

Review Article

Determining transition state structure using kinetic isotope effects[†]

KENNETH C. WESTAWAY*

Department of Chemistry and Biochemistry, Laurentian University, Sudbury, Ont., Canada P3E 2C6

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Abstract: Kinetic isotope effects (KIEs) have been found to be the most powerful tool available to physical organic chemists for determining the mechanism of reactions and for estimating the structure of their transition states. Various types of KIEs including primary-leaving group-, nucleophile-, and α -carbon KIEs and secondary alpha- and beta-deuterium KIEs are introduced. The factors that affect the magnitude of each of these KIEs are covered in some detail. Finally, the use of these KIEs to determine the mechanism of a reaction and to estimate the structure of the transition state for a reaction is discussed. Copyright © 2007 John Wiley & Sons, Ltd.

Keywords: primary-leaving group KIEs; primary nucleophile KIEs; primary α -carbon KIEs; secondary alpha deuterium KIEs; secondary beta deuterium KIEs; transition state structure; S_N2; nucleophilic substitution

One of the most powerful techniques for determining the mechanism of a reaction and for determining the structure of the transition state of the rate-determining step of a reaction is a kinetic isotope effect (KIE). Two types of KIEs, primary and secondary, have been used to determine transition state structure.

PKIEs

A primary KIE is found when the bond to the isotopically labeled atom is breaking or forming in the transition state of the rate-determining step of the reaction. Although KIE theory is best understood in terms of highly complex equations,^{1–4} the approach here will be to develop the concept using a simplified version of the KIE equation:^{5,6}

$$k_L/k_H = (k_L/k_H)_{\text{Tunnel}} \times (v_L^\ddagger/v_H^\ddagger) \times [1 + \underbrace{\sum G(u_i)\Delta u_i}_{\text{KIE}_T} - \underbrace{\sum G(u_i^\ddagger)\Delta u_i^\ddagger}_{\text{TDF}}] \quad (1)$$

$\underbrace{\hspace{10em}}_{\text{TIF}}$

*Correspondence to: K. C. Westaway, Department of Chemistry and Biochemistry, Laurentian University, Sudbury, Ont., Canada P3E 2C6. E-mail: Kwestaway@laurentian.ca

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where k_L is the rate constant for the reaction with the lighter isotope, k_H is the rate constant for the reaction with the heavier isotope,

$$G(u_i) = \left[\frac{1}{2} - 1/u_i + 1/(e^{u_i} - 1) \right]$$

and $\Delta u_i = hc/kT(\Delta v_i)$. The terms h , c , k , and T are Planck's constant, the speed of light, Boltzmann's constant and the absolute temperature, respectively. The Δv_i and Δv_i^\ddagger terms represent the isotope effect on the vibrational frequencies of the reactant and transition state, respectively. In a simple approach to KIE theory, it has been assumed that both the tunneling contribution to the KIE, KIE_T , and the imaginary frequency ratio or temperature-independent factor, TIF, are much smaller than the temperature-dependent factor, TDF. As a result, it has been accepted that the KIE, k_L/k_H , is primarily determined by the TDF, i.e. by the changes in the force constants of the bond(s) to the isotope(s) that occur when the reactants are converted into the transition state of the rate-determining step of a reaction.

If the bond to the isotopically labelled atom is broken in a reaction, but bond breaking has not occurred at the transition state of the rate-determining step of the overall reaction, there is no change in the force constants involving the isotopic atom (the second and third terms in the TDF factor, Equation (1), will be equal) and the $\text{KIE} = 1.000$. If there is a decrease in the

force constant(s) to the isotopically labelled atom(s) on going to the transition state of the rate-determining step of the reaction (the bond to the isotope is breaking in the transition state of the rate-determining step of a reaction), the third term of TDF will be smaller than the second term and a $\text{KIE} > 1.000$ will be observed. Conversely, when the bond to the isotopically labelled atom is forming in the transition state of the rate-determining step of a reaction, the third term in the TDF will be larger than the second term and an inverse (< 1.000) KIE can be observed. This means KIEs are very useful for determining the mechanism of a reaction because they identify the bonds that are changing in the transition state of the rate-determining step of the reaction. Also, because the decrease (increase) in the force constants (the vibrational energy) to the isotope(s) on going to the transition state of the rate-determining step of the reaction is thought to be related to the change in the length of the bond to the isotope(s), the magnitude of the KIE (normal or inverse) can be used to estimate the length of the bonds to the isotope in the transition state of a reaction. This obviously allows one to suggest a structure for the transition state of a reaction.

Three types of primary KIEs have been used to determine the structure of the transition state of a reaction.

Leaving group KIEs

A primary heavy atom-leaving group KIE is observed when the bond to the isotopic atom is breaking in the transition state. Typical examples of primary-leaving group KIEs include a nitrogen (k^{14}/k^{15}) KIE for the reactions of quaternary ammonium salts,⁷ a sulfur (k^{32}/k^{34}) KIE for the reactions of sulfonium salts,⁸ and chlorine (k^{35}/k^{37})⁹ and bromine (k^{79}/k^{81})¹⁰ KIEs for the reactions of chlorides and bromides, respectively. A comprehensive review of this type of KIE has been published by Shiner and Wilgis.¹¹ In a simple approach to these KIEs, the bonding (the vibrational energy) to the isotopically labeled atom in the leaving group is reduced on going to the transition state; hence, both the TDF and the KIE, Equation (1), will be > 1.000 . Since it has been assumed that the magnitude of the isotope effect is directly related to the amount of $\text{C}_\alpha\text{-LG}$ bond rupture in the transition state, the dotted line in Figure 1, the magnitude of these KIEs should provide detailed information about the amount of $\text{C}_\alpha\text{-LG}$ bond rupture in the transition state.

Recently, however, the traditional interpretation of this type of KIE has been questioned.¹² The transition state structures and chlorine KIEs for 26 different $\text{S}_\text{N}2$ (nucleophilic substitution) reactions, Equation (2), with

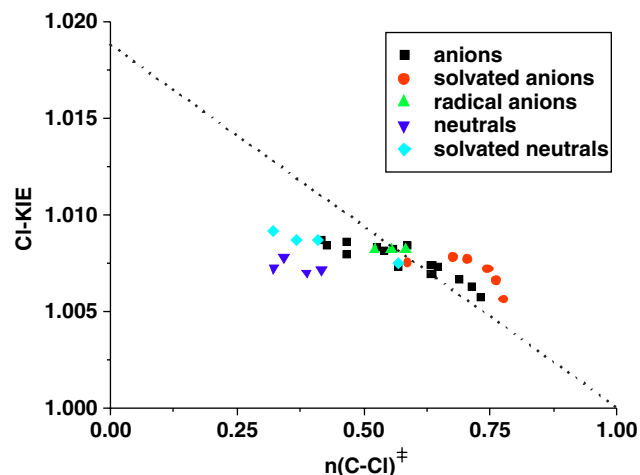
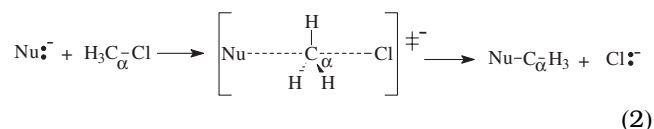


Figure 1 The dependence of the chlorine KIE on the Wiberg $\text{C}_\alpha\text{-Cl}$ transition state bond order for the $\text{S}_\text{N}2$ reactions of methyl chloride with 26 different nucleophiles. The dashed line is the KIE estimated using the BEBOVIB approach. Reprinted with permission from Reference 12. Copyright (2004) American Chemical Society. (The figure is available in color online at www.interscience.wiley.com/Journal/jlcr.)

methyl chloride were calculated



quantum mechanically at the B1LYP/aug-cc-pVDZ level of theory. When the KIEs were plotted against the $\text{C}_\alpha\text{-Cl}$ transition state bond order (Figure 1), the calculated KIEs did not follow the expected relationship but were almost identical ranging from 1.0056 to 1.0091 even though the $\text{C}_\alpha\text{-Cl}$ transition state bond order varied from 0.32 (fairly reactant-like) to 0.73 (very product-like). Clearly, the KIE does not change with the amount of $\text{C}_\alpha\text{-Cl}$ bond rupture in the transition state as had previously been thought. It is worth noting that adding water to the calculation using a solvent continuum model neither altered the chlorine KIEs nor the conclusion, significantly.

As expected, the plot of the percent extension of the $\text{C}_\alpha\text{-Cl}$ bond on going to the transition state varied linearly with the transition state bond order with a correlation coefficient of 0.994. This indicates that the transition state bond order is directly related to the percent extension (the length) of the $\text{C}_\alpha\text{-Cl}$ bond in the transition state even though the transition state bonds are much longer, and weaker, than the normal bonds. The failure of the KIE to respond to the change in the percent $\text{C}_\alpha\text{-Cl}$ bond rupture in the transition state as expected by the simple theory, arises because $[\text{KIE}_\text{T} \times \text{TIF}]$, Equation (1), represents a significant

portion (between 14 and 40%) of the KIE and is not related to the amount of C_x -Cl bond rupture in the transition state structure in any way (Figure 2). It is important to note, however, that the TDF is related to transition state structure as the simple theory predicts (Figure 3). This is important because it means a chlorine KIE, and presumably other leaving group KIEs, can be used to determine the relative amount of

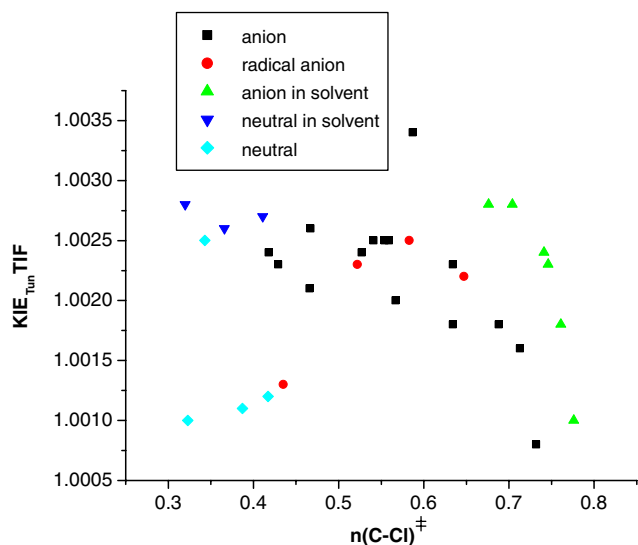


Figure 2 The dependence of the $[KIE_T \times TIF]$ on the C_x -Cl transition state bond order. Reprinted with permission from Reference 12. Copyright (2004) American Chemical Society. (The figure is available in color online at www.interscience.wiley.com/Journal/jlcr.)

