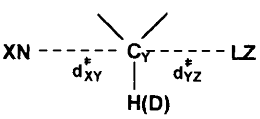
Secondary Kinetic Isotope Effects Involving Deuterated Nucleophiles

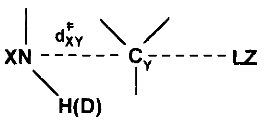
Ikchoon Lee
Department of Chemistry, Inha University, Inchon 402, Korea

1 Introduction

The key to elucidation of the organic reaction mechanism is the transition state (TS). Determination of TS structure and the manner in which TS structure varies with structural changes in the reacting system is one of the most important problems in physical organic chemistry. In this respect secondary α-deuterium kinetic isotope effects (KIEs) have provided a useful means to determine the TS structures involved in nucleophilic substitution reactions and also how the reactants, especially through changes in substituents, alter the structure of the S_N2 TS.[1] Applications of the secondary α-deuterium KIE (k_H/k_D) to the studies of the S_N2 TS have been involved, however, primarily with deuterated substrates,[1] C α–H(D), (I). In this case, k_H/k_D is determined by the overall tightness ($d^\ddagger_{XY} + d^\ddagger_{YZ}$) of the TS. Quite recently, the secondary α-deuterium KIEs involving deuterated nucleophiles (II) have been used in characterization of TS structure; here the secondary α-deuterium nucleophile KIE (Nu-KIE) reflects the extent of bond making only ($d^\ddagger_{XY}$). The application of this method has proved to be useful in determining variations of S_N2 TSs with substituents and in providing experimental evidence in support of the mechanistic interpretation based on the cross-interaction constants, ρ_{ij}, especially when it is supplemented by the secondary α-deuterium substrate KIE (C α-KIE).



(I)



(II)

In this article, some of the more important applications of the secondary α-deuterium KIEs involving deuterated nucleophiles are reviewed in conjunction with the mechanistic criteria based on the cross-interaction constants.

2 Theory

2.1 Secondary α-Deuterium Kinetic Isotope Effect

The secondary KIE results from isotopic substitution at a bond not being broken in the reaction and arises solely from changes of zero-point energies of ordinary vibration. The magnitude of secondary kinetic isotope effects can be approximately given by equation 1.

$$k_H/k_D = \exp\{-\tfrac{1}{2}[u^\ddagger_H - u^\ddagger_D - (u^0_H - u^0_D)]\} \qquad (1)$$

where $u^\ddagger_i$ and u^0_i represent $h\nu/kT$ for the TS and reactant respectively. Using an approximate relationship $\nu_D = \nu_H/1.35$, this can be further simplified into equation 2.[2]

$$\begin{aligned} k_H/k_D &= \exp\left\{-\frac{0.1865}{T}(\nu^\ddagger_H - \nu^0_H)\right\} \\ &= \exp\left(-\frac{0.1865}{T}\cdot\Delta\nu^\ddagger\right) \qquad (2) \end{aligned}$$

Thus any vibrational mode for which the frequency decreases ($\Delta\nu^\ddagger < 0$) on going to the TS contributes a factor greater than unity ($k_H/k_D > 1.0$) and any vibrational mode for which the frequency increases ($\Delta\nu^\ddagger > 0$) contributes a factor less than unity ($k_H/k_D < 1.0$).

It has been accepted that the magnitude of k_H/k_D reflects primarily changes in the out-of-plane bending vibrations when the reactant is converted into the TS. Streitwieser and coworkers[3] have analysed a commonly observed secondary α-deuterium KIE occurring when deuterium substitution is made at a carbon that changes hybridization, and concluded that in going from sp^3 to sp^2 the out-of-plane bending vibration contributes a factor of approximately 1.41; it is however typically around 1.15 to 1.25. For a reaction in which hybridization changes from sp^2 to sp^3, the effect becomes inverted, $k_H/k_D < 1.0$, with a minimum of roughly $1/1.41 = 0.71$ for a TS closely resembling sp^3 hybridized product, typical values being between 0.8 to 0.9.

In accordance with this analysis, when deuterium is substituted in the substrate, (I), the C α-KIE can be either normal ($k_H/k_D > 1.0$) for a loose S_N2 TS with a decrease in the out-of-plane bending frequency ($\Delta\nu^\ddagger < 0$), or inverse ($k_H/k_D < 1.0$) when the TS is tight with $\Delta\nu^\ddagger > 0$. The k_H/k_D value reflects the overall tightness of the S_N2 TS and in effect reflects the extent of both bond-making ($d^\ddagger_{XY}$) and bond breaking ($d^\ddagger_{YZ}$).

In contrast, when deuterium is incorporated in the nucleophile (II) the Nu-KIE can only be inverse ($k_H/k_D < 1.0$) in a normal S_N2 TS of the single step, concerted, backside attack processes, since the vibrational frequencies of N–H(D) invariably increases on going to the TS ($\Delta\nu^\ddagger > 0$) due to an increase in steric crowding in the bond-making process.

Recently this commonly accepted view of the origin of the secondary α-deuterium KIE as arising from changes in bending frequencies has been challenged. It has been shown theoretically that the secondary α-deuterium KIE arises mostly from changes in stretching, not bending, frequencies.[4] The results have even predicted a smaller value of k_H/k_D (< 0) for an overall looser TS,[4d] which is in direct contrast to the trend, *i.e.* a larger value, predicted by the conventional theory of the secondary α-deuterium KIE.

More recently, however, further theoretical works have clearly shown that the conventional view is correct after all.[5] Poirier *et al.*[5b] have stressed that the secondary α-deuterium KIE is related to the *'space' available for the out-of-plane bending vibrations in the TS*. Thus the secondary α-deuterium KIE is determined by the looseness, *i.e.* the distance between the nucleophile and leaving group ($d^\ddagger_{XY} + d^\ddagger_{YZ}$), of the S_N2 TS; a greater k_H/k_D value is observed for a looser TS.

