C_6H_4Z \tag{1}$$

$$2XC_6H_4CH_2NH_2(D_2) + CH_3CH_2OSO_2C_6H_4Z \xrightarrow[65.0°C]{MeCN}$$
$$XC_6H_4CH_2NH(D)CH_2CH_3 + XC_6H_4CH_2NH_3{}^+(D_3)$$
$$+ {}^-OSO_2C_6H_4Z \tag{2}$$

$$2XC_6H_4CH_2NH_2(D_2) + YC_6H_4COCH_2OSO_2C_6H_4Z \xrightarrow[45.0°C]{MeCN}$$
$$XC_6H_4CH_2NH(D)CH_2COC_6H_4Y + XC_6H_4CH_2NH_3{}^+(D_3)$$
$$+ {}^-OSO_2C_6H_4Z \tag{3}$$

Results and Discussion

Kinetic isotope effects observed with deuterated benzylamine nucleophiles for reactions 1-3 are summarized in Tables 1-3. The results in Tables 1 and 2 show that the k_H/k_D values are smaller than one; replacements of both amine hydrogens, H_a and H_b, on N in the benzylamine nucleophile leads to an iverse secondary α-deuterium KIE, TS (I), since the N-H and N-D bending vibrations are hindered in the TS relative to the initial state.[5] Reactions of benzyl benzenesulfonates (BBS) with anilines[6] are known to proceed by a dissociative S_N2 mechanism with a relatively loose TS. The

Table 1. The Kinetic Isotope Effects Observed with Deuterated Benzylamine Nucleophiles for Reaction:

$$XC_6H_4CH_2NH_2(D_2) + YC_6H_4CH_2OSO_2C_6H_4Z \xrightarrow[30.0°C]{MeCN}$$

X	Y	Z	$k_H(M^{-1}s^{-1})$	$k_D(M^{-1}s^{-1})$	k_H/k_D
			4.197×10^{-1}	4.501×10^{-1}	
p-CH₃O	H	p-NO₂	4.246	4.491	$0.94_0 \pm 0.007^b$
			4.214	4.470	$(0.89_8 \pm 0.007)^c$
			$4.21_9 \pm 0.02_5{}^d$	$4.48_7 \pm 0.01_6$	
			1.263×10^{-2}	1.332×10^{-2}	
p-CH₃O	H	p-CH₃	1.250	1.328	$0.95_2 \pm 0.009$
			1.275	1.330	$(0.95_5 \pm 0.007)$
			$1.26_3 \pm 0.01_3$	$1.32_7 \pm 0.00_4$	
			2.501×10^{-1}	2.631×10^{-1}	
p-Cl	H	p-NO₂	2.478	2.602	$0.95_3 \pm 0.007$
			2.496	2.614	
			$2.49_2 \pm 0.01_2$	$2.61_6 \pm 0.01_5$	
			$7.66_2 \times 10^{-3}$	7.952×10^{-3}	
p-Cl	H	p-CH₃	7.592	7.843	$0.96_6 \pm 0.009$
			7.601	7.861	
			$7.61_8 \pm 0.03_8$	$7.88_5 \pm 0.05_8$	

[a]Standard deviation. [b]Standard error[10]$= 1/k_D[(\Delta k_H)^2 + (k_H/k_D)^2 \times (\Delta k_D^2)]^{1/2}$. [c]The values in parentheses are those for the reactions with anilines.[4a,d]

Table 2. The Kinetic Isotope Effects Observed with Deuterated Benzylamine Nucleophiles for Reaction:

