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A Theoretical Study of the Relationship between Secondary α-Deuterium Kinetic Isotope Effects and the Structure of S_N2 Transition States

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Abstract: The reactant and transition-state structures for several S_N2 reactions between different nucleophiles and methyl and ethyl chloride and fluoride have been calculated at the HF/6-13+G* level. The secondary α-deuterium kinetic isotope effects for these reactions were calculated with Sim's BEBOVIB-IV program. The results demonstrate that the magnitude of these isotope effects is determined by an inverse stretching vibration contribution and a normal bending vibration contribution to the isotope effect. The stretching vibration contribution to the isotope effect is essentially constant for each substrate while the bending vibration contribution varies with the nucleophile and the looseness of the S_N2 transition state. Thus, the out-of-plane bending vibration model for relating the magnitude of secondary α-deuterium kinetic isotope effects to transition-state structure is correct. The bending vibration contribution to the isotope effect is greater in the ethyl substrate reactions than in the methyl substrate reactions. As a result, larger isotope effects and looser transition states are found for the S_N2 reactions of larger substrates. Looser transition states and larger isotope effects are also observed for the S_N2 reactions with softer nucleophiles.

Introduction

Secondary α-deuterium kinetic isotope effects (KIEs) have been widely used to determine (i) the mechanism of S_N reactions and (ii) how substituents alter the structure of the S_N2 transition state.[1] Although these uses of secondary α-deuterium KIEs are based on experimental evidence, it has been accepted that the magnitude of a secondary α-deuterium KIE is primarily the result of changes that occur in the C_α–H(D) out-of-plane bending vibrations when the reactant is converted into the transition state.[1,2] Since the out-of-plane bending vibrations remain almost the same or become even higher energy when the tetrahedral substrate is converted into the trigonal bipyramidal S_N2 transition state, the secondary α-deuterium KIE for an S_N2 reaction is either small and normal or inverse. If the reaction occurs via the unimolecular nucleophilic substitution (S_N1) mechanism, the C_α–H(D) out-of-plane bending vibrations become lower energy when the tetrahedral substrate is converted into the trigonal planar-like transition state, and the secondary α-deuterium KIE is large and normal.

Secondary α-deuterium KIEs have also been used to determine the structure of S_N2 transition states.[1,3–8] For a particular substrate, a tighter transition state, with short nucleophile–α-carbon and/or α-carbon–leaving group bonds, will have high-energy C_α–H(D) out-of-plane bending vibrations and the secondary α-deuterium KIE will be small. If the S_N2 transition state is looser, with longer nucleophile–α-carbon and/or α-carbon–leaving group bonds, the C_α–H(D) out-of-plane bending vibrations will be lower energy and a larger secondary α-deuterium KIE will be found, Figure 1.

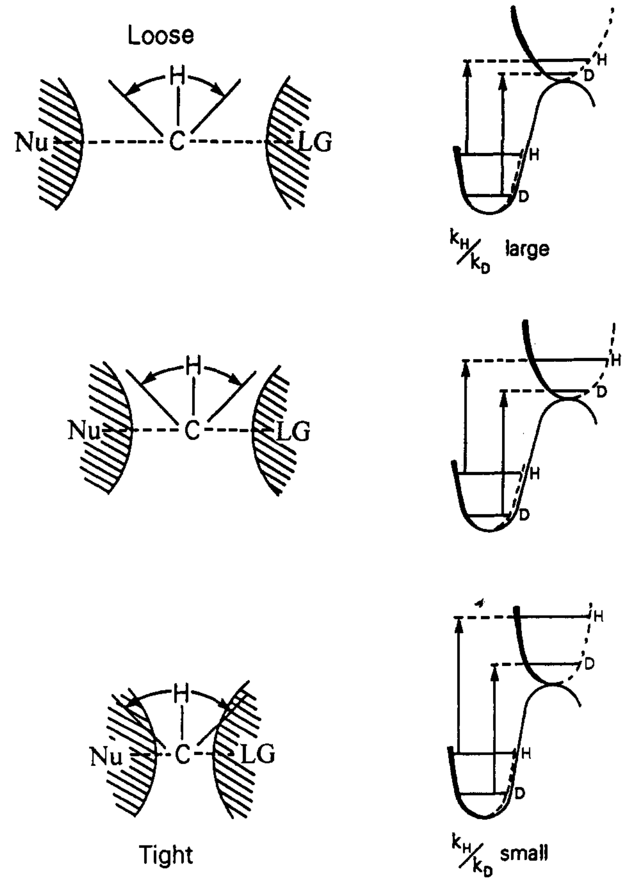

Figure 1. The relationship between the looseness (the nucleophile–leaving group distance) of the S_N2 transition state and the magnitude of the secondary α-deuterium KIE as determined by the C_α–H(D) out-of-plane bending vibrations.

Although it has been accepted that the secondary α-deuterium

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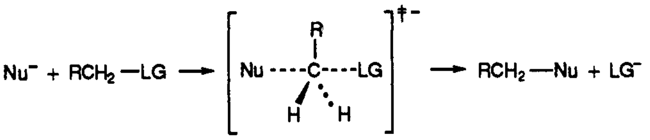
KIE is determined primarily by the out-of-plane bending vibrations of the C_α–H(D) bonds in the reactant and the transition state, recent theoretical calculations by Truhlar and co-workers[9,10] and by Wolfe and Kim[11] have suggested that the inverse KIEs in S_N2 reactions are primarily the result of changes in the C_α–H(D) stretching vibrations rather than the C_α–H(D) out-of-plane bending vibrations. Wolfe and Kim also reported that the C_α–H bond lengths were virtually identical in a wide variety of transition states and concluded that the trends in these KIEs are determined ultimately by differences in the C_α–H bond lengths of the reacting molecules and not by the C_α–H(D) bonds in the S_N2 transition state. This means that secondary α-deuterium KIEs have been interpreted incorrectly and that a smaller KIE is associated with a looser, rather than a tighter, S_N2 transition state. It is important that this alternate interpretation of secondary α-deuterium KIEs be tested because these KIEs are widely used to determine the mechanism of S_N reactions and substituent effects on the structure of the S_N2 transition state.

Computational Method

In this study, HF/6-31+G* level calculations have been used to obtain the force constants and optimized geometries for the reactants and the S_N2 transition states for the reactions



where the nucleophile (Nu) = F, Cl, OH, SH, NH_2, or SCH_3, R = H or CH_3, and the leaving group (LG) = F or Cl.

