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A New Interpretation of Chlorine Leaving Group Kinetic Isotope Effects; A Theoretical Approach

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Received April 21, 2004

The chlorine leaving group kinetic isotope effects (KIEs) for the S_N2 reactions between methyl chloride and a wide range of anionic, neutral, and radical anion nucleophiles were calculated in the gas phase and, in several cases, using a continuum solvent model. In contrast to the expected linear dependence of the chlorine KIEs on the $C_\alpha-Cl$ bond order in the transition state, the KIEs fell in a very small range (1.0056−1.0091), even though the $C_\alpha-Cl$ transition state bond orders varied widely from approximately 0.32 to 0.78, a range from reactant-like to very product-like. This renders chlorine KIEs, and possibly other leaving-group KIEs, less useful for studies of reaction mechanisms than commonly assumed. A partial explanation for this unexpected relationship between the $C_\alpha-Cl$ transition state bond order and the magnitude of the chlorine KIE is presented.

Introduction

In their 50 year history, kinetic isotope effects (KIEs) have been considered one of the most sensitive tools for studying mechanisms and determining the structure of the transition states of chemical and enzymatic reactions.[1] With the advent of very fast computers and highly efficient algorithms, it has become possible to precisely describe transition states (TSs) quantum mechanically, at least for simple reactions, and to predict KIEs on the basis of these TS structures. Recently, we compared[2] values of computed KIEs with the experimental values for the simple S_N2 reaction described by eq 1 between cyanide ion and ethyl chloride (Nu: $= CN^-$, R = Et, and LG = Cl) in DMSO at 30 °C

$$\text{Nu:} + \text{R-LG} \rightarrow \text{Nu-R} + \text{LG} \qquad (1)$$

This study yielded two surprising results. First, although many different levels of theory, including post-Hartree−Fock levels, were employed, none of the over 40 theoretical methods predicted all of the experimental isotope effects. This may be because one needs to use multireference wave functions for calculating the structure of a TS and/or anharmonicity may play a role since bonds being broken and/or formed are much longer in the TS than they are in the stable reactant and product structures.[2,3] Second, the intuitive rules and/or simple theory used to interpret the experimental KIEs (such as the rules in the BEBOVIB theory[3]) placed the transition state in a very different position along the reaction coordinate than the quantum mechanical calculations, i.e., the TS suggested by the qualitative interpretation of the experimental KIEs was very product-like whereas the TS predicted by theory was very reactant-like. The discrepancy in the position of the TS along the reaction coordinate could be resolved if the reasonably large chlorine leaving group KIE observed for the reaction did not mean that the $C_\alpha-Cl$ bond was long in the TS as the simple theory suggests. Because the experimental KIEs are frequently interpreted qualitatively using simple theory this study attempts to resolve this problem by investigating the relationship between the leaving group chlorine KIE and TS structure. Knowing how to interpret chlorine leaving group isotope effects is important because in recent years a renaissance of chlorine KIE studies has occurred as a result of of developments in experimental procedures of chlorine isotope ratio analyses[5] as well as their application to biological systems of ecological importance.[6]

Method

The comparison of the adequacy of different levels of theory for calculating the KIEs for the ethyl chloride-cyanide S_N2 reaction[2] showed that the best results were

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10.1021/jo049327z CCC: $27.50

obtained when B3LYP and B1LYP DFT functionals[7] were used in combination with the aug-cc-pVDZ basis set[8] to determine the transition structure for the reaction. Then, the KIEs were calculated from the normal vibrational modes of ethyl chloride and the transition structure. Because the B1LYP functional was developed with calculations of IR frequencies in mind and contains fewer adjustable parameters, the B1LYP/aug-cc-pVDZ level has been chosen for the present calculations. The chlorine KIEs for the S_N2 reactions between 25 different nucleophiles (Nu:) and methyl chloride (R = Me, LG = Cl, eq 1) were calculated. All calculations were performed in Gaussian03 using default convergence criteria.[9] The effect of tunneling has been estimated using the Wigner approximation.[10] Each transition state was characterized by exactly one imaginary frequency corresponding to the methyl group transfer between the Nu: and the LG (Cl).