$$XC_6H_4CH_2NH_2(D_2) + C_2H_5OSO_2C_6H_4Z \xrightarrow[65.0°C]{MeCN}$$

| X	Z	$k_H(M^{-1}s^{-1})$	$k_D(M^{-1}s^{-1})$	k_H/k_D
		1.979×10^{-2}	2.219×10^{-2}	
p-CH₃O	p-NO₂	1.992	2.225	$0.90_5 \pm 0.005^b$
		1.975	2.212	$(0.86_9 \pm 0.009)^c$
		$1.98_2 \pm 0.00_9{}^d$	$2.18_9 \pm 0.00_7$	
		1.650×10^{-3}	1.844×10^{-3}	
p-CH₃O	p-CH₃	1.653	1.830	$0.90_6 \pm 0.009$
		1.671	1.816	$(0.86_2 \pm 0.008)$
		$1.658 \pm 0.01_1$	$1.83_0 \pm 0.01_4$	
		1.014×10^{-2}	1.119×10^{-2}	
p-Cl	p-NO₂	1.012	1.109	$0.90_4 \pm 0.008$
		1.001	1.120	
		$1.00_9 \pm 0.00_7$	$1.11_8 \pm 0.00_6$	
		5.324×10^{-4}	5.967×10^{-4}	
p-Cl	p-CH₃	5.401	6.025	$0.89_9 \pm 0.009$
		5.386	5.934	
		$5.37_0 \pm 0.04_1$	$5.97_5 \pm 0.04_6$	

[a]Standard deviation. [b]Standard error. [c]The values in parentheses are those for the reactions with anilines.[4b]

tightest TS, with $X = p\text{-}OCH_3$ and $Z = p\text{-}NO_2$, has somewhat greater k_H/k_D indicating a looser structure than the corresponding reaction of BBS with aniline nucleophiles.[4] A weaker-nucleophile $(X = p\text{-}Cl)$ and a worse LG $(Z = p\text{-}CH_3)$ appear to give a less tight bondformation in the TS i.e., and earlier

Table 3. The Kinetic Isotope Effects Observed with Deuterated Benzylamine Nucleophiles for Reaction

$$XC_6H_4CH_2NH_2(D_2) + YC_6H_4COCH_2OSO_2C_6H_4Z \xrightarrow[45.0°C]{MeCN}$$

X	Y	Z	$k_H(M^{-1}s^{-1})$	$k_D(M^{-1}s^{-1})$	k_H/k_D
			3.130×10^{-1}	2.890×10^{-1}	
p-CH₃O	H	p-NO₂	3.129	2.852	$1.08_9 \pm 0.008^b$
			3.122	2.862	$(1.02_9 \pm 0.008)^c$
			$3.12_4 \pm 0.01_6{}^d$	$2.86_8 \pm 0.01_9$	
			1.880×10^{-1}	$1.73_4 \times 10^{-1}$	
p-CH₃O	H	p-CH₃	1.901	1.74_2	$1.09_1 \pm 0.008$
			1.897	1.72_9	$(1.03_4 \pm 0.009)$
			$1.89_3 \pm 0.01_1$	$1.73_5 \pm 0.00_7$	
			1.044×10^{-1}	0.949×10^{-1}	
p-Cl	H	p-NO₂	1.036	0.951	$1.09_2 \pm 0.007$
			1.041	0.955	
			$1.04_0 \pm 0.00_4$	$0.95_2 \pm 0.00_3$	
			5.065×10^{-2}	4.576×10^{-2}	
p-Cl	H	p-CH₃	5.085	4.544	$1.10_9 \pm 0.008$
			5.067	4.602	
			$5.07_2 \pm 0.01_1$	$4.57_4 \pm 0.02_9$	

[a]Standard deviation. [b]Standard error. [c]The values in parentheses are those for the reactions with anilines.[4b,c]


$$XC_6H_4\text{-}CH_2\text{-}N \cdots C \cdots OSO_2C_6H_4Z$$

R = CH₃ or C₆H₄

(I)
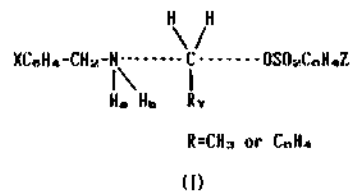
TS for bond-making, than a stronger nucleophile $(X = p\text{-}CH_3 O)$ and a better LG $(Z = p\text{-}NO_2)$. This reactivity trend is expected from a negative $\rho_{XZ}{}^{6,7a}$ $(\rho_{XZ} < 0$ in eq. (4), since the definition of $\rho_{XZ}{}^{6,7}$ eq. (4), requires that a stronger nucleophile and a better LG should lead to a later TS along the reaction coordinate.

$$\rho_{XZ} = \frac{\partial \rho_Z}{\partial \sigma_X} = \frac{\partial \rho_X}{\partial \sigma_Z} \tag{4}$$

