A Theoretical Investigation of α-Carbon Kinetic Isotope Effects and Their Relationship to the Transition-State Structure of S_N2 Reactions

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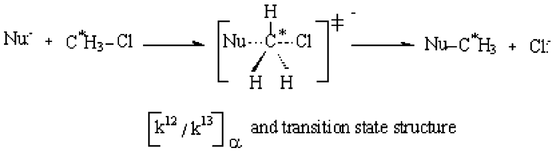
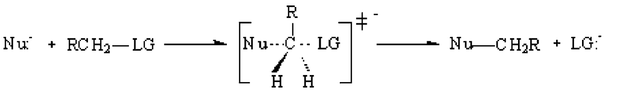


The transition structures and α-carbon $^{12}C/^{13}C$ kinetic isotope effects for 22 S_N2 reactions between methyl chloride and a wide variety of nucleophiles have been calculated using the B1LYP/aug-cc-pVDZ level of theory. Anionic, neutral, and radical anion nucleophiles were used to give a wide range of S_N2 transition states so the relationship between the magnitude of the α-carbon kinetic isotope effect and transition-state structure could be determined. The results suggest that the α-carbon $^{12}C/^{13}C$ kinetic isotope effects for S_N2 reactions will be large (near the experimental maximum) and that the curve relating the magnitude of the KIE to the percent transfer of the α-carbon from the nucleophile to the leaving group in the transition state has a broad maximum. This means very similar KIEs will be found for early, symmetric, and late transition states and that one cannot use the magnitude of these KIEs to estimate transition-state structure.

Introduction

α-Carbon kinetic isotope effects (KIEs) have been used to determine the mechanism and estimate the structure of the transition state of S_N2 reactions for some time.[1] Small α-carbon KIEs near 1% are indicative of a carbocation S_N (an S_N1) reaction, while larger KIEs of up to 8% for a $^{12}C/^{13}C$ KIE,[2] 16% for a $^{12}C/^{14}C$ KIE,[3] and 22% for an $^{11}C/^{14}C$ KIE[4] are indicative of an S_N2 mechanism, eq 1.



$$Nu^- + RCH_2{-}LG \longrightarrow \left[Nu\cdots\overset{R}{\underset{H\ \ H}{C}}\cdots LG\right]^{\ddagger -} \longrightarrow Nu{-}CH_2R + LG^- \quad [1]$$

Simple theory suggests that the relationship between the magnitude of the α-carbon KIE and the transition-state structure for an S_N2 reaction is given by a Melander−Westheimer-type curve with a maximum KIE observed for a symmetric transition state where the α-carbon is 50% transferred from the leaving group to the nucleophile in the transition state and smaller isotope effects for unsymmetric transition states.[1,3,5−7] It is worth noting that this curved relationship has been reported by Yamataka and Ando for the S_N2 reactions between benzyl para-substituted benzenesulfonates and *N*,*N*-dimethyl-*p*-toluidine in acetone at 35 °C.[3] However, an examination of the literature has shown that almost all of the α-carbon KIEs that have been reported for S_N2 reactions are large and near the experimental maximum KIE, Table 1.[4−15] In fact, the smallest α-carbon KIE

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TABLE 1. Experimental α-Carbon KIEs Measured for S_N2 Reactions