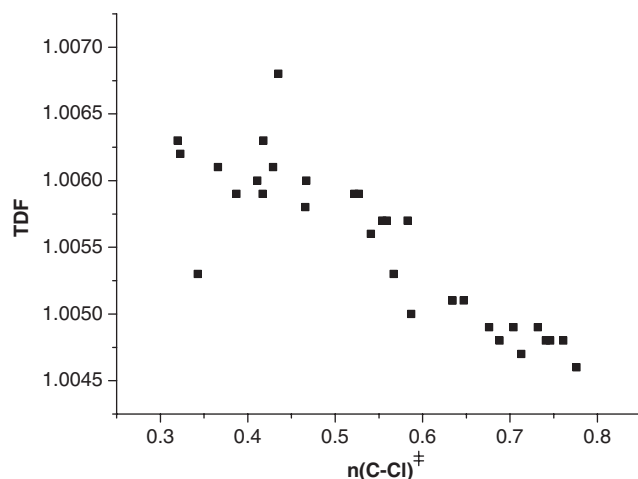


Figure 3 The TDF term versus the Wiberg C_x -Cl transition state bond order for the S_N2 reactions between methyl chloride and 26 different nucleophiles. Reprinted with permission from Reference 12. Copyright (2004) American Chemical Society.

C_x -LG bond rupture in the transition state of a reaction if one calculates the transition structure, the KIE_T , TIF, and the TDF for the reaction and compares the TDF values.

Finally, it is also important to note that the chlorine-leaving group KIEs can be used to determine the effect of a change in solvent¹³ and, in most cases, the substituent effect¹⁴ on transition state structure as the simple theory predicts. The effect of a change of solvent has been investigated using the S_N2 reactions between cyanide ion and ethyl chloride in two very different solvents, DMSO and THF (Table 1).¹³ The slightly smaller chlorine-leaving group KIE indicates that the C_x -Cl transition state bond is slightly shorter in the reaction in THF. Smaller $(k_H/k_D)_\beta$ and $(k^{12}/k^{13})_{Nuc}$ KIEs in THF suggest that the $NC-C_x$ transition state bond is also shorter in THF (*vide infra*). Unfortunately, the α -carbon $^{11}C/^{14}C$ KIEs cannot be related to a change in transition state structure (*vide infra*).

The results in Table 2 show that the magnitude of the chlorine-leaving group KIE can be used to determine the relative amount of C_x -Cl bond rupture in the transition states of reactions differing by a para-substituent. The smaller KIE found when a more electron-withdrawing substituent is on the benzene ring of the substrate indicates that the amount of C_x -Cl bond rupture in the transition state decreases when a more electron-withdrawing substituent is present.¹⁴ The results in Tables 1 and 2 suggest that leaving

Table 1 The secondary β -deuterium-, the α -carbon $^{11}C/^{14}C$ -, the nucleophile carbon $^{12}C/^{13}C$ -, and the chlorine-leaving group KIEs found for the S_N2 reaction between ethyl chloride and tetrabutylammonium cyanide in anhydrous DMSO and THF at 30°C

KIE	DMSO	THF
k^{35}/k^{37}	1.00699 ± 0.00026	1.00659 ± 0.00012
$(k_H/k_D)_\beta$	1.014 ± 0.003	1.003 ± 0.001
$(k^{12}/k^{13})_{Nuc}$	1.0009 ± 0.0007	0.9990 ± 0.0007
$(k^{11}/k^{14})_\alpha$	1.208 ± 0.019	1.212 ± 0.021

Table 2 The chlorine-leaving group KIEs for the S_N2 reactions between cyanide ion and three para-substituted benzyl chlorides at 20°C in THF

Para-substituent	k^{35}/k^{37}
CH ₃	1.00609 ± 0.00014^a
H	1.00591 ± 0.00004
Cl	1.00546 ± 0.00016

^aStandard deviation for five separate experiments measuring the KIE.

group KIEs can be used to study the effect of a change in solvent or in a para-substituent on transition state structure. This is because neither of these changes affect the $[\text{KIE}_T \times \text{TIF}]$ significantly. As a result, the change in the KIE is due to the change in the TDF (transition state structure).

Nucleophile KIEs

A primary incoming nucleophile or nucleophile KIE is observed when the bond to the isotope is being formed in the transition state, e.g. when the isotope is the nucleophilic atom in an $\text{S}_\text{N}2$ reaction. Since there is no bonding between the nucleophile and the substrate in the initial state (the second term in the TDF in Equation (1) is zero or constant¹⁵) but bonding in the transition state (the third term in the TDF in Equation (1) is finite), the TDF factor is less than one. Finally, since the magnitude of the third term in the TDF increases with the amount of bonding between the nucleophile and the α -carbon in the transition state, the KIE decreases as the amount of Nu-C $_\alpha$ bonding in the transition state

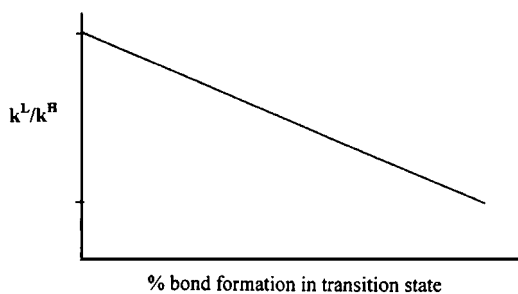


Figure 4 The incoming group KIE versus the percent bond formation in the transition state.

Table 3 The nucleophile nitrogen- and secondary α -deuterium KIEs for the $\text{S}_\text{N}2$ reactions between para-substituted N,N -dimethylanilines and methyl iodide in ethanol at 25°C

Para-substituent on the nucleophile	k^{14}/k^{15}	$(k_{\text{H}}/k_{\text{D}})_\alpha$	Relative transition state structure
CH ₃	1.0036	0.927	N—C $_\alpha$ —I
H	1.0032	0.968	N—C $_\alpha$ —I
C(O)CH ₃	0.9989	1.143	N—C $_\alpha$ —I

Table 4 The nucleophile $^{11}\text{C}/^{14}\text{C}$ carbon- and secondary α -deuterium KIEs for the $\text{S}_\text{N}2$ reactions between meta-chlorobenzyl-para-substituted benzenesulfonates and cyanide ion in 0.5% aqueous acetonitrile at 0°C

Para-substituent on the leaving group	k^{11}/k^{14}	$(k_{\text{H}}/k_{\text{D}})_\alpha$	Relative transition state structure
CH ₃	1.0119	1.028	NC—C $_\alpha$ —O
H	1.0111	1.012	NC—C $_\alpha$ —O
Cl	1.0096	1.009	NC—C $_\alpha$ —O

increases (Figure 4). The maximum value of the KIE is >1.000 when there is little bonding to the isotopic atom in the transition state because both the KIE_T and the TIF, although very small, are greater than 1.000. However, a smaller nucleophile KIE will be observed when there is more Nu-C $_\alpha$ bonding in the transition state of the rate-determining step of the reaction. Examples of nucleophile KIEs that have been used to determine the relative transition state structures of $\text{S}_\text{N}2$ reactions are nucleophile nitrogen (k^{14}/k^{15}) KIEs¹⁶ where nitrogen nucleophiles are used (Table 3) and k^{11}/k^{14} carbon KIEs where cyanide ion is the nucleophile¹⁷ (Table 4). In Tables 3 and 4, a smaller nucleophile KIE indicates that the bond between the nucleophile and the α -carbon is shorter (more fully formed) when a more electron-withdrawing substituent is in the nucleophile and the leaving group, respectively, of the reaction. A larger $(k_{\text{H}}/k_{\text{D}})_\alpha$ indicates a looser transition state structure (*vide infra*).

KIEs where the isotope is transferred between two atoms in the transition state

An example of this type of primary KIE is observed when the α -carbon is labelled in an $\text{S}_\text{N}2$ reaction. α -Carbon KIEs have been extensively used to determine the mechanism of S_N reactions.¹⁸ Small α -carbon $^{12}\text{C}/^{13}\text{C}$ KIEs near 1% are indicative of a carbenium ion S_N (an $\text{S}_\text{N}1$) reaction, while larger KIEs of up to 8% for a $^{12}\text{C}/^{13}\text{C}$ KIE are indicative of an $\text{S}_\text{N}2$ mechanism.

