Substituent Effects on Transition-state Structures for Dissociative and Associative S_N2 Reactions

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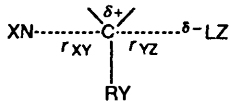
α-Deuterium secondary kinetic isotope effects (KIEs) have been investigated for the reactions of anilines with benzyl, methyl and ethyl benzenesulfonates involving deuteriated aniline nucleophiles and substrates. The secondary KIEs observed are normal, $k_H/k_D > 1.0$, only for the deuteriated benzyl system and are of an inverse type, $k_H/k_D < 1.0$, for the deuteriated methyl and ethyl systems as well as for all the deuteriated nucleophiles. These results suggest that the relief of steric strain by bond breaking of the leaving group prevails over the steric congestion incurred by bond formation of the nucleophile in the reactions of the benzyl compound (dissociative S_N2 mechanism), in contrast to the reverse trend, *i.e.*, the strain incurred by bond formation of the nucleophile is greater than the relief of steric congestion by bond breaking of the leaving group in the reactions of alkyl compounds (associative S_N2 mechanism). The effects of substituents in the nucleophile (X) and leaving group (Z) on the secondary KIEs are in complete agreement with the transition-state variation predicted by the sign and magnitude of the cross-interaction constant, ρ_{XZ}.

The transition-state (TS) structure of a concerted bimolecular nucleophilic substitution (S_N2) reaction can be relatively loose or tight depending on whether bond breaking has progressed further (dissociative, **1**) or lesser (associative, **2**) than bond formation.[1-3] One way of distinguishing between these two types is to vary substituent Y in the substrate and determine the Hammett ρ_Y value, which will be negative (positive) in **1** (in **2**) indicating that the reaction centre carbon is positively (negatively) charged in the TS. However, a more quantitative measure of the TS structure is provided by the cross-interaction constant, ρ_{XZ} in eqns. (1) and (2).[3] The parameter ρ_{XZ} is a



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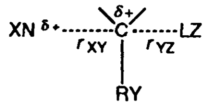

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$$\log(k_{XZ}/k_{HH}) = \rho_X\sigma_X + \rho_Z\sigma_Z + \rho_{XZ}\sigma_X\sigma_Z \qquad (1)$$

$$\rho_{XZ} = \frac{\partial^2 \log k_{XZ}}{\partial\sigma_X\partial\sigma_Z} = \frac{\partial\rho_Z}{\partial\sigma_X} = \frac{\partial\rho_X}{\partial\sigma_Z} \qquad (2)$$

second-derivative parameter obtained by subjecting rate constants for a dual-substituted [X in the nucleophile and Z in the leaving group (LG)] reaction system, k_{XZ}, to multiple linear regression using eqn. (1). It has been shown that the sign of ρ_{XZ} represents two different types of substituent (X and Z) effects on the TS structure;[2,4] when ρ_{XZ} is negative, eqn. (2) requires that a stronger nucleophile ($\delta\sigma_X < 0$) and a better LG ($\delta\sigma_Z > 0$) lead to a later TS, *i.e.*, $\delta\rho_Z > 0$ and $\delta\rho_X < 0$, whereas they lead to an earlier TS when ρ_{XZ} is positive. Thus the effects of substituents in the nucleophile and LG on the degree of bond formation (Δr_{XY}) and bond breaking (Δr_{YZ}), respectively, (primary effects) can be represented as eqns. (3), while those on the degree of bond cleavage (Δr_{YZ}) and bond formation (Δr_{XY}), respectively

$$\Delta r_{XY} = a\sigma_X \qquad \Delta r_{YZ} = a'\sigma_Z \qquad (3)$$

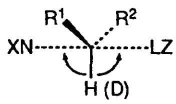
(secondary effect) can be expressed as eqns. (4),[3h] where

$$\Delta r_{XY} = b\sigma_Z \qquad \Delta r_{YZ} = b'\sigma_X \qquad (4)$$

$a, a' > 0$ and $b, b' < 0$ for $\rho_{XZ} < 0$ and conversely $a, a' < 0$ and $b, b' > 0$ for $\rho_{XZ} > 0$. In the former case, *i.e.*, $\rho_{XZ} < 0$, the substituent effects on TS variation conform to those predicted quantum mechanically[3,8] (QM Model) while in the latter, *i.e.*, $\rho_{XZ} > 0$, the TS variation is consistent with that predicted by a potential energy surface (PES Model)[3,9] diagram with the Hammond effect[10] (thermodynamic effect) on the reaction coordinate diagonal.