The nucleophiles ranged in nucleophilicity from very weak (water) to very strong (NH_2^-). Although the majority of the nucleophiles were anionic (Cl^-, F^-, SH^-, CN^-, SCN^-, Br^-, BH_4^-, SeH^-, OCl^-, OBr^-, OF^-, $NHCl^-$, OCF_3^-, N_3^-, CCH^-, NH_2^-, and OH^-), five reactions with neutral nucleophiles (H_2O, pyridine, 4-nitropyridine, NH_3, and PH_3) and three with radical anions ($S^{\bullet-}$, $SO^{\bullet-}$, and $Se^{\bullet-}$) were included to cover a wide range of transition structures. The reactions with the radical anions were treated using the UHF formalism.[11]

Solvents were modeled using the PCM continuum solvent model[12] with the conductor field model of electrostatic interactions (COSMO[12c]). Default solvent parameters implemented in Gaussian03 were used. The ISOEFF98 program[13] was used for KIE calculations.

Results and Discussion

The chlorine leaving group KIEs for the 25 S_N2 reactions are presented in Table 1, and the dependence of the chlorine KIEs on the Wiberg C_α−Cl bond order[14] in the TS is presented in Figure 1. The qualitative correlation based on the BEBOVIB method assumes that the relation between the bond order and the bond length is semilogarithmic[15] and that the force constant changes linearly with the bond order. This predicts a linear relationship (dotted line in Figure 1) between the chlorine KIE and the C_α−Cl bond order in the TS with no isotope effect when the transition state bond order approaches unity (reactant) and a maximum KIE for a transition state bond order = 0, i.e., where the C_α−Cl bond is fully broken in the TS. It is impossible to determine the maximum chlorine leaving group KIE. However, several estimates of the maximum chlorine KIE have been made. Maccoll[16a] and Buddenbaum and Shiner[16b] have suggested the maximum TDF at 25 °C to be equal to 1.014 on the bsis of the vibrational frequency of a C−Cl bond (860 cm^{-1}). Using the actual vibrational frequency for methyl chloride (732.2 cm^{-1}),[16c] the maximum TDF is 1.013. However, it is important to note that none of these maxima include the contribution from the tunneling or the imaginary frequency contribution to the KIE. If the average TIF and tunneling factors found in Table 1 are included, the maximum KIE would be approximately 1.02. This is in good agreement with the value of 1.019 reported by Paneth.[16d] In addition, Sims and co-workers[16e] also suggested a maximum chlorine leaving group KIE in an S_N2 reaction would be greater than 1.02.

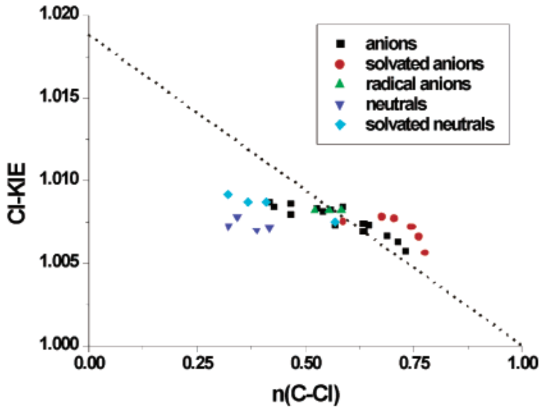

FIGURE 1. Dependence of the chlorine KIE on the Wiberg C_α−Cl transition state bond order for the S_N2 reactions of methyl chloride with 25 different nucleophiles. The dashed line is the KIE estimated using the BEBOVIB approach.

The results in Table 1 and Figure 1 show that the KIEs calculated quantum mechanically do not follow the BEBOVIB line for S_N2 reactions. In fact, all of the KIEs (for anionic, neutral, and radical anion nucleophiles) fall in a very small range even though the Wiberg TS bond orders and reactivity, vary significantly, i.e., the chlorine KIEs only vary from 1.0091 to 1.0056 (by 0.0035) even though the C_α−Cl transition state bond order varies from 0.32 to 0.73, or from fairly reactant-like to very product-like. This means that reactions with a C_α−Cl TS bond

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TABLE 1. Transition Structures and Chlorine Leaving Group KIEs for S_N2 Reactions between Methyl Chloride and Several Different Nucleophiles at 298 °C