The relationship between the magnitude of the KIE and transition state structure is more complicated than for the other primary KIEs because bond formation and bond breaking are occurring at the isotope concurrently. This means that there are new stretching vibrations in the transition state that are not present

in the reactants.^{19,20} For instance, in a linear three-center transition state such as those found in an S_N2 reaction, the transition state has two independent stretching vibrations (Figure 5). The asymmetric transition state vibration represents translational motion along the reaction coordinate and has an imaginary force constant, while the symmetric transition state vibration has a real force constant.^{19–21} If the motion is truly symmetric, the central atom will be motionless in the vibration and the frequency of the symmetric vibration will not depend on the mass of this atom, i.e. the vibrational frequency will be the same for both isotopically substituted transition states (Figure 6(a)). This means that the difference in activation energy is the difference between the zero-point energies (ZPE) of the symmetric stretching vibrations in the initial state and a maximum KIE will be observed. In instances where bond breaking is either more or less advanced than bond formation, the central atom in the symmetric vibration is not motionless and the stretching frequency depends on the mass of the central atom (Figure 6(b)). In these cases, there will be a ZPE difference for the symmetric vibrations of the isotopically substituted molecules at the transition state and a smaller KIE will be observed. This means that the relationship between the magnitude of the KIE and the percent transfer of the central atom in the transition

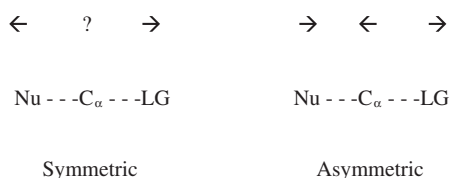


Figure 5 The symmetric and asymmetric stretching vibrations for an S_N2 transition state.

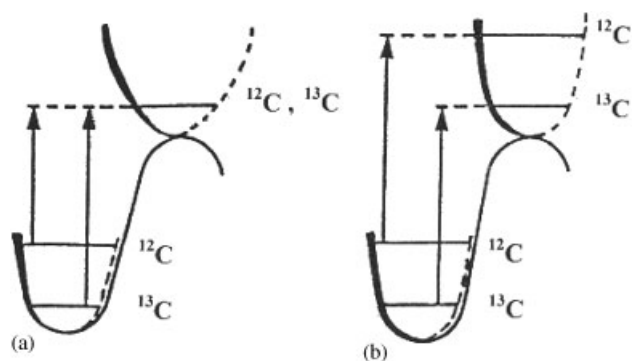


Figure 6 The reaction coordinate diagram for the symmetric stretching vibration when the central atom is (a) symmetrically placed between the Nu and LG (Figure 5) and (b) is closer to either the Nu or LG (Figure 5).

state is curved with a maximum KIE when the α -carbon (the isotopically labeled atom) is 50% transferred from the nucleophile to the leaving group in the transition state (the solid line in Figure 7).

A recent review of the literature²² showed that virtually all of the α -carbon KIEs reported for S_N2 reactions are near the experimental maximum KIE of approximately 8% for a ¹²C/¹³C KIE, 16% for a ¹²C/¹⁴C KIE, and 22% for a ¹¹C/¹⁴C KIE. Since the smallest α -carbon KIE reported for an S_N2 reaction is 80% of the largest observed KIE, the qualitative conclusion would be that all these S_N2 reactions have symmetric or almost symmetric transition states. This is unreasonable because α -carbon KIEs have been measured for S_N2 reactions with very different nucleophiles and leaving groups and in different solvents and must have very different transition state structures. Recently, the α -carbon ¹²C/¹³C KIEs for 22 S_N2 reactions between different nucleophiles and methyl chloride were calculated at the B1LYP/aug-cc-pVDZ level of theory to investigate the relationship between the magnitude of these KIEs and transition state structure.²² The nucleophiles ranged from very weak (F⁻) to very strong (C \equiv N⁻ and SH⁻) and included anionic, neutral, and radical anion nucleophiles to cover a wide range of transition state structures. A plot of the α -carbon KIEs versus the C_α-Cl transition state bond order (Figure 7) shows that all of the calculated KIEs are within 1% of the largest KIE even though the C_α-Cl transition state bond orders vary from 0.32 to 0.73, the Nu-C_α transition state bond orders vary from 0.21 to 0.70, and the transition states range from very reactant-like to very product-like. Since large α -carbon KIEs are observed for transition states that are early, symmetric,

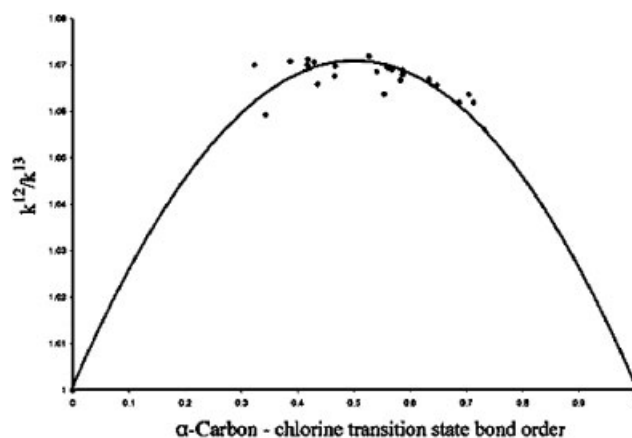


Figure 7 The α -carbon KIE versus the C_α-Cl transition state bond orders for the S_N2 reactions between methyl chloride and 22 different nucleophiles at 298°C. Reprinted with permission from Reference 22. Copyright (2005) American Chemical Society.

or late, the curve in Figure 7 must have a very broad maximum.

It is worth noting that the $[\text{KIE}_T \times \text{TIF}]$ plays a significant role in determining the magnitude of these KIEs, i.e. the KIE_T ranged from 5.0 to 19.1% of the total KIE, the TIF accounted for between 44.9 and 53.3% of the total KIE, and the $[\text{KIE}_T \times \text{TIF}]$ represented between 55.0 and 70.4% of the total KIE. As with the chlorine (leaving group) KIEs, none of the TIF, the KIE_T , or the $[\text{KIE}_T \times \text{TIF}]$ were related to the transition state structure. Finally, the TDF versus the transition state bond $C_\alpha\text{-Cl}$ order did not show the bell-shaped curve the simple theory predicts. This is undoubtedly because the TDF values varied over a very small range, i.e. from 1.0200 to 1.0278, even though there was a huge change in transition state structure. It is worth noting that adding water to the calculation using a solvent continuum model did not change the KIE significantly; hence, solvent does not appear to be the reason for the observed lack of curvature in the KIE versus transition state structure curve.

Because all the α -carbon KIEs found in $\text{S}_{\text{N}}2$ reactions are near the maximum value for these KIEs, α -carbon KIEs are not useful in determining transition state structure. However, although one cannot use these KIEs to determine the transition state structure of $\text{S}_{\text{N}}2$ reactions, these KIEs remain an important tool for determining the mechanism of S_{N} reactions (*vide supra*).

Secondary KIEs

A secondary KIE is observed when the bond(s) to the isotopically labelled atom(s) are not being broken or formed in the transition state of the rate-determining step of the reaction. A secondary KIE is much smaller than a primary KIE because the bonds to the isotope do not undergo the large changes in force constant like those that occur when the bond to the isotope is either forming or breaking in the transition state. As a result, only two types of secondary KIEs, secondary α -deuterium- and secondary β -deuterium KIEs, have been studied in any detail. A secondary α -deuterium KIE $(k_{\text{H}}/k_{\text{D}})_\alpha$ is observed when the hydrogen(s) on the α -carbon are replaced by deuterium atom(s) and a secondary β -deuterium KIE, $(k_{\text{H}}/k_{\text{D}})_\beta$, is observed when the hydrogen(s) on a β -carbon are replaced by deuterium atom(s).

Secondary α -deuterium KIEs

Secondary α -deuterium KIEs have been extensively used to determine the mechanism of S_{N} reactions. S_{N} reactions proceeding via a carbenium ion intermediate,

i.e. $\text{S}_{\text{N}}1$ reactions, have large, normal, isotope effects, $(k_{\text{H}}/k_{\text{D}})_{\alpha\text{-D}}$, between 75 and 100% of the theoretical maximum values for each leaving group, i.e. 1.22 for fluoride, 1.15 for chloride, 1.13 for bromide, 1.09 for iodide, 1.19 for ammonia, and 1.22 for benzenesulfonate.²³ Smaller α -deuterium KIEs, originally thought to be $\leq 1.04_{\alpha\text{-D}}$ for primary substrates,²⁴ are observed for reactions proceeding via the $\text{S}_{\text{N}}2$ mechanism. Two reviews^{24,25} discuss the origin of these KIEs in detail.

Although these KIEs are affected slightly by steric and inductive effects,²⁵ the magnitude of these KIEs is primarily due to changes in the $C_\alpha\text{-H(D)}$ vibrations on going from the reactants to the transition state, i.e. they depend on the change in ZPE on going to the transition state. When the force constants for the $C_\alpha\text{-H(D)}$ bonds in the transition state are smaller than those in the reactant, the ZPE difference is smaller in the transition state. This, in turn, means the free energy of activation is greater for the deuterated reactant, i.e. k_{H} will be greater than k_{D} and the secondary α -deuterium KIE will be >1.000 (Figure 8(a)). When the $C_\alpha\text{-H(D)}$ force constants are greater in the transition state than in the reactant, an isotope effect of less than one is observed (Figure 8(b)).

