Using Secondary α Deuterium Kinetic Isotope Effects To Determine the Symmetry of S_N2 Transition States

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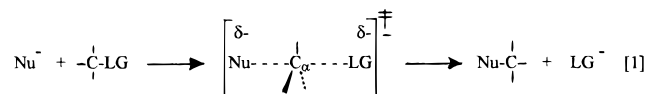
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Abstract: The secondary α deuterium and heavy atom kinetic isotope effects found for two different S_N2 reactions suggest that the magnitude of secondary α deuterium kinetic isotope effects can be determined by the length of only the shorter (stronger) reacting bond in an unsymmetrical S_N2 transition state rather than by the usual nucleophile−leaving group distance. Although this means the interpretation of these isotope effects is more complex than has been recognized, the results suggest that they can be used to determine whether an S_N2 transition state is symmetrical or unsymmetrical.

Introduction

Secondary α deuterium and heavy atom kinetic isotope effects (KIEs) have been widely used to determine how changing a substituent on the nucleophile, the substrate, or the leaving group alters the structure of an S_N2 transition state (eq 1).[1−5]

$$Nu^- + \;-\overset{|}{\underset{|}{C}}-LG \longrightarrow \left[\overset{\delta-}{Nu}---\overset{|}{\underset{|}{C_\alpha}}---\overset{\delta-}{LG} \right]^{\ddagger} \longrightarrow Nu-\overset{|}{\underset{|}{C}}- + \; LG^- \quad [1]$$

Recent work has shown that the magnitude of a secondary α deuterium KIE is determined by the changes that occur in both the C_α−H(D) stretching and out-of-plane bending vibrations when the reactant is converted into the transition state.[6,7] However, a study of the secondary α deuterium KIEs for a series of S_N2 reactions of methyl or ethyl chlorides and fluorides with several different nucleophiles has shown that the magnitude of these KIEs for a series of S_N2 reactions *with the same leaving group* is determined by the changes that occur in the out-of-plane bending vibrations when the reactant is converted into the transition state.[7] This means the magnitude of the KIEs for a series of S_N2 reactions *with the same leaving group* is determined by the nucleophile−leaving group distance (tightness) of the transition state[7,8] (Figure 1). Although this relationship has been widely used to relate the magnitude of secondary α deuterium KIEs to transition state structure,[1−5] it seemed possible that the magnitude of these KIEs might not be determined by the nucleophile−leaving group distance in a very unsymmetrical S_N2 transition state. For instance, if the S_N2 transition state were unsymmetrical (Figure 2), the magnitude of the secondary α deuterium KIE (the changes in the C_α-H(D) out-of-plane bending vibrations when the reactant is converted into the transition state) might only depend on the length of the

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(2) Westaway, K. C.; Waszczylo, Z. *Can. J. Chem.* **1982,** *60,* 2500.
(3) Yamataka, H.; Ando, T. *J. Am. Chem. Soc.* **1979,** *101,* 266.
(4) Harris, J. M.; Shafer, S. G.; Moffat, J. R.; Becker, A. R. *J. Am. Chem. Soc.* **1979,** *101,* 3295.
(5) Lee, I. *Chem. Soc. Rev.* **1995,** 223.
(6) Wolfe, S.; Kim, C.-K. *J. Am. Chem. Soc.* **1991,** *113,* 8056.
(7) Poirier, R. A.; Wang, Y.; Westaway, K. C. *J. Am. Chem. Soc.* **1994,** *116,* 2526.
(8) Barnes, J. A.; Williams, I. H. *J. Chem. Soc., Chem. Commun.* **1993,** 1286.
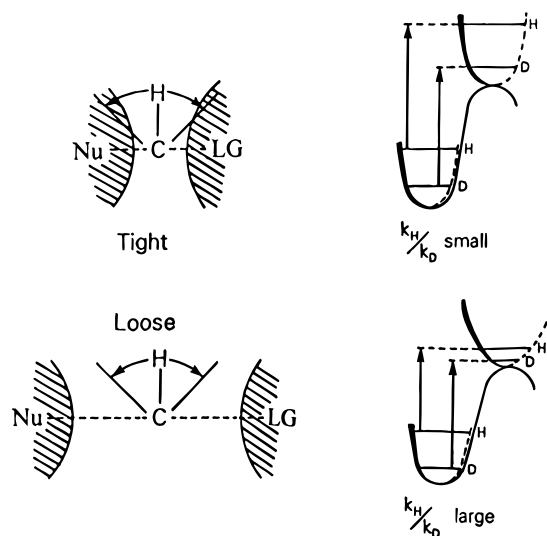

Figure 1. Relationship between the looseness (the nucleophile−leaving group distance) of the S_N2 transition state and the magnitude of the secondary α deuterium KIE as determined by the C_α−(H)D out-of-plane bending vibrations.
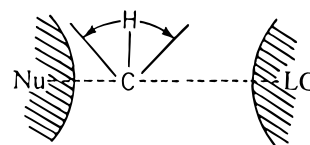

Figure 2. C_α−(H)D out-of-plane bending vibrations for an unsymmetrical S_N2 transition state.

shorter reacting bond rather than on the nucleophile−leaving group distance.