On the other hand, the magnitude of the cross-interaction constant is inversely related to the distance between the two interacting reaction centres,[2,3,11] r_{XY}, r_{YZ} or r_{XZ} ($= r_{XY} + r_{YZ}$); thus $|\rho_{XZ}|$ is substantially greater (since r_{XZ} is smaller) in an associative S_N2 reaction, **2**, than in a dissociative S_N2 reaction, **1**.

Kinetic isotope effects (KIEs) are expected when the force-constant changes in the activation process involving the isotopically substituted position. α-Deuterium secondary isotope effects, k_H/k_D, are known to arise mainly from hybridization change ($sp^3 \longrightarrow sp^2$) at the α-carbon in the reactant, and are usually significantly less than 1.4.[12] The inverse secondary KIE, $k_H/k_D < 1.0$, is observed in some S_N2 processes due to interference by the LG and/or the incoming nucleophile with the stretching[13] as well as the out-of-plane bending motion of the carbon–hydrogen bond, **3**.[13,14] The more the isotopic atom



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is constrained in the TS than in the reactant, the smaller the value of k_H/k_D becomes;[13,14] thus the size of k_H/k_D reflects the relief or increase of steric strain around the isotopic atom involved in the activation process of a reaction in a given set of circumstances. The majority of α-deuterium KIE studies are

Table 1 The cross-interaction constants, ρ_{XZ} and β_{XZ}, for the reactions of benzyl benzenesulfonates with anilines (R1a) and benzylamines (R1b), and of alkyl benzenesulfonates with anilines (R2a) and benzylamines (R2b)

Reaction		T/°C	$\rho_{XZ}(\beta_{XZ})$	
			Solvent	
			MeOH	MeCN
R1(a)	$XC_6H_4NH_2 + C_6H_5CH_2OSO_2C_6H_4Z$	30.0	−0.10[1] (−0.06)	−0.12[5] (−0.07)
R1(b)	$XC_6H_4CH_2NH_2 + C_6H_5CH_2OSO_2C_6H_4Z$	20.0		−0.07[6] (−0.13)
R2(Ma)	$XC_6H_4NH_2 + CH_3OSO_2C_6H_4Z$	65.0	0.30[2b] (0.18)	0.32[2b] (0.20)
R2(Mb)	$XC_6H_4CH_2NH_2 + CH_3OSO_2C_6H_4Z$	65.0		0.18[2b] (0.26)
R2(Ea)	$XC_6H_4NH_2 + CH_3CH_2OSO_2C_6H_4Z$	65.0	0.33[2b] (0.19)	0.34[2b] (0.21)
R2(Eb)	$XC_6H_4CH_2NH_2 + CH_3CH_2OSO_2C_6H_4Z$	65.0		0.19[2b] (0.28)

conducted with deuteriated substrates.[14] In this type of study, however, the effect, k_H/k_D, reflects the changes in both the degree of bond formation (Δr_{XY}) and bond cleavage (Δr_{YZ}) so that some ambiguities as to which change is the main factor are unavoidable.[15] In overcoming this difficulty, the use of a deuteriated nucleophile, *e.g.* $XC_6H_4ND_2$, has proved to be useful, since the secondary KIE in this case reflects solely the change occurred in the bond formation process.[12,15]