Since the $C_\alpha\text{-H(D)}$ stretching vibration becomes stronger as the sp^3 hybridized substrate is converted into the sp^2 hybridized carbenium ion in an $\text{S}_{\text{N}}1$ reaction, an inverse KIE, not the large, normal, KIEs observed for $\text{S}_{\text{N}}1$ reactions, would be observed if the KIE were primarily determined by the $C_\alpha\text{-H(D)}$ stretching vibrations. As a result, the origin of secondary α -deuterium KIEs was originally attributed to the change in the $C_\alpha\text{-H(D)}$ out-of-plane bending vibrations on going from the reactant to the transition state. This was because the $C_\alpha\text{-H(D)}$ out-of-plane bending vibrations would be easier (lower energy) in the transition state

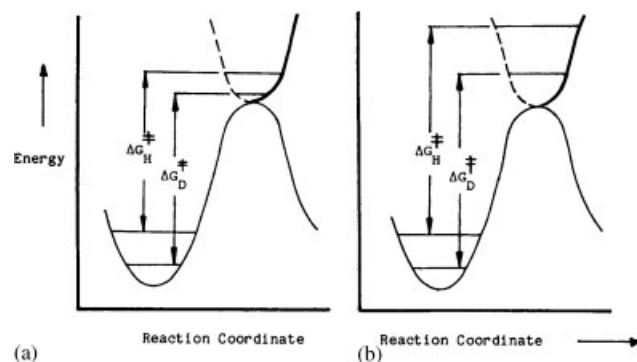


Figure 8 The reaction coordinate diagram for the secondary α -deuterium KIE for an S_{N} reaction with (a) smaller force constants for the $C_\alpha\text{-H(D)}$ bonds in the transition state and (b) greater force constants for the $C_\alpha\text{-H(D)}$ bonds in the transition state.

when the tetrahedral substrate is converted into the trigonal planar carbenium ion and the bond angle of the (D)H-C_x-H(D) bonds increases from approximately 109.5° in the substrate to nearly 120° in the transition state (Figure 9). Since the C_x-H(D) out-of-plane bending vibrations are easier (lower energy) in the transition state, the large KIE that is found for S_N1 reactions is expected (Figure 8(a)). In an S_N2 reaction on the other hand, the tetrahedral substrate is converted into a pentavalent transition state (Figure 9). This would increase the energy of the C_x-H(D) out-of-plane bending vibrations and lead to the small, normal, or inverse KIEs that are observed for S_N2 reactions (Figure 8(b)).

This explanation for the origin of these KIEs suggested how the magnitude of these KIEs was related to the structure of the transition state of an S_N2 reaction. It was proposed that the magnitude of these KIEs in an S_N2 reaction was determined by the amount of steric crowding at the C_x-H(D) bonds by the leaving group and the nucleophile in the transition state, i.e. the transition state C_x-H(D) out-of-plane bending vibrations would be higher energy (the ZPE is larger) when the transition state is tighter with shorter C_x-Nu and/or C_x-LG bonds. This meant that a smaller KIE would be found for a reaction with a tighter transition state with shorter Nu-C_x and/or C_x-LG bonds (Figure 10).

Recently, however, this explanation has been revised. The first indication that the origin of these KIEs was more complicated than the simple theory suggested, came from theoretical calculations by Williams,²⁶ by Truhlar and coworkers^{27,28} and by Wolfe and Kim.²⁹ All these workers reported that the major contribution to the secondary α-deuterium KIE in S_N2 reactions was due to the C_x-H(D) stretching vibrations rather than the C_x-H(D) out-of-plane bending vibrations. However, although the magnitude of a secondary α-deuterium KIE for an S_N2 reaction is primarily determined by the change in the C_x-H(D) stretching vibrations on going

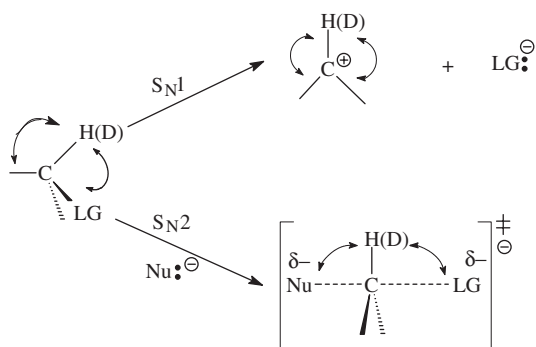


Figure 9 The C_x-H(D) out-of-plane bending vibrations in the substrate and in the S_N1 and S_N2 transition states.

to the transition state, a theoretical study by Poirier *et al.*³⁰ showed that the C_x-H(D) bending vibrations are also important in determining the magnitude of these KIEs and that they are dominant in determining the relationship between the magnitude of these KIEs and the transition state structure of S_N2 reactions. These workers calculated the transition structures and secondary α-deuterium KIEs for the S_N2 reactions where the nucleophile was F⁻, Cl⁻, OH⁻, SH⁻, NH₂⁻, or SCH₃⁻ and the substrate was either methyl fluoride or chloride. In this study, the KIE was expressed as

$$(k_{\text{H}}/k_{\text{D}}) = (k_{\text{H}}/k_{\text{D}})_{\text{trans}}(k_{\text{H}}/k_{\text{D}})_{\text{vib}}(k_{\text{H}}/k_{\text{D}})_{\text{rot}}(k_{\text{H}}/k_{\text{D}})_{\text{T}} \quad (3)$$

where the tunneling term $(k_{\text{H}}/k_{\text{D}})_{\text{T}}$ was determined using the Wigner correction and the vibrational contribution to the KIE, $(k_{\text{H}}/k_{\text{D}})_{\text{vib}}$, was factored into a stretching contribution $((k_{\text{H}}/k_{\text{D}})_{\text{stretch}})$ and a bending contribution, $((k_{\text{H}}/k_{\text{D}})_{\text{bend}})$:

$$(k_{\text{H}}/k_{\text{D}})_{\text{vib}} = (k_{\text{H}}/k_{\text{D}})_{\text{stretch}}(k_{\text{H}}/k_{\text{D}})_{\text{bend}} \quad (4)$$

the total KIEs, the total vibrational contribution, and both the stretching and bending contributions to the KIE for 11 S_N2 reactions with methyl chloride and methyl fluoride (Table 5) confirmed that the stretching vibration contribution to the $(k_{\text{H}}/k_{\text{D}})_{\text{s}}$ for all the methyl fluoride and chloride reactions was large and

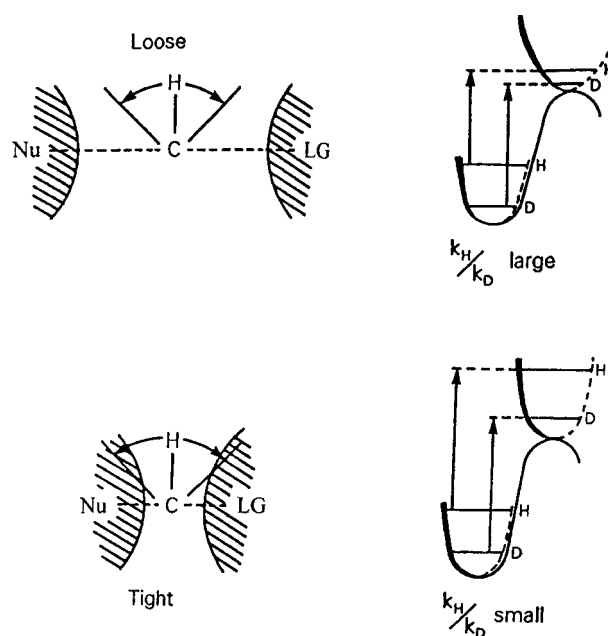


Figure 10 The relationship between the looseness (the nucleophile-leaving group distance) of the S_N2 transition state and the magnitude of the secondary α-deuterium KIE as determined by the C_x-H(D) out-of-plane bending vibrations in the transition state. Reprinted with permission from Reference 37. Copyright (1997) American Chemical Society.

Table 5 The HF/6-31 + G* KIEs and the vibrational contributions to the KIEs for 11 S_N2 reactions of methyl fluoride and methyl chloride with several different nucleophiles at 25°C

Nucleophile	$(k_{\text{H}}/k_{\text{D}})_{\alpha}$	$(k_{\text{H}}/k_{\text{D}})_{\text{stretch}}$	$(k_{\text{H}}/k_{\text{D}})_{\text{bend}}$	$(k_{\text{H}}/k_{\text{D}})_{\text{vib}}$	R_{TS}
<i>Methyl fluoride KIEs</i>					
F ⁻	0.846	0.677	0.978	0.656	3.6930
OH ⁻	0.871	0.686	1.024	0.648	3.7845
NH ₂ ⁻	0.904	0.692	1.054	0.643	3.9055
Cl ⁻	1.002	0.665	1.157	0.762	4.2611
SH ⁻	1.010	0.663	1.215	0.701	4.3088
<i>Methyl chloride KIEs</i>					
F ⁻	0.882	0.705	1.098	0.711	4.2611
OH ⁻	0.907	0.714	1.128	0.704	4.3714
NH ₂ ⁻	0.897	0.716	1.112	0.665	4.4599
Cl ⁻	0.935	0.680	1.178	0.739	4.7880
SH ⁻	0.953	0.690	1.197	0.688	4.8844
SCH ₃ ⁻	0.953	0.701	1.221	0.552	4.8713

inverse as Williams, Truhlar *et al.*, and Wolfe and Kim reported. The bending contributions to the KIE, on the other hand, were close to or greater than 1.000. However, since the magnitude of $(k_{\text{H}}/k_{\text{D}})_{\text{stretch}}$ is greater than $(k_{\text{H}}/k_{\text{D}})_{\text{bend}}$, as Truhlar and Wolfe and Kim reported, the total KIEs are inverse, or small and normal, as expected for the S_N2 reactions of methyl compounds. However, an examination of Table 5 shows that the $(k_{\text{H}}/k_{\text{D}})_{\text{stretch}}$ is effectively constant for each leaving group, i.e. it varies from 0.66 to 0.69 (by only 0.03) when the nucleophile changes from F⁻ to SH⁻ in the methyl fluoride reactions and from 0.68 to 0.72 (by only 0.04) when the nucleophile changes from F⁻ to SH⁻ in the methyl chloride reactions. $(k_{\text{H}}/k_{\text{D}})_{\text{bend}}$, on the other hand, changes from 0.98 to 1.22, i.e. by 0.24 in the methyl fluoride reactions, and by 0.12, i.e. from 1.10 to 1.22, in the methyl chloride reactions. Thus, the change in $(k_{\text{H}}/k_{\text{D}})_{\text{bend}}$ is eight times greater than the change in $(k_{\text{H}}/k_{\text{D}})_{\text{stretch}}$ for the methyl fluoride reactions and is three times greater for the methyl chloride reactions! Obviously, the bending vibration contributions to the KIE are much more sensitive to a change of nucleophile than the stretching vibration contribution in both reactions. Moreover, since $(k_{\text{H}}/k_{\text{D}})_{\text{stretch}}$ is effectively constant, *but different, for each leaving group*, the change in $(k_{\text{H}}/k_{\text{D}})_{\alpha}$ with a change in nucleophile is obviously determined by the change in $(k_{\text{H}}/k_{\text{D}})_{\text{bend}}$. This conclusion was confirmed because plots of $(k_{\text{H}}/k_{\text{D}})_{\alpha}$ versus $(k_{\text{H}}/k_{\text{D}})_{\text{bend}}$ (Figure 11) had correlation coefficients (r) of 0.985 for the methyl chloride reactions and 0.983 for the methyl fluoride reactions, respectively, whereas they were only 0.645 and 0.776, respectively, for the $(k_{\text{H}}/k_{\text{D}})_{\alpha}$ versus $(k_{\text{H}}/k_{\text{D}})_{\text{stretch}}$ plot (Figure 12). The important observation, however, was that both the $(k_{\text{H}}/k_{\text{D}})_{\alpha}$ and $(k_{\text{H}}/k_{\text{D}})_{\text{bend}}$

correlated very well with R_{TS} , the nucleophile-leaving group (Nu-LG) distance in the S_N2 transition state, where

$$R_{\text{TS}} = [C_{\alpha}-\text{Nu}]_{\text{TS}} + [C_{\alpha}-\text{LG}]_{\text{TS}} \quad (5)$$