This discrepancy between the views of the two theoretical

Ikchoon Lee received his B.S. from Seoul National University and his Ph.D. (1962) from the University of London. He began his academic career at Seoul National University from which he moved to his present position at Inha University where he is Professor of Chemistry. His research interests lie in the field of physical organic chemistry with emphasis on the mechanistic studies of organic reactions in solution by exprimental and theoretical approaches.

groups seems to arise from two different reference (initial) states adopted for relating bond length changes to the secondary α-deuterium KIEs Bond length changes relative to the encounter complex rather than the reactant appear to lead to the unconventional, and indeed untenable, view as to the origin of the secondary α-deuterium KIE

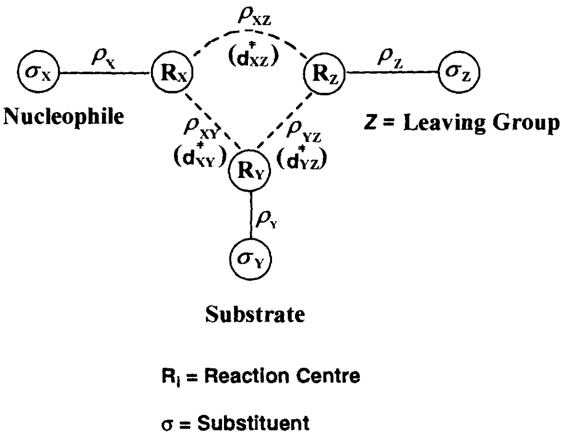
2.2 Cross-interaction Constant

A simple second order expression, equation 3, is arrived at by a Taylor series expansion of log k_{ij}, where k_{ij} is a rate constant for a dually substituted reaction system, around $\sigma_i = \sigma_j = 0$ and neglecting pure second-order and higher order terms [6] The indicies i and j represent X,Y and/or Z in a typical S_N2 TS, Scheme 1 The cross-interaction constant ρ_{ij} can be alternatively given by equation 4, and represents the *change in the intensity of interaction* between substituents σ_i and σ_j on going to the TS,[6b] *i e* , it corresponds to an activation parameter

$$\log(k_{ij}/k_{HH}) = \rho_i\sigma_i + \rho_j\sigma_j + \rho_{ij}\sigma_i\sigma_j \tag{3}$$

$$\rho_{ij} = \frac{\partial^2 \log k_{ij}}{\partial\sigma_i\,\partial\sigma_j} = \frac{\partial\rho_j}{\partial\sigma_i} = \frac{\partial\rho_i}{\partial\sigma_j} \tag{4}$$

It has been shown[6] that ρ_{XY} (< 0) and ρ_{YZ} (> 0) have opposite signs and their magnitudes reflect the extent of bond-making and breaking, respectively, in a normal S_N2 reaction proceeding through a concerted back-side attack mechanism In contrast, the sign of ρ_{XZ} can be either positive or negative and determines types of TS variation with respect to substituent changes in the nucleophile($\delta\sigma_X$) and leaving group ($\delta\sigma_Z$) When ρ_{XZ} is positive a stronger nucleophile ($\delta\sigma_X < 0$) and/or a stronger nucleofuge ($\delta\sigma_Z > 0$) lead to an earlier TS with a lesser extent of bond making ($\delta\rho_X > 0$) and bond breaking ($\delta\rho_Z < 0$), whereas when ρ_{XZ} is negative the opposite is true, *i e* , a later TS is obtained with a stronger nucleophile and/or a stronger nucleofuge The magnitude of ρ_{XZ} provides a measure of the overall TS tightness



Scheme 1

It is inversely related to $d^{\ddagger}_{XZ}(d^{\ddagger}_{XY} + d^{\ddagger}_{YZ})$, *the greater the magnitude of* ρ_{XZ}, *the tighter is the TS*, *i e* , the shorter is the $d^{\ddagger}_{XZ}$ It is to be noted, however, that $d^{\ddagger}_{XZ}$ is not exactly same as the sum of two distances, $d^{\ddagger}_{XY} + d^{\ddagger}_{YZ}$, since the angle $R_X{-}R_Y{-}R_Z$ is in most cases smaller than 180°, thus $d^{\ddagger}_{XZ} \leq d^{\ddagger}_{XY} + d^{\ddagger}_{YZ}$

One the other hand, in the carbonyl addition–elimination processes with rate limiting breakdown of a tetrahedral intermediate, the signs of ρ_{XY}(> 0) and ρ_{YZ} (< 0) are opposite to those corresponding ones for the normal S_N2 processes[7], and the sign of ρ_{XZ} is always positive For this type of mechanism, the magnitude of ρ_X, ρ_Z, ρ_{XY}, and ρ_{YZ} tends to be large

3 Applications

3.1 Transition State Variations for Associative and Dissociative S_N2 Reactions

For a typical S_N2 reaction at a primary carbon, *e g* ethyl benzenesulfonates, ρ_{XZ} is positive (Table 1) [8] Since ρ_{XZ} is positive, an earlier TS with a lower degree of bond-making and bond-breaking is expected for a stronger nucleophile and/or a stronger nucleofuge Comparison of the k_H/k_D values for X = p-CH_3O and m-NO_2 shows that the magnitude for both substrate and nucleophile secondary KIE, C α-KIE and Nu-KIE, are larger for the former, a stronger nucleophile This indicates that the stronger nucleophile forms a looser TS due to a lesser extent of bond making This is also true for a stronger nucleofuge when Z = p-NO_2 and p-CH_3 are compared We note that the k_H/k_D values for the Cα-KIE and Nu-KIE change in parallel, *i e* , the trend of change in the Cα-KIE follows that in the Nu-KIE, indicating that the Cα-KIE is dominated by the extent of bond making This is due to a tight TS formed by a large extent of bond-making with a low degree of bond cleavage, *i e* , the reaction proceeds by an associative S_N2 mechanism

Table 1 Secondary α-deuterium KIEs for the reactions of ethyl arenesulfonates with anilines in acetonitrile at 65 0°C[14]

$$CH_3CH_2(D_2)OSO_2C_6H_4Z + XC_6H_4NH_2(D_2) \xrightarrow[65\ 0\,°C]{CH_3CN}$$

(ρ_{XZ} = + 0 33)