Nu:	r (C−Cl)[a]	% (C−Cl)[b]	n (C−Cl)[c]	charge Cl[d]	r (C−Nu)[e]	n (C−Nu)[f]	charge Nu[g]	KIE_T[h]	TIF[i]	TDF[j]	Cl-KIE[k]	% $\frac{KIE_T \times TIF}{(Cl\text{-}KIE)}$
Cl^-	2.364	30.6	0.467	−0.647	2.364	0.467	−0.647	1.0005	1.0021	1.0060	1.0086	30.2
F^-	2.076	14.7	0.713	−0.471	2.257	0.218	−0.824	1.0002	1.0014	1.0047	1.0063	25.4
F^- aq[l]	2.218	21.8	0.587	−0.588	2.026	0.285	−0.816	1.0008	1.0019	1.0048	1.0075	36.0
SH^-	2.229	23.2	0.559	−0.564	2.628	0.408	−0.678	1.0005	1.0020	1.0057	1.0082	30.5
CN^-	2.200	21.6	0.567	−0.560	2.462	0.380	−0.787	1.0005	1.0015	1.0053	1.0073	27.4
SCN^-	2.399	32.5	0.429	−0.640	2.384	0.495	−0.600	1.0005	1.0018	1.0061	1.0084	27.4
Br^-	2.428	34.1	0.418	−0.673	2.458	0.530	−0.547	1.0004	1.0020	1.0063	1.0087	27.6
BH_4^-	2.214	22.3	0.587	−0.554	1.702	0.230	−0.707	1.0010	1.0024	1.0050	1.0084	40.5
SeH^-	2.266	25.2	0.527	−0.576	2.709	0.445	−0.636	1.0004	1.0020	1.0059	1.0083	28.9
OCl^-	2.148	18.7	0.647	−0.518	2.158	0.282	−0.788	1.0004	1.0018	1.0051	1.0073	30.1
$S^{\bullet -}$	2.222	22.8	0.554	−0.562	2.630	0.422	−0.677	1.0005	1.0020	1.0057	1.0082	30.5
OBr^-	2.164	19.6	0.634	−0.526	2.136	0.294	−0.783	1.0005	1.0018	1.0051	1.0074	31.1
OF^-	2.094	15.7	0.688	−0.480	2.232	0.256	−0.825	1.0003	1.0015	1.0048	1.0066	27.3
$NHCl^-$	2.038	12.6	0.732	−0.436	2.483	0.233	−0.812	1.0001	1.0007	1.0049	1.0057	14.0
$NHCl^-$ aq[l]	2.068	14.2	0.704	−0.484	2.429	0.249	−0.809	1.0007	1.0021	1.0049	1.0077	36.4
NH_3	2.528	39.6	0.343	−0.681	1.788	0.581	0.132	1.0006	1.0019	1.0053	1.0078	32.1
NH_3 aq[l]	2.235	22.8	0.569	−0.601	2.180	0.338	0.019	1.0007	1.0017	1.0050	1.0075	32.0
OCF_3^-	2.386	31.8	0.466	−0.655	1.941	0.371	−0.737	1.0005	1.0016	1.0058	1.0079	26.6
N_3^-	2.274	25.6	0.541	−0.597	2.142	0.328	−0.761	1.0006	1.0019	1.0056	1.0081	30.9
$SO^{\bullet -}$	2.179	20.4	0.583	−0.520	2.669	0.361	−0.663	1.0004	1.0021	1.0057	1.0082	30.5
PH_3	2.532	39.9	0.323	−0.632	2.112	0.699	0.511	1.0002	1.0008	1.0062	1.0072	13.9
pyridine	2.439	34.7	0.417	−0.625	1.859	0.486	0.129	1.0003	1.0009	1.0059	1.0071	16.9
4-nitropyridine	2.470	36.5	0.387	−0.634	1.813	0.517	0.122	1.0003	1.0008	1.0059	1.0070	15.7
$C{\equiv}CH^-$	2.130	17.7	0.634	−0.518	2.433	0.318	−0.752	1.0004	1.0014	1.0051	1.0069	26.1
H_2O aq[l]	2.433	34.4	0.411	−0.709	1.906	0.405	0.190	1.0007	1.0020	1.0060	1.0087	31.1
H_2O THF	2.494	37.8	0.366	−0.733	1.845	0.445	0.201	1.0006	1.0020	1.0061	1.0087	29.9
H_2O ether	2.494	37.8	0.320	−0.711	1.845	0.486	0.191	1.0006	1.0022	1.0063	1.0091	30.8
NH_2^- aq[l]	2.024	11.8	0.741	−0.447	2.598	0.227	−0.868	1.0005	1.0019	1.0048	1.0072	33.3
NH_2^- DMSO[l]	2.019	11.6	0.746	−0.443	2.602	0.223	−0.871	1.0005	1.0018	1.0048	1.0072	32.0
NH_2^- THF[l]	2.005	10.8	0.761	−0.428	2.628	0.211	−0.876	1.0003	1.0015	1.0048	1.0066	27.3
NH_2^- ether[l]	1.991	10.0	0.776	−0.412	2.655	0.198	−0.883	1.0001	1.0009	1.0046	1.0056	17.9
OH^- aq[l]	2.106	16.4	0.676	−0.513	2.284	0.259	−0.824	1.0008	1.0020	1.0049	1.0078	35.9
$Se^{\bullet -}$	2.260	24.8	0.522	−0.576	2.713	0.458	−0.633	1.0004	1.0019	1.0059	1.0082	28.1