Recently we have been involved in α-deuterium secondary KIE studies using both deuteriated nucleophiles[15] and substrates in order to examine the effects of both changes in bond formation and bond breaking on the S_N2 TS structures. In this work, we report on the α-deuterium secondary KIEs for the typical reaction series proceeding with dissociative (R1) and associative (R2) S_N2 mechanisms. The effects of substituents in the nucleophile (X) and LG (Z) on the TS variation are shown to agree with those expected from the sign and magnitude of ρ_{XZ}.[3]

$$2XC_6H_4NH_2 + C_6H_5CH_2OSO_2C_6H_4Z \longrightarrow C_6H_5CH_2NHC_6H_4X + XC_6H_4N^+H_3 + {}^-OSO_2C_6H_4Z \qquad (R1)$$

$$2XC_6H_4NH_2 + ROSO_2C_6H_4Z \longrightarrow RNHC_6H_4X + C_6H_4N^+H_3 + {}^-OSO_2C_6H_4Z \qquad (R2)$$

$$R = CH_3 \text{ or } C_2H_5$$

Results and Discussion

The relevant cross-interaction constants for R1 and R2 are summarized in Table 1. We note that the signs of ρ_{XZ}[1,2] (and β_{XZ})* for reaction series R1 are negative, whereas they are positive for R2. This means that a stronger nucleophile, *e.g.* X = *p*-CH_3O, and a better LG, *e.g.* Z = *p*-NO_2, should lead to a later TS for the former, while they should lead to an earlier TS for the latter. On the other hand, the magnitude of ρ_{XZ} (and β_{XZ})* for the R2 series is 2–3 times greater than that for the R1 series† indicating a much tighter TS with a closer distance, r_{XZ}, between the two reaction centres, *N* and *O*, in the nucleophile and LG (*i.e.* an associative mechanism **2**) for R2 than for R1.

The KIEs for R1 determined with α-deuteriated substrates are reported in Table 2 together with those obtained with the *N*-deuteriated nucleophiles. The S_N2 reactions of benzyl derivatives with relatively good LGs are known to proceed with a loose TS, **1**, in which bond breaking is ahead of bond formation so that the benzylic hydrogens experience the relief of steric strain in proceeding from reactant to TS;[15-17] thus the α-deuterium secondary KIEs become normal, $k_H/k_D > 1.0$, as observed (Table 2) even though the reaction is clearly an S_N2 displacement. The normal secondary KIEs in Table 2 therefore support the loose TS structure *i.e.*, dissociative (**1**) for R1, as evidenced by the small magnitude of ρ_{XZ} (and β_{XZ}).[15] Similar normal α-deuterium (or α-tritium) secondary KIEs have been reported for the S_N2 displacement at benzylic carbon under various reaction conditions by Westaway *et al.*[16,17] and Ando *et al.*[18] The reactions of benzyl derivatives in these studies show secondary KIEs ranging from 1.03–1.27, and hence the values reported in Table 2 are well within this range. We note that this relatively narrow range of secondary KIEs is covered despite the various reaction conditions used in the measurements. We can conclude that in the loose TS (**1**) for the S_N2 reactions of benzyl derivatives, leaving-group participation by relieving steric strain of the substrate is the major factor determining the α-deuteriated (benzylic hydrogens) substrate secondary KIEs; the incoming nucleophile is relatively far away forming a rather long bond to the α-carbon and the relief in the steric strain by bond cleavage outweighs the steric congestion caused by bond formation of the nucleophile.

Although the distance r_{XY} may be large, the two N–H bending as well as stretching vibrations[13] in the aniline and benzylamine nucleophiles are bound to be hindered to some extent since the N–C_α bond is partially formed in proceeding from the reactant to the TS. This should cause an increase in the N–H bending[15-17] as well as stretching force constants[13] resulting in an inverse secondary KIE, $k_H/k_D < 1.0$, but a normal secondary KIE, $k_H/k_D > 1.0$, will not be observed unless other effects, *e.g.* hydrogen bond formation,[15] apart from steric congestion are involved in the TS. The inverse secondary KIEs

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* β_{XZ} is defined similarly as ρ_{XZ} in eqn. (1) using pK_X and pK_Z instead of σ_X and σ_Z. Its magnitude represents the intensity of direct interaction between two interacting reaction centres. Thus its magnitude is not affected, in contrast to fall-off of ρ_{XZ} by one half, by an intervening non-conjugating group (*e.g.* CH_2 in $XC_6H_4CH_2NH_2$) between the substituent and the reaction centre.