The secondary α deuterium and heavy atom KIEs found for two different S_N2 reactions (*vide infra*) suggest (i) that the magnitude of some secondary α deuterium KIEs is not determined by the nucleophile−leaving group distance but only by the length of the shorter reacting bond in the S_N2 transition state and (ii) that there are two general types of S_N2 transition states. One is a central (nearly symmetrical) transition state with reasonably short nucleophile−α carbon and α carbon−leaving group bonds where the magnitude of the KIE is determined by the nucleophile−leaving group distance. The second type of S_N2 transition state is unsymmetrical with the

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Table 1. Nitrogen (Leaving Group) KIEs for the S_N2 Reactions between Several *Para*-Substituted Sodium Thiophenoxides and Benzyldimethylphenylammonium Nitrate in DMF at 0 °C

para substituent on the thiophenoxide ion	k^{14}/k^{15}
CH$_3$O	1.01580
	1.01536
	1.01658
	1.01711
av	1.0162 ± 0.0007[a]
H	1.01599
	1.01717
	1.01683
	1.01623
	1.01680
av	1.0166 ± 0.0004
Cl	1.01625
	1.01724
	1.01684
	1.01707
	1.01584
av	1.0166 ± 0.0005

[a] The error is the standard deviation of the mean.

Table 2. Secondary α Deuterium KIEs for the S_N2 Reactions between Several *Para*-Substituted Sodium Thiophenoxides and Benzyldimethylphenylammonium Nitrate in DMF at 0 °C
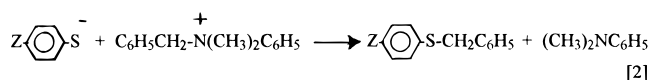
para substituent on the thiophenoxide ion	$(k_H/k_D)_\alpha$
CH$_3$O	1.238 ± 0.017[a]
	1.219 ± 0.019
	1.210 ± 0.012
	1.217 ± 0.014
av	1.221 ± 0.012[b]
H	1.212 ± 0.015
	1.228 ± 0.010
	1.210 ± 0.022
av	1.215 ± 0.011
Cl	1.204 ± 0.019
	1.229 ± 0.018
	1.211 ± 0.014
av	1.215 ± 0.013

[a] The error in each KIE = $1/k_D[(\Delta k_H)^2 + (k_H/k_D)^2(\Delta k_D)^2]^{1/2}$, where Δk_H and Δk_D are the standard deviations for the rate constants for the undeuterated and deuterated substrates, respectively. In each KIE experiment, three rate constants for the undeuterated and three for the deuterated substrates were measured simultaneously to reduce the effect of any temperature changes during the reaction and or differences between batches of solvent. [b] The error is the standard deviation of the mean.

strongest reacting bond shorter than the weaker reacting bond. For these transition states, the magnitude of the secondary α deuterium KIE is determined by only the shorter (stronger) reacting bond.

Results and Discussion

The first set of KIEs which suggest that the magnitude of a secondary α deuterium KIE is not always determined by the nucleophile−leaving group distance in the S_N2 transition state was obtained for the S_N2 reactions[9] between several *para*-substituted thiophenoxide ions and benzyldimethylphenylammonium ion in DMF (eq 2).

$$Z\text{-}\langle O \rangle\text{-}S^- + C_6H_5CH_2\text{-}N(CH_3)_2C_6H_5 \longrightarrow Z\text{-}\langle O \rangle\text{-}S\text{-}CH_2C_6H_5 + (CH_3)_2NC_6H_5$$

$$[2]$$

The nitrogen (leaving group) and the secondary α deuterium KIEs for these reactions were measured at 0 °C in DMF at an ionic strength of 0.904. The inert salt, sodium nitrate, was used to keep the ionic strength constant throughout the reaction so accurate rate constants (KIEs) could be determined. The nitrogen KIEs for these reactions (Table 1), are identical. The secondary α deuterium KIEs found for these reactions (Table 2) are also all the same within experimental error.

The conventional approach to interpreting the identical nitrogen and secondary α deuterium KIEs would be that the transition state structure does not change when the substituent on the nucleophile is altered. This suggestion seems highly unlikely, however, because (i) no one has observed this behavior in any study and (ii) it is unreasonable to conclude that a change in nucleophile, which changes the rate constant by a factor of 6.4, would not alter the energy and, therefore, the structure of the transition state.

A second, and more likely, possibility is that the change in nucleophile alters the structure of the transition state but that the change in transition state structure does not cause a change in the nitrogen or the secondary α deuterium KIEs. If one

assumes that the nitrogen leaving group KIEs can be interpreted in the usual fashion, i.e., that the magnitude of the KIE increases with the percent $C_\alpha-N$ bond rupture in the transition state,[10] then all three reactions have identical amounts of $C_\alpha-N$ bond rupture in the transition state. This interpretation is reasonable because the magnitude of a nitrogen leaving group KIE only depends on the change in the vibrational energy of the C_α-N bond (the amount of $C_\alpha-N$ bond rupture[11]) on going from the reactant to the transition state. If this is the case, then interpreting the secondary α deuterium KIEs is not straightforward. In fact, identical secondary α deuterium KIEs could be found for two different reactions if the transition states were unsymmetrical and the bond to one of the reacting nucleophiles in the transition state was very long. In this instance, the magnitude of the KIE would only be determined by the shorter reacting bond in the S_N2 transition state (Figure 2) because the other nucleophile in the transition state would be too far away to affect the $C_\alpha-H(D)$ out-of-plane bending vibrations (frequencies). Therefore, when a substituent in the nucleophile is altered, the change in the magnitude of the KIE would be determined by only the changes that occur in the shorter reacting bond and not by the nucleophile−leaving group distance in the S_N2 transition state.

A detailed examination of the nitrogen and secondary α deuterium KIEs that have been measured for the S_N2 reaction between benzyldimethylphenylammonium ion and thiophenox-

(9) All the reactions were second order, first order in both the substrate and the nucleophile up to at least 67% of completion. The second order kinetic plots were linear with correlation coefficients of ≥0.999. This, the Hammett ρ values obtained by changing the substituent on the nucleophile and the nitrogen (leaving group) KIEs,[1] indicates that these reactions are all S_N2 processes.