[a] Length of the C_α−Cl TS bond in angstroms. [b] Percent elongation of the C_α−Cl TS bond = 100 × (length of the C_α−Cl TS bond − length of the C_α−Cl bond in the reactant)/length of the C_α−Cl bond in the reactant. [c] Wiberg C_α−Cl TS bond order. [d] Mulliken charge on the developing chloride ion in the TS. [e] Length of the Nu−C_α bond in the TS in angstroms. [f] Wiberg Nu−C_α TS bond order. [g] Mulliken charge on the nucleophile in the TS. [h] Wigner tunneling contribution to the chlorine KIE. [i] Temperature-independent term or imaginary frequency contribution to the chlorine KIE. [j] Temperature-dependent term or the vibrational energy contribution to the chlorine KIE. [k] Chlorine leaving group KIE = KIE_T × TIF × TDF. [l] Calculated using the PCM continuum solvent model with the conductor field model of electrostatic interactions (COSMO).

order in this range, covering most nucleophiles, have almost identical chlorine KIEs. Therefore, although differences in the magnitude of the chlorine KIE can probably still be used to show differences in the C_α−Cl TS bond order in a single reaction studied under different conditions and perhaps in reactions where a substituent has been changed, drawing any conclusion about TS structure from the magnitude of the chlorine KIEs from different reactions will be virtually impossible. This is because the difference between the chlorine KIE found for different reactions is not necessarily due to changes in the C_α−Cl TS bond order. For example, the reactions with neutral nucleophiles have smaller chlorine KIEs even though they have C_α−Cl TS bond orders smaller than those of the reactions with anions and radical anions. This makes chlorine KIEs less useful for studies of reaction mechanisms than assumed previously because one cannot use the magnitude of the chlorine KIE from one reaction to suggest whether another reaction has a shorter or longer C_α−Cl bond (a larger or smaller bond order) in the TS.

In several cases, the PCM continuum solvent model[12] with the conductor field model of electrostatic interactions (COSMO) was employed[13] to examine the effect of solvent on the KIE versus the Wiberg TS bond order plot, Figure 1. Inclusion of water as the solvent increases the chlorine KIE and decreases the C_α−Cl TS bond order for the anionic nucleophiles (F^-, NH_2^-, and $NHCl^-$) but increases the KIE and increases the bond order of the C_α−Cl TS bond when water is the nucleophile and decreases the KIE and decreases the C_α−Cl the bond order when NH_3 is the nucleophile. Some of the different behavior found for the neutral and negatively charged nucleophiles may be due to changes in solvation of the S_N2 TS,[17] but the relationship between the KIE and solvent is evidently complex. The important observation, however, is that although including solvent in the calculation alters the KIE, it does not affect the major conclusion of this study, i.e., that one cannot use the magnitude of the chlorine KIE from one reaction to suggest whether another reaction has a shorter or longer C_α−Cl bond (a larger or smaller bond order) in the TS because the KIE is not related to the TS C_α−Cl bond order.