All reactant and transition-state structures were optimized with the MUNGAUSS[12] program using the OC[13] and VA05AD[14] optimization methods, respectively. All the transition states had only one imaginary frequency after diagonalization of the force constant matrix. The Hartree–Fock force constants were calculated analytically using GAUSSIAN 86[15] at the HF/6-31+G* level and scaled by a factor of 0.81. Sims' BEBOVIB-IV program[16] modified to accept the ab initio geometries and force constants, was used to carry out a vibrational analysis on the HF/6-31+G* level reactant and transition-state structures and to calculate the secondary α-deuterium KIEs at 25 °C. All the isotope effects are the observed (k_H/k_D), not $(k_H/k_D)/\alpha$-D.

The total KIE can be expressed as the product of a translational, a rotational, a vibrational, and a tunneling term,

$$k_H/k_D = (k_H/k_D)_{trans}\,(k_H/k_D)_{rot}(k_H/k_D)_{vib}\,(k_H/k_D)_{tunneling}$$

where the tunneling term was determined using the Wigner correction.[16] The vibrational contribution to the KIE can be factored into a stretching contribution and a bending contribution,

$$(k_H/k_D)_{vib} = (k_H/k_D)_{stretching}(k_H/k_D)_{bending}\,(k_H/k_D)_{other}$$

where the $(k_H/k_D)_{stretching}$ term contains the contribution from the C_α–H(D) stretching vibrations to the KIE and the $(k_H/k_D)_{bending}$ term contains the contribution from the C_α–H(D) bending vibrations. Three stretching vibrations and five bending vibrations were used to calculate the $(k_H/k_D)_{stretching}$ and $(k_H/k_D)_{bending}$ terms, respectively, for the methyl chloride and methyl fluoride reactions. Two stretching and seven bending vibrations were used to calculate the $(k_H/k_D)_{stretching}$ and $(k_H/k_D)_{bending}$ terms, respectively, for the ethyl chloride and ethyl fluoride reactions. The seven bending vibrations were those where substituting a deuterium for a hydrogen altered the frequency of a vibration found between 1500 and 500 cm^{-1} by at least 20%.

Table 1. The Change in the Magnitude of the Secondary α-Deuterium KIEs with a Change in Nucleophile in the S_N2 Reactions of Several 3-X,5-Y-Substituted Pyridines with Methyl Iodide in 2-Nitropropane at 25 °C

3-X	5-Y	(k_H/k_D)
CH_3	CH_3	0.908
CH_3	H	0.851
H	H	0.850
Cl	H	0.835
Cl	Cl	0.810

Results and Discussion

The relationship between the magnitude of the secondary α-deuterium KIE and transition-state structure is investigated in an effort to discover the factors that determine the magnitude of these KIEs in S_N2 reactions. In particular, this study will determine whether these KIEs are primarily determined by changes in the stretching vibrations as proposed by Wolfe and Kim[11] or whether they are the result of changes in the out-of-plane bending vibrations as had been previously believed.[1]

Wolfe and Kim indicated that (i) the secondary α-deuterium KIE is primarily determined by changes that occur in the C_α–H stretching vibrations as the reactant is converted to the transition state and (ii) that the magnitude of the KIE is determined by the length of the C_α–H bond in the reactant. If Wolfe and Kim are correct, these KIEs would be independent of the nucleophile used in an S_N2 reaction. Experimental evidence clearly shows that this is not the case.[1] For example, Harris et al.[17] found that the secondary α-deuterium KIE varies markedly when the nucleophile is varied in the S_N2 reactions between 3,5-disubstituted pyridines and methyl iodide, Table 1. In another study, Westaway and Lai[18] found that the secondary α-deuterium KIE changes from 1.13 to 1.03 when the nucleophile changes from a free ion to an ion pair in the S_N2 reaction between thiophenoxide ion and *n*-butyl chloride in DMSO. Since neither of these changes in nucleophile affect the C_α–H bonds of the reactant, the KIEs should not change if Wolfe and Kim are correct.

A second argument against the proposals of Wolfe and Kim is that the secondary α-deuterium KIE for a unimolecular nucleophilic substitution (S_N1) reaction would be smaller than 1.00 if the stretching vibration contribution to the KIE were more important than the bending vibration contribution. This would be observed because the C_α–H bonds are shorter (stronger) in the carbocation-like transition state and in the carbocation intermediate than in the reactant. However, the secondary α-deuterium KIEs found in S_N1 reactions are not inverse, but are large and normal, i.e., they are >1.07/α-D and can be as large as 1.25/α-D.[19] This suggests that the bending vibrations are more important than the stretching vibrations in determining the magnitude of the KIE. In fact, Wolfe and Kim's calculated **equilibrium** isotope effect (EIE) for the conversion of methyl chloride into the methyl carbocation and chloride ion supports

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Table 2. The HF/6-31+G* KIEs and Vibrational Contributions to the KIEs for the S_N2 Reactions of Methyl Fluorides and Chlorides with Various Nucleophiles at 25 °C

nucleophile	total KIE	$\left(\frac{k_H}{k_D}\right)_{\text{stretching}}$	$\left(\frac{k_H}{k_D}\right)_{\text{bending}}$	$\left(\frac{k_H}{k_D}\right)_{\text{vib}}$	$L_{T.S.}$	$R_{T.S.}$
Methyl Fluoride KIEs						
F	0.846	0.677	0.978	0.656	69.2	3.6930
OH	0.871	0.686	1.024	0.648	72.8	3.7845
NH_2	0.904	0.692	1.054	0.643	75.8	3.9055
Cl	1.002	0.665	1.157	0.762	74.5	4.2611
SH	1.010	0.663	1.215	0.701	72.4	4.3088
Methyl Chloride KIEs						
F	0.882	0.705	1.098	0.711	74.5	4.2611
OH	0.907	0.714	1.128	0.704	79.7	4.3714
NH_2	0.897	0.716	1.112	0.665	80.2	4.4599
Cl	0.935	0.680	1.178	0.739	68.0	4.7880
SH	0.953	0.690	1.197	0.688	70.9	4.8844
SCH_3	0.953	0.701	1.221	0.552	70.1	4.8713

this conclusion. The stretching vibration contribution to the EIE for this reaction was inverse at 0.93 whereas the bending vibration contribution was a large and normal 2.17.

The calculated total KIEs, the total vibrational contribution, and both the stretching and bending contributions to the KIE for 13 methyl chlorides and fluorides are presented in Table 2. The first observation is that all the stretching contributions to the KIE ($(k_H/k_D)_{\text{stretching}}$) are large and inverse as Truhlar et al. and Wolfe and Kim have reported.[9-11] The bending contributions to the KIE ($(k_H/k_D)_{\text{bending}}$) on the other hand, are close to or greater than unity. The magnitude of $(k_H/k_D)_{\text{stretching}}$ is greater than $(k_H/k_D)_{\text{bending}}$ for all the methyl fluoride and chloride reactions. As a result, the KIEs are inverse, or small and normal, as expected for methyl compounds.[1,20,21] These observations are in agreement with the results of Wolfe and Kim. In fact, where they can be compared, the KIEs in this work are in excellent agreement with those reported by Wolfe and Kim. Wolfe and Kim reported KIEs of 0.84 for the methyl fluoride and 0.94 for the methyl chloride identity reactions. In this study, the KIEs for these reactions were 0.846 and 0.935, respectively, Table 2.