(10) Saunders, W. H. *Chem. Scripta* **1975**, *8*, 27.

(11) Some of the vibrational energy lost when the $C_\alpha-N$ bond breaks in the transition state will be partially replaced by the increased vibrational energy associated with the strengthening of the N−C(phenyl) bond, i.e., by conjugation between the dimethylamino group and the benzene ring in the transition state.[1] Although the KIE's ability to detect a change in the extent of $C_\alpha-N$ bond rupture is reduced slightly by this factor, reactions with identical KIEs must have identical amounts of $C_\alpha-N$ bond rupture in the transition state. The conjugation effect is thought to be small because (i) the wavenumber of the absorption of the N−C(phenyl) bond only increases by approximately 300 cm^{-1}, i.e., from approximately 1000 cm^{-1} in the reactant to 1300 cm^{-1} in the product, and (ii) large nitrogen KIEs of 1.0202 have been found in these reactions.[1] The largest nitrogen KIE that has been reported for an S_N2 reaction of a quaternary ammonium salt is 1.0226.[12]

(12) Smith, P. J.; Pollock, C. A.; Bourns, A. N. *Can. J. Chem.* **1975**, 53, 1319.

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Table 3. Secondary α Deuterium and Primary Nitrogen KIEs for the S_N2 Reaction between Sodium Thiophenoxide and Benzyldimethylphenylammonium Nitrate at Different Ionic Strengths in DMF at 0 °C

ionic strength	$(k_H/k_D)_\alpha$	k^{14}/k^{15}
0.904	1.215 ± 0.011[a]	1.0166 ± 0.0004[b]
0.64	1.179 ± 0.007	1.0200 ± 0.0007

[a] The error in the KIE $= 1/k_D[(\Delta k_H)^2 + (k_H/k_D)^2(\Delta k_D)^2]^{1/2}$, where Δk_H and Δk_D are the standard deviations for the rate constants for the undeuterated and deuterated substrates, respectively. [b] The error is the standard deviation of the mean of five different measurements.

ide ion (eq 2) at two different ionic strengths shows that the transition states for the high ionic strength reactions where the constant KIEs have been observed are, indeed, unsymmetrical. The identical nitrogen KIEs of 1.0165 found at the high ionic strength (Table 1) are not large, i.e., they are only approximately one-third of the theoretical maximum nitrogen KIE of 1.044.[13,14] Also, the nitrogen KIE found for the reaction with sodium thiophenoxide at the high ionic strength ($k^{14}/k^{15} = 1.0166 \pm 0.0004$) is significantly smaller than the nitrogen KIE of 1.0200 ± 0.0007 found[1] for the same reaction at an ionic strength of 0.64 (Table 3). Thus, C_α–N bond rupture is not well advanced in the transition states of the high ionic strength reactions. This suggests that the transition states are reactant-like with reasonably short C_α–N bonds.

The identical secondary α deuterium KIEs of 1.22 found for the reactions at high ionic strength, on the other hand, are very large (approximately 11%/α-D).[15] In fact, they are the largest that have been found for an S_N2 reaction of a quaternary ammonium ion. This indicates that the transition state is very loose.[7] Since the C_α–N bond is short and the transition states are very loose, the S–C_α bond must be very long in these transition states. Thus, the KIE data suggests that the high ionic strength reactions with constant nitrogen and secondary α deuterium KIEs have very reactant-like transition states with short C_α–N bonds and very long S–C_α bonds.

Two other pieces of information suggest the S–C_α bonds are long in the high ionic strength transition states. The $(k_H/k_D)_\alpha$ of 1.215 ± 0.011 found for the thiophenoxide ion reaction in this study is significantly larger than the $(k_H/k_D)_\alpha = 1.179 \pm 0.007$ found[1] for the same reaction at an ionic strength of 0.64 (Table 3). Since the C_α–N bond is shorter (*vide supra*) and

Table 4. Rate Constants and Hammett ρ Values for the Reactions between *Para*-Substituted Sodium Thiophenoxides and Benzyldimethylphenylammonium Nitrate at Different Ionic Strengths in DMF at 0 °C

para substituent on the thiophenoxide ion	rate constant $\times 10^3$ (L/(M s))	
	ionic strength $\mu = 0.904$	ionic strength $\mu = 0.64$
CH_3O	30.1 ± 0.8[a]	46.2 ± 3.3[a]
H	10.9 ± 0.3	12.8 ± 1.0
Cl	4.67 ± 0.07	6.13 ± 0.65
ρ	-1.62 ± 0.01	-1.76 ± 0.19
correlation coefficient	1.000	0.994

[a] The error is the standard deviation of the mean of at least three different measurements.

the secondary α hydrogen-deuterium KIEs are larger in the high ionic strength reactions, the transition states for these reactions must have very long S–C_α bonds and be unsymmetrical.

The Hammett ρ value also suggests that the S–C_α transition state bond is very long in the reactions with $(k_H/k_D)_\alpha = 1.22$. A Hammett $\rho = -1.62 \pm 0.01$ was observed in the reaction where $(k_H/k_D)_\alpha = 1.22$ whereas a larger Hammett ρ value of -1.76 ± 0.19 was found in the reaction with $(k_H/k_D)_\alpha = 1.179$ (Table 4). Since a larger ρ value is observed when the change in charge on the sulfur atom on going from the reactants to the transition state is larger, i.e., when there is more nucleophile–α carbon bond formation in the transition state, the reaction with the larger $(k_H/k_D)_\alpha$ must have a longer S–C_α transition state bond.[22] Thus, the conclusion based on the ρ values supports that based on relative magnitudes of the secondary α deuterium KIEs, i.e., that the transition states in the reactions with the identical KIEs have longer S–C_α bonds. Finally, since the reaction at low ionic strength has a symmetrical transition state,[1] the transition states in the reactions with the constant KIEs must be reactant-like with very long S–C_α and short C_α–N bonds.