$[C_{\alpha}-\text{Nu}]_{\text{TS}}$ and $[C_{\alpha}-\text{LG}]_{\text{TS}}$ are the lengths of the C_α-Nu and C_α-LG transition state bonds, respectively. The plot of $(k_{\text{H}}/k_{\text{D}})_{\alpha}$ versus R_{TS} (Figure 13) has $r = 1.000$ and 0.973 for the methyl fluoride and methyl chloride reactions, respectively, and the $(k_{\text{H}}/k_{\text{D}})_{\text{bend}}$ versus R_{TS} plot (Figure 14) has $r = 0.987$ and 0.957 for the methyl fluoride and chloride reactions, respectively. These plots indicate that as R_{TS} increases (the transition state becomes looser), both the $(k_{\text{H}}/k_{\text{D}})_{\text{bend}}$ and $(k_{\text{H}}/k_{\text{D}})_{\alpha}$ increase as the bending vibration model predicts. Therefore, although the stretching vibration plays a significant role in determining the magnitude of the KIE for S_N2 reactions of a substrate *with a particular leaving group*, $(k_{\text{H}}/k_{\text{D}})_{\text{bend}}$ and the trend in $(k_{\text{H}}/k_{\text{D}})_{\alpha}$ are determined by the looseness of the S_N2 transition state.

It is important to note that the $(k_{\text{H}}/k_{\text{D}})_{\alpha}$ for the ethyl chloride and ethyl fluoride S_N2 reactions with several nucleophiles showed the same relationship between the α-deuterium KIE and transition state structure (R_{TS}). However, the (bending/stretching) contribution to the KIE is significantly greater for the S_N2 reactions of ethyl substrates, i.e. it increased from 0.48 for the methyl chloride reactions to 0.88 for the reactions of ethyl chloride and from 0.17 to 0.22 for the methyl and ethyl fluoride reactions. Thus, the bending vibrations play a greater role in determining the magnitude of the $(k_{\text{H}}/k_{\text{D}})_{\alpha}$ for the reactions of more complex substrates. This accounts for the change from the inverse $(k_{\text{H}}/k_{\text{D}})_{\alpha}$ s often found for the S_N2 reactions of methyl substrates

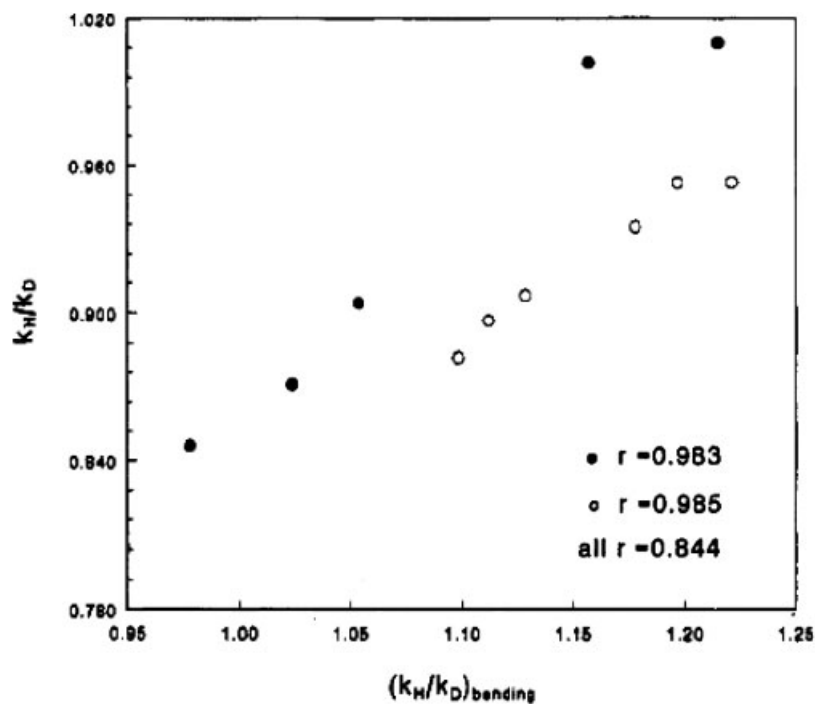


Figure 11 The total KIE versus the bending vibration contribution to the KIE for the S_N2 reactions of methyl chloride and methyl fluoride in Table 5 with various nucleophiles. The open circles are for the methyl chloride reactions and the solid circles are for the methyl fluoride reactions. Reprinted with permission from Reference 30. Copyright (1994) American Chemical Society.

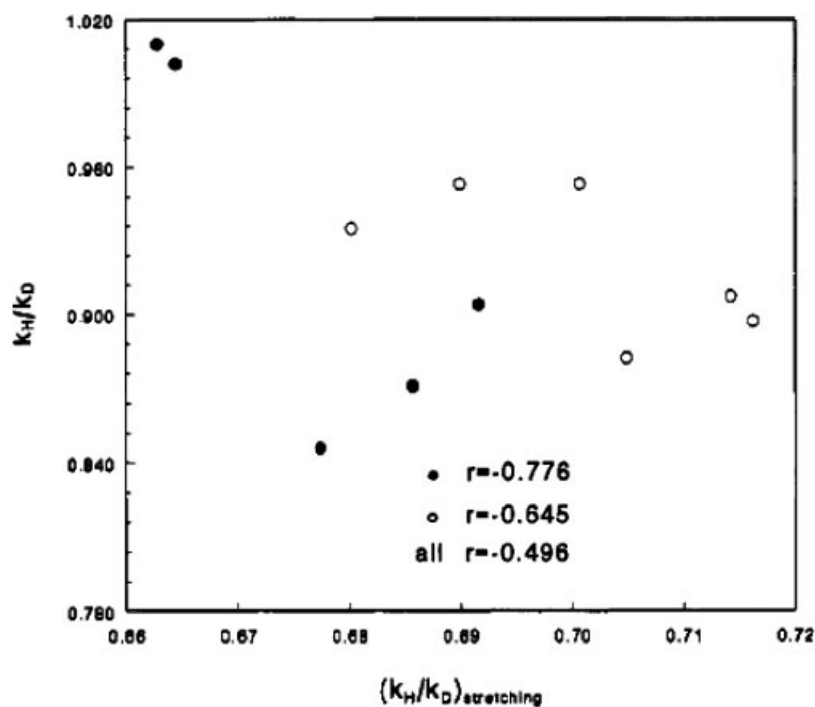


Figure 12 The total KIE versus the stretching vibration contribution to the KIE for the S_N2 reactions of methyl chloride and methyl fluoride in Table 5 with various nucleophiles. The open circles are for the methyl chloride reactions and the solid circles are for the methyl fluoride reactions. Reprinted with permission from Reference 30. Copyright (1994) American Chemical Society.

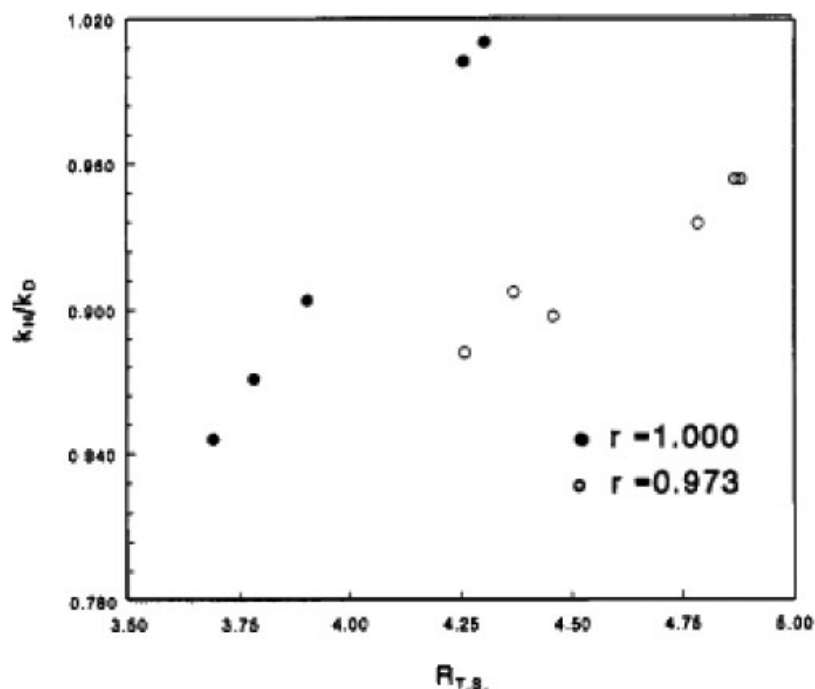


Figure 13 The total KIE versus R_{TS} for the S_N2 reactions of methyl chloride and methyl fluoride in Table 5 with various nucleophiles. The open circles are for the methyl chloride reactions and the solid circles are for the methyl fluoride reactions. Reprinted with permission from Reference 30. Copyright (1994) American Chemical Society.