† The magnitude of ρ (and β) is inversely related to the reaction temperature so that the values for R2 at 65.0 °C in Table 1 should become even greater at the lower temperatures of 20–30 °C at which the ρ (and β) values are reported for R1. See G. W. Klumpp, *Reactivity in Organic Chemistry*, Wiley, New York, 1982, p. 275.

Table 2 Kinetic isotope effects for the reactions of α-deuteriated benzyl benzenesulfonates with anilines in acetonitrile at 30.0 °C

X	Z	Substrate KIE k_H/dm^3 mol^{-1} s^{-1}	k_D/dm^3 mol^{-1} s^{-1}	k_H/k_D	Nucleophile KIE k_H/k_D[a]	k_H/k_D[b]
p-CH$_3$O	p-NO$_2$	65.83×10^{-3}	60.29×10^{-3}			
		66.78	60.51	$1.10_2 \pm 0.010$[c]	0.89_8	0.94_0
		66.38	59.74	(1.05_0)[d]	(0.94_8)	(0.97_0)
		$66.3_3 \pm 0.4_8$[e]	$60.1_8 \pm 0.4_0$			
p-CH$_3$O	p-CH$_3$	2.697×10^{-3}	2.467×10^{-3}			
		2.687	2.434	$1.09_6 \pm 0.009$	0.95_5	0.95_2
		2.693	2.470	(1.04_7)	(0.97_7)	(0.97_6)
		$2.69_2 \pm 0.00_5$	$2.45_7 \pm 0.02_0$			
m-NO$_2$	p-NO$_2$	8.491×10^{-4}	7.811×10^{-4}			
		8.507	7.725	$1.09_5 \pm 0.007$	0.95_1	0.95_3[f]
		8.551	7.798	(1.04_6)	(0.97_5)	(0.97_6)
		$8.51_6 \pm 0.03_1$	$7.77_8 \pm 0.04_6$			
m-NO$_2$	p-CH$_3$	1.620×10^{-4}	1.490×10^{-4}			
		1.617	1.486	$1.08_9 \pm 0.005$	0.97_3	0.96_6[f]
		1.613	1.478	(1.04_3)	(0.98_8)	(0.98_3)
		$1.61_7 \pm 0.00_4$	$1.48_5 \pm 0.00_6$			

[a] $XC_6H_4NH_2(D_2)$, at 30.0 °C.[15a,c] [b] $XC_6H_4CH_2NH_2(D_2)$, at 30.0 °C.[15e] [c] Standard error[7] $= 1/k_D[(\Delta k_H)^2 + (k_H/k_D)^2(\Delta k_D)^2]^{\frac{1}{2}}$. [d] Per deuterium. [e] Standard deviation. [f] X = p-Cl.

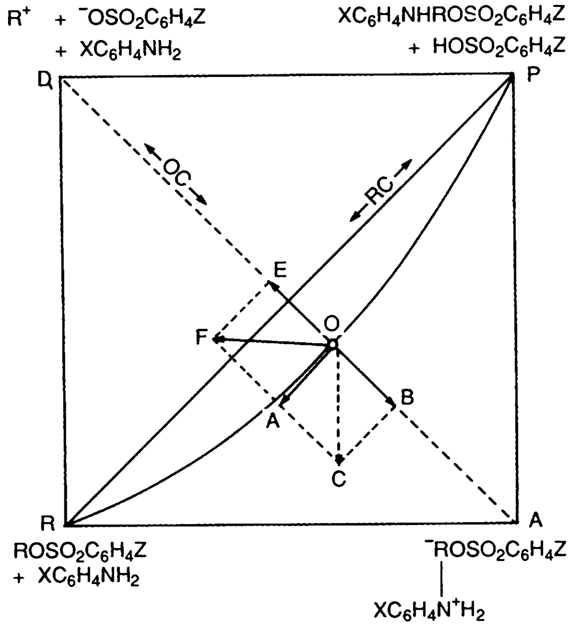

Fig. 1 The potential energy surface (PES) diagram for an associative S_N2 reaction. RC and OC denote the reaction and orthogonal coordinates, respectively.

involving deuteriated nucleophiles should, therefore, reflect solely an increase in the steric strain felt by the nucleophile so that they can be a measure only of the distance r_{XY}. The inverse secondary KIEs are indeed observed with the N-deuteriated nucleophiles in Table 2. The size of k_H/k_D is smaller for aniline suggesting that the N–H vibrations are more hindered in aniline relative to benzylamine.