X	Z	k_H/k_D C_α-KIE	 Nu-KIE
p-CH_3O	p-NO_2	0 98(4)	0 86(9)
p-CH_3O	p-CH_3	0 98(1)	0 86(2)
m-NO_2	p-NO_2	0 96(2)	0 85(8)
m-NO_2	p-CH_3	0 95(3)	0 85(1)

These type of effects are clearer in Table 2 [9] A stronger nucleophile, *e g* , X = p-CH_3O, is seen to give a larger k_H/k_D value for the Cα-KIE indicating a looser TS overall but with a smaller primary substrate-carbon KIE, $^{12}k/^{14}k$, value due to a lower extent of bond cleavage, this shows clearly that the loose overall TS indicated by the larger substrate k_H/k_D value is dominated by a lower degree of bond making since the extent of bond cleavage is lower Exactly the same trend is reported by Harris *et al* ,[10] for the reactions of methyl iodide with substituted pyridines the TS for a Menschutkin-type reaction is looser overall with a larger k_H/k_D value but the extent of bond cleavage is smaller with a smaller primary substrate-carbon KIE for a stronger nucleophile Thus *when* ρ_{XZ} *is positive, a lower degree of bond-making as well as bond-breaking is observed for a stronger nucleophile and/or a stronger nucleofuge* This type of TS variation with substituents X and Z are consistent with that predicted

Table 2 KIEs for the reactions of methyl p-bromobenzenesulfonate with N,N-dimethylanilines in acetonitrile at 55 0 °C[9]

$$C(^{14}C)H_3(D_3)OSO_2C_6H_4Br + XC_6H_4N(CH_3)_2 \xrightarrow[55\ 0\,°C]{CH_3CN}$$

X	k_H/k_D (C_α-KIE)	$^{12}k/^{14}k$
p-CH_3O	0 98(3)	1 14(9)
p-CH_3	0 97(1)	1 15(2)
H	0 97(1)	1 16(2)
p-Br	0 95(3)	1 16(2)
m-Br	0 95(8)	1 16(3)

by the potential energy surface (PES),[11] or More O'Ferrall–Jencks[12] diagram, and is controlled by thermodynamic effects [6a]

The results in Table 3 provide a relatively rare example of negative ρ_{XZ} [13] The ρ_{XZ} is not only negative but also the magnitude is relatively small This means that the TS is rather loose as evidenced by the normal secondary α-deuterium KIEs, Cα-KIE of $k_H/k_D > 1\ 0$, observed for the deuterated substrate The trends of change in the k_H/k_D values[14] are exactly opposite to what we have seen above for the case of positive ρ_{XZ} Now a stronger nucleophile and/or nucleofuge lead to a later TS with a greater degree of bond-making and -breaking For example, comparison of k_H/k_D for X = *p*-CH$_3$O and *m*-NO$_2$ indicates that for the stronger nucleophile, *i e* , the former, substrate k_H/k_D ($> 1\ 0$) is greater indicating that the TS is overall looser, but nucleophile k_H/k_D ($< 1\ 0$) is smaller indicating a tighter bond formation This means that a stronger nucleophile leads to a greater extent of bond cleavage as well as bond formation, the looser overall structure predicted by a larger substrate k_H/k_D value being dominated by the greater extent of bond cleavage

Table 3 Secondary α-deuterium KIEs for the reaction of benzyl arenesulfonates with anilines in acetonitrile at 30 0 °C[14]

$$C_6H_5CH_2(D_2)OSO_2C_6H_4Z + XC_6H_4NH_2(D_2) \xrightarrow[30\ 0\,^{\circ}C]{CH_3CN}$$

		k_H/k_D	
X	Z	(C_α-KIE)	(Nu-KIE)
p-CH$_3$O	*p*-NO$_2$	1 10(2)	0 89(8)
p-CH$_3$O	*p*-CH$_3$	1 09(6)	0 95(5)
m-NO$_2$	*p*-NO$_2$	1 09(5)	0 95(1)
m-NO$_2$	*p*-CH$_3$	1 08(9)	0 97(3)

This type of TS variation is in accord with that predicted by quantum mechanics and is controlled by intrinsic effects [6a]

The Cα-KIE in this case is dominantly influenced by the extent of bond cleavage, since the progress of bond cleavage is more advanced than that of bond-making, the reaction proceeds by a dissociative S_N2 mechanism

3.2 Tightness of S_N2 Transition States

Determinations of secondary KIEs involving deuterated nucleophiles, Nu-KIE, and the cross-interaction constant ρ_{XZ} have led to some interesting results concerning the structure of TSs for S_N2 processes at primary and secondary carbon centres

The magnitude of ρ_{XZ}, which is inversely proportional to the tightness of S_N2 TSs, has been found to be a relatively large constant value at a primary carbon (= 0 29—0 40 in MeCN or MeOH at 45 0—65 0 °C), whereas it is a smaller constant at a secondary carbon centre (= 0 10—0 13 in MeCN at 65 0 °C), irrespective of the size of the group attached to the reaction centre (Table 4) [15a] These constant ρ_{XZ} values suggest that the TS is tight or loose ($d^{\ddagger}_{XZ}$ in Scheme 1 is short or long) depending on whether the reaction centre (R$_Y$) carbon (Scheme 1) is primary or secondary, but the TS tightness varies very little with regard to the group attached to the reaction centre, R$_Y$

This constancy of the TS tightness has been confirmed by a high level *ab initio* MO calculations using polarization (*) and diffuse (+) functions with inclusion of the electron correlation effect at the MP2 level, (MP2/6 − 31 + G*//MP2/6 − 31 + G*),[15b] on the reaction $X^- + RX \rightleftarrows XR + X^-$ with various primary and secondary R groups for X = F and Cl [15a] The overall tightness, $d^{\ddagger}_{(X\ \ X)}$, was indeed constant for each nucleophile, X = F and Cl For X = Cl the constant values were greater than those for X = F with seven primary ($d^{\ddagger}_{(Cl\ \ Cl)} = 4\ 67 \pm 0\ 02$ Å) and nine secondary ($d^{\ddagger}_{(Cl\ \ Cl)} = 4\ 80 \pm 0\ 03$ Å) carbon centres studied The theoretical difference in the tightness of *ca* 0 1 Å $\{\Delta d^{\ddagger}_{(Cl\ \ Cl)} = d^{\ddagger}(sec) - d^{\ddagger}(prim) = (4\ 80 - 4\ 67)\ \text{Å} = 0\ 1\ \text{Å}\}$ for X = Cl corresponds to the experimental difference in ρ_{XZ} of *ca* 0 2 ($\Delta\rho_{XZ} = \rho_{XZ}(prim) - \rho_{XZ}(sec) = 0\ 33 - 0\ 12 = 0\ 2$) This theoretical analysis lends credence and reliability to the mechanistic significances of the cross-interaction constants and in particular the inverse proportionality established experimentally between the magnitude of ρ_{XZ} and the overall TS tightness