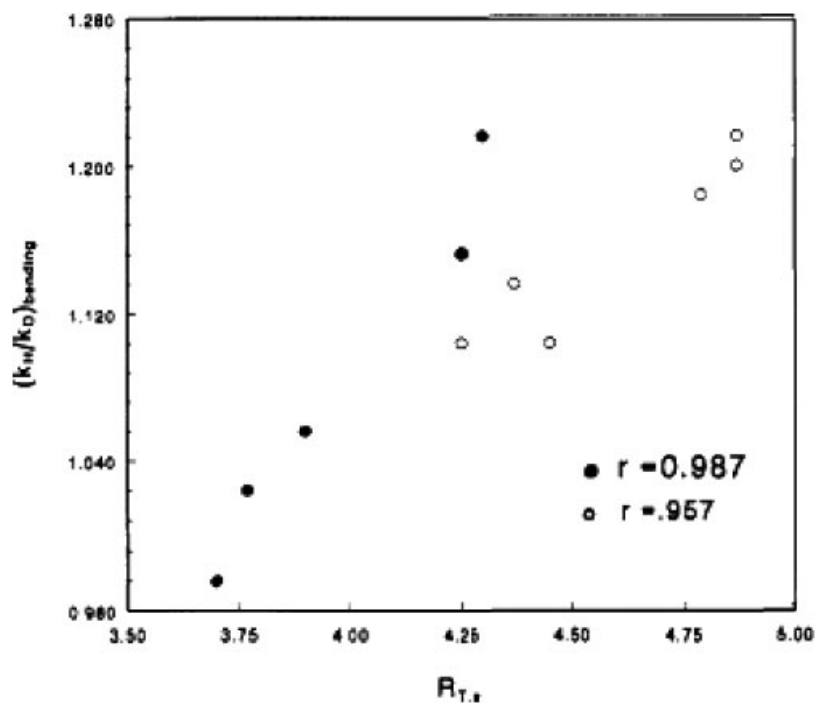


Figure 14 The bending vibration contribution to the KIE versus R_{TS} for the S_N2 reactions of methyl chloride and methyl fluoride in Table 5 with various nucleophiles. The open circles are for the methyl chloride reactions and the solid circles are for the methyl fluoride reactions. Reprinted with permission from Reference 30. Copyright (1994) American Chemical Society.

to the normal $(k_H/k_D)_{\alpha}$ s found for the S_N2 reactions of larger (more complex) substrates, such as ethyl and benzyl.

Finally, it is worth noting that the above conclusions are supported by both theoretical and experimental evidence. A theoretical study by Barnes and Williams³¹ found the $(k_H/k_D)_{\alpha}$ s for the S_N2 reactions of methyl-, ethyl-, and isopropyl chlorides were composed of an almost constant, inverse, $C_{\alpha}-H(D)$ stretching vibration contribution and a normal $C_{\alpha}-H(D)$ bending vibration contribution that increased as the transition state became looser. Another theoretical study by Glad and Jensen³² concluded that (i) the $C_{\alpha}-H(D)$ stretching vibration contribution was important for determining the magnitude of the total KIE; (ii) the change in the KIE with transition state looseness was primarily due to the changes that occur in the $(D)H-C_{\alpha}-H(D)$ out-of-plane bending and umbrella bending vibrations; and (iii) that neither the other transition state vibrations nor the rotational or the translational contributions to the KIE have a significant effect on the magnitude of the KIE. Their results also led them to conclude that the KIE was

larger for a looser transition state. Finally, an experimental study by Bierbaum and coworkers³³ measured the secondary α -deuterium KIEs for the S_N2 reactions of methyl fluoride, chloride, bromide, and iodide with several different nucleophiles in the gas phase. They also calculated the KIEs for these reactions using several levels of theory. All of the calculated KIEs and the experimental KIEs for the methyl chloride S_N2 reactions correlated with the R_{TS} looseness parameter for each leaving group (Figure 15). The authors suggested that the KIE versus R_{TS} relationship failed for the experimental methyl bromide and iodide reactions (Figure 15) because the methyl bromide and iodide reactions occur so rapidly in the gas phase that statistical thermodynamics and transition state theory do not apply. The important observation, however, is that there is evidence from both experiment and theory indicating that the R_{TS} model works for S_N2 reactions with the same leaving group.

Although the magnitude of these KIEs has been attributed to other factors,^{34,35} the R_{TS} model seems to be the best way of interpreting the secondary α -deuterium KIEs in S_N2 reactions with the same leaving

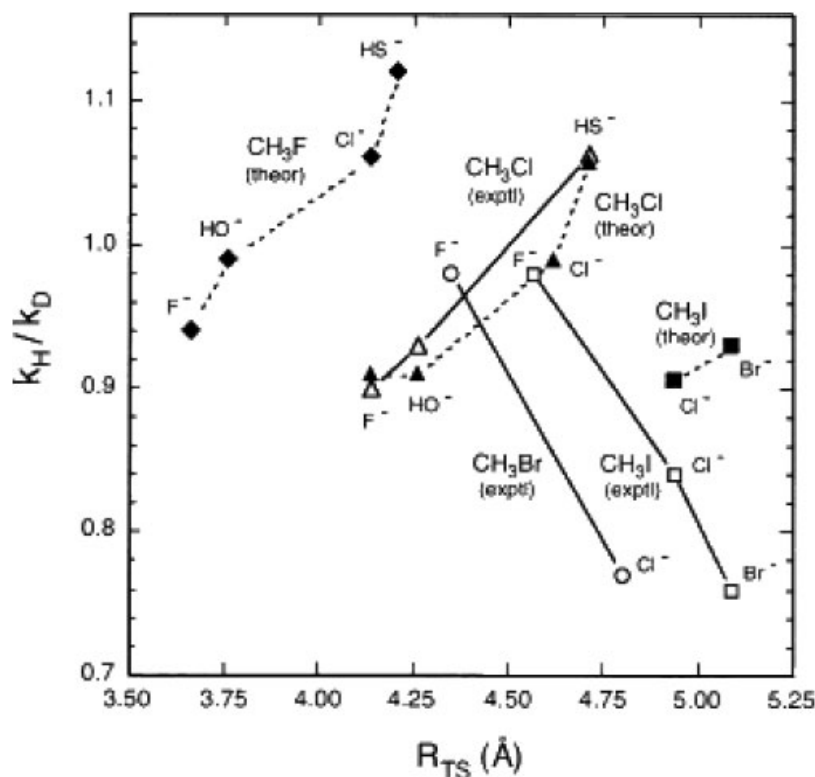
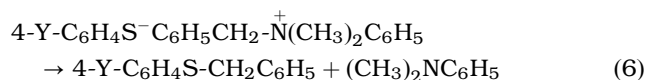


Figure 15 The experimental (open symbols) and theoretical (closed symbols) secondary α -deuterium KIEs for the S_N2 reactions of methyl halides with various nucleophiles in the gas phase. The R_{TS} values were obtained from the theoretical calculations of the transition structure using transition state theory at the MP2/6-31 + G*, MP2/6-31 + G(d), MP2/PDZ, or MP2/PTZ level. Although R_{TS} varied with the level of theory, the correlations remained. Reprinted with permission from Reference 33. Copyright (2001) Elsevier.

group. However, Davico and Bierbaum³⁶ have suggested that crowdedness, rather than looseness, of the transition state is a better way of understanding the magnitude of a secondary α -deuterium KIE for reactions with polyatomic nucleophiles and diatomic nucleophiles with heavy atoms that are off the Nu-C_x-LG axis and can sterically hinder the C_x-H(D) bending vibrations in the transition state. In these cases, the C_x-H(D) bending vibrations will be of higher energy than expected for a particular R_{TS} (looseness of the transition state) and a smaller KIE than predicted by the R_{TS} model will be observed. Thus, while monatomic and diatomic nucleophiles with a hydrogen atom, such as those used by Poirier *et al.*, follow the looseness or R_{TS} model, polyatomic or diatomic nucleophiles with two or more heavy atoms can affect the C_x-H(D) bending vibrations in the transition state and the magnitude of the KIE.

Another factor that affects the magnitude of a secondary α -deuterium KIE is the symmetry of the S_N2 transition state. If one of the reacting bonds is short and the other is very long in an unsymmetric S_N2 transition state (Figure 16), a change in the length of the longer bond would not affect the C_x-H(D) bending vibrations in the transition state significantly. In these cases, the magnitude of the KIE would only be determined by changes in the length of the shorter reacting bond in the transition state. The set of KIEs that suggested that the magnitude of a secondary α -deuterium KIE might be determined by only the change in the shorter of the Nu-C_x and C_x-LG bonds in the transition state was found with the S_N2 reactions between several para-substituted thiophenoxide ions and benzyldimethylphenylammonium ion³⁷ (Equation (6)). Both the nitrogen (leaving group)- and secondary α -deuterium KIEs found for



these reactions at 0°C in DMF at an ionic strength of 0.904 M, (Table 6), are identical considering the

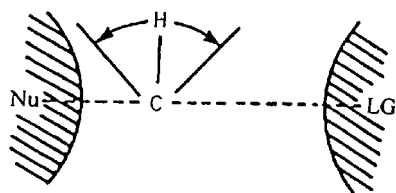


Figure 16 The C_x-H(D) out-of- plane bending vibrations in an unsymmetric S_N2 transition state. Reprinted with permission from Reference 37. Copyright (1997) American Chemical Society.

experimental errors. The simplest interpretation of these identical KIEs is that the transition state does not change when the substituent on the nucleophile is altered. This suggestion seemed 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. These KIEs could be understood if one assumed 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_x-N bond rupture in the transition state.¹⁴ If this is the case, all three reactions have identical amounts of C_x-N bond rupture in the transition state. Then, if the transition state structure changes with the change in nucleophile, the change in transition state structure must occur in the S-C_x bond. Identical secondary α -deuterium KIEs could be observed if the transition states were unsymmetric with very long S-C_x and short C_x-N transition state bonds. In this case, the magnitude of the secondary α -deuterium KIE would only be determined by the shorter (C_x-N) reacting bond (Figure 16) because the nucleophilic sulfur atom would be too far away to affect the C_x-H(D) bending vibrations in all three transition states. Since the change in transition state structure with substituent occurs in the very long S-C_x transition state bonds and the C_x-N transition state bonds are not altered by the change in substituent, the secondary α -deuterium KIEs are identical for the three reactions.