Although the data in Table 1 and Figure 1 clearly show that the magnitude of the chlorine KIE is *not* related to

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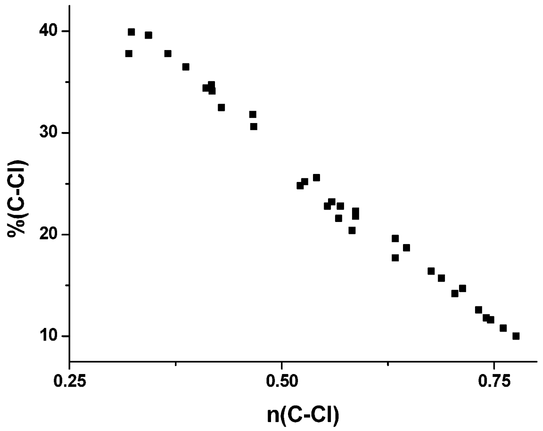

FIGURE 2. Percent extension of the C_α−Cl versus Wiberg C_α−Cl transition state bond order the transition state bond for the S_N2 reactions of methyl chloride with 25 different nucleophiles.

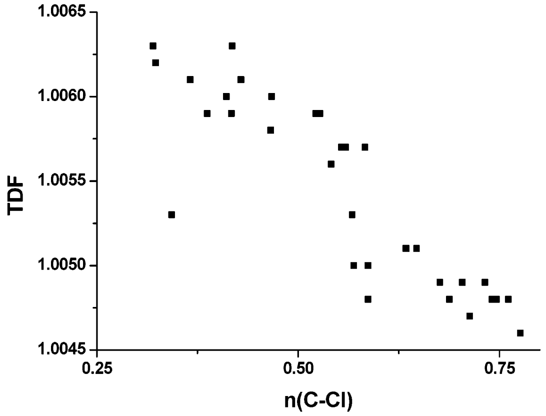

FIGURE 3. TDF term versus the Wiberg C_α−Cl transition state bond order for the S_N2 reactions between methyl chloride and 25 different nucleophiles.

the C_α−Cl bond order in the TS, it was important to determine whether there is any link between the chlorine KIE and TS structure. One question that has been considered recently is whether there is a direct relationship between the TS bond order and the percent extension (increase) in the length of the C_α−Cl bond in the TS. The plot of the percent extension of the C_α−Cl bond in the TS versus the bond order, Figure 2, is linear with a correlation coefficient of −0.994. This clearly indicates that the TS bond order is directly related to the percent extension of the C_α−Cl bond in the TS even though the transition state bonds are much longer and weaker than normal bonds. This observation is important because chemists have questioned whether this relationship would hold for weak bonds in a TS.

The leaving group KIE (Cl−KIE), Table 1, can be expressed as the product of three terms, a tunneling contribution to the KIE (KIE_T), a temperature-independent (TIF) term, and a temperature-dependent (TDF) term, eq 2, where $G(u_i) = [1/2 - 1/u_i + 1/(e^ui - 1)]$ and

$$\underbrace{k^{35}/k^{37}}_{\text{Cl-KIE}} = \underbrace{(k^{35}/k^{37})_{\text{Tunnel}}}_{\text{KIE}_T} \times \underbrace{(\nu^{\neq 35}/\nu^{\neq 37})}_{\text{TIF}} \times \underbrace{(1 + \Sigma G(u_i)\Delta u_i - \Sigma G(u_i^{\neq})\Delta u_i^{\neq})}_{\text{TDF}} \qquad (2)$$

$\Delta u_i = hc/kT(\Delta\nu_i)$. The terms h, c, k, and T are Planck's constant, the speed of light, Boltzmann's constant, and the absolute temperature, respectively. The $\Delta\nu_i$ term represents the isotope effect on the vibrational frequencies of the reactant and transition state.[18] On considering eq 2, it was realized that the TDF term gives the simple (BEBOVIB) relationship between TS structure and the magnitude of the leaving group KIE, i.e., that the KIE increases with the percent bond rupture in the TS. Therefore, the TDF term should be directly related to the C_α−Cl bond order (the percent extension) in the TS. The plot, Figure 3, shows that this is, indeed, the case. In fact, only ammonia does not fit this dependence. Given the very wide range nucleophiles used in this study, i.e., varying from poor (H_2O) to excellent (SH^- and CN^-), the agreement is unexpectedly good. The correlation coefficient for the plot is −0.926 when the outlier NH_3 is discarded. We were not able to discover why NH_3 is an outlier. However, it is clear that the qualitatively expected dependence of the magnitude of an isotope effect on the bond order holds for the thermodynamic ("equilibrium") part represented by the TDF factor, eq 2. It is worth noting that the least squares (best) straight line through the data in Figure 3 does not pass through either the maximum (1.014 for the TDF term) or minimum (1.000) value of the chlorine KIE. This suggests the relationship between the TDF term of the KIE and the C_α−Cl transition state bond order must be curved at very small and very large n_{C-Cl}.