k^L/k^H	reaction	solvent	T (°C)	ref
k^{12}/k^{13}				
1.071 ± 0.008	$CN^- + CH_3{-}Cl$	water	31	8
1.071 ± 0.005	$CN^- + CH_3{-}I$	water	31	9
1.082 ± 0.007	$CN^- + CH_3{-}Br$	water	31	8
1.09 ± 0.05	3,4-dihydroxyacetophenone + *S*-adenosyl-L-methionine	water	37	5
1.08 ± 0.02	*S*-methyldibenzothiophenium ion + CH_3O^-	methanol	25	15
k^{12}/k^{14}				
1.117 ± 0.011	*N*,*N*-dimethyl-*p*-toluidine + $CH_3{-}I$	methanol	48.5	12
1.120 ± 0.001	*N*,*N*-diethylaniline + $CH_3{-}I$	methanol	62.7	12
1.134 ± 0.047	*N*,*N*-dimethyl-*o*-toluidine + $CH_3{-}I$	methanol	62.7	12
1.119−1.162	benzyl-*p*-substituted benzenesulfonates + *N*,*N*-dimethyl-*p*-toluidine	acetone	35	14
1.137−1.151	*m*-bromobenzyl-*p*-substituted benzenesulfonates + *N*,*N*-dimethyl-*p*-toluidine	acetone	35	14
1.140−1.148	benzyl-*p*-substituted benzenesulfonates + *N*,*N*-dimethyl-*p*-methoxyaniline	acetone	35	14
1.135−1.158	benzyl-*p*-substituted benzenesulfonates + *N*,*N*-dimethylaniline	acetone	35	14
1.129 ± 0.003	benzyl-*p*-chlorobenzenesulfonate + *N*,*N*-dimethyl-*m*-toluidine	acetone	35	14
1.117 ± 0.004	benzyl-*p*-chlorobenzenesulfonate + *N*,*N*-dimethyl-*p*-bromoaniline	acetone	35	14
1.127 ± 0.006	benzyl-*m*-nitrobenzenesulfonate + *N*,*N*-dimethyl-*m*-nitroaniline	acetone	35	14
k^{11}/k^{14}				
1.208 ± 0.019	$CN^- + CH_3CH_2{-}Cl$	DMSO	30	6
1.189 ± 0.012	2,4-lutidine + $CH_3{-}I$	acetonitrile	30	11
1.221 ± 0.006	triethylamine + $CH_3{-}I$	dimethoxymethane	15	11
1.192 ± 0.001	$OH^- + CH_3{-}I$	50% dioxane−water	25	4

reported for an S_N2 reaction is 80% of the largest-observed KIE so the qualitative conclusion would be that all the S_N2 reactions where an α-carbon KIE has been measured have symmetric or almost symmetric transition states. This is unreasonable, however, because (i) unsymmetric transition states have been proposed for many S_N2 reactions[16−18] and (ii) the α-carbon KIEs have been measured for S_N2 reactions with very different nucleophiles and leaving groups and in different solvents. Since these reactions must have different transition-state structures, it is very surprising that all S_N2 reactions have large α-carbon KIEs.

Until the dependence of these KIEs on transition-state structure is known with certainty, α-carbon KIEs will only be useful for indicating the mechanism of the reaction but will not be particularly useful for determining transition-state structure. Very fast computers and highly efficient algorithms that have been developed recently have enabled chemists to precisely describe transition states (TSs) quantum mechanically, at least for simple reactions, and to predict KIEs on the basis of these TS structures.[6] The relationship between the magnitude of the α-carbon KIE and the structure of the S_N2 transition state has been investigated in this study by calculating the TS structure and the α-carbon KIEs for a wide range of S_N2 reactions with methyl chloride.

Method

The transition structures and the α-$^{12}C/^{13}C$ KIEs for 22 S_N2 reactions between different nucleophiles (Nu:) and methyl chloride (R = H, LG = Cl, eq 1) were calculated using the B1LYP/aug-cc-pVDZ level of theory. This method was chosen because (i) a comparison of the adequacy of 42 different levels of theory for calculating the KIEs for the ethyl chloride−cyanide S_N2 reaction[6] showed that the best results were obtained when B3LYP and B1LYP DFT functionals[19] were used in combination with the aug-cc-pVDZ basis set[20] to determine the transition structure for the reaction and (ii) the B1LYP functional was developed with calculations of IR frequencies in mind and contains fewer adjustable parameters. Then, the α-$^{12}C/^{13}C$ KIEs were calculated from the normal vibrational modes of methyl chloride and the transition structure.[21] All calculations were performed in Gaussi-