If one assumes (i) that the transition states for the reactions with the constant nitrogen and secondary α deuterium KIEs are reactant-like with very long S–C_α and short C_α–N bonds, (ii) that the structure of the transition state is altered by the change in substituent on the nucleophile, and (iii) that changing the substituent in the nucleophile does not alter the amount of C_α–N bond rupture in the transition state (the nitrogen KIE) significantly (*vide supra*), then a change in substituent must change the length of the S–C_α transition state bond. However, since the transition state is unsymmetrical and very reactant-like, the changes in the length of the S–C_α bond occur too far from the α carbon to affect the C_α–(H)D out-of-plane bending vibrations in the transition state (the magnitude of the secondary α deuterium KIE, Figure 2) and identical secondary α deuterium KIEs[26] are found for all three of the S_N2 reactions between benzyldimethylphenylammonium ion and *para*-substituted thiophenoxide ions. In this instance, the magnitude of the secondary α deuterium KIEs in these reactions is only determined by what happens to the shorter C_α–N bond when the substituent is changed. Since the C_α–N bond does not change

(13) Maccoll, A. *Annu. Rep. A: Chem. Soc. (London)* **1974**, *71*, 77.

(14) Buddenbaum, W. E.; Shiner, V. J., Jr. In *Isotope Effects on Enzyme-Catalyzed Reactions*; Cleland, W. W., O'Leary, M. H., Northrop, D. B., Eds.; University Park Press: London, 1977; p 18.

(15) The maximum secondary α deuterium KIE for an ammonia leaving group is $1.17/_{\alpha\text{-D}}$.[16,17] This means the minimum KIE expected for a carbocation S_N reaction would be approximately $1.12/_{\alpha\text{-D}}$.[18] Shiner and co-workers suggested that the maximum KIE expected for an S_N2 reaction is $1.04/_{\alpha\text{-D}}$.[19] The large secondary α deuterium KIEs = 1.22 ($1.105/_{\alpha\text{-D}}$) found for these S_N2 reactions have been attributed to the relief of steric crowding around the C_α–H(D) bonds in the substrate as the bond to the very sterically crowded *N,N*-dimethylaniline leaving group lengthens on going to the transition state[1,20,21] and to the fact that the thiophenoxide ion is too far away from the α carbon to affect the C_α–H(D) out-of-plane bending vibrations in the transition state.

(16) Hartshorn, S. R.; Shiner, V. J., Jr. *J. Am. Chem. Soc.* **1972**, *94*, 9002.

(17) Shiner, V. J., Jr.; Neumann, T. E. *Z. Naturforsch.* **1989,** *44a*, 337.

(18) Westaway, K. C. In *Secondary Hydrogen-Deuterium Kinetic Isotope Effects and Transition State Structure in S_N2 Processes In Isotopes in Organic Chemistry*; Buncel, E., Lee, C. C., Eds.; Elsevier: New York, 1987; Vol. 7, p 312.

(19) Humski, K.; Sendijarevic, V.; Shiner, V. J., Jr. *J. Am. Chem. Soc.* **1974**, *96*, 6187.

(20) Westaway, K. C., *Tetrahedron Lett.* **1975**, 4229.

(21) Westaway, K. C. In *Secondary Hydrogen-Deuterium Kinetic Isotope Effects and Transition State Structure in S_N2 Processes In Isotopes in Organic Chemistry*; Buncel E., Lee, C. C., Eds.; Elsevier: New York, 1987; Vol. 7, pp 311–316.

(22) Hoz et al.[23] used theoretical calculations on homolytic cleavage reactions to question using Hammett ρ values to determine transition state structure. However, linear free energy relationships such as ρ values are currently used to indicate differences in transition state structure[24,25] and there is no experimental evidence to show which position is correct. The authors believe that ρ values from closely related systems can be used to indicate transition state structure because the changes in the structure of the S_N2 transition state suggested by ρ values have been confirmed by KIE data.[1,2]

(23) Hoz, S.; Basch, S; Goldberg, M. J. *J. Am. Chem. Soc.* **1992**, *114*, 4364.

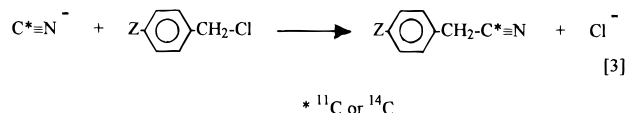(24) Stefanidis, D.; Jencks, W. P. *J. Am. Chem. Soc.* **1993**, *115*, 6045.

(25) Lee, I.; Lee, W. H.; Lee, H. W. *J. Phys. Org. Chem.* **1990**, *3*, 545.

when the substituent in the nucleophile is altered, neither the nitrogen nor the secondary α deuterium KIEs change when the substituent on the nucleophile is altered.

These conclusions are interesting because they are consistent with the predictions of the "bond strength hypothesis"[27] which suggests that "there will be a significant change in the weaker reacting bond but little or no change in the stronger reacting bond in an S_N2 transition state when a substitutent in the nucleophile, the substrate, or the leaving group is altered in an S_N2 reaction". Since the C−S bond is weaker than the C−N bond in these S_N2 reactions,[27] the "bond strength hypothesis" would predict that adding an electron-withdrawing substituent to the nucleophile should not affect the C_α−N bond significantly but should lead to a significant change in the weaker S−C_α bond. These are the exact changes suggested on the basis of the KIEs.