Table 4 The ρ_{XZ} values for the reactions of ROSO$_2$C$_6$H$_4$Z with XC$_6$H$_4$NH$_2$

	R	Solvent	T(°C)	ρ_{XZ}	ref
Primary Compounds	CH$_3$	MeCN	65 0	0 32	8
		MeOH	65 0	0 30	8
	C$_2$H$_5$	MeCN	65 0	0 34	8
		MeOH	65 0	0 33	8
	CH$_2$=CHCH$_2$	MeCN	45 0	0 37	21
	CH$_2$=C(CH$_3$)CH$_2$	MeCN	45 0	0 40	*b*
	CH≡CCH$_2$	MeCN	45 0	0 29	*c*
	(CH$_3$)$_3$CCH$_2$	MeOH	55 0	0 31	*d*
	(CH$_3$)$_3$SiCH$_2$	MeCN	65 0	0 33	*e*
		MeOH	65 0	0 31	*e*
Secondary Compounds	Isopropyl	MeCN	65 0	0 10	*f*
	2-butyl	MeCN	65 0	0 12	18
	2-pentyl	MeCN	65 0	0 13	18
	2-hexyl	MeCN	65 0	0 13	18
	3-pentyl	MeCN	65 0	0 12	18
	3-hexyl	MeCN	65 0	0 12	18
	cyclobutyl	MeCN	65 0	0 11	16
	cyclopentyl	MeCN	65 0	0 11	16
	cyclohexyl	MeCN	65 0	0 11	16
	cycloheptyl	MeCN	65 0	0 11	16

(*a*) H K Oh, H J Koh, and I Lee, *J Chem Soc Perkin Trans 2*, 1991, 1981 (*b*) H K Oh, C H Shin, and I Lee, *J Phys Org Chem* , 1992, **5**, 731 (*c*) H K Oh, I H Cho, M J Jin, and I Lee, *J Phys Org Chem* , in press (*d*) H J Koh, H W Lee, and I Lee, *J Chem Soc Perkin Trans 2*, 1994, 253 (*e*) H K Oh, C H Shin, and I Lee, *J Chem Soc Perkin Trans 2*, 1993, 2411 (*f*) H K Oh, Y B Kwon, and I Lee, *J Phys Org Chem* , 1993, **6**, 357

Under the same experimental condition (in MeCN at 65 °C), the Nu-KIEs were, for example, $k_H/k_D = 0\ 86(2)$ and 0 90(5) for the reactions of ethyl[14] (primary) and cyclopentyl[16] (secondary) benzenesulfonates, respectively, with deuterated anilines In fact, the k_H/k_D values for the Nu-KIE at secondary carbon centres are all greater than that for the ethyl compound (Table 5) This is again consistent with a more advanced bond-making expected from a greater value of ρ_{XZ} indicating a tighter TS for a primary carbon centre

Table 5 Secondary α-deuterium nucleophile KIEs (Nu-KIE) for the reactions of anilines with secondary alkyl arenesulfonates in acetonitrile at 65 0 °C

$$ROSO_2C_6H_4Z + XC_6H_4NH_2(D_2) \xrightarrow[65\ 0\,^{\circ}C]{MeCN}$$

	R	$\Sigma E_S{}^c$	k_H/k_D
acyclic[18] series	2-butyl[a]	− 0 07	0 93(4)
	3-pentyl	− 0 14	0 92(0)
	2-pentyl	− 0 36	0 90(9)
	2-hexyl	− 0 39	0 89(3)
	3-hexyl	− 0 43	0 88(0)
alicyclic[16] series	cyclobutyl[b]	—	0 91(3)
	cyclopentyl	—	0 90(5)
	cyclohexyl	—	0 89(0)
	cycloheptyl	—	0 87(8)

[a] For X = *p* NO$_2$ and Z = *p*-CH$_3$O [b] For X = *p* Cl and Z = *p*-CH$_3$ Total Taft's polar substituent constant, P W Taft Jr , Steric Effects in Organic Chemistry ed M Newman Wiley New York 1956 Chapter 13

Another quite interesting result emerged from the studies of Nu-KIE for the S_N2 reactions at secondary carbon centres: a smaller k_H/k_D (< 1.0) is observed in the reaction of a sterically more hindered secondary carbon centre, Table 5.[16] This may be interpreted as (i) due simply to a greater steric hindrance of the substrate to the approaching nucleophile, or (ii) due to a greater extent of bond making in the TS, which will also incur a greater steric hindrance, for the more crowded reaction centre. Experimental as well as theoretical evidence supports the latter interpretation: *the smaller* k_H/k_D (< 1.0) *observed for the more crowded system reflects mainly a more extensive bond making in the TS*.

For the alicyclic series, the magnitude of ρ_X (ρ_{nuc}) and β_X (β_{nuc}), and also of ρ_Z (ρ_{lg}) and β_Z (β_{lg}), increases with increasing ring size. For example, in the reactions with anilines ρ_X (and β_X) increases successively from -0.92 (0.33) to -1.58 (0.57) as the ring size grows from cyclobutyl to cycloheptyl, indicating that the degree of bond making increases successively and the TS shifts towards a later position along the reaction coordinate. The reaction energies, ΔE_0, calculated by the semiempirical AM1-MO method indicated that as the ring size grows the exothermicity of the reaction decreases, or alternatively the endothermicity increases successively. According to the Bell–Evans–Polanyi (BEP) principle[17] a more endothermic reaction should lead to a later TS with a greater extent of bond-making, in agreement with the above interpretation of the decreasing (Nu-KIE) k_H/k_D (< 1.0) value.