Because the TDF varies directly with the C_α−Cl bond order in the TS, it is obvious that the product [KIE_T × TIF], corresponding to the dynamic ("kinetic") part of eq 2, is what destroys the simple relationship experimentalists have been using (the TDF term) to relate the magnitude of a leaving group KIE to TS structure. The last column of Table 1, which gives [KIE_T × TIF] as a percentage of the Cl−KIE, shows that this is the case. Two points are important. First, [KIE_T × TIF] represents a significant portion ($\geq$14%) of the Cl−KIE. Second, the [KIE_T × TIF] term varies both randomly and markedly throughout the series, i.e., from a low of 14% to a high of 40% of the Cl−KIE, Figure 4. In fact, no relationship could be found between the [KIE_T × TIF] term and TS structure. Because the product of the tunneling and the TIF term does not vary with TS structure in any obvious way and accounts for a significant portion of the Cl−KIE, it is this factor that leads to the unexpected results shown in Figure 1. Experimentalists using the simple theory (the TDF term) have assumed the [KIE_T × TIF] term was small and did not affect the magnitude of the Cl−KIE significantly. This study has shown that this is obviously not the case. This means one cannot estimate TS structure from a leaving group KIE without determining the [KIE_T × TIF] in a theoretical calculation so that one can isolate the TDF from the experimental KIE. It also means that all of the published chlorine KIEs will have to be reevaluated with respect to the TS structure.

This last point is illustrated by the exhaustive study of the KIEs for the S_N2 reaction between ethyl chloride

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[18] Westaway, K. C.; Fang, Y.-r; Persson, J.; Matsson, O. *J. Am. Chem. Soc.* **1998**, *120*, 3340.

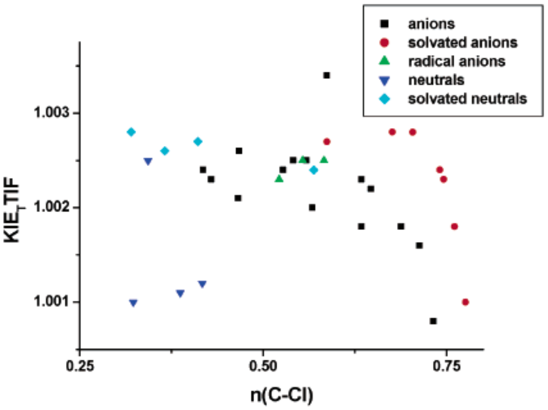

FIGURE 4. [KIE$_T$ × TIF] versus the Wiberg $C_\alpha-Cl$ transition state bond order for the S_N2 reactions between methyl chloride and 25 different nucleophiles.

TABLE 2. KIEs Found for S_N2 Reaction between Ethyl Chloride and Cyanide in DMSO at 30 °C[2]

measured KIE	experimental KIE
$(k_H/k_D)_{\alpha-D2}$	0.990 ± 0.004
$(k_H/k_D)_{\beta-D3}$	1.014 ± 0.003
k^{35}/k^{37}	1.0070 ± 0.0003
$(k^{11}/k^{14})_\alpha$	1.21 ± 0.02
k^{12}/k^{13}	1.0009 ± 0.0007
k^{14}/k^{15}	1.0002 ± 0.0006