Since for R1 the ρ_{XZ} value is negative, the constants a and a' are positive [eqn. (3)] and b and b' are negative [eqn. (4)]. The TS variation, Δr_{XY} and Δr_{YZ}, expected from these relations are indeed borne out in the KIE results in Table 2. For X = p-CH$_3$O, a stronger nucleophile, and for Z = m-NO$_2$, a better LG, the k_H/k_D (<1.0) values involving N-deuteriated nucleophiles are invariably smaller indicating a greater sterically-congested bond-forming process due to the primary [$\sigma_X < 0$ and $a > 0$ in eqn. (3)] and secondary [$\sigma_Z > 0$ and $b < 0$ in eqn. (4)] effects on the TS structure, respectively. Likewise for X = p-CH$_3$O [$\sigma_X < 0$ and $b' < 0$ in eqn. (4)] and Z = m-NO$_2$ [$\sigma_Z > 0$ and $a' > 0$ in eqn. (3)], the normal secondary KIEs ($k_H/k_D > 1.0$) involving an α-deuteriated substrate (benzylic hydrogens) are greater, indicating a greater degree of relief in the steric strain by bond cleavage of the LG. Similar trends in TS variations are found with the results of Westaway[16,17] and Ando;[18] a stronger nucleophile, X = p-CH$_3$O, and a better LG, Z = p-Cl, lead to a greater normal secondary KIE ($k_H/k_D > 1.0$)[16] and primary nitrogen KIE ($k^{14}/k^{15} > 1.0$)[16] involving isotopic nitrogen in the LG.

The secondary KIEs for R2 are summarized in Tables 3–5. In contrast to the normal secondary substrate KIEs for R1 ($k_H/k_D > 1.0$) observed in Table 2, we obtain inverse KIEs for R2 irrespective of whether the isotopic atoms are incorporated in the substrate (Tables 3 and 5) or in the nucleophile (Tables 4 and 5). This means that the incoming nucleophiles increase steric strain even though bond breaking of the leaving group has taken place in the TS. This is a clear indication that TS **2** is much tighter than TS **1** as the greater magnitudes of ρ_{XZ} (and β_{XZ}) in Table 1 suggest. Moreover, the effects of substituents in the nucleophile (X) and leaving group (Z) on the TS variation of the R2 series are quite opposite to those of the R1 series, which is consistent with the opposite sign of ρ_{XZ} (and β_{XZ}) for the two series. The smaller k_H/k_D values obtained for the ethyl series relative to those for the methyl system are consistent with a somewhat tighter TS predicted based on the greater ρ_{XZ} (and β_{XZ}) values in Table 1 for the ethyl compounds.[2b]

Since ρ_{XZ} is positive, a stronger nucleophile and a better leaving group should lead to an earlier TS [eqn. (2)], as predicted by the PES diagram, Fig. 1. Note that in this diagram the reaction coordinate (RC) diagonal represents the Hammond effect (effect on thermodynamic barrier) and the orthogonal coordinate (OC) diagonal represents the anti-Hammond or Thornton effect (effect on intrinsic barrier), and

Table 3 Kinetic isotope effects for the reactions of deuteriated methyl benzenesulfonates with anilines in acetonitrile at 65.0 °C