In fact, the TS tightness for the reactions at the alicyclic secondary alkyl carbon centres is constant, as the constant experimental ρ_{XZ} and theoretical $d^{\ddagger}_{(Cl-Cl)}$ values indicated, but shifts toward a later position along the reaction coordinate with a more and more *asymmetric* TS structure as the ring size grows,[16] *i.e.*, the extent of bond-making as well as bond-breaking increases successively in the TS as the ring size becomes larger from cyclobutyl to cycloheptyl.

For the acyclic secondary carbon series,[18] theoretical results also supported relatively constant overall TS tightness with a greater degree of bond-making for a more crowded system (as expressed by an increase in the Taft's steric constant, ΣE_s in Table 5).

A tighter bond formation for a sterically more hindered system is in fact consistent with the BEP principle,[17] since a sterically hindered TS is prone to lead to a hindered, higher energy product, which in turn leads to a greater endothermicity. We can therefore conclude that *a tighter bond is formed at a sterically more demanding reaction centre in the normal* S_N2 *reactions*.[19]

3.3 Failure of the Magnitude of $\rho_X(\rho_{nuc})$ as a Measure of the Extent of Bond-making

The magnitude of $\rho_X(\rho_{nuc})$ in S_N2 reactions is often loosely related to the extent of bond making in the TS within a series of reactions. In most cases this is true. For the reactions of benzyl chloride and bromide with anilines the Nu-KIE, k_H/k_D, decreases as the electron-withdrawing power of substituent Y becomes stronger, *i.e.* for Y = *p*-NO_2 indicating that the extent of bond-making increases. In agreement with this trend, the magnitude of ρ_X also increases,[20] as shown in Table 6.

However, for an associative S_N2 reaction series in which negative charge develops at Cα in the TS with $\rho_Y > 0$, an inverse proportionality between the magnitude of ρ_X and the extent of bond-making is obtained. The trends of change in Nu-KIE, k_H/k_D, for the reactions of benzoyl chlorides with anilines are shown in Table 7.[20]

Reference to this table reveals that k_H/k_D (< 1.0) increases, and hence the extent of bond-making decreases, with a stronger electron-withdrawing substituent in the ring ($\delta\sigma_Y > 0$) in direct contrast to the trend found for benzyl halides above. The magnitude of ρ_X, however, grows with an increase in the electron-withdrawing power of substituent Y, which is contrary to the putative proportionality between $|\rho_X|$ and the extent of bond making. This shows that care should be exercised in the interpretation of $|\rho_X|$ as a measure of bond formation within a series of S_N2 reactions.

One may argue that different mechanisms apply to the two reaction series, *i.e.*, for benzyl and benzoyl series. The following experimental evidence rules out this possibility. (i) For both reaction series, the sign of ρ_{XY} was found to be negative suggesting a normal S_N2 mechanism, despite the fact that for benzyl halide series the reactivity–selectivity parameter, $W = \rho_X\rho_Y/\rho_{XY}$[21b] or $\rho_X\rho_Y\rho_{XY}$[21a] is negative and the reactivity–selectivity principle (RSP)[22] holds, but for benzoyl chloride series W is positive and RSP is not valid.[22] (ii) Similar trends (as benzoyl) are also observed for the reaction series of benzenesulfonyl chloride,[23] for which a normal S_N2 mechanism has been reported to apply. (iii) The carbonyl addition–elimination mechanism with rate-limiting breakdown of a tetrahedral intermediate can be ruled out, since for this type of mechanism the Nu-KIE k_H/k_D values are greater than one,[24] unlike the benzoyl chloride series for which the values are less than one (Table 7). Also for this type of mechanism, ρ_{XY} is positive and W is negative so that RSP is valid: in fact RSP holds in general for this type of mechanism. (iv) The mechanism with a hydrogen-bonded four-centre TS can be ruled out, since for such a process

Table 6 Secondary α-deuterium nucleophile KIEs (k_H/k_D for Nu-KIE) for the reactions of benzyl bromides with anilines in acetonitrile at 25.0 °C.[20]

$$YC_6H_4CH_2Br + XC_6H_4NH_2(D_2) \xrightarrow[25.0\,°C]{MeCN}$$

X \ Y	*p*-CH_3	H	*p*-Cl	*m*-Cl	*p*-NO_2	ρ_Y
p-CH_3	0.93(2)	0.92(8)	0.92(6)	0.92(1)	0.91(7)	−0.48 (−0.46)[a]
H	0.93(9)	0.93(5)	0.92(8)	0.92(5)	0.92(3)	−0.55 (−0.55)
p-Cl	0.94(5)	0.93(9)	0.93(9)	0.93(4)	0.93(2)	−0.65 (−0.64)
m-Cl	0.95(9)	0.95(5)	0.94(9)	0.94(7)	0.94(1)	−0.75 (−0.74)
p-NO_2	0.97(1)	0.96(6)	0.96(4)	0.95(8)	0.95(5)	−0.91 (−0.90)
ρ_X	−1.37 (−1.39)[a]	−1.45 (−1.46)	−1.55 (−1.57)	−1.63 (−1.64)	−1.79 (−1.81)	

[a] With $XC_6H_4ND_2$

Table 7 Secondary α-deuterium nucleophile KIEs (k_H/k_D for Nu-KIE) for the reactions of benzoyl chlorides with anilines in acetonitrile at 25.0 °C [20]

$$YC_6H_4COCl + XC_6H_4NH_2(D_2) \xrightarrow[25.0\,°C]{MeCN}$$

X \ Y	p-CH$_3$	H	p-Cl	m-Cl	p-CN	p-NO$_2$	m,m'-(NO$_2$)$_2$	ρ_Y
p-CH$_3$O	0.90(5)	0.90(8)	0.92(1)	0.92(8)				2.23 (2.21)[a]
p-CH$_3$	0.90(0)	0.90(4)	0.91(7)	0.92(1)				2.16 (2.14)
H	0.89(6)	0.89(7)	0.90(8)	0.91(7)	0.93(0)	0.94(6)		1.89 (1.87)
p-Cl	0.88(9)	0.89(5)	0.90(6)	0.91(0)	0.92(0)	0.93(9)		1.81 (1.79)
m-Cl	0.88(5)	0.89(1)	0.90(5)	0.91(0)	0.91(3)	0.92(5)		1.66 (1.64)
m-NO$_2$	0.83(6)	0.83(8)	0.86(7)	0.88(0)	0.88(9)	0.89(3)	0.92(4)	1.31 (1.28)
p-NO$_2$	0.82(0)	0.82(4)	0.84(3)	0.86(3)	0.87(8)	0.87(8)	0.89(5)	1.24 (1.24)
ρ_X	−2.11 (−2.07)[a]	−2.28 (−2.24)	−2.46 (−2.43)	−2.57 (−2.54)	−2.77 (−2.74)	−2.84 (−2.80)	−3.22 (−3.20)	