and cyanide in DMSO at 30 °C, Table 2.[2] With the exception of the chlorine leaving group KIE, all of the KIEs were consistent with a transition state that had a short $C_\alpha-Cl$ bond and/or a short $NC-C_\alpha$ bond. On the basis of the simple theory of leaving group KIEs, which assumed the TIF and tunneling corrections to the KIE were very small, the authors concluded that the TS was product-like with a short $NC-C_\alpha$ bond and a long $C_\alpha-Cl$ bond because the chlorine leaving group KIE of 1.0070 was large, i.e., approximately 50% of the theoretical maximum TDF term, indicating there was significant $C_\alpha-Cl$ bond rupture in the TS. If this was true, the only alternative was that the TS was product-like with a fairly long $C_\alpha-Cl$ bond and a short $NC-C_\alpha$ bond. Forty-two different levels of theory, on the other hand, predicted the TS was reactant-like with a short $C_\alpha-Cl$ bond and a long $NC-C_\alpha$ bond. The results in this manuscript demonstrate that one cannot conclude the $C_\alpha-Cl$ TS bond is long because of a reasonably large chlorine KIE, i.e., the chlorine KIE of 1.0070 could be for a TS with either a short or a long $C_\alpha-Cl$ bond. Given this new information, the TS based on the experimental KIEs could be reactant-like with a long $NC-C_\alpha$ and a short $C_\alpha-Cl$ bond as theory predicted. Although it does not prove the TS is reactant-like, it could be reactant-like, resolving the discrepancy between theory and experiment. In this regard, it is worth noting that only a few of the 42 theoretical methods calculated the chlorine KIE within the experimental error.

It is important to note that the veracity of the calculated KIEs was checked in several ways. First, the effect of choosing the Wiberg TS bond order was investigated. The simplest Wiberg[19] definition, which is based on the Mulliken[20] partial atomic charges,[21] was used to calculate the $C_\alpha-Cl$ bond order for Figure 1. Although partial atomic charges have less physical meaning as the basis set is increased, the dependence of the chlorine KIEs on the $C_\alpha-Cl$ TS bond order should not be affected by the choice of the Wiberg bond order since the same basis set was used in all of the calculations. However, to ensure that the choice of bond order did not affect the conclusions, the dependence of the chlorine KIEs on the $C_\alpha-Cl$ TS bond order was determined using Pauling's bond orders with the coefficient value of 0.3[15] and 0.6, a value suggested by Houk[22] for calculating the bond orders in TSs. The choice of bond order only shifted the range of bond orders in the TSs but did not change the overall conclusion. It is important to note that the dependence of the chlorine KIE on the $C_\alpha-Cl$ bond length in the TS (percentage elongation of this bond) is qualitatively the same as that found using the Wiberg bond order and leads to the same conclusions. This is a result of the linear correlation between the percentage elongation of the $C_\alpha-Cl$ bond in TS and the Wiberg bond order, Figure 2. This observation is important because chemists have questioned whether this relationship would hold for weak bonds in a TS.

Next, the effect of anharmonicity was investigated. Isotopic frequencies of the transition state for the reaction between methyl chloride and ammonia were determined within the harmonic and anharmonic approximation. The TIF found using the anharmonic approximation is only slightly smaller than that with the harmonic approximation (1.0010 versus 1.0012, respectively). Anharmonicity in the TS causes the semiclassical chlorine KIE to be smaller by 0.0017. The major contribution comes from the symmetric $C_\alpha-Cl$ stretching vibration in the NH_3-CH_3Cl TS. Available methods do not allow calculations of the anharmonic frequencies for highly symmetric molecules such as methyl chloride. However, it is expected that the effect of anharmonicity of the methyl chloride will be close to that found for the transition state. Therefore, 0.0017 is the upper limit, and the overall effect of anharmonicity should be very small since it will be reduced by the anharmonicity of the substrate. This means anharmonicity will only have a very small effect on the chlorine KIE. The important observation is that neither the type of TS bond order nor the anharmonicity affect the conclusions based on Figure 1.

The effect of specific solvent–solute interactions on the KIE was also investigated. One problem with the continuum solvent models used (vide supra) to determine how solvent affects the leaving group KIE, is that they neglect explicit solvent–solute interactions. Some reactions were investigated by including in calculations explicit water molecule(s) that hydrogen bond to the developing chloride ion in the TS (the results not reported). The direction of changes of chlorine leaving group KIEs calculated with one or two explicit water molecule(s) are the same as those obtained with the continuum solvent model. They do not fall on the same TDF versus TS bond order curve since the C–Cl bond is not the only bond to the chlorine atom. The important observation, however, is that although including explicit water molecules in the calculation altered the KIE, it does not affect