X	Z	k_H/dm^3 mol^{-1} s^{-1}	k_D/dm^3 mol^{-1} s^{-1}	k_H/k_D
p-CH$_3$O	p-NO$_2$	2.108×10^{-2}	2.103×10^{-2}	
		2.090	2.101	$0.99_3 \pm 0.007$[a]
		2.068	2.106	(0.99_8)[b]
		$2.08_9 \pm 0.02_0$[c]	$2.10_3 \pm 0.00_3$	
p-CH$_3$O	p-CH$_3$	1.422×10^{-3}	1.450×10^{-3}	
		1.446	1.449	$0.99_0 \pm 0.008$
		1.433	1.448	(0.99_7)
		$1.43_4 \pm 0.01_2$	$1.44_9 \pm 0.00_1$	
m-NO$_2$	p-NO$_2$	5.948×10^{-4}	6.067×10^{-4}	
		5.894	6.124	$0.97_4 \pm 0.007$
		5.945	6.073	(0.99_1)
		$5.92_9 \pm 0.03_0$	$6.08_8 \pm 0.03_1$	
m-NO$_2$	p-CH$_3$	3.823×10^{-5}	3.932×10^{-5}	
		3.799	3.895	$0.97_1 \pm 0.009$
		3.831	3.966	(0.99_0)
		$3.81_8 \pm 0.01_7$	$3.93_1 \pm 0.03_6$	

[a] Standard error. [b] Per deuterium. [c] Standard deviation.

Table 4 Kinetic isotope effects for the reactions of methyl benzenesulfonates with N-deuteriated anilines in acetonitrile at 65.0 °C

X	Z	k_H/dm^3 mol^{-1} s^{-1}	k_D/dm^3 mol^{-1} s^{-1}	k_H/k_D
p-CH$_3$O	p-NO$_2$	2.108×10^{-2}	2.123×10^{-2}	
		2.090	2.109	$0.98_4 \pm 0.007$[a]
		2.068	2.136	(0.99_2)[b]
		$2.08_9 \pm 0.02_0$[c]	$2.12_3 \pm 0.01_4$	
p-CH$_3$O	p-CH$_3$	1.422×10^{-3}	1.468×10^{-3}	
		1.446	1.459	$0.97_8 \pm 0.008$
		1.433	1.470	(0.98_9)
		$1.43_4 \pm 0.01_2$	$1.46_6 \pm 0.00_6$	
m-NO$_2$	p-NO$_2$	5.948×10^{-4}	6.142×10^{-4}	
		5.894	6.104	$0.96_8 \pm 0.009$
		5.945	6.138	(0.98_4)
		$5.92_9 \pm 0.06_4$	$6.12_8 \pm 0.02_1$	
m-NO$_2$	p-CH$_3$			
				0.96_3[14b] ± 0.009
				(0.98_1)

[a] Standard error. [b] Per deuterium. [c] Standard deviation.

the secondary effect of a substituent (the effect of σ_X on bond breaking and σ_Z on bond formation) is deduced by a vector sum of the two primary effects (effects of σ_X on bond formation and σ_Z on bond breaking).[*], [3h] A stronger nucleophile will stabilize the right hand corners, P and A, so that the primary effect along the RC diagonal (Hammond effect) requires the movement of the original TS, O, toward the point A while that along the OC diagonal (anti-Hammond effect) requires a shift toward B so that the (vector) sum of the two primary effects leads to the secondary shift, a shift toward C, *i.e.* $\overrightarrow{OC} = \overrightarrow{OA} + \overrightarrow{OB}$. Thus a stronger nucleophile should shift the TS, O, toward a more reactant-like structure for bond breaking, *i.e.*, a lesser degree of bond breaking. Likewise, a better leaving group shifts the TS toward F as a result of the sum of the two primary effects, $\overrightarrow{OA} + \overrightarrow{OE}$, resulting in a lesser degree of bond formation. Our inverse secondary KIEs reported in Tables 3–5 are in complete agreement with these predictions from the PES diagram. Thus a stronger nucleophile (X = p-CH$_3$O) invariably gives a larger k_H/k_D value as a result of the lesser degree of bond formation (a primary effect, $\overrightarrow{OA}$), and bond breaking (a secondary effect, $\overrightarrow{OC}$). Similarly (Tables 4 and 5) for a better leaving group (Z =