[a] With $XC_6H_4ND_2$

the Nu-KIE k_H/k_D values observed are greater than one,[25] in this TS partial depronation of N−H(D) leads to a primary KIE (*vide infra*)

3.4 Front-side Attack S_N2 Mechanism

Back-side S_N2 attack on the cumyl system will be difficult owing to steric inhibition by the two methyl groups on Cα, and instead the front-side approach of a nucleophile becomes energetically favourable. For reaction 5, the magnitude of ρ_{XZ} is relatively large negative (= −0.75) indicating that the nucleophile (X) and the leaving group (Z) are in close proximity with a strong interaction in the TS, Figure 1a. The results in Table 8[26] indicates that variations of $|\rho_X|$ and ρ_Z are in agreement with those expected from a negative ρ_{XZ} value, a stronger nucleophile (X = p-CH$_3$O) and nucleofuge (Z = p-NO$_2$) lead to a later TS (a greater extent of bond-making and cleavage indicated by the greater $|\rho_X|$ and ρ_Z, respectively). However, in contrast to this trend of increasing $|\rho_X|$, *i e*, a greater degree of bond-making expected if the reaction were a normal S_N2 process of back-side attack, k_H/k_D becomes greater suggesting a lesser extent of bond-making as the electron-withdrawing power of substituent Z increases.

$$2\,XC_6H_4NH_2 + YC_6H_4C(CH_3)_2OSO_2C_6H_4Z \rightarrow YC_6H_4C(CH_3)_2NHC_6H_4X + XC_6H_4NH_3^+ + {}^-OSO_2C_6H_4Z \qquad (5)$$

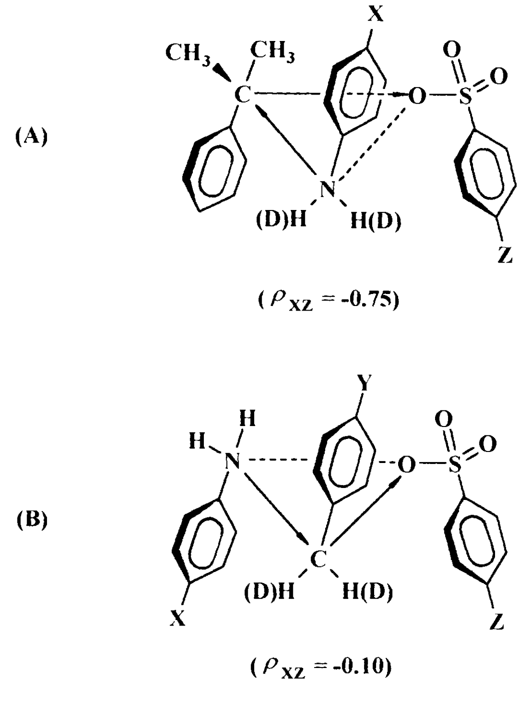


Figure 1 Proposed TS structures for the reactions of (A) cumyl arenesulfonates with anilines and (B) benzyl arenesulfonates with anilines

Examination of the TS structure in Figure 1a shows that the reaction centre of aniline, N, plays a role of Cα in the normal S_N2 reaction of benzyl benzenesulfonates, Figure 1b, for which the substrate KIE, Cα-KIE, is normal (k_H/k_D > 1.0), Table 3, and the trend of change in the k_H/k_D values is dominantly influenced by the extent of bond cleavage in the TS. The TS structure in Figure 1a indicates that as the leaving group departs farther

Table 8 Secondary α-deuterium nucleophile KIEs (k_H/k_D for Nu-KIE) for the reactions of cumyl arenesulfonates with anilines in acetonitrile at 55.0 °C [26]

$$C_6H_5C(CH_3)_2OSO_2C_6H_4Z + XC_6H_4NH_2(D_2) \xrightarrow[55.0\,°C]{MeCN}$$

X \ Z	p-CH$_3$	H	p-Cl	p-NO$_2$	ρ_Z
p-CH$_3$O	0.92(4)	0.94(6)	0.99(1)	1.00(3)	0.82 (0.78)[a]
p-CH$_3$	0.92(0)	0.94(1)	0.98(4)	1.00(3)	0.74 (0.70)
H	0.91(3)	0.93(9)	0.97(6)	1.00(9)	0.62 (0.57)
p-Cl	0.90(4)	0.93(5)	0.97(1)	1.00(7)	0.36 (0.31)
m-NO$_2$	0.90(1)	0.90(3)	0.90(3)	0.90(5)	0.08 (0.07)
p-NO$_2$	0.88(7)	0.90(1)	0.89(6)	0.90(1)	0.04 (0.03)
m,m'-(NO$_2$)$_2$	—	—	—	—	−0.01
ρ_X	−2.63 (−2.62)[a]	−2.73 (−2.71)	−2.79 (−2.78)	−3.15 (−3.10)	

[a] With $XC_6H_4ND_2$

away the N–H vibrational mode is sterically relieved to increase the k_H/k_D value Since the sign of ρ_{XZ} is negative, the leaving group moves farther away from the reaction centre carbon, Cα, when the nucleophile and/or nucleofuge become stronger leading to a sterically more relieved N–N moiety, as a result the k_H/k_D value becomes greater, as indeed is observed in Table 8 The combined analysis of the sign and magnitude of ρ_{XZ} with the trend of change in the Nu-KIE, k_H/k_D, leads us to conclude that the S_N2 reaction of cumyl arenesulfonate with aniline proceeds by a front-side attack mechanism