*The k_H/k_D values in Table 2 indicate again that the reactions of benzylamine nucleophiles lead to looser TS_s than the corresponding reactions with aniline nucleophiles. In the reactions of ethyl benzenesulfonates (EBS) with anilines,[8] the TS was found to be relatively tight and a stronger nucleophile and a better LG were found to give an earlier TS as requireed by a positive $\rho_{XZ}{}^{8,9}$ $(\rho_{XZ} > 0$ in eq. (4)). Reference to Table 2 reveals that the variation of k_H/k_D with substituents X and/or Z is very small indeed, albeit a similar reactivity trend of an earlier TS with a stronger nucleophile and a better LG can barely be recognized. A small degree of k_H/k_D variation with the substituents may result from a loosei TS, however.

The reactions of phenacyl benzenesulfonates (PAB) with anilines[9a] were characterized by an extremely small ρ_{XY}, cross-interaction between the substituents in the nucleophile and the substrate, as a result of resonance shunt phenomenon[7c,9]; the electronic effect from a substituent in the nucleo-

phile (X) to that in the substrate (Y) is bypassed to the carbonyl group, as in (II), before reaching substituent Y.

(II)
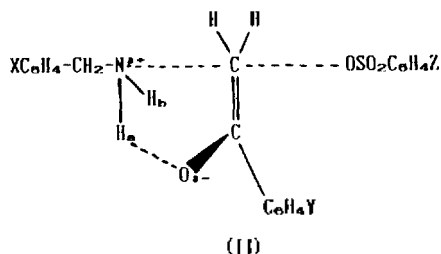
It was found that the two reactions of EBS[8] and PAB[9a] with anilines are very similar: (i) The ρ_{XZ} values are positive[8,9] and hence an earlier TS is expected from a stronger nucleophile and/or a better LG. (ii) The magnitudes of ρ_{XZ} are large and strikingly similar so that the two must proceed by an associative S_N2 mechanism[8,9] with a tight TS. In contrast to these similarities, the observed KIE, exhibited a striking difference: the k_H/k_D values for the reactions of EBS were smaller than unity as noted above but the reactions of PAB had the k_H/k_D values of greater than one. This unexpected difference was rationalized with resonance shunt phenomenon[7c,9] in the TS for the reactions of PAB. A consequence of this effect was that the N-H$_a$ bond stretching due to hydrogen bonding of H$_a$ toward the carbonyl oxygen can give a primary KIE ($k_H/k_D>1.0$)[4b,c] which will be reduced by a concomitant inverse secondary α-deuterium KIE of the N-H$_b$ bending viration. Since ρ_{XZ} was positive for this reaction,[9] an earlier TS was obtained with a stronger nucleophile and/or a better LG.

The k_H/k_D values in Table 3 show that the reactions of PAB with benzylamines are similar to those with anilines[4b,c]: the KIE, are greater than one, indicating the N-H$_a$ bond stretching due to resonance shunt effect.[7c,9] The magnitudes of k_H/k_D are, however, somewhat greater than those for the aniline reactions. This suggests that the TS structure is such that the N-H, bending mode is less hindered but the N-H$_a$ streching is not much affected by a somewhat loose TS in the benzylamine reactions. A lesser degree of steric hindrance for the N-H$_b$ bending will result in a relatively greater k_H/k_D, since the observed k_H/k_D values are given by the product of the two effects due to N-H$_a$ and N-H$_b$. The variations of k_H/k_D with substituents X and Z are in accord with those expected from the positive ρ_{XZ} values[9] i.e., an earlier TS with a stronger nucleophile and/or a better LG having a smaller k_H/k_D due to a lesser degree of bond-making.

Experimental

Meterials and measurements of KIE are as described previously.[4,6,8,9] Preparation of deuterated benzylamine: Benzylamine was dissolved in excess D_2O under nitrogen atmosphere and left over 5 hours at 25.0°C. The deuterated benzylamine was extracted with dry ethyl ether and dried again over $MgSO_4$. After expulsion of solvent, the analysis (NMR) of dried deuterated benzylamine has more than 99% deuterium content; the k_H/k_D values were thus not corrected for the deuterium content.

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