Finally, another interesting conclusion is that the stronger C_α−N bond is shorter than the weaker S−C_α bond in these reactant-like, unsymmetrical, S_N2 transition states.

The same phenomenon, i.e., that the secondary α deuterium KIE is only determined by the length of the shortest reacting bond rather than by the nucleophile−leaving group distance in the S_N2 transition state, has been found in a completely different reaction system. Recently, Matsson, Westaway, and co-workers[28] used $^{11}C/^{14}C$ incoming group KIEs, Hill and Fry's chlorine leaving group KIEs,[29] and Fry's $^{12}C/^{14}C$ α carbon KIEs[30] to model the transition states for a series of S_N2 reactions[31] between *para*-substituted benzyl chlorides and cyanide ion (eq 3). Both the chlorine[29] and the incoming group

$$C^* \equiv N^- \ + \ Z\langle\bigcirc\rangle CH_2\text{-}Cl \longrightarrow Z\langle\bigcirc\rangle CH_2\text{-}C^*\equiv N \ + \ Cl^-$$

[3]

$$*\ ^{11}C\ \text{or}\ ^{14}C$$

$^{11}C/^{14}C$ [28] KIEs (Table 5) decrease when a more electron-withdrawing substituent is added to the benzene ring of the substrate. A more detailed analysis of these KIEs[28] showed that the change in the C_α−Cl bond (the change in the KIE with respect to the maximum chlorine KIE) is approximately 6 times greater than the change in the N≡C−C_α bond (the change in the KIE with respect to the maximum $^{11}C/^{14}C$ incoming group KIE) when the substituent on the benzene ring is altered. This means that adding a more electron-withdrawing substituent to the benzene ring of the substrate shortens the C_α−Cl bond significantly but has little or no effect on the C_α−C≡N bond (Figure 3).

(26) The magnitude of the secondary α deuterium KIE is determined by the changes that occur in the both the C_α−H(D) stretching and out-of-plane bending vibrations when the reactant is converted into the transition state. However, the stretching contribution to the KIE is constant *for each leaving group* regardless of transition state structure.[7] Therefore, the magnitude of the KIE for reactions *with the same leaving group* can be interpreted in terms of the changes in the C_α−H(D) out-of-plane bending vibrations.

(27) Westaway, K. C. *Can. J. Chem.* **1993**, *71*, 2084.

(28) Matsson, O.; Persson, J.; Axelsson, B. S.; Långström, B.; Fang, Y.-R.; Westaway, K. C. *J. Am. Chem. Soc.* **1996**, *118*, 6350.

(29) Hill, J. W.; Fry, A. *J. Am. Chem. Soc.* **1962**, *84*, 2763.

(30) Fry, A. In *Isotope Effects in Organic Reactions*; Collins, C. J., Bowman, N. S., Eds.; ACS Publication 167; Van Nostrand Reinhold: New York, 1970; p 380.

(31) A reviewer suggested that these reactions might shift from an S_N2 to a mixed S_N2–S_N1 mechanism or from a mixed S_N2–S_N1 mechanism to an S_N1 mechanism when electron-donating groups were on the benzene ring of the substrate. The second-order kinetic plots for all the substrates were linear with correlation coefficients of ≥0.999 up to at least 55% of completion. Also, a significant shift in mechanism should cause a significant decrease in the incoming group $^{11}C/^{14}C$ KIE and a significant increase in the secondary α deuterium KIE. The kinetics and the almost identical incoming group $^{11}C/^{14}C$ and secondary α deuterium KIEs found for these reactions indicate that all of these reactions are S_N2 processes.

Table 5. $^{35}Cl/^{37}Cl$ Leaving Group, the Incoming Group $^{11}C/^{14}C$, the Secondary α Deuterium and the $^{12}C/^{14}C$ α Carbon KIEs for the S_N2 Reactions between *Para*-Substituted Benzyl Chlorides and Cyanide Ion in 20% Aqueous DMSO at 30 °C

para substituent	k^{35}/k^{37} [a]	k^{11}/k^{14}	$(k_H/k_D)_\alpha$	k^{12}/k^{14} [b]
CH₃	1.0079 ± 0.0004	1.0104 ± 0.0001	1.008 ± 0.003[c]	1.090
H	1.0072 ± 0.0003	1.0105 ± 0.002	1.011 ± 0.001	1.102
Cl	1.0060 ± 0.0002	1.0070 ± 0.001	1.002 ± 0.003	1.106

[a] Measured in 20% aqueous dioxane at 30.00 °C.[29] [b] Measured in 20% aqueous dioxane at 40 °C. No error limits were given for these KIEs.[30] [c] Measured at 30.000 ± 0.002 °C. The error in the KIE = $1/k_D[(\Delta k_H)^2 + (k_H/k_D)^2(\Delta k_D)^2]^{1/2}$, where Δk_H and Δk_D are the standard deviations for the rate constants for the undeuterated and deuterated substrates, respectively. In each KIE experiment, at least three rate constants for the undeuterated and three for the deuterated substrates were measured simultaneously to reduce the effect of any temperature changes during the reaction and or differences between batches of solvent.
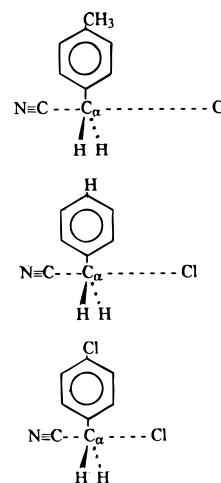

Figure 3. Relative structures for the S_N2 transition states for the reactions of *para*-substituted benzyl chlorides with cyanide ion.