3.5 Temperature Dependence of the Cross-interaction Constants

According to equation 2, the secondary KIE, a selectivity parameter, is a function of temperature and the selectivity decreases as the temperature rises Thus the Nu-KIE, for which frequencies of the out-of-plane bending vibration increase on going to the TS ($\Delta\nu^\ddagger > 0$ and hence $k_H/k_D < 1\ 0$), will approach to 1 0 as the temperature rises, $\Delta T > 0$ This approach of k_H/k_D ($< 1\ 0$) to 1 0 should indicate a decrease in the selectivity and a looser TS with a lesser extent of bond-making, this in turn will be reflected in the decreased size of $|\rho_{XY}|$ as well as of $|\rho_{XZ}|$ Examples are shown in Table 9 [27]

Table 9 Temperature effects on the magnitude of ρ_{XY}[22] and ρ_{XZ}[27b]

Reaction	T(°C)	ρ_{XY}
$XC_6H_4NH_2 + YC_6H_4CH_2Br$	25	− 0 47
	35	− 0 43
	45	− 0 40
$XC_6H_4NH_2 + YC_6H_4CH_2Cl$	35	− 0 44
	45	− 0 42
	55	− 0 39
$XC_6H_4NH_2 + YC_6H_4COCl$	25	− 0 85
	35	− 0 81
		ρ_{XZ}
$XC_6H_4NH_2 + Y(Z)C_6H_4COOCOC_6H_5$	25	1 46
	35	1 25
	45	1 19

$$k_H/k_D = \exp\left\{-\frac{0\ 1865}{T}(\nu_H^\ddagger - \nu_H^0)\right\} = \exp\left(-\frac{0\ 1865}{T}\Delta\nu^\ddagger\right) \qquad (2)$$

3.6 S_N1 Processes

Since for the S_N1 processes the nucleophile does not participate in the TS, ρ_{XY} and ρ_{XZ} are zero,[6] *i e* , there is no interaction between the nucleophile and substrate, and leaving group respectively, in the TS, and hence the Nu-KIEs cannot be observed, $k_H/k_D = 1\ 0$ This has been confirmed for the reaction of α-*t*-butylbenzyl arenesulfonates with anilines, equation 6 For this reaction cross-interactions ρ_{XY} and ρ_{XZ} were zero and the Nu-KIE, k_H/k_D, was practically unity,[28] the ρ_{YZ} values were, however, large and positive in methanol–acetonitrile mixtures (= 0 6—1 0) correctly reflecting a relatively large extent of bond cleavage involved in the S_N1 TS

$$2\,XC_6H_4NH_2 + YC_6H_4CHC(CH_3)_3OSO_2C_6H_4Z \rightarrow XC_6H_4NHCHC(CH_3)_3C_6H_4Y + {}^+NH_3C_6H_4X + {}^-OSO_2C_6H_4Z \qquad (6)$$

3.7 A Four-centre S_N2 TS with a Primary Kinetic Isotope Effect

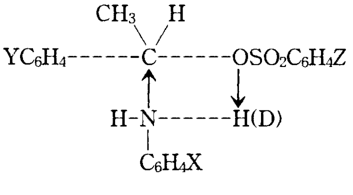
The reaction of 1-phenylethyl arenesulfonates with anilines, equation 7, exhibited a large negative ρ_{XZ} (= − 0 56) suggesting that the two, nucleophile and leaving group, are in close proximity in the TS Based on various experimental results, the TS is believed to involve a four-centre hydrogen-bonded type, (III), which is a result of frontal attack [25] The k_H/k_D values in Table 10 are indeed in accord with this proposal The size of k_H/k_D is large, exceeding the limit of secondary KIEs ($k_H/k_D \leq 1\ 41$) and the four-centre TS is seen to be more stable by forming a stronger hydrogen bond for a weaker nucleophile and/or nucleofuge This is consistent with the greater deprotonation occurring when the aniline has an electron-withdrawing substituent (weaker nucleophile to facilitate proton nucleofuge) to localize more electronic charge on the reaction-centre oxygen atom leading to a greater electrostatic attraction of the proton An earlier TS is formed with a weaker nucleophile and/or nucleofuge since in this reaction ρ_{XZ} is negative A relatively early TS formed with a hydrogen bond between the nitrogen and oxygen atoms (III) is also indicated by the relatively small magnitude of ρ_{XY} (= − 0 21) and ρ_{YZ} (= 0 11) observed The primary KIE ($k_H/k_D > 1\ 0$) due to the partial deprotonation of one of the two N–H(D) bonds should have been greater than the observed value since the out-of-plane bending vibrational frequencies of the other N–H(D) bond are increased in the TS due to steric hindrance and give an inverse effect ($k_H/k_D < 1\ 0$), and the combined result of the two is actually observed When the nucleophile is changed to *N,N*-dimethylaniline, the size of ρ_{XZ} decreases to − 0 24, which is still somewhat high because of closer approach of the nucleophile towards the leaving group in the partial front-side attack, but without the deprotonation involved in the four-centre-type TS

$$2\,XC_6H_4NH_2 + YC_6H_4CH(CH_3)_3OSO_2C_6H_4Z \rightarrow XC_6H_4NHCH(CH_3)_3C_6H_4Y + {}^+NH_3C_6H_4X + \ OSO_2C_6H_4Z \qquad (7)$$

Table 10 Kinetic isotope effects for the reactions of 1-phenylethyl arenesulfonates with deuterated anilines in acetonitrile at 35 0 °C[25c]

$$YC_6H_4CH(CH_3)OSO_2C_6H_4Z + XC_6H_4NH_2(D_2) \xrightarrow[30\ 0\ ^\circ C]{MeCN}$$

X	Y	Z	k_H/k_D
p-CH_3O	H	*p*-NO_2	1 70(3)
p-CH_3O	H	*p*-CH_3	1 96(4)
m-NO_2	H	*p*-NO_2	2 34(8)
m-NO_2	H	*p*-CH_3	2 58(3)



(III)