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[*] This is similar to the Marcus equation, which represents a reaction barrier as a sum of intrinsic and thermodynamic barriers. The secondary effect deduced in the PES diagram with the Hammond effect along the reaction coordinate diagonal is thermodynamic in nature, whereas with the anti-Hammond (intrinsic) effect along the reaction coordinate diagonal the intrinsic effect is obtained as a vector sum of two primary effects *i.e.*, the nature of the secondary effect deduced by the sum of the two primary effects is dictated by the major effect, which is adopted as the reaction coordinate diagonal.[3h]

Table 5 Kinetic isotope effects for the reactions of α-deuteriated ethyl benzenesulfonates with anilines in acetonitrile at 65.0 °C

		Substrate KIE			Nucleophile KIE	
X	Z	k_H/dm^3 mol^{-1} s^{-1}	k_D/dm^3 mol^{-1} s^{-1}	k_H/k_D	k_H/k_D[a]	k_H/k_D[b]
p-CH$_3$O	p-NO$_2$	2.549×10^{-3}	2.570×10^{-3}			
		2.510	2.581	$0.98_4 \pm 0.010$[c]	0.86_9	0.90_5
		2.531	2.555	(0.99_2)[d]	(0.93_2)	(0.95_1)
		$2.52_9 \pm 0.01_9$[e]	$2.56_9 \pm 0.01_3$			
p-CH$_3$O	p-CH$_3$	1.321×10^{-4}	1.340×10^{-4}			
		1.307	1.342	$0.98_1 \pm 0.011$	0.86_2	0.90_5
		1.329	1.350	(0.99_1)	(0.92_8)	(0.95_2)
		$1.31_9 \pm 0.01_3$	$1.34_4 \pm 0.00_5$			
m-NO$_2$	p-NO$_2$	6.699×10^{-5}	6.983×10^{-5}			
		6.758	6.953	$0.96_2 \pm 0.006$	0.85_8	0.90_4[f]
		6.721	7.012	(0.98_1)	(0.92_6)	(0.95_1)
		$6.72_6 \pm 0.03_0$	$6.99_3 \pm 0.04_6$			
m-NO$_2$	p-CH$_3$	1.459×10^{-5}	1.534×10^{-5}			
		1.475	1.526	$0.95_3 \pm 0.010$	0.85_1	0.89_9[f]
		1.461	1.553	(0.97_6)	(0.92_3)	(0.94_8)
		$1.46_5 \pm 0.00_9$	$1.53_8 \pm 0.01_4$			

[a] $XC_6H_4NH_2(D_2)$, at 65.0 °C.[15b] [b] $XC_6H_4CH_2NH_2(D_2)$, at 65.0 °C.[15e] [c] Standard error. [d] Per deuterium. [e] Standard deviation. [f] X = p-Cl.

p-NO$_2$) the k_H/k_D value is larger than that for a worse leaving group (Z = p-CH$_3$) as a result of the lesser degree of bond breaking (a primary effect, $\overrightarrow{OE}$) and bond formation (a secondary effect, $\overrightarrow{OF}$). In both cases, the effect of bond formation is more important than that of bond breaking on the TS structure. Again in Tables 3 and 5, the k_H/k_D values involving deuteriated substrates indicate that the effect of LG is very small relative to that of the nucleophile on bond formation.

Similar KIE studies on the associative-type S$_N$2 reactions of methyl derivatives have been reported in the literature.[19,20] In all cases, inverse secondary KIEs are observed and a stronger nucleophile is shown to lead to a greater k_H/k_D value in agreement with our results. The primary KIEs involving the isotopic carbon in the methyl group[20] are also in line with our conclusions: a stronger nucleophile always gives a smaller primary carbon KIE (k^{12}/k^{14} or k^{12}/k^{13} is smaller)[20] indicating a lesser degree of bond breaking, a secondary substituent effect corresponding to $\overrightarrow{OC}$ in Fig. 1.