This suggestion that the transition states for these reactions are unsymmetric with long S-C_x and short C_x-N bonds was confirmed by a comparison of the nitrogen-leaving group and secondary α -deuterium KIEs for the S_N2 reaction between benzyldimethylphenylammonium ion and thiophenoxide ion (Equation (6)) at two different ionic strengths.³⁸ The KIEs in Table 7 show that the transition state for the 0.904 M ionic strength reaction is, indeed, unsymmetric with long S-C_x and short C_x-N bonds. The nitrogen KIE of 1.0165 found at the high ionic strength for the reaction of the

Table 6 Nitrogen-leaving group- and secondary α -deuterium KIEs for the S_N2 reactions between several para-substituted sodium thiophenoxides and benzyldimethylphenylammonium nitrate in DMF at 0°C at an ionic strength of 0.940 M

Para-substituent on the thiophenoxide ion	k^{14}/k^{15}	$(k_{\text{H}}/k_{\text{D}})_{\alpha}$
CH ₃ O	1.0162 ± 0.0007	1.221 ± 0.012
H	1.0166 ± 0.0004	1.215 ± 0.011
Cl	1.0166 ± 0.0005	1.215 ± 0.013

Table 7 The nitrogen-leaving group and secondary α -deuterium KIEs and Hammett ρ_{Nuc} values for the $\text{S}_{\text{N}}2$ reaction between sodium thiophenoxide and benzyldimethylphenylammonium nitrate at different ionic strengths in DMF at 0°C

Ionic strength (M)	k^{14}/k^{15}	$(k_{\text{H}}/k_{\text{D}})_z$	Hammett ρ_{Nuc}
0.904	1.0165 ± 0.0004	1.215 ± 0.011	-1.62 ± 0.01
0.64	1.0200 ± 0.0007	1.179 ± 0.007	-1.76 ± 0.19

benzyldimethylphenylammonium ion (Table 6) is only 38% of the theoretical maximum nitrogen KIE of 1.044^{39} and is significantly smaller than the nitrogen KIE of 1.0200 found for the same reaction at an ionic strength of 0.64 (Table 7). Therefore, $\text{C}_z\text{-N}$ bond rupture is not well advanced (the $\text{C}_z\text{-N}$ bond must be reasonably short) in the transition state of the high ionic strength reaction. The secondary α -deuterium KIE of 1.215 for the high ionic strength reaction, on the other hand, is the largest (approximately 11%/ $\alpha\text{-D}$) that has been found for an $\text{S}_{\text{N}}2$ reaction of a quaternary ammonium ion and is significantly larger than the $(k_{\text{H}}/k_{\text{D}})_z = 1.179$ found for the same reaction at an ionic strength of 0.64 M (Table 7). Since the $\text{C}_z\text{-N}$ bond is shorter and the secondary α -deuterium KIE is larger in the high ionic strength reaction, the transition state for the high-ionic strength reactions must be very loose with very long S-C_z bonds. Thus, the KIE data suggest that the high ionic strength reactions with constant nitrogen and secondary α -deuterium KIEs (Table 6) have very reactant-like transition states with short $\text{C}_z\text{-N}$ and very long S-C_z bonds. It is worth noting that the small Hammett ρ_{Nuc} value -1.62 observed for the high ionic strength reaction (Table 7) indicates the S-C_z transition state bond is longer (less formed) in the high ionic strength reaction. Finally, it is worth noting that this suggestion that the S-C bond changes while there is little or no change in the C-N bonds in these transition states, is supported by Westaway's 'Bond Strength Hypothesis'⁴⁰ 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 $\text{S}_{\text{N}}2$ transition state when a substituent in the nucleophile, the substrate, or the leaving group is altered.' Since the $\text{C}_z\text{-S}$ bond is weaker than the $\text{C}_z\text{-N}$ bond in these $\text{S}_{\text{N}}2$ reactions, the 'Bond Strength Hypothesis' predicts that changing the nucleophile should not affect the $\text{C}_z\text{-N}$ bond significantly but should lead to a significant change in the weaker S-C_z bond.

Secondary α -deuterium KIEs can also be used to determine the symmetry of an $\text{S}_{\text{N}}2$ transition state.⁴¹ The data in Table 8 show there are two different substituent effects on the secondary α -deuterium KIEs of the $\text{S}_{\text{N}}2$ reactions of benzyl substrates. The KIEs of some $\text{S}_{\text{N}}2$ reactions decrease markedly when the substituent is more electron withdrawing, while in

other $\text{S}_{\text{N}}2$ reactions, the KIEs are almost independent of substituent. In $\text{S}_{\text{N}}2$ reactions with symmetric transition states, the Nu-C_z and $\text{C}_z\text{-LG}$ transition state bonds have comparable bond orders, the $\text{C}_z\text{-H(D)}$ bending vibrations are affected by both the Nu-C_z and $\text{C}_z\text{-LG}$ transition state bonds, and the magnitude of the secondary α -deuterium KIE is determined by the Nu-LG transition state distance (R_{TS}). In these reactions, the secondary α -deuterium KIE decreases markedly (by between 2.8 and 12%) when a more electron-withdrawing substituent is added to the benzene ring on the α -carbon, the nucleophilic atom, or the leaving group. In $\text{S}_{\text{N}}2$ reactions with unsymmetric transition states, the $\text{C}_z\text{-H(D)}$ bending vibrations are only affected by the changes in the shortest reacting bond. In all the reactions with unsymmetric transition states 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 $\text{S}_{\text{N}}2$ transition state when a substituent on the nucleophile, the leaving group, or the substrate is altered⁴⁰, the secondary α -deuterium KIE should be insensitive to a change in substituent. In fact, the change in the secondary α -deuterium KIE with substituent is always less than 1% (the average change is 0.5%) even when the substituent changes from strongly electron-donating to strongly electron-withdrawing. It is worth noting that this behavior has been observed for $\text{S}_{\text{N}}2$ reactions whether the change in substituent is in the nucleophile, the leaving group, or the substrate; hence, it seems to be a general phenomenon.

The secondary α -deuterium KIEs in $\text{S}_{\text{N}}2$ reactions are also affected by the presence of a bulky-leaving group. This was first suggested by Westaway and Ali⁷ who attributed the extremely large secondary α -deuterium KIEs of between 1.151 and 1.207 ($1.073\text{--}1.099/\alpha\text{-D}$) (The maximum value expected for a secondary α -deuterium KIE in an $\text{S}_{\text{N}}2$ reaction was $\leq 1.04/\alpha\text{-D}$) found for the $\text{S}_{\text{N}}2$ reactions of benzyldimethyl-*p*-substituted phenylammonium ions and thiophenoxide ion (Equation (7)) to the great relief of the steric crowding of the $\text{C}_z\text{-H(D)}$

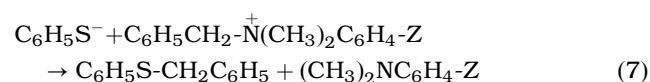


Table 8 The secondary α -deuterium KIEs for S_N2 reactions with symmetric transition states where the magnitude of the KIE varies with the nucleophile-leaving group distance and for unsymmetric transition states where the magnitude of the KIE is determined by the length of only the shortest, and strongest, reacting bond

Substrate/nucleophile	$(k_H/k_D)_\alpha$, para-substituent (Z)						Δ KIE (%)
	CH ₃ O	CH ₃	H	Cl	Br	NO ₂	
<i>S_N2 reactions with symmetric transition states</i>							
Z-BzCl ^a /PhS ⁻	1.126	1.096	1.056	1.046	1.039		8.7
Z-BzCl/H ₂ O			1.096		1.032		6.3
Z-BzCl/H ₂ O in 10% aq CH ₃ CN			1.059		1.008		5.1
Z-BzOBs/H ₂ O in 90% aq EtOH			1.124			1.004	12.0
Z-BzCl/H ₂ O			1.092	1.061			3.1
Z-BzBr/S ₂ O ₃ ²⁻			1.063			1.032	3.1
Z-BzBr/N ₃ ⁻			1.024			0.996	2.8
Z-BzBr/OH ⁻	1.028		0.984				4.4
4-BzN ⁺ Me ₂ Ph-Z/PhS ⁻	1.207		1.179	1.151			5.6
<i>S_N2 reactions with unsymmetric transition states</i>							
BzN ⁺ Me ₂ Ph/Z-PhS ⁻	1.221		1.215	1.215			0.6
Z-BzCl/CN ⁻		1.008	1.011	1.002			0.99
4-BzOSO ₂ Ph-Z/4-MeOPhNH ₂	1.096					1.102	0.6
4-BzOSO ₂ Ph-Z/4-NO ₂ PhNH ₂	1.098					1.095	0.3
MeOSO ₂ Ph-Z/4-MeOPhNH ₂	0.990					0.993	0.3
MeOSO ₂ Ph-Z/ m-NO ₂ PhNH ₂	0.971					0.974	0.3
EtOSO ₂ Ph-Z/4-MeOPhNH ₂	0.981					0.984	0.3
EtOSO ₂ Ph-Z/m-NO ₂ PhNH ₂	0.953					0.962	0.9
<i>Secondary α-tritium KIEs</i>							
4-BzOSO ₂ Ph-Cl/4-Z-PhNH ₂	1.061	1.055	1.042		1.048		1.9
m-BrBzOSO ₂ Ph-Cl/4-Z-PhNH ₂	1.033		1.026			1.033	0.7

^aBz = -C₆H₄-CH₂

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bending vibrations in the substrate due to the bulky-leaving group, on going to a loose transition state with a long bond to the leaving group (Figure 8(a)). This explanation for these unexpectedly large KIEs is reasonable because the fairly small Hammett ρ_{Nuc} of -1.70 (the equilibrium ρ_{Nuc} value for this process is -3.30)⁴² indicated that the S-C_x transition state bonds were long. The large nitrogen-leaving group KIEs ranging from 1.0197 to 1.0202 (approximately 50% of the theoretical maximum nitrogen KIE)³⁹ and a Hammett ρ_{LG} of +2.04 (the equilibrium Hammett ρ_{LG} value for this reaction would be approximately +4)⁴³ indicated that there was substantial C_x-N bond rupture in the transition state.