A comparison of the stretching and the bending vibration contributions to the total KIE clearly shows that there is a much wider variation in $(k_H/k_D)_{\text{bending}}$ than in $(k_H/k_D)_{\text{stretching}}$. For example, $(k_H/k_D)_{\text{stretching}}$ only varies from 0.66 to 0.69, i.e., it changes by only 0.03 when the nucleophile changes from F^- to SH^- in the methyl fluoride reactions and only from 0.68 to 0.72 or by 0.04 when the nucleophile changes from F^- to SCH_3^- in the methyl chloride reactions. $(k_H/k_D)_{\text{bending}}$, 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 $(k_H/k_D)_{\text{bending}}$ is eight times greater than the change in $(k_H/k_D)_{\text{stretching}}$ 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 contributions in both the reactions that have been investigated. Therefore, the change in the total KIE with a change in nucleophile is primarily determined by the change in $(k_H/k_D)_{\text{bending}}$ and is not the result of changes in the stretching vibrations.

An examination of the secondary α-deuterium KIEs for the S_N2 reactions of methyl chloride and methyl fluoride with various nucleophiles, Table 2, illustrates that the KIEs are, indeed, determined by the bending vibrations. The plots of the total KIE versus $(k_H/k_D)_{\text{stretching}}$ and $(k_H/k_D)_{\text{bending}}$, Figures 2 and 3, respectively, clearly show that the total KIE correlates well with $(k_H/k_D)_{\text{bending}}$ whereas the total KIE is not related to $(k_H/k_D)_{\text{stretching}}$. In fact, the correlation coefficient for the total KIE versus $(k_H/k_D)_{\text{bending}}$ plot is 0.844 for all the methyl substrate reactions while that for the $(k_H/k_D)_{\text{stretching}}$ plot is only −0.496. The difference in the correlation coefficients for the bending and stretching plots is even more striking if the methyl chloride and methyl fluoride series are examined separately. The correlation coefficient for the methyl chloride total KIE versus $(k_H/k_D)_{\text{bending}}$ is 0.985 whereas it is only −0.645 versus $(k_H/k_D)_{\text{stretching}}$. Similar results are found for the methyl fluoride reactions. The correlation coefficients for the total KIE versus $(k_H/k_D)_{\text{bending}}$ and $(k_H/k_D)_{\text{stretching}}$ for the methyl fluoride reactions are 0.983 and −0.776, respectively. The trends in these KIEs are, therefore, in agreement with the commonly accepted view that the KIE is determined by changes in the bending vibrations and not by changes in the stretching vibrations as suggested by Wolfe and Kim. It is important to note that the KIEs for the identity reactions have been included in these plots and therefore the identity reaction KIEs behave in the same way as the other KIEs. It is also important to note that if changes in the bending vibrations are responsible for the trends in the KIE, a S_N2 reaction with a looser transition state would be expected to have a larger KIE. For example, the larger $(k_H/k_D)_{\text{bending}}$ found for the methyl chloride

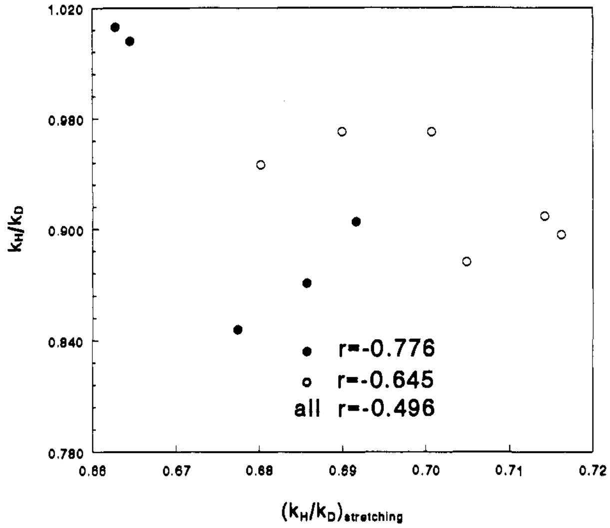

Figure 2. The total KIE versus the stretching vibration contribution to the KIE for S_N2 reactions of methyl chloride and methyl fluoride with various nucleophiles. The open circles are for the methyl chloride reactions and the solid circles are for the methyl fluoride reactions.

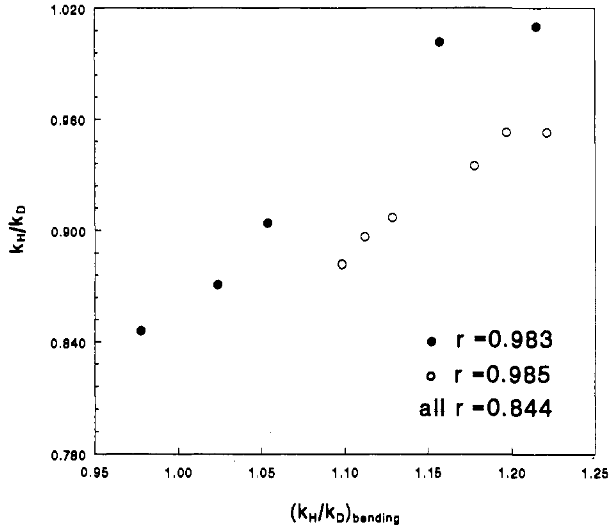

Figure 3. The total KIE versus the bending vibration contribution to the KIE for S_N2 reactions of methyl chloride and methyl fluoride with various nucleophiles. The open circles are for the methyl chloride reactions and the solid circles are for the methyl fluoride reactions.

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Table 3. The HF/6-31+G* KIEs and Vibrational Contributions to the KIEs for the S_N2 Identity Reactions of Methyl Substrates at 25 °C

nucleophile leaving group	total KIE	$\left(\frac{k_H}{k_D}\right)_{\text{stretching}}$	$\left(\frac{k_H}{k_D}\right)_{\text{bending}}$	$\left(\frac{k_H}{k_D}\right)_{\text{vib}}$	$L_{T.S.}$	$R_{T.S.}$
F	0.846	0.677	0.978	0.656	69.2	3.6930
OH	0.816	0.634	1.301	0.616	75.4	3.8608
SH	0.851	0.645	1.077	0.643	72.2	4.9482
Cl	0.935	0.680	1.178	0.739	68.0	4.7880

identity reaction (1.178 compared to 0.978 for the methyl fluoride identity reaction) suggests that the methyl chloride transition state is looser than the methyl fluoride transition state and that there is less "steric hindrance" exerted on the out-of-plane bending vibrations in the methyl chloride transition state.