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TABLE 2. Transition-State Bond Orders for the C_α−Nu and the C_α−Cl Bonds and the α-Carbon KIEs for the S_N2 Reactions between Methyl Chloride and 22 Different Nucleophiles at 298 °C

Nu:	$n_{(C-Cl)}$ [a]	$n_{(C-Nu)}$ [b]	Δn [c]	KIE_T [d]	TIF[e]	TDF[f]	C13 KIE[g]	%(KIE_T·TIF)
Cl^-	0.467	0.467	0.000	1.0071	1.0342	1.0271	1.0698	59.6
F^-	0.713	0.218	0.495	1.0042	1.0313	1.0254	1.0620	57.5
SH^-	0.559	0.408	0.151	1.0069	1.0340	1.0273	1.0695	59.1
$C\equiv N^-$	0.567	0.380	0.187	1.0091	1.0330	1.0256	1.0690	61.4
SCN^-	0.429	0.495	−0.066	1.0079	1.0343	1.0271	1.0707	60.1
Br^-	0.418	0.530	−0.112	1.0063	1.0358	1.0278	1.0713	59.4
BH_4^-	0.587	0.230	0.357	1.0118	1.0314	1.0233	1.0680	64.2
SeH^-	0.527	0.445	0.082	1.0068	1.0359	1.0278	1.0720	59.8
OCl^-	0.647	0.282	0.365	1.0071	1.0327	1.0246	1.0656	61.0
$S^{\bullet-}$	0.554	0.422	0.132	1.0068	1.0339	1.0219	1.0637	64.2
OBr^-	0.634	0.294	0.340	1.0079	1.0332	1.0246	1.0670	61.7
OF^-	0.688	0.256	0.432	1.0042	1.0313	1.0254	1.0620	57.5
$NHCl^-$	0.732	0.233	0.499	1.0028	1.0281	1.0246	1.0562	55.0
NH_3	0.343	0.581	−0.238	1.0077	1.0305	1.0200	1.0593	64.9
$NH_3^{\bullet-}$	0.435	0.359	0.076	1.0085	1.0303	1.0258	1.0659	59.3
OCF_3^-	0.466	0.371	0.095	1.0101	1.0340	1.0223	1.0677	65.6
N_3^-	0.541	0.328	0.213	1.0092	1.0326	1.0254	1.0685	61.5
$SO^{\bullet-}$	0.583	0.361	0.222	1.0057	1.0325	1.0272	1.0667	57.6
PH_3	0.323	0.699	−0.376	1.0089	1.0328	1.0269	1.0700	60.0
Pyridine	0.417	0.486	−0.069	1.0117	1.0362	1.0207	1.0700	69.0
Pyr-NO_2	0.387	0.517	−0.131	1.0130	1.0364	1.0200	1.0708	70.4
$C\equiv CH^-$	0.634	0.318	0.316	1.0071	1.0324	1.0257	1.0665	59.9
$NHCl^-_{aq}$ [h]	0.704	0.249	0.455	1.0090	1.0303	1.0232	1.0637	62.1
F^-_{aq} [h]	0.587	0.285	0.303	1.0131	1.0310	1.0234	1.0689	64.6

[a] The Wiberg bond order of the C_α−Cl TS bond. [b] The Wiberg bond order of the Nu−C_α TS bond. [c] $\Delta n = [(C_\alpha-Cl)_{TS\ bond\ order} - (C_\alpha-Nu)_{TS\ bond\ order}]$. [d] The Wigner tunneling contribution to the α-carbon KIE. [e] The temperature-independent term or the imaginary frequency contribution to the α-carbon KIE. [f] The temperature-dependent term or the vibrational energy contribution to the α-carbon KIE. [g] The α-carbon KIE = KIE_T × TIF × TDF. [h] Calculated using the PCM continuum solvent model with the conductor field model of electrostatic interactions (COSMO).[24, 25]

an03 using default convergence criteria.[22] Each transition state was characterized by exactly one imaginary frequency corresponding to the methyl group transfer between the Nu: and the LG (Cl). The effect of tunneling has been estimated using the Wigner approximation.[23] The PCM continuum solvent model[24] with the conductor field model of electrostatic interactions (COSMO)[25] was employed for two different reactions, the S_N2 reactions between fluoride ion and $NHCl^-$ with methyl chloride, to estimate the effect of solvent on the α-carbon KIE.