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[19] Wiberg, K. B. *Tetrahedron* **1968**, *24*, 1083.
[20] Mulliken, R. S. *J. Chem. Phys.* **1955**, *23*, 1833.
[21] Green, D. F.; Tidor, B. *J. Phys. Chem. B* **2003**, *107*, 10261.
[22] Houk, K. N.; Gustafson, S. M.; Black, K. A. *J. Am. Chem. Soc.* **1977**, *114*, 8565.

the major conclusion of this study, i.e., that one cannot use the magnitude of the chlorine KIE from one reaction to suggest whether another reaction has a shorter or longer C_α−Cl bond (a larger or smaller bond order) in the TS because the KIE is not related to the TS C_α−Cl bond order.

Our findings indicate that in several cases the contribution of tunneling accounts for over 10% of the observed chlorine leaving group KIE. This is in agreement with previous reports that heavy atom tunneling can be significant for heavy atom KIEs.[23]

Finally, the validity of the calculated KIEs has been examined in the light of the published values of these KIEs. Four chlorine leaving group KIEs have been measured for S_N2 reactions with methyl chloride. Le Noble and Miller[24a] reported values of 1.0036 and 1.0038 for the S_N2 reactions with pyridine and 2,6-lutidine, respectively, at 100 °C in bromobenzene, and Swain and Hershey[24b] found KIEs of 1.0071 and 1.0064 with quinuclidine and triethylamine, respectively, in 1,2-dimethoxyethane at 25 °C. All of these values are within the range of KIEs found in Table 1. The chlorine KIEs found for the S_N2 reactions of ethyl chloride[2] and benzyl chloride with cyanide ion[24c] also fall within the range of values in Table 1. However, some larger KIEs, which fall outside the range of the calculated values, have been found for the S_N2 reactions of other alkyl chlorides. For instance, Graczyk et al.[24d] found chlorine leaving group KIEs between 1.0093 and 1.0096 for the S_N2 reaction between *n*-butyl chloride and thiophenoxide ion in several protic, aprotic, and dipolar aprotic solvents. Because substrates with larger alkyl groups are thought to have looser TSs, chlorine KIEs were also calculated for the S_N2 reactions between ethyl, propyl, and butyl chlorides and SH^- to approximate the system where Graczyk et al. found the very large chlorine KIEs. As expected, the calculated KIEs for the substrates with the larger alkyl groups are greater than that calculated for the methyl chloride−SH^- reaction, i.e., they increase from 1.0083 to 1.0089 as the size of the alkyl group in the substrate increases from methyl to butyl, Table 3. Although the calculated KIEs are slightly smaller than the experimental values, adding solvent will increase the KIEs slightly, Table 1. Given the increase in the magnitude of the KIE with the increase in substrate size and the effect of adding solvent, the calculated KIEs are in excellent agreement with the experimental KIEs. This confirms that the calculations give the correct KIEs.

TABLE 3. Calculated Chlorine KIEs for S_N2 Reactions of Several Alkyl Chlorides with SH^- at 298 °C

substrate	Cl−KIE
CH_3Cl	1.0082
C_2H_5Cl	1.0087
C_3H_7Cl	1.0091
C_4H_9Cl	1.0090
C_4H_9Cl (with PhS^-)	1.0089

Finally, this study has clearly shown that it is dangerous (impossible) to estimate the length of a C_α−Cl TS bond from the magnitude of a chlorine leaving group KIE. Therefore, it is important to determine whether the relationship between the magnitude of the leaving group KIE and TS bond order found for chlorine leaving group KIEs applies to other leaving-group KIEs. This study is underway.

Acknowledgment. This work was supported by grant 3-T09A-023-30 from the State Committee for Scientific Research, Poland, the Swedish Science Research Council (VR), and the Natural Science and Engineering Research Council of Canada (NSERC). P.P. acknowledges an Emerson Center (Emory University) visiting fellowship.

Supporting Information Available: Transition state structures, all characterized by one imaginary frequency, at the B1LYP/aug-cc-pVDZ level of theory and corresponding energies (in au). Nucleophiles are identified in the first line. The use of the continuum solvent model C-PCM (as implemented in Gaussian03) is indicated in parentheses where appropriate. This material is available free of charge via the Internet at http://pubs.acs.org.

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