Wolfe and Kim[11] reported that the magnitude of the KIEs for identity S_N2 reactions was inversely proportional to a "looseness" parameter,

$$L_{T.S.} = (\%\text{C–Nu} + \%\text{C–LG})$$

where the percent increase in the length of the C–LG bond in going from the reactant to the transition state, %C–LG, can be expressed as

$$\%\text{C–LG} = ((\text{C–LG}_{T.S.} - \text{C–LG}_{react})/\text{C–LG}_{react}) \times 100\%$$

and $\text{C–LG}_{T.S.}$ and C–LG_{react} are the length of the α-carbon-leaving group bond in the transition state and reactant, respectively. A similar equation gives %C–Nu for the nucleophile–α-carbon bond. (Wolfe and Kim used the C–Nu and C–LG bond lengths in the encounter and product complexes rather than the substrate and product to calculate the %C–Nu and %C–LG. A comparison of Wolfe and Kim's $L_{T.S.}$ values for the methyl fluoride and methyl chloride identity reactions with those in Table 4 shows that Wolfe and Kim's $L_{T.S.}$ values are only 3% smaller than those obtained using the substrate C–LG and product C–Nu bond lengths.) The inverse relationship between the KIE and the looseness parameter, $L_{T.S.}$, found by Wolfe and Kim suggested that a reaction with a looser transition state will have a smaller KIE and implies that trends in the KIE are (i) not due to changes in the bending vibrations but are due to changes in the stretching vibrations and (ii) that the secondary α-deuterium KIEs have been incorrectly related to transition-state structure.

The inverse relationship found for the identity reactions by Wolfe and Kim is observed when the KIEs for our series of identity reactions are plotted versus the looseness parameter, $L_{T.S.}$, Table 3. However, the correlation coefficient for the plot of the total KIE versus $L_{T.S.}$ for our identity reactions is only −0.302 rather than the −0.934 found by Wolfe and Kim for their identity reactions. In fact, the small correlation coefficient found in this work suggests there is no correlation between the KIE and $L_{T.S.}$. This lack of a correlation between the KIE and $L_{T.S.}$ is more clearly seen when the KIEs for the non-identity methyl fluoride and methyl chloride reactions are considered, Figure 4. The correlation coefficient for the total KIE versus $L_{T.S.}$ for all the reactions of the methyl substrates is only −0.121 and even the correlation coefficients found when the methyl fluoride reactions and methyl chloride reactions are considered separately are low, i.e., 0.421 in the methyl fluoride and −0.719 in the methyl chloride series, respectively.

This lack of a relationship between the total KIE and $L_{T.S.}$ can be shown in another way. Both the Wolfe–Kim and this study have found that the two identity reactions, methyl fluoride with fluoride ion and methyl chloride with chloride ion, have the same $L_{T.S.}$ value, Table 4. Since these two reactions have the same "looseness", Wolfe and Kim would predict that they should have the same KIE. The KIEs are very different, however, i.e., the KIE for the methyl fluoride reaction is 0.846 while that for the methyl chloride identity reaction is 0.935. Obviously, this difference in the KIEs is not caused by a change in $L_{T.S.}$ and it must be concluded that the KIE and $LT_{.S.}$ are not directly related.

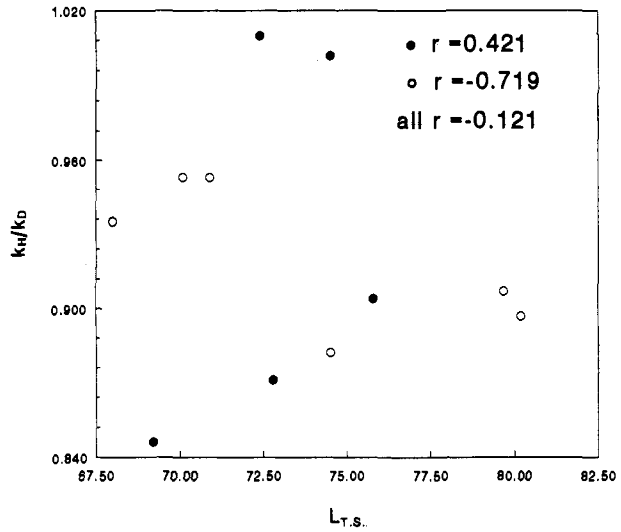

Figure 4. The total KIE versus $L_{T.S.}$ for S_N2 reactions of methyl chloride and methyl fluoride with various nucleophiles. The open circles are for the methyl chloride reactions and the solid circles are for the methyl fluoride reactions.

Table 4. Properties of the S_N2 Transition States for the Identity Reactions of Methyl Fluoride and Methyl Chloride

property	CH_3–F + F^-	CH_3–Cl + Cl^-	difference
α-Carbon-Leaving Group Bond Length (Å)			
reactant	1.3719	1.7864	
transition state	1.8465	2.3904	
C_α–H Bond Length (Å)			
reactant	1.0806	1.0779	0.0027
transition state	1.0609	1.0615	0.0006
$L_{T.S.}$	69.2	68.0	1.2
$(k_H/k_D)_{\text{stretching}}$	0.677	0.680	0.003
$(k_H/k_D)_{\text{bending}}$	0.978	1.178	0.200
total k_H/k_D	0.846	0.935	0.089

An examination of the data in Table 4 shows why the KIEs in these two identity reactions are different. The $(k_H/k_D)_{\text{stretching}}$ are virtually identical for the two reactions. However, there is a large difference in $(k_H/k_D)_{\text{bending}}$ and in the total KIE for the two reactions even though they have the same $L_{T.S.}$. This again demonstrates that changes in the bending vibrations are more important than changes in the stretching vibrations in determining the magnitude of secondary α-deuterium KIEs. It is important to note that an identical analysis of all of the identity reactions in this study, as well as in the Wolfe–Kim study, Table 5, shows that changes in $(k_H/k_D)_{\text{bending}}$ have a greater effect on the magnitude of the KIE than changes in $(k_H/k_D)_{\text{stretching}}$. For example, the absolute value of the difference between $(k_H/k_D)_{\text{stretching}}$ for each identity reaction and $(k_H/k_D)_{\text{stretching}}$ for the methyl fluoride identity reaction in both studies is small, Table 5. The corresponding differences between the $(k_H/k_D)_{\text{bending}}$ values are larger for all but one of the identity reactions. On average, the absolute values of the differences between the $(k_H/k_D)_{\text{bending}}$ values for the identity reactions in this study are almost nine times greater than the corresponding differences in $(k_H/k_D)_{\text{stretching}}$ and are more than twice the differences in $(k_H/k_D)_{\text{stretching}}$ for the identity reactions in the Wolfe–Kim study. Thus, it must be concluded that the difference in the KIEs for even the identity reactions is primarily due changes in the bending vibrations.