The nucleophiles ranged in nucleophilicity from very poor (F^-) to excellent ($C\equiv N^-$ and SH^-). While the majority of the nucleophiles were anionic (Cl^-, F^-, SH^-, $C\equiv N^-$, SCN^-, Br^-, BH_4^-, SeH^-, OCl^-, OBr^-, OF^-, $NHCl^-$, OCF_3^-, N_3^- and $C\equiv CH^-$), four neutral nucleophiles (pyridine, 4-nitropyridine, NH_3, and PH_3) and three radical anions ($S^{\bullet-}$, $SO^{\bullet-}$, and $NH_3^{\bullet-}$) were included to cover a wide range of transition structures. The reactions with the radical anions were treated using the UHF formalism.[26]

Results and Discussion

The transition-state bond orders for the C_α−Nu and the C_α−Cl bonds and the α-carbon KIEs for the S_N2 reactions between methyl chloride and 22 different nucleophiles are presented in Table 2. A plot of the KIEs versus the Wiberg C_α−Cl bond order,[27] Figure 1, shows that all of the calculated KIEs are within 1% (the approximate experimental error) of the largest KIE even though the transition structures for these S_N2 reactions are very different. For instance, the C_α−Cl transition-state bond orders vary from approximately 0.32 to 0.73 while the C_α−Nu transition-state bond orders vary from from 0.21 to 0.70 and the Δn values (the [C_α−Cl transition-state bond order − the C_α−Nu transition-state bond order]) varies from −0.38 to +0.50. Since a positive Δn indicates a reactant-like transition state and a negative Δn is found for a product-like transition state, the transition-state structures cover the range from very reactant-like to very product-like. Thus, the calculated KIEs suggest that the curve describing the dependence of the α-carbon KIE on transition-state structure, Figure 1, has a very broad maximum and that large α-carbon KIEs would be observed for transition states that are early, symmetric, or late.

An examination of the literature, Table 1, showed that all of the α-carbon KIEs that have been measured for S_N2 reactions are large. This obviously agrees with the calculated KIEs in Table 2. However, it is worth noting that not all S_N2 reactions seem to have a broad curve relating transition-state structure to the magnitude of the KIE suggested by Figure 1. One of several sets of α-carbon KIEs measured for the reactions between *p*-benzyl-*p*-substituted benzenesulfonates and *p*-substituted *N*,*N*-dimethylanilines[13,14] appears to have significant curvature to the magnitude of the KIE versus the para substituent on the leaving group plot, i.e., the KIEs for the reaction series between benzyl-*p*-substituted benzenesulfonates with *N*,*N*-dimethyl-*p*-toluidine, varies from 1.119 ± 0.003, to 1.149 ± 0.004, to 1.162 ± 0.008, to 1.156 ± 0.005, to 1.147 ± 0.002 when the substituent