4 Conclusion

(i) The mechanistic interpretation of the size of secondary KIEs (k_H/k_D) based on the conventional view as to the origin of the effects is consistent with the variation of TS structures predicted by the sign and magnitude of the experimental cross-interaction constants, ρ_{ij}

(ii) The cross-interaction constants and the secondary KIEs supplement each other as useful means for the elucidation of TS structures

Acknowledgments The author thanks all the collaborators who participated in this series of works on the secondary kinetic isotope effects involving deuterated nucleophiles He also thanks the Korea Science and Engineering Foundation, the Ministry of Education, the Korea Research Center for Theoretical Physics and Chemistry, and Inha University for support of this series of works

5 References

1 (*a*) K C Westaway and S F Ali, *Can J Chem*, 1979, **57**, 1354 (*b*) K C Westaway and Z Waszczylo, *Can J Chem*, 1982, **60**, 2500 (*c*) V P Vitullo, J Grabowski, and S Sridharam, *J Am Chem Soc*, 1980, **102**, 6463 (*d*) R A J O'Hair, G E Darico, J Hacaloglu, T T Dang, C H DePuy, and V M Bierbaum, *J Am Chem Soc*, 1994, **116**, 609

2 (*a*) L Melander and W H Saunders, 'Reaction Rates of Isotopic Molecules', Wiley New York, 1980 (*b*) T H Lowry and K S Richardson, 'Mechanism and Theory in Organic Chemistry', 3rd Edn , Harper and Row, New York, 1987, p 232

3 A Streitwieser, R H Jagow, R C Fahey, and S Suzuki, *J Am Chem Soc*, 1958, **80**, 2326

4 (*a*) S Wolfe and C K Kim, *J Am Chem Soc*, 1991, **113**, 8056 (*b*) X G Zhao, S C Tucker, and D G Truhlat, *J Am Chem Soc*, 1991, **113**, 826 (*c*) I H Williams, *J Am Chem Soc*, 1984 **106**, 7206 (*d*) R J Boyd, C K Kim, Z Shi, N Weinberg, and S Wolfe, *J Am Chem Soc*, 1993, **115**, 10147

5 (*a*) J A Barnes and I A Williams, *J Chem Soc, Chem Commun*, 1993, 1286 (*b*) R A Poirier, Y Wang, and K C Westaway, *J Am Chem Soc*, 1994, **116**, 2526

6 (*a*) I Lee, *Adv Phys Org Chem*, 1992, **27**, 57 (*b*) I Lee *J Phys Org Chem*, 1992, **5**, 736

7 I Lee, *Bull Korean Chem Soc*, 1994, **15**, 985

8 I Lee, Y H Choi, K W Rhyu, and C S Shim, *J Chem Soc, Perkin Trans 2*, 1989, 1881

9 T Ando, T Kimma, and H Yamataka, 'Nucleophilicity', ed J M Harris and S P McManus, American Chemical Society, Washington D C , 1987, Chapter 7

10 J M Harris, M S Paley, and T W Prasthofer, *J Am Chem Soc*, 1981, **103**, 5915

11 (*a*) A Pross and S S Shaik, *J Am Chem Soc*, 1981, **103**, 3702 (*b*) D J Mitchell, H B Schlegel, S S Shaik, and S Wolfe, *Can J Chem*, 1985, **63**, 1642

12 (*a*) R A More O'Ferrall, *J Chem Soc (B)*, 1970, 274 (*b*) W P Jencks, *Chem Rev*, 1972, **72**, 705

13 I Lee, S C Sohn, Y J Oh, and B C Lee, *Tetrahedron*, 1986, **42**, 4713

14 I Lee, H J Koh, B S Lee, D S Sohn, and B C Lee, *J Chem Soc Perkin Trans 2*, 1991, 1741

15 (*a*) I Lee, C K Kim, D S Chung, and B S Lee, *J Org Chem*, 1994, **59**, 4490 (*b*) W J Hehre, L Radom, P v R Schleyer, and J A Pople, 'Ab Initio Molecular Orbital Theory', Wiley, New York, 1986, Chapter 4

16 H K Oh, Y B Kwon, I H Cho, and I Lee, *J Chem Soc, Perkin Trans* 2, 1994, 1697

17 M J S Dewar and R C Dougherty, 'The PMO Theory of Organic Chemistry', Plenum, New York, 1975, p 212

18 H K Oh, Y B Kwon, D S Chung, and I Lee, unpublished results

19 (*a*) W J le Noble and T Asano, *J Am Chem Soc*, 1975, **97**, 1778 (*b*) W J le Noble and A R Miller, *J Org Chem*, 1979, **44**, 889

20 I Lee, H J Koh, and B C Lee, *J Phys Org Chem*, 1994, **7**, 50

21 (*a*) O Exner, *J Chem Soc, Perkin Trans 2*, 1993, 973 (*b*) I Lee, B S Lee, H J Koh, and B D Chang, *Bull Korean Chem Soc*, 1995, **16**, 277

22 (*a*) A Pross, *Adv Phys Org Chem*, 1997, **14**, 69 (*b*) E Buncel and H Wilson, *J Chem Educ*, 1987, **64**, 475

23 B C Lee, D S Sohn, J H Yoon, S M Yang, and I Lee, *J Korean Chem Soc*, 1993, **14**, 621

24 F M Menger and J H Smith, *J Am Chem Soc*, 1972, **94**, 3824

25 (*a*) I Lee, H Y Kim, H K Kang, and H W Lee, *J Org Chem*, 1988, **53**, 2678 (*b*) I Lee, C S Shim, H W Lee, and B S Lee, *Bull Korean Chem Soc*, 1991, **12**, 255 (*c*) I Lee, H J Koh, and H W Lee, *J Chem Res*, 1990, (S), 282

26 H J Koh, H W Lee, and I Lee, *J Chem Soc, Perkin Trans 2*, 1994, 125

27 (*a*) I Lee, H J Koh, B C Lee, and B S Park, *Bull Korean Chem Soc*, 1994, **15**, 576 (*b*) B C Lee, J H Yoon, C G Lee, and I Lee, *J Phys Org Chem*, 1994, **7**, 273

28 I Lee, M S Choi, and H W Lee, *J Chem Res*, 1994, (S) 92, (M) 0568—0587