The importance of the bending vibrations in determining the magnitude of the KIE and the lack of a correlation between the KIE and $L_{T.S.}$ suggests that the $L_{T.S.}$ parameter is not a good

Table 5. A Comparison of $(k_H/k_D)_{stretching}$ and $(k_H/k_D)_{bending}$ for Various Identity Reactions with $(k_H/k_D)_{stretching}$ and $(k_H/k_D)_{bending}$ for the Methyl Fluoride Identity Reaction

identity reaction	$(k_H/k_D)_{stretching}$	|difference|[a]	$(k_H/k_D)_{bending}$	|difference|[b]
		This Study		
Cl	0.680	0.003	1.178	0.200
OH	0.634	0.036	1.301	0.329
SH	0.645	0.032	1.077	0.099
average		0.024		0.209
		The Wolfe and Kim Study		
Cl	0.71	0.03	1.33	0.19
OF	0.91	0.17	0.90	0.24
CN	0.70	0.04	1.12	0.02
OCH_3	0.56	0.18	1.42	0.28
NC	0.72	0.02	0.96	0.18
HC≡C	0.68	0.06	0.99	0.15
average		0.083		0.177

[a] This absolute value was obtained by subtracting $(k_H/k_D)_{stretching}$ for the identity reaction shown from the $(k_H/k_D)_{stretching}$ for the methyl fluoride identity reaction, i.e., from 0.677 in this study and from 0.74 in the Wolfe–Kim study. [b] This absolute value was obtained by substracting $(k_H/k_D)_{bending}$ for the identity reaction shown from $(k_H/k_D)_{bending}$ for the methyl fluoride identity reaction, i.e., from 0.978 in this study and from 1.14 in the Wolfe–Kim study.

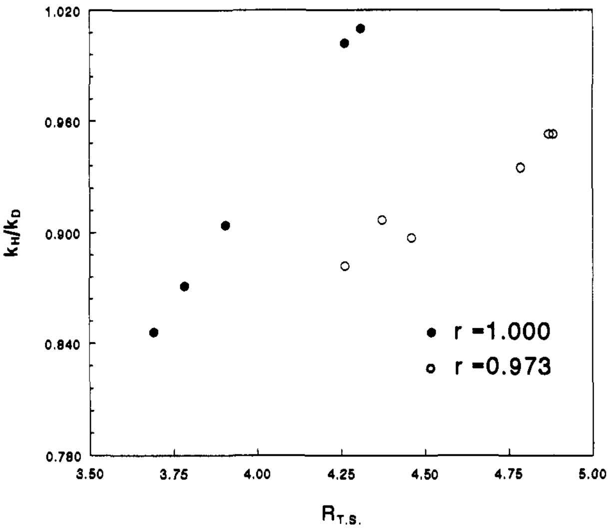

Figure 5. The total KIE versus $R_{T.S.}$ for S_N2 reactions of methyl chloride and methyl fluoride with various nucleophiles. The open circles are for the methyl chloride reactions and the solid circles are for the methyl fluoride reactions.

measure of the looseness of the transition state. Since the trends in the KIE are due to changes in the bending vibrations, one would expect the magnitude of the KIE would be related to the "space" available for the out-of-plane bending vibrations in the transition state, i.e., to the distance between the nucleophile and the leaving group in the S_N2 transition state. To test this hypothesis, the nucleophile–leaving group distance in the S_N2 transition state, $R_{T.S.}$, where

$$R_{T.S.} = C\text{–}Nu_{T.S.} + C\text{–}LG_{T.S.}$$

and $C\text{–}Nu_{T.S.}$ and $C\text{–}LG_{T.S.}$ are the lengths of the nucleophile–α-carbon and α-carbon-leaving group transition state bonds, respectively, was obtained from the HF/6-31+G* transition states of all the methyl fluoride and methyl chloride reactions in Table 2. Then, the total KIE, the $(k_H/k_D)_{stretching}$, and the $(k_H/k_D)_{bending}$ for these reactions were plotted against $R_{T.S.}$, Figures 5–7. The plot of the total KIE versus $R_{T.S.}$, Figure 5, had correlation coefficients of 1.000 for the methyl fluoride reactions and 0.973 for the methyl chloride reactions. In contrast, the plot of $(k_H/k_D)_{stretching}$ versus $R_{T.S.}$, Figure 6, have correlation coefficients of only −0.710 for the methyl chloride reactions and −0.778 for the methyl fluoride reactions. Clearly, $(k_H/k_D)_{stretching}$ does not correlate well with $R_{T.S.}$. $(k_H/k_D)_{bending}$, on the other hand, correlates very well with $R_{T.S.}$. The correlation coefficient for the $(k_H/k_D)_{bending}$ versus $R_{T.S.}$ plot, Figure 7, is 0.957 for the methyl chloride reactions and 0.987 for the methyl fluoride reactions. Thus, as $R_{T.S.}$ increases (the transition state becomes looser), both $(k_H/k_D)_{bending}$ and the total KIE increase as the out-of-plane bending vibration model predicts. These plots also demonstrate that, 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, **$(k_H/k_D)_{bending}$ and the trend in the total KIE is determined by the looseness of the S_N2 transition state.**

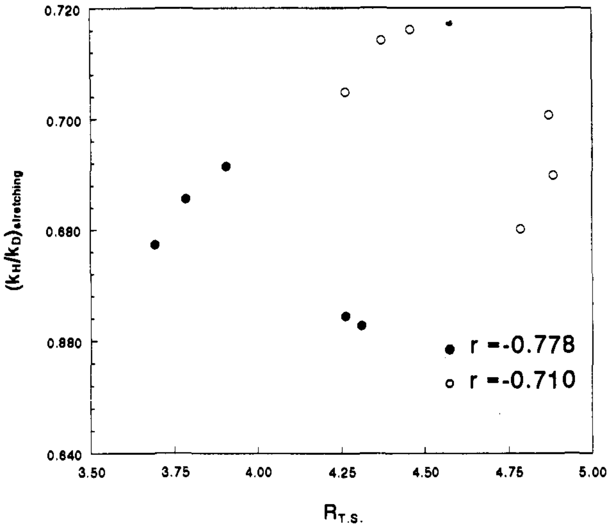

Figure 6. The stretching vibration contribution to the KIE versus $R_{T.S.}$ for S_N2 reactions of methyl chloride and methyl fluoride with various nucleophiles. The open circles are for the methyl chloride reactions and the solid circles are for the methyl fluoride reactions.

