Determining the Transition-State Structure for Different S_N2 Reactions Using Experimental Nucleophile Carbon and Secondary α-Deuterium Kinetic Isotope Effects and Theory

Kenneth C. Westaway,*,† Yao-ren Fang,† Susanna MacMillar,‡ Olle Matsson,*,‡
Raymond A. Poirier,*,§ and Shahidul M. Islam§

Department of Chemistry and Biochemistry, Laurentian University, Sudbury, ON, Canada, P3E 2C6,
Department of Biochemistry and Organic Chemistry, Uppsala University, P.O. Box 576,
SE-751 23 Uppsala, Sweden, and Department of Chemistry, Memorial University,
St. John's, NL, Canada, A1B 3X7

Nucleophile $^{11}C/^{14}C$ [k^{11}/k^{14}] and secondary α-deuterium [$(k_H/k_D)_\alpha$] kinetic isotope effects (KIEs) were measured for the S_N2 reactions between tetrabutylammonium cyanide and ethyl iodide, bromide, chloride, and tosylate in anhydrous DMSO at 20 °C to determine whether these isotope effects can be used to determine the structure of S_N2 transition states. Interpreting the experimental KIEs in the usual fashion (i.e., that a smaller nucleophile KIE indicates the Nu−C_α transition state bond is shorter and a smaller $(k_H/k_D)_\alpha$ is found when the Nu−LG distance in the transition state is shorter) suggests that the transition state is tighter with a slightly shorter NC−C_α bond and a much shorter C_α−LG bond when the substrate has a poorer ***halogen*** leaving group. Theoretical calculations at the B3LYP/aug-cc-pVDZ level of theory support this conclusion. The results show that the experimental nucleophile $^{11}C/^{14}C$ KIEs can be used to determine transition-state structure in different reactions and that the usual method of interpreting these KIEs is correct. The magnitude of the experimental secondary α-deuterium KIE is related to the nucleophile−leaving group distance in the S_N2 transition state (R_{TS}) for reactions with a halogen leaving group. Unfortunately, the calculated and experimental $(k_H/k_D)_\alpha$'s change oppositely with leaving group ability. However, the calculated $(k_H/k_D)_\alpha$'s duplicate both the trend in the KIE with leaving group ability and the magnitude of the $(k_H/k_D)_\alpha$'s for the ethyl *halide* reactions when different scale factors are used for the high and the low energy vibrations. This suggests it is critical that different scaling factors for the low and high energy vibrations be used if one wishes to duplicate experimental $(k_H/k_D)_\alpha$'s. Finally, neither the experimental nor the theoretical secondary α-deuterium KIEs for the ethyl tosylate reaction fit the trend found for the reactions with a halogen leaving group. This presumably is found because of the bulky (sterically hindered) leaving group in the tosylate reaction. From every prospective, the tosylate reaction is too different from the halogen reactions to be compared.

1. Introduction

Although many different types of kinetic isotope effects (KIEs) have been used to probe the structure of S_N2 transition states,[1−10] most of the studies used leaving group KIEs to estimate the relative lengths of the C_α−LG bond in the transition state.[2,5,8,11,12] Until recently, the interpretation of these KIEs was thought to be straightforward (i.e., it was believed that a larger leaving group KIE was indicative of greater C_α−LG bond rupture in the transition state). However, a recent theoretical investigation of chlorine leaving group KIEs[13] indicated that the interpretation of these KIEs was not as straightforward as had been previously thought. This study showed that the chlorine leaving group KIEs for 26 S_N2 reactions with methyl chloride fell in a very narrow range of values and that there was no relationship between the magnitude of the KIE and the C_α−Cl bond length in the transition state!