We have shown in this work that the secondary KIEs observed for the typical dissociative (R1) and associative (R2) S$_N$2 reactions are in complete agreement with those predicted by the sign and magnitude of the cross-interaction constants ρ_{XZ}. Notably, the opposite signs of ρ_{XZ} (or β_{XZ}) for the two series, R1 and R2, reflect correctly the opposite trend of substituent effects on the TS variation; a later TS for R1 ($\rho_{XZ} < 0$) but an earlier TS for R2 ($\rho_{XZ} > 0$) for a stronger nucleophile and/or a better leaving group.

Experimental

General.—Materials were as described previously.[15] Deuteriated substrates were prepared as follows.

$C_6H_5CD_2OH$. A method similar to that used by Westaway *et al.*,[17] was adopted.

$C_6H_5CD_2OSO_2C_6H_4$-p-NO$_2$. To a 250 cm^3 three-necked flask containing dry ether (70 cm^3) was added $C_6H_5CD_2OH$ (2.2 g, 0.020 mol). After the addition of pyridine (1.68 g, 0.021 mol) to this solution, p-NO$_2$C$_6$H$_4$SO$_2$Cl (4.01 g, 0.018 mol), dissolved in 100 cm^3 dry ether, was added dropwise. The reaction temperature was kept at 0 °C. After completion of the dropwise addition the system was refluxed for 12 h at 25 °C. The pyridine salt was then filtered off and the ether layer washed with cool water four or five times. Magnesium sulphate (5.02 g) was added to the ether layer and the whole was left to stand for 2 h to effect drying. After removal of MgSO$_4$ by filtration and ether by evaporation, the product, $C_6H_5CD_2OSO_2C_6H_4$-p-NO$_2$, was recrystallized twice from light petroleum. A similar method was used for the preparation of $C_6H_5CD_2OSO_2C_6H_4$-p-CH$_3$.

$CD_3OSO_2C_6H_4$-p-NO$_2$. To a 250 cm^3 three-necked flask containing dry ether (50 cm^3) was added CD$_3$OD (Merck) (1.02 g, 0.028 mol). After the addition of pyridine (2.30 g, 0.029 mol), p-NO$_2$C$_6$H$_4$SO$_2$Cl (4.80 g, 0.022 mol) dissolved in 100 cm^3 dry ether, was added dropwise at 0 °C. The system was then refluxed for 6 h at 25 °C. The product was isolated and purified by similar procedures as above. A similar method was also adopted for the preparation of $CD_3OSO_2C_6H_4$-p-CH$_3$.

$CH_3CD_2OSO_2C_6H_4$-p-NO$_2$. To a 250 cm^3 three-necked flask containing dry ether (50 cm^3) was added CH$_3$CD$_2$OH (Aldrich) (0.77 g, 0.016 mol). After the addition of pyridine (1.18 g, 0.015 mol), p-NO$_2$C$_6$H$_4$SO$_2$Cl (3.10 g, 0.014 mol) dissolved in 100 cm^3 dry ether, was added dropwise at 0 °C. The system was then refluxed for 6 h at 25 °C. The product was isolated and purified by similar procedures as above.

A similar method was also adopted for the preparation of $CH_3CD_2OSO_2C_6H_4$-p-CH$_3$. The deuterium content of the deuteriated substrates was checked initially by NMR analysis, which showed negligible (almost undetectable) undeuteriated peaks in all cases. We modestly estimate 98% purity. We then carried out a mass spectrometric analysis confirming that the substrates are deuterated more than 98%.

Kinetic Procedures.—Rates were measured conductimetrically. Pseudo first-order rate constants, k_1^{obs}, were determined by the Guggenheim method, and second-order rate constants, k_2, were then obtained from the slope of a plot of k_1^{obs} *versus* [aniline] with a greater than four-fold excess of aniline. The linearity of the plot with more than four-fold excess of aniline was good, with correlation coefficients better than 0.999 with a 99% confidence limit. The three k_2 values observed were then averaged and the error limits are given in Tables 2–5.

Acknowledgements

We thank the Ministry of Education and the Korea Science and Engineering Foundation for support of this work.

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Paper 1/02697F
Received 6*th June* 1991
Accepted 8*th July* 1991