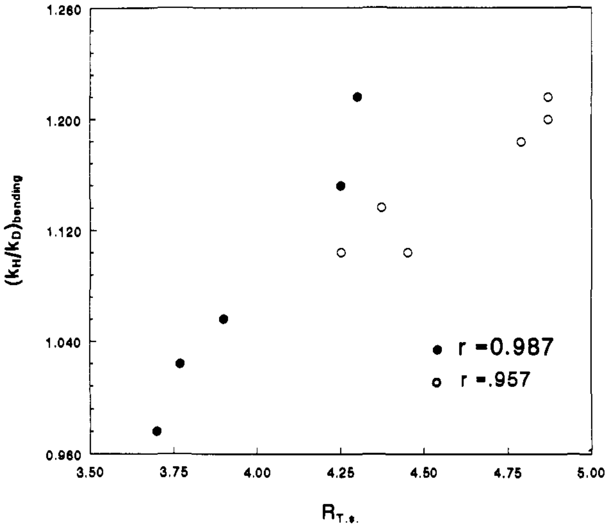

Figure 7. The bending vibration contribution to the KIE versus $R_{T.S.}$ for S_N2 reactions of methyl chloride and methyl fluoride with various nucleophiles. The open circles are for the methyl chloride reactions and the solid circles are for the methyl fluoride reactions.

Finally, the results in Figure 8 indicate that the $L_{T.S.}$ parameter used by Wolfe and Kim is not related to the looseness $R_{T.S.}$ of the S_N2 transition state. In fact, the correlation coefficient of the $L_{T.S.}$ versus $R_{T.S.}$ plot is only 0.767 and 0.412 for the methyl chloride and methyl fluoride reactions, respectively. Obviously, whatever $L_{T.S.}$ is measuring, it is not the looseness of the transition state. The origin of the problem is probably that the energy required to increase the length of a bond by a certain percentage is different for each bond. This is because the energy to stretch

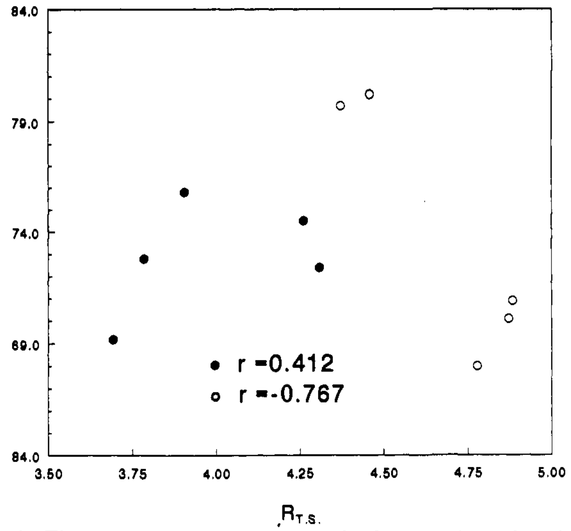

Figure 8. The $L_{T.S.}$ parameter versus $R_{T.S.}$ for S_N2 reactions of methyl chloride and methyl fluoride with various nucleophiles. The open circles are for the methyl chloride reactions and the solid circles are for the methyl fluoride reactions.

a bond depends on the strength of the bond and on the curvature of its potential energy surface. For example, increasing the length of a short (strong) bond by 30% would change the total Nu---LG distance in the transition state by a much smaller amount than changing the length of a long (weak) bond by 30%. Since the KIE is related to $(k_H/k_D)_{\text{bending}}$ and the Nu---LG distance in the S_N2 transition state, the correlation with $L_{T.S.}$ is poor. In fact, $L_{T.S.}$ would only be expected to work for a series of reactions where the reacting bonds had similar energy surfaces and ground-state bond lengths.

A closer examination of the Wolfe–Kim plot of the total KIE versus $L_{T.S.}$ suggests that this may, in fact, be the case. It appears that there are three different groups of identity reactions, each of which have similar KIEs, rather than a whole range of identity reactions with different KIEs. The Cl^- identity reaction of a second-row nucleophile with a shallow energy well is in one group. The reactions where the nucleophiles and leaving groups are electronegative first row elements and the energy wells are narrow and deep, i.e., the F^-, CN^-, FO^-, and CH_3O^- reaction, comprise the second group. The third group is the NC^-, and the $HC{\equiv}C^-$ reactions of carbon atoms with even deeper energy wells. The identity reactions in this study also fall in two groups rather than on a single straight line. Again, the identity reactions with the second-row nucleophiles, Cl^- and HS^-, have larger KIEs and much looser transition states than the reactions where the nucleophilic atoms are first-row elements, i.e., OH^- and F^-, Table 3. In fact, larger KIEs and looser transition states are observed in all the reactions where softer (second row element nucleophiles) are used in both the identity and non-identity reactions, Tables 2, 3, and 6.

Table 6. The HF/6-31+G* KIEs and Vibrational Contributions to the KIEs for the S_N2 Reactions of Ethyl Fluorides and Chlorides with Various Nucleophiles at 25 °C

nucleophile	total KIE	$\left(\frac{k_H}{k_D}\right)_{\text{stretching}}$	$\left(\frac{k_H}{k_D}\right)_{\text{bending}}$	$\left(\frac{k_H}{k_D}\right)_{\text{vib}}$	$L_{T.S.}$	$R_{T.S.}$
		Ethyl Fluoride KIEs				
F	0.914	0.809	0.995	0.790	75.0	3.7729
OH	0.935	0.809	1.008	0.810	79.1	3.8725
NH_2	0.940	0.816	1.030	0.810	80.6	3.8725
Cl	1.034	0.792	1.137	0.877	83.0	4.3991
		Ethyl Chloride KIEs				
F	0.960	0.791	1.145	0.836	83.0	4.3991
OH	0.976	0.792	1.168	0.852	88.7	4.5204
Cl	1.017	0.784	1.223	0.870	78.5	4.9750
SH	1.018	0.781	1.214	0.872	80.0	5.0486

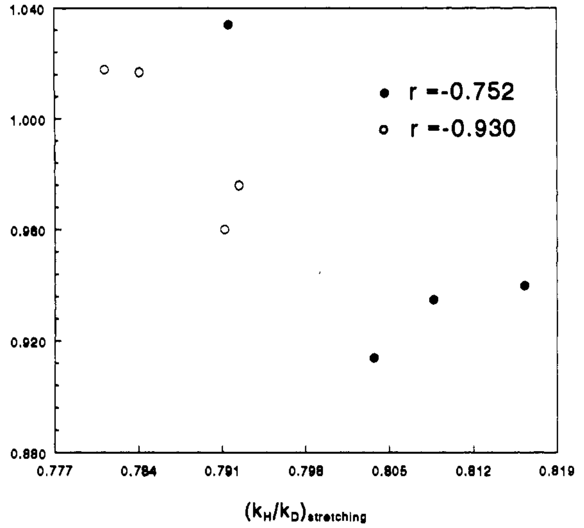

Figure 9. The total KIE versus the stretching vibration contribution to the KIE for S_N2 reactions of ethyl chloride and ethyl fluoride with various nucleophiles. The open circles are for the ethyl chloride reactions and the solid circles are for the ethyl fluoride reactions.