The secondary α deuterium KIEs for these reactions were determined in an effort to learn in more detail how the transition state changes when the *para* substituent on the benzene ring is altered. All of these KIEs (Table 5) are small and normal. This was surprising because (i) the secondary α deuterium KIEs found for the S_N2 reactions of many *para*-substituted benzyl substrates, particularly those with electron-donating substituents, are large and normal[32] and (ii) because the KIEs do not decrease significantly when a more electron-withdrawing substituent is added to the substrate. In fact, the maximum change in these KIEs is less than 1%, and the KIE for the unsubstituted benzyl chloride reaction is greater than that for the *p*-methylbenzyl chloride reaction. Normally, the small change observed in the secondary α deuterium KIE would lead one to conclude that the nucleophile−leaving group distance in the transition state does not change significantly when the substituent on the benzene ring is altered. However, the chlorine KIEs indicate that the C_α−Cl bond shortens significantly and that the N≡C−C_α bond shortens slightly when a more electron-withdrawing substituent is added to the benzene ring.[28] Thus, the nucleophile−leaving group distance in these S_N2 transition states decreases when a more electron-withdrawing substituent is added to the benzene ring of the substrate. If the magnitude of the secondary α deuterium KIEs were determined by the nucleophile−leaving group distance in the transition state, the

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KIEs should decrease significantly when a more electron-withdrawing *para* substituent is added to the substrate.

The only way to rationalize the almost constant secondary α deuterium KIEs found for these reactions is to assume that these benzyl chloride−cyanide ion S_N2 transition states are also unsymmetrical and that only the shorter reacting bond determines the magnitude of the KIE. A comparison of the chlorine and the secondary α deuterium KIEs in Table 5 shows that the magnitudes of the chlorine and the secondary α deuterium KIEs are clearly not related. The secondary α deuterium and the incoming group $^{11}C/^{14}C$ KIEs, on the other hand, change in the same way with substituent. In fact, although the changes that are found in the secondary α and the incoming group carbon KIEs are very small, they parallel each other exactly, i.e., the largest KIEs are observed when the *para* substituent on the benzene ring is hydrogen and the smallest KIEs are found when the *para* substituent is chlorine. Obviously, the factors that affect the secondary α deuterium KIEs also affect the incoming carbon KIEs. This suggests that these transition states have a short $N\equiv C-C_\alpha$ bond and that the $C_\alpha-Cl$ bonds in these transition states are long, i.e., that the transition states are unsymmetrical and product-like (Figure 3). As a result, the changes that occur in the $C_\alpha-Cl$ bond when the *para* substituent on the benzene ring is altered do not affect the C_α-(H)D out-of-plane bending vibrations significantly and the magnitude of the secondary α deuterium KIE is only determined by the length of the shorter $N\equiv C-C_\alpha$ transition state bond.

Pearson and Fry[30] measured the $^{12}C/^{14}C$ α carbon KIEs (Table 5) for the S_N2 reactions between cyanide ion and three *para*-substituted benzyl chlorides at 40 °C in 20% aqueous dioxane, the solvent that was used to measure the chlorine KIEs for these reactions. If it is assumed that these KIEs measured in 20% aqueous dioxane would be similar to those found in the 20% aqueous DMSO used in this study,[28] the $^{12}C/^{14}C$ KIEs can be used to model the transition states for these reactions in even more detail. The α carbon $^{12}C/^{14}C$ KIE increases as a more electron-withdrawing group is added to the benzene ring of the substrate. Since the maximum α carbon KIE is observed when the S_N2 transition state is symmetrical, i.e., when the α carbon is bonded with equal strength to the nucleophile and the leaving group in the transition state,[33,34] the transition state for the *p*-chlorobenzyl chloride reaction is the most symmetrical. Although the α carbon KIE found for the *p*-chlorobenzyl chloride reaction is near the maximum expected for these KIEs,[13,14] these KIEs only indicate that the *p*-chlorobenzyl chloride transition state is the most symmetrical and that the benzyl chloride and *p*-methylbenzyl chloride transition states are more unsymmetrical. The chlorine KIEs indicate that the $C_\alpha-Cl$ transition state bond length decreases significantly when a more electron-withdrawing substituent is present in the substrate.[28] The incoming group carbon KIEs, on the other hand, suggest there is only a very small decrease in the length of the $N\equiv C-C_\alpha$ bond when a more electron-withdrawing substituent is on the substrate. The only way a more symmetrical transition state can be achieved by adding a more electron-withdrawing substituent is if these transition states are product-like, i.e., with short $N\equiv C-C_\alpha$ and long $C_\alpha-Cl$ bonds. Then, shortening the $C_\alpha-Cl$ bond by adding a more electron-withdrawing substituent makes the $C_\alpha-Cl$ bond more equal in strength to the short $N\equiv C\text{- - -}C_\alpha$ transition state bond (a more symmetrical transition state) and a larger $^{12}C/^{14}C$ α carbon KIE is observed (Figure 3).

The only concern with the above interpretation is the large magnitude of the $^{11}C/^{14}C$ incoming group KIEs. BEBOVIB-IV calculations[28] suggest that the incoming group KIE should be inverse (near 0.87) for a product like-transition state with a short $N\equiv C-C_\alpha$ and a long $C_\alpha-Cl$ bond. However, only a product-like transition state with a short $N\equiv C-C_\alpha$ and long $C_\alpha-Cl$ bond is consistent with the $^{35}Cl/^{37}Cl$, the secondary α deuterium, the $^{12}C/^{14}C$ α carbon, and the trend in the $^{11}C/^{14}C$ incoming group carbon KIEs found in these reactions. The explanation for the large magnitude of the $^{11}C/^{14}C$ incoming group carbon KIEs found in this system is not obvious.