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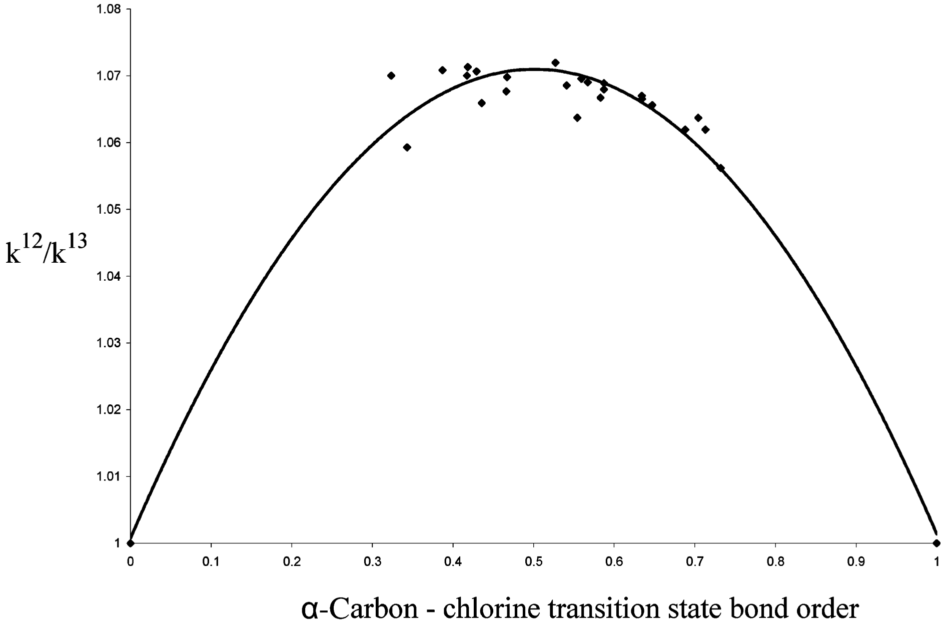

FIGURE 1. α-Carbon KIEs versus the C_α−Cl transition-state bond orders for the S_N2 reactions between methyl chloride and 22 different nucleophiles at 298 °C.

on the leaving group is changed from m-NO_2, to p-Cl, to H, to p-CH_3, to p-CH_3O^-, respectively. Although this suggests the curvature predicted by the simple theory, this conclusion seems unwarranted. When the para substituent in the leaving group is varied from p-Cl, to H, to p-CH_3, to p-CH_3O, the KIEs are almost the same when one considers the experimental errors in the KIEs. In fact, only the KIE where the para substituent is m-NO_2 is significantly different from the other values in the series. Also, the other experiment where the leaving group was varied in this series of reactions, i.e., in the reactions between the m-bromobenzyl-p-substituted benzenesulfonates and N,N-dimethyl-p-toluidine,[14] do not show the curved relationship found in the above series of reactions. Finally, all the other changes in the α-carbon KIEs due to substituent changes found in this series of reactions[14] have little or no change in the KIE with substituent; i.e., they display the same behavior as the calculated α-carbon KIEs in Table 2. As a result, although we do not understand why the KIE for the reaction where the substituent is m-NO_2 in the benzyl-p-substituted benzenesulfonate − N,N-dimethyl-p-toluidine reaction series is so low that it creates the illusion of curvature suggested by the simple theory, the curvature for this series of reactions seems far from proven.

The relationship between the magnitude of the KIE and transition-state structure for S_N2 reactions is obviously dependent on the shape of the KIE versus the percent transfer of the α-carbon between the leaving group and the nucleophile in the transition state curve, Figure 1. A curve with a narrow maximum means that the α-carbon KIE is very sensitive to transition-state structure whereas a broader curve implies that the KIE is not very sensitive to a change in transition state structure. Earlier attempts using the BEBO (bond energy-bond order) approach[28] to calculate the α-carbon KIEs for several S_N2 reactions showed that the choice of reaction-coordinate motion affects both the magnitude of the KIE and its relationship to transition-state structure. Yamataka and Ando[13] reported that adding an interaction constant that couples the bending and stretching vibrations in the reaction-coordinate motion[28] increased the magnitude of the α-carbon KIE. This bend−stretch coupling also broadened the curve relating the KIE to bond order for the forming or breaking bonds so that a wide range of transition-state structures gave near-maximum KIEs. Matsson and co-workers also used BEBOVIB calculations and the same type of reaction coordinate motion as Yamataka and Ando to estimate the α-$^{11}C/^{14}C$ KIEs for the S_N2 reactions between methyl iodide and hydroxide ion[4] or N,N-dimethyl-p-toluidine.[10] They found that varying the interaction force constants determined whether a narrow or a broad curve described the dependence of the KIE on transition-state structure. For instance, in the methyl iodide−hydroxide ion reaction, they found that a bond order for the forming O−C_α bond ranging from 0.30 to 0.55 when the interaction force constants were allowed to vary, or from 0.15 to 0.65 when the interaction force constants were fixed, gave a curve where the α-carbon KIE was ≥77% of the maximum value of 1.22.[4] This suggested that the magnitude of the KIE was not sensitive to changes in transition-state structure. This has been confirmed by the quantum mechanical calculations, i.e., the very broad, almost flat, top of the α-carbon KIE versus the C_α−Cl transition-state bond order curve, Figure 1, confirms that S_N2 reactions with an early, a central, and a late transition state have α-carbon KIEs close to the experimental maximum value. This unfortunately, means that α-carbon KIEs will not be very useful in determining transition-state structure of S_N2 reactions. It is worth noting, however, that although the data in Figure 1 seems to show the curvature expected for the α-carbon KIE versus percent