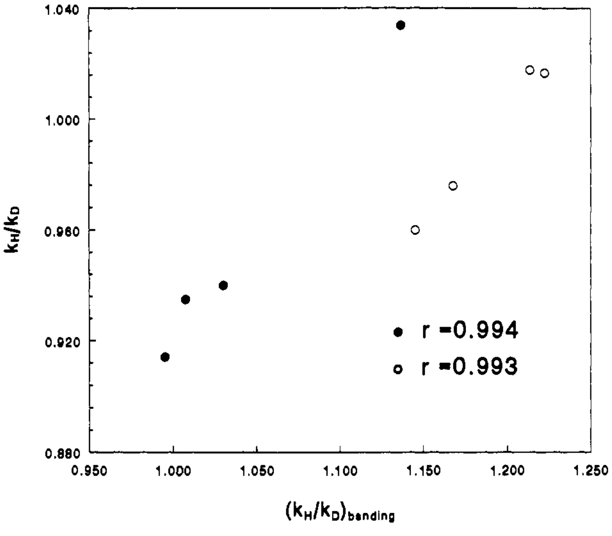

Figure 10. The total KIE versus the bending vibration contribution to the KIE for S_N2 reactions of ethyl chloride and ethyl fluoride with various nucleophiles. The open circles are for the ethyl chloride reactions and the solid circles are for the ethyl fluoride reactions.

Reactions of Ethyl Substrates

An analysis of the KIEs for the ethyl chloride and ethyl fluoride S_N2 reactions, Table 6, demonstrates that the relationship between the secondary α-deuterium KIE and transition-state structure found for the methyl substrates also exists for the ethyl substrates. For example, the correlation coefficients for the plot of the total KIE versus $(k_H/k_D)_{\text{stretching}}$, Figure 9, were only −0.930 (this high correlation coefficient is misleading because the line connects two sets of two points with similar KIEs, Figure 9) and −0.752 for the ethyl chloride and ethyl fluoride reactions, respectively. The correlation coefficients for the plot of the total KIE versus $(k_H/k_D)_{\text{bending}}$, on the other hand, were 0.993 for the ethyl chloride and 0.994 for the ethyl fluoride reactions, Figure 10. As was found for the methyl compounds, the $(k_H/k_D)_{\text{bending}}$ versus $R_{T.S.}$ plot, Figure 11, had high correlation coefficients for both the ethyl chloride reactions (0.976) and the ethyl fluoride reactions (0.996). High correlation coefficients were also observed for the total KIE versus $R_{T.S.}$ plots, Figure 12, i.e., the correlation coefficients for the ethyl chloride and ethyl fluoride reactions are 0.995 and 0.992, respectively. These high correlations between

Table 7. The Relative Importance[a] of the Bending and Stretching Vibrational Contributions to the HF/6-31+G* KIEs for the S_N2 Reactions of Methyl and Ethyl Substrates at 25 °C

substrates	average $\|\%(k_H/k_D)_{stretching}\|$,[b] %	average $\|\%(k_H/k_D)_{bending}\|$,[c] %	$(\|(k_H/k_D)_{bending}\|/\|(k_H/k_D)_{stretching}\|)$
CH_3-Cl	29.9	14.3	0.48
C_2H_5-Cl	21.3	18.8	0.88
CH_3-F	32.0	5.3	0.17
C_2H_5-F	19.4	4.3	0.22

[a] The values used to calculate these averages and ratios were from reactions where the same nucleophile reacted with both the ethyl and methyl substrates. [b] The |% stretching KIE| = $(1.0000 - (k_H/k_D)_{stretching}) \times 100\%$. [c] The |% bending KIE| = $((k_H/k_D)_{bending} - 1.0000) \times 100\%$.

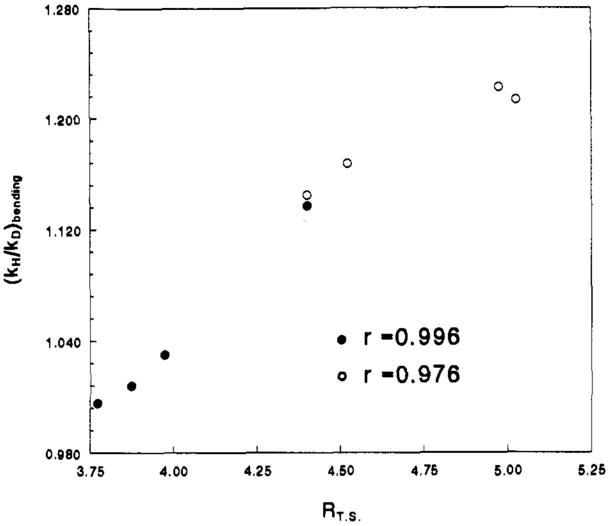

Figure 11. The bending vibration contribution to the KIE versus $R_{T.S.}$ for S_N2 reactions of ethyl chloride and ethyl fluoride with various nucleophiles. The open circles are for the ethyl chloride reactions and the solid circles are for the ethyl fluoride reactions.

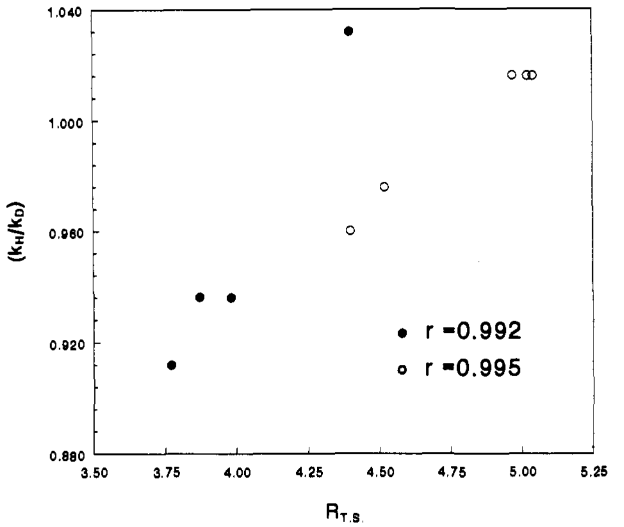

Figure 12. The total KIE versus $R_{T.S.}$ for S_N2 reactions of ethyl chloride and ethyl fluoride with various nucleophiles. The open circles are for the ethyl chloride reactions and the solid circles are for the ethyl fluoride reactions.

the total KIE and $(k_H/k_D)_{bending}$, between $(k_H/k_D)_{bending}$ and $R_{T.S.}$, and between the total KIE and $R_{T.S.}$ confirm that (i) the magnitude of the secondary α-deuterium KIE is determined by the changes that occur in the bending vibrations as the reactant is converted into the transition state and (ii) that the magnitude of the KIE is related to the Nu---LG distance in the transition state as the out-of-plane bending vibration model suggests.