It is interesting to note that the changes that occur in transition state structure are consistent with the "bond strength hypothesis"[27] even though the change in substituent in these reactions is in the substrate rather than in the nucleophile as it was in the first reaction. As expected, the weaker $C_\alpha-Cl$ bond changes significantly and there is little or no change in the stronger $N\equiv C-C_\alpha$ bond when the substituent in the substrate is altered. It is also worth noting that, again, the weaker $C_\alpha-Cl$ reacting bond is long and the stronger $N\equiv C-C_\alpha$ reacting bond is short in these unsymmetrical transition states. Thus, the behavior is identical to that observed in the first reaction even though the change in substituent has been made at different positions.

The secondary α deuterium KIEs reported in this paper suggest that the magnitude of the KIE for an S_N2 reaction can be determined either (i) by the nucleophile−leaving group distance in a symmetrical transition state or (ii) by the length of the shorter (stronger) reacting bond of an unsymmetrical transition state. A comparison of the secondary α deuterium KIEs for several S_N2 reactions of benzyl substrates[1,2,32,35−42] (Table 6) shows that there are two different substituent effects on the magnitude of secondary α deuterium KIEs. In some S_N2 reactions, these KIEs decrease markedly when a more electron-withdrawing substituent is present while in other S_N2 reactions they are virtually independent of substituent. On the basis of the results presented above, it is proposed that the reactions where the secondary α deuterium KIE varies with substituent have reasonably tight, symmetrical transition states while those where the KIE is independent of substituent have unsymmetrical S_N2 transition states where the strongest reacting bond is short and determines the magnitude of the KIE.

In the S_N2 reactions with symmetrical transition states, the nucleophile−α carbon and α carbon−leaving group transition state bonds have comparable bond orders, the C_α-(H)D out-of-plane bending vibrations are affected by both the nucleophile and the leaving group, and the magnitude of the secondary α deuterium KIE is determined by the nucleophile−leaving group distance in the S_N2 transition state. In these reactions (Table 6), the secondary α deuterium KIEs decrease markedly (by between 2.8 and 12%) when a more electron-withdrawing substituent is added to the benzene ring in the substrate[2,35−38] or the leaving group.[1]

In S_N2 reactions with an unsymmetric transition state, the C_α−(H)D out-of-plane bending vibrations that determine the

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Table 6. Some Secondary α Deuterium KIEs for S_N2 Reactions with Symmetrical Transition States Where the Magnitude of the KIE Varies with the Nucleophile−Leaving Group Distance in the Transition State and for Unsymmetrical Transition States Where the Magnitude of the KIE Is Determined by the Length of Only the Shortest and Strongest Reacting Bond

substrate/nucleophile	$(k_H/k_D)_\alpha$ *para* substituent (Z)						ΔKIE (%)	ref
	CH_3O	CH_3	H	Cl	Br	NO_2		
S_N2 Reactions with Symmetrical Transition States								
Z-BzCl[a]/$C_6H_5S^-$	1.126	1.096	1.056	1.046		1.039	8.7	2
Z-BzCl/H_2O		1.096			1.032		6.3	35
Z-BzCl/H_2O in 10% aq CH_3CN			1.059		1.008		5.1	35
Z-BzOBs/H_2O in 90% aq EtOH			1.124			1.004	12.0	36
Z-BzCl/H_2O			1.092	1.061			3.1	37
Z-BzBr + $S_2O_3^{2-}$			1.063			1.032	3.1	38
Z-BzBr + N_3^-			1.024			0.996	2.8	38
Z-BzBr + OH^-	1.028		0.984				4.4	38
$\overset{+}{Bz}NMe_2$⟨◯⟩—Z/$C_6H_5S^-$	1.207		1.179	1.151			5.6	1
S_N2 Reactions with Unsymmetrical Transition States								
$\overset{+}{Bz}NMe_2C_6H_5$/Z–$C_6H_4S^-$	1.221		1.215	1.215			0.6	this study
Z-BzCl/CN^-		1.008	1.011	1.002			0.99	this study
$BzOSO_2$⟨◯⟩—Z/CH_3O—⟨◯⟩—NH_2	1.096					1.102	0.6	39
$BzOSO_2$⟨◯⟩—Z/m-O_2N—⟨◯⟩—NH_2	1.098					1.095	0.3	39
$MeOSO_2$⟨◯⟩—Z/CH_3O—⟨◯⟩—NH_2	0.990					0.993	0.3	39
$MeOSO_2$⟨◯⟩—Z/m-O_2N—⟨◯⟩—NH_2	0.971					0.974	0.3	39
$EtOSO_2$⟨◯⟩—Z/CH_3O—⟨◯⟩—NH_2	0.981					0.984	0.3	39
$EtOSO_2$⟨◯⟩—Z/m-O_2N—⟨◯⟩—NH_2	0.953					0.962	0.9	39
Secondary α Tritium KIEs[b]								
$BzOSO_2$⟨◯⟩—Cl/Z—⟨◯⟩—NMe_2	1.061	1.055	1.042		1.048		1.9	40
m-Br—⟨◯⟩—CH_2OSO_2⟨◯⟩—Cl/Z—⟨◯⟩—NMe_2	1.033		1.026		1.033		0.7	40