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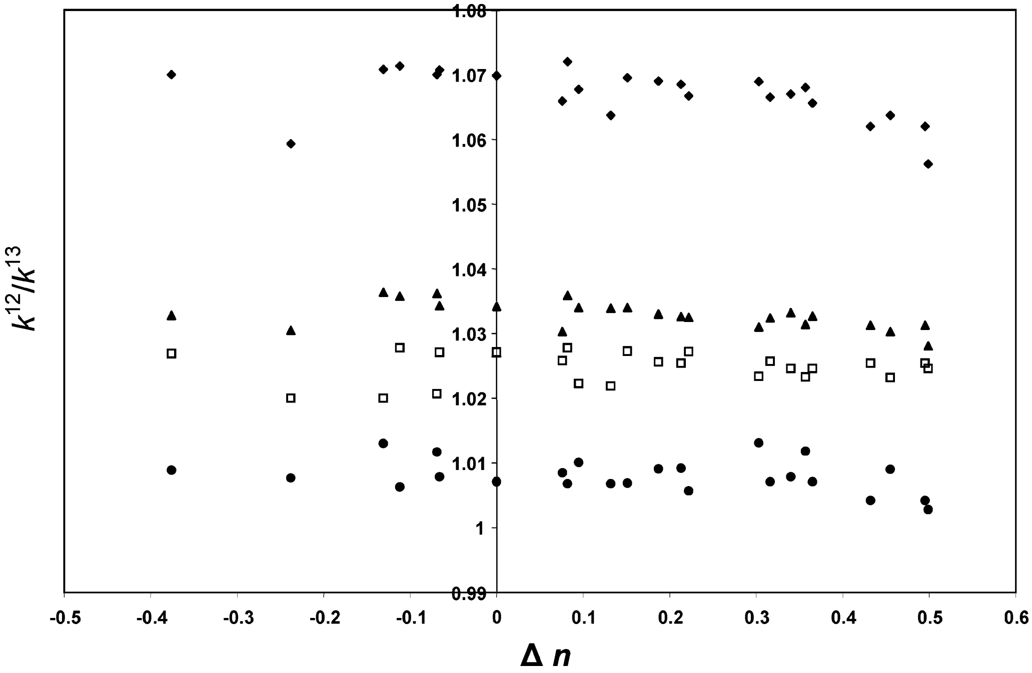

FIGURE 2. KIE_T (●), TIF (▲), TDF (□), and α-carbon KIEs (◆) versus Δ*n*, the [$C_\alpha-Cl$ transition-state bond order − the $C_\alpha-Nu$ transition state bond order], for the S_N2 reactions between methyl chloride and 22 different nucleophiles. Positive Δ*n* values are for reactant-like transition structures and negative values are for product-like transition structures.

transfer of the α-carbon from the leaving group to the nucleophile curve, the curvature is too small to be useful for determining transition-state structure.