The Relative Importance of Bending and Stretching Vibrations to the Secondary α-Deuterium KIE

An analysis of the results in Table 7 shows that the relative contribution of the stretching and bending vibrations to the secondary α-deuterium KIE is quite different for the S_N2 reactions of methyl and ethyl substrates. The stretching contribution to the KIE can be expressed as the absolute percent stretching KIE

$$|\% \text{ stretching KIE}| = (1.0000 - (k_H/k_D)_{stretching}) \text{ X } 100\%$$

and the absolute value of the bending contribution to the KIE is given by

$$|\% \text{ bending KIE}| = ((k_H/k_D)_{bending} - 1.0000) \text{ X}/100\%$$

The data in Table 7 show that the |% stretching KIE| is much larger than the |% bending KIE| for methyl substrates. In fact, the average ratio of the (bending/stretching) contribution to the KIE is 0.48 for the methyl chloride reactions and 0.17 for the methyl fluoride reactions. As a result, the KIEs for the methyl substrate reactions are inverse or very small and normal.

The ratio of the (bending/stretching) contribution to the KIE is significantly greater for the S_N2 reactions of ethyl substrates, i.e., it increases from 0.48 for the methyl chloride reactions to 0.88 for the S_N2 reactions of ethyl chloride. The same change in the ratio of the (bending/stretching) contributions to the KIE are seen for the methyl and ethyl fluoride reactions. Here, the (bending/stretching) contribution to the KIE increases from 0.17 to 0.22 when the substrate is changed from methyl fluoride to ethyl fluoride. This clearly demonstrates that the bending vibrations play a greater role in determining the magnitude of the secondary α-deuterium KIE for the reactions of more complex substrates. In fact, the KIE arising from the bending vibrations is normal for all but one of the ethyl substrate reactions. Therefore, the change from the large and inverse KIEs found for the methyl substrates to larger (less inverse or normal) KIEs found with the ethyl substrates is due to the increased contribution of the bending vibrations to the KIE. This increasing importance of $(k_H/k_D)_{bending}$ to the total KIE is undoubtedly responsible for the larger KIEs found in the S_N2 reactions of larger (more complex) substrates such as ethyl and benzyl. Finally, it is worth noting that the larger KIEs found in the S_N2 reactions of larger substrates are accompanied by a greater $R_{T.S.}$ value (looseness of the S_N2 transition state).

Table 8. The Experimental Ratio of the Secondary α-Deuterium KIEs for the S_N2 Reactions of Ethyl and Methyl Substrates

LG	Me-LG KIE	Et-LG KIE	Et-LG KIE/Me-LG KIE
OTs	0.985	1.020	1.036
Br	0.959	0.990	1.032
OMs	0.985	1.02	1.036

Finally, a good test of these calculations is to compare the calculated KIE ratios for the S_N2 reactions of several methyl and ethyl chlorides and fluorides against the experimental results. The experimental methyl/ethyl KIE ratios are 1.04 for several different S_N2 reactions,[1] Table 8. The calculated KIE ratios in Table 9 agree qualitatively with experiment in that increasing the size of the alkyl group from methyl to ethyl increases the KIE by a reasonably constant 1.07 ± 0.022. Even the magnitude of the increase in the KIE is reproduced fairly well by the calculations, i.e., the calculated KIE ratios range from 1.03 to 1.09. The fact that calculated KIEs increase with the size of the alkyl group of the α-carbon suggests that the calculated KIEs are reasonable.

Table 9. The HF/6-31+G* Secondary α-Deuterium KIEs for the S_N2 Reactions of Several Methyl and Ethyl Chlorides and Fluorides

nucleophile	Me–LG KIE	Et–LG KIE	Et–LG KIE/Me–LG KIE
	Methyl and Ethyl Fluoride Reactions		
F	0.846	0.914	1.08
Cl	1.002	1.034	1.03
OH	0.871	0.935	1.07
NH_2	0.904	0.940	1.04
	Methyl and Ethyl Chloride Reactions		
F	0.882	0.960	1.09
Cl	0.935	1.017	1.09
SH	0.953	1.018	1.07
OH	0.907	0.976	1.08
			av 1.07 ± 0.02

Conclusions

1. The out-of-plane bending vibration model that has been used to interpret secondary α-deuterium KIEs is basically correct, i.e., changes that occur in the bending vibrations as the reactants are converted into the transition state determine the magnitude of the KIE for a particular substrate. Although the KIE is determined by both the stretching and the bending vibrations, the stretching vibration contribution to the secondary α-deuterium KIE is virtually constant for each substrate, e.g., all the methyl chloride reactions have almost identical $(k_H/k_D)_{\text{stretching}}$ values. The bending vibrations, on the other hand, change markedly when the nucleophile changes. Therefore, the magnitude of the secondary α-deuterium KIE for a particular substrate is determined by the bending vibration contribution to the KIE. It is worth noting that a recent study based on AM1 calculations has reached the same conclusion.[22]

2. The magnitude of a secondary α-deuterium KIE in an S_N2 reaction is determined by both an inverse stretching and a normal bending contribution to the KIE. The stretching contribution to the total KIE is greater than the bending contribution for methyl substrates and the KIEs are inverse or small and normal. The stretching contribution to the KIE is less important for larger substrates such as ethyl. As a result, the larger KIEs found for the S_N2 reactions of larger substrates are observed because the normal $(k_H/k_D)_{\text{bending}}$ plays a greater role in determining the magnitude of the KIE.

3. The stretching contribution to the total KIE is approximately constant for a particular substrate and varies with the leaving group.

4. $(k_H/k_D)_{\text{bending}}$, which determines the magnitude of the KIE for a particular substrate, is related to $R_{\text{T.S.}}$, the internuclear distance between the nucleophile and the leaving group in the S_N2 transition state. This means both $(k_H/k_D)_{\text{bending}}$ and the total KIE are related to the looseness of the S_N2 transition state.

5. Wolfe and Kim's $L_{\text{T.S.}}$ parameter is not a good measure of the "looseness" of an S_N2 transition state.

6. Larger bending contributions and looser transition states are found when softer (second row) nucleophiles are used in a series of S_N2 reactions with the same leaving group.

7. The approach used in this study may enable chemists to assign "experimental transition state structures" based on the magnitude of the secondary α-deuterium KIE.

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[22] Barnes, J. A.; Williams, I. H. *J. Chem. Soc., Chem. Commun.* **1993**, 1286.