[a] Bz = —⟨◯⟩—CH_2

[b] Secondary α tritium KIEs are much larger and more sensitive to a change in transition state structure than secondary α deuterium KIEs.

magnitude of the secondary α deuterium KIEs are only affected by the nucleophile in the shortest reacting bond. In all the reactions with an unsymmetrical transition state found to date, the stronger reacting bond is short and the weaker reacting bond is long. Since the "bond strength hypothesis" predicts that little or no change will occur in the stronger (the shortest) reacting bond in an S_N2 transition state when a substituent on the nucleophile, the leaving group, or the substrate is altered,[27] the secondary α deuterium KIE will be insensitive to a change in substituent. In fact, the change in the secondary α deuterium KIE with substituent (Table 6) is always less than 1% (the average change is 0.5%) even when the substituent is changed from strongly electron-donating to strongly electron-withdraw- ing. Finally, it is worth noting that this behavior has also been observed for S_N2 reactions where the change in substituent is in the nucleophile[39,40] (*vide supra*), the leaving group,[39,41] or the substrate[42] (*vide supra*).

The data in Table 6 clearly show that there is two different substituent effects on the secondary α deuterium KIEs of S_N2 reactions, and the KIE data in this manuscript suggest that this is because there are both symmetric and unsymmetric S_N2 transition states and that the relationship between the secondary α deuterium KIE and transition state structure is different for the two types of transition states. While this makes interpreting secondary α deuterium KIEs more difficult, it appears that the change in a secondary α deuterium KIE with substituent will be a good indicator for determining whether an S_N2 transition state is symmetric or unsymmetric.

Conclusions

The KIE data suggest that the magnitude of a secondary α deuterium KIE is not always determined by the nucleophile− leaving group distance in an S_N2 transition state. In S_N2 reactions with unsymmetric transition states, the magnitude of the secondary α deuterium KIE is determined by the length of only the shorter (stronger) reacting bond. Finally, it appears that the change in the secondary α deuterium KIE when a substituent in the nucleophile, the substrate, or the leaving group is changed in an S_N2 reaction can indicate whether the transition state is symmetric or unsymmetric.

Experimental Section

Nitrogen KIEs for the S_N2 Reactions between *Para*-Substituted Sodium Thiophenoxides and Benzyldimethylphenylammonium Ion in DMF at 0 °C. The procedure used to synthesize the benzyldi-

methylphenylammonium nitrate and measure the nitrogen KIE has been described by Westaway and Ali.[1] The only difference was that these KIEs were measured at an ionic strength of 0.90 rather than an ionic strength of 0.64. The ionic strength was adjusted by adding sodium nitrate to the solvent.

The Secondary α Deuterium KIEs for the S_N2 Reactions between *Para*-Substituted Sodium Thiophenoxides and Benzyldimethylphenylammonium Ion in DMF at 0 °C. The preparation of the benzyldimethylphenylammonium nitrate and the benzyl-1,1-d_2-dimethylphenylammonium nitrate have been described.[1] The procedure used to measure the second-order rate constants is also described.[1] The least-squares kinetic plots had correlation coefficients of at least 0.999 and the kinetics were followed to at least 55% of completion. The secondary α deuterium KIEs were obtained by dividing the average (from three separate kinetic runs done using the same stock solutions and at the same time) rate constant for the reaction of the undeuterated substrate with that for the reaction of the deuterated substrate. The KIEs measured with different batches of solvent on different days were identical.

Secondary α Deuterium KIEs for the S_N2 Reactions between Cyanide Ion and *Para*-Substituted Benzyl Chlorides in 20% Aqueous DMSO at 30 °C. The undeuterated *para*-substituted benzyl chlorides were purchased from Aldrich and purified by treatment with sodium bisulfite,[43] dried, and distilled prior to use. The deuterated *para*-substituted benzyl chlorides were synthesized according to the procedure described by Westaway and Waszczylo.[2] The tetraethylammonium cyanide (TEACN) (Aldrich) was used without further purification. Once opened, the TEACN was stored in a vacuum desiccator.

The secondary α deuterium KIEs were calculated from the second-order rate constants for the reactions of the undeuterated and deuterated substrates. Approximately 0.018 g (accurately weighed) of TEACN was dissolved in 2.50 mL of 20% (v/v) aqueous DMSO (Caledon, distilled in glass) containing 2.625×10^{-4} mol/L of the internal standard, *p*-nitrotoluene (Aldrich), under an extra-dry nitrogen (Praxair) atmosphere in an IR[2] glovebag. After this solution had temperature equilibrated for at least one hour at 30.000 ± 0.002 °C, the kinetic run was begun by injecting approximately 0.039 g (0.030 mL) (accurately weighed) of the appropriate *para*-substituted benzyl chloride into the 2.50-mL solution. Between 10 and 14 10-μL samples were withdrawn at various times and injected into an HPLC consisting of a Waters 600 multisolvent delivery system, a 3.9 mm × 15 cm, 3 μm Nova-Pak C18 column, a Waters programmable multiwavelength UV detector, and an HP 3396A integrator. The mobile phase was 55% aqueous acetonitrile for the benzyl chloride reaction and 60% aqueous acetonitrile for the reactions of the *p*-methyl- and the *p*-chlorobenzyl chlorides. The flow rate was 1.2 mL/min, and the ultraviolet detector was set at 260 nm. The concentration of the product, the *para*-substituted benzyl cyanide, was calculated from a calibration curve of the area ratio of the *p*-substituted benzyl cyanide/internal standard peaks and the known concentration of *p*-nitrotoluene.[44] Several experiments showed that the internal standard did not affect the products or the rate of the reaction. The second-order rate constants were calculated in the usual way.[45]

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