The α-carbon KIE, Table 2, can be expressed as the product of three factors, a tunneling contribution to the KIE, a temperature-independent factor or TIF, which is the imaginary frequency ratio, and a temperature-dependent factor or TDF, which is the vibrational product, the excitation, and the zero-point energy factors,[29] eq 2.

$$k^{12}/k^{13} = \underbrace{(k^{12}/k^{13})_{\text{tunnel}}}_{\text{KIE}_\text{T}} \times \underbrace{(v^{\ddagger 12}/v^{\ddagger 13})}_{\text{TIF}} \times \underbrace{(\text{VP})(\text{EXC})(\text{ZPE})}_{\text{TDF}} \quad (2)$$

Each of the terms in eq 2 were calculated in an effort to understand the origin of the α-carbon KIE. As was reported recently for the chlorine (leaving group) KIEs,[30] the results in Table 2 show that both the KIE_T and the TIF terms play a significant role in determining the magnitude of the α-carbon KIE. For instance, the tunneling contribution ranges from 5.0 to 19.1% of the KIE[31] and the TIF term accounts for an even larger percentage (from 44.9 to 53.3%) of the total KIE. In fact, the product of the KIE_T and the TIF terms represent between 55.0 and 70.4% of the total KIE. As with the chlorine (leaving group) KIEs,[30] none of the TIF, the KIE_T, or the product of the KIE_T and the TIF terms, Figure 2, were related to the transition-state structure. Finally, it is important to note that the TDF term versus Δ*n* does not show any significant curvature either, Figure 2. Although one might argue that there does appear to be some curvature in the KIE with transition-state structure, Figure 1, the curvature, if any, is very small. This undoubtedly is because the TDF values only range from 1.0200 to 1.0278, Table 2, even though there is a large change in transition-state structure.

The PCM continuum solvent model[24] with the conductor field model of electrostatic interactions (COSMO)[25] was employed for two different reactions, the S_N2 reactions between fluoride ion and $NHCl^-$ with methyl chloride, to estimate the effect of solvent on the α-carbon KIE. In both reactions, the KIE is slightly (by 0.007 or 0.7%) larger when water is added in the solvent continuum model. The difference in the KIE is almost completely caused by a change in the imaginary frequency, i.e., the imaginary frequency increases from −281.9 to −524.8 cm^{-1} for the fluoride ion reaction and from −237.1 to −434.3 cm^{-1} in the $NHCl^-$ reaction for the reactions with carbon 12 at the α-carbon. However, the change in the KIE on adding solvent is small; i.e., it is only 0.7% and comparable to the error in measuring these KIEs. This small effect of solvent on the magnitude of these KIEs is substantiated by the fact that the experimental KIEs measured in many very different solvents, Table 1, are all at or near the experimental maximum. Also, the $^{11}C/^{14}C$ α-carbon KIE (the largest of the α-carbon KIEs and therefore the most sensitive to a change in solvent) measured for the S_N2 reaction between ethyl chloride and cyanide ion did not change when the solvent was changed from DMSO (dielectric constant =

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(29) Melander, L.; Saunders, W. H., Jr. In *Reaction Rates of Isotopic Molecules*; Wiley-Interscience: J. Wiley and Sons: New York, 1980; pp 19−26.

(30) Dybala-Defratyka, A.; Rostkowski, M.; Matsson, O.; Westaway, K. C.; Paneth, P. *J. Org. Chem.* **2004**, *69*, 4900.

(31) As expected, the TIF terms for the chlorine leaving group KIE only represented between 1.5 and 12.1% of the total KIE.

49) to THF (dielectric constant = 7.32).[32] Since this very large change in solvent did not change the KIE, it appears that these KIEs are not significantly affected by solvent as the small change on adding solvent to the calculations suggests.

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Note Added after ASAP Publication. There were presentation errors in eq 2 in the version published ASAP April 19, 2005; the corrected version was published April 25, 2005.

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[32] Gordon, A. J.; Ford, R. A. In *The Chemist's Companion*; J. Wiley and Sons: New York, 1972; pp 6, 7.