Other workers have reported unusually large secondary α -deuterium KIEs in S_N2 reactions with bulky-leaving groups. For instance, KIEs of 1.09 and 1.10/ _{α -D} and of 1.178 and 1.184/ _{α -D}⁴⁵ were reported for reactions with the bulky *N,N*-dimethylaniline-leaving group and Craze *et al.*⁴⁶ found very large KIEs ranging from 1.05 to 1.16/ _{α -D} when the leaving group was the bulky 2,4-dinitrophenoxide ion. Unusually large secondary α -

deuterium KIEs ranging from 1.07 to 1.18/ _{α -D} were also found for S_N2 reactions with the *N,N*-dimethyl-*m*-nitroaniline ion-leaving group.⁴⁷ It has even been suggested that the lone pairs of electrons on the oxygens of perchlorate- and arenesulfonate-leaving groups affect the C_x-H(D) bending vibrations in the ground state and are responsible for the larger α -deuterium KIEs found in these S_N2 reactions.⁴⁸

Although we do not know how to interpret secondary α -deuterium KIEs for S_N2 reactions with different leaving groups, overwhelming evidence from theoretical calculations has shown that the KIE is primarily determined by contributions from an inverse C_x-H(D) stretching vibration, which is effectively constant for each leaving group, and an inverse, or normal, C_x-H(D) bending vibration contribution that increases with transition state looseness (the steric crowding around C_x in the transition state). The stretching contribution to the total KIE is usually greater than the bending contribution for the S_N2 reactions of methyl substrates; hence, the KIEs for these S_N2 reactions are inverse or small and normal. However, the stretching contribution

to the KIE becomes less important as the size of the substrate increases so larger, normal, KIEs are found for the S_N2 reactions of larger substrates such as ethyl and benzyl where the normal $(k_H/k_D)_{\text{bend}}$ contribution plays a greater role in determining the magnitude of the KIE. Both experiment and theory suggests that the R_{TS} model based on the looseness of transition states *with the same leaving group* is valid for reactions with small nucleophiles. However, the R_{TS} model does not apply to reactions with large nucleophiles with heavy atoms off the Nu-C_x-LG axis. Here, the KIE is based on the crowdedness of the transition state, although, unfortunately, it will likely be impossible to estimate the effect of these off axis atoms on the magnitude of the KIE. Finally, theory has suggested that other factors such as the Nu-C_x-LG bond angle in the transition state and the change in the C_x-LG stretching force constant on going to the transition state may affect the magnitude of these KIEs.

Experimental evidence has suggested that (i) the secondary α -deuterium KIE in S_N2 reactions is determined by only the length of the shortest reacting bond in unsymmetric transition states; (ii) the symmetry of the transition state can be determined from the change in the KIE with substituent; and (iii) reactions with large, bulky leaving groups increase the KIE significantly. All these factors that affect the magnitude of the KIE obviously make it difficult to compare the structure of the transition states in different reactions based on the magnitude of the secondary α -deuterium KIEs. However, it is believed that the magnitude of these KIEs can be used to show how substituents, a change in solvent, and ion pairing^{49,50} affect the structure of the transition state of an S_N2 reaction. In these cases, the magnitude of the KIE appears to be related to the looseness of the transition state (R_{TS}) for the reaction.

Secondary β -deuterium KIEs

An elegant study by Shiner and Humphrey^{51,52} showed that the secondary β -deuterium KIEs that arise when hydrogen(s) on the β -carbon are replaced by deuterium(s) are composed of a steric KIE (the C $_{\beta}$ -D bonds are shorter than the C $_{\beta}$ -H bonds⁵³), an inductive effect KIE (D is more electron donating than H⁵³), and a hyperconjugative (the weaker C $_{\beta}$ -H bonds stabilize the transition state more than C $_{\beta}$ -D bonds via hyperconjugation⁵³) KIE that is related to the amount of positive charge on the α -carbon in the transition state. The steric contribution to the KIE is small because the deuterium(s) are not at the reaction center and inverse because the deuterated transition state is always less sterically crowded. The inductive contribution to these KIEs is also small because the deuterium(s) are not at the reaction center and there is only a partial positive charge on C $_{\alpha}$ in the transition state. In fact, both the steric and inductive components of the KIE are usually $\leq 1\%/_{\beta-D}$.⁵³ The hyperconjugative component of the KIE is always >1.000 and is invariably the largest contributor to the KIE. As expected, the hyperconjugative KIE is large for a carbenium ion S_N reaction and small for an S_N2 reaction where the positive charge on C $_{\alpha}$ in the transition state is small. Therefore, large secondary β -deuterium KIEs of $\geq 1.07/_{\beta-D}$ are observed for carbenium ion S_N reactions and small KIEs of $\leq 1.05/_{\beta-D}$ are indicative of an S_N2 mechanism.⁵¹ For example, the secondary β -deuterium KIE/ $_{\beta-D}$ increases from approximately 1.02 for ethyl compounds (Table 9), which undoubtedly react by an S_N2 mechanism, to approximately 1.10/ $_{\beta-D}$ ($(K_H/K_D)_{\beta} = 2.417$) for a *t*-butyl compound that reacts by a limiting S_N1 mechanism.⁵¹ While this means these KIEs can be used to determine the mechanism of a reaction, they can also be used to estimate transition

Table 9 The secondary β -deuterium KIEs for some S_N2 reactions

Substrate	Nucleophile	Temperature (°C)	$(k_H/k_D)_{\beta-D}$
CD ₃ CH ₂ -OTs	H ₂ O	60	1.006
CD ₃ CH ₂ -OMs	H ₂ O	60	1.009
CD ₃ CH ₂ -Br	H ₂ O	80	1.011
CD ₃ CH ₂ -I	H ₂ O	80	1.012
CD ₃ CH ₂ -OTf	TFE	25	1.03
CD ₃ CH ₂ -OTf	acetic acid	25	1.04
CD ₃ CH ₂ -OTf	formic acid	25	1.05
CF ₃ C≡CCHCD ₃ -OBs	50% aq. EtOH	45	1.018
CF ₃ C≡CCHCD ₃ -OBs	30% aq. EtOH	45	1.019
HC≡CCHCD ₃ -OBs	95% EtOH	45	1.027
CD ₃ CH ₂ -Cl	CN ⁻ /DMSO	30	1.005
(CD ₃) ₃ C-Cl	60% aq. EtOH	25	1.103

state structure. A larger KIE will be observed for reactions with a greater positive charge on C_α because the hyperconjugative component of the KIE is larger.

As with the secondary α-deuterium KIEs, the magnitude of a secondary β-deuterium KIE is affected by several factors. For example, in carbenium ion S_N reactions, the magnitude of the KIE is strongly dependent on the stereochemistry of the developing carbenium ion in the transition state. Shiner and coworkers^{51,54,55} found that the magnitude of the KIE is reduced from 1.30/_{β-D} when the dihedral angle between the C_β-H bond and the empty 2p atomic orbital on the α-carbon in the transition state is 0° to 1.07/_{β-D} when the dihedral angle is 30°, to only 1.01/_{β-D} when the dihedral angle is 60° and is inverse at 0.99 when the dihedral angle is 90°. This is not a serious problem, however, because small β-deuterium KIEs are only found in the carbenium ion reactions of bicyclic and other sterically crowded systems where free rotation about the C_α-C_β bonds is restricted.

Another factor affecting the magnitude of these KIEs is conjugation between the positive charge on the α-carbon of the carbenium ion and a strongly electron-donating group. For example, the β-deuterium KIEs for the hydrolyses of several 1-para-substituted phenylethyl chlorides (1.07 to 1.05/_{β-D}) are between the values expected for a carbenium ion and an S_N2 mechanism and a very small KIE of 1.036/_{β-D} is observed when the para-substituent is the methoxy group, even though all these substrates react via a carbenium ion mechanism with the formation of the solvent-separated ion pair rate-determining.⁵¹ The very small KIE is found for the reaction with the para-methoxy substituent because the highly conjugated (very stable) 1-para-methoxyphenylethyl carbenium ion is stabilized by conjugation to the methoxy group and does not need to be stabilized by hyperconjugation.

Finally, strong solvation of the developing carbenium ion in the transition state also causes a marked reduction in the secondary β-deuterium KIE. For example, the β-deuterium KIE in the solvolysis of isopropyl tosylate is reduced from 1.13/_{β-D} in trifluoroethanol, which does not solvate the developing carbenium ion strongly, to 1.08/_{β-D} in water where the carbenium ion is strongly solvated.⁵⁶ Again, the hyperconjugation component of the KIE is reduced because the solvent stabilizes the developing carbenium ion in the transition state.

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