The KIE is the product of the tunneling KIE (KIE_T), the imaginary frequency ratio, or temperature independent factor, (TIF‡), and the temperature dependent factor (TDF) that

represents the isotope effect on the vibrations in the reactant (TDF_R) and transition state (TDF‡), respectively.[14,15] According to eq 1,

$$
\underbrace{\frac{k_L}{k_H}}_{KIE_T} = \underbrace{\left(\frac{k_L}{k_H}\right)_T}_{} \times \underbrace{\left(\frac{\nu_L^{\ddagger}}{\nu_H^{\ddagger}}\right)}_{TIF^{\ddagger}} \times \underbrace{\prod_i^{3N-6} \frac{\mu_{iH}^R \sinh(\mu_{iL}^R/2)}{\mu_{iL}^R \sinh(\mu_{iH}^R/2)}}_{TDF_R} \times \underbrace{\prod_i^{3N^{\ddagger}-7} \frac{\mu_{iL}^{\ddagger} \sinh(\mu_{iH}^{\ddagger}/2)}{\mu_{iH}^{\ddagger} \sinh(\mu_{iL}^{\ddagger}/2)}}_{TDF^{\ddagger}}
$$

(1)

where R represents the reactant, ‡ indicates the transition state, $\mu_i = h\nu_i/k_B T$, ν_i is the vibrational frequencies, and L and H represent species with the light and heavy isotopes, respectively. Dybala-Defratyka et al.[13] found that the relationship between the magnitude of the experimental chlorine leaving group KIE and the C_α−Cl bond length in the transition state fails because the (KIE_T × TIF‡) portion of the KIE accounted for a significant portion of the total KIE and is not related to transition-state structure in any discernible way. This means that although the TDF‡ was related to the length of the C_α−Cl bond in the transition state, one cannot use the magnitude of the KIE to estimate the length of the C_α−Cl transition-state bond. This then

　* Authors to whom correspondence should be addressed. E-mail: kwestaway@laurentian.ca; olle.matsson@biorg.uu.se; rpoirier@mun.ca.
　† Laurentian University.
　‡ Uppsala University.
　§ Memorial University.

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led one to question whether one could use the magnitude of a nucleophile KIE to estimate the relative lengths of the $Nu-C_\alpha$ transition-state bond in different reactions or whether they would suffer from the same problem as the leaving group KIEs. This latter possibility seemed likely because the basic equation is the same and the nucleophile KIE measures the reverse of the leaving group KIEs (i.e., the amount of $Nu-C_\alpha$ bond formation rather than the amount of $C_\alpha-LG$ bond rupture in the transition state). This experimental and theoretical study of the nucleophile carbon KIEs for several S_N2 reactions with different leaving groups and presumably very different transition states, examines whether the magnitude of the nucleophile KIEs from different reactions can be used to determine the relative lengths of the $Nu-C_\alpha$ transition-state bond in S_N2 reactions.

2. Computational Method

The calculations for the S_N2 reactions between cyanide ion and ethyl chloride, bromide, iodide, and tosylate were done at the RHF/6-31+G(d), the B3LYP/6-31+G(d), and the B3LYP/aug-cc-pVDZ levels of theory. The last method was chosen because it gave the closest KIEs to the experimental values in a thorough examination of the readily available methods for calculating the transition-state structure and the KIEs in the ethyl chloride−cyanide ion S_N2 reaction.[16] All calculations were performed with Gaussian03[17] using default convergence criteria. For third row elements, the standard 6-31G basis set[18] was found to be more reliable than the Binning−Curtiss basis set[19] (BC6-31G) available in Gaussian03.[20] However, for bromine both the 6-31G and BC6-31G basis sets were used. Huzinaga's double-ζ basis set[21] was used for iodine. Unscaled frequencies were used for most of the calculations. The only exception was that scaled frequencies were used for calculating some of the secondary α-deuterium KIEs. Each transition structure had one imaginary frequency corresponding to the transfer of the α carbon from the leaving group to the carbon of the cyanide ion nucleophile. The effect of tunneling (KIE_T) was calculated using the Wigner approximation.[22] Because a recent study[15] showed that a significant change in solvent does not change the structure of a type I (where the nucleophilic atoms in the transition state have the same charge) S_N2 transition state significantly, the lack of solvent in the calculations was not expected to have a significant effect on the results. However, this conclusion was tested by optimizing the transition-state structures and calculating the KIEs in both the gas phase and in DMSO using the polarizable continuum model (PCM) as implemented in Gaussian03. All the KIEs were calculated with the ISOEFF98 program.[23]

3. Results and Discussion

The nucleophile $^{11}C/^{14}C$ KIEs for the S_N2 reactions between cyanide ion and ethyl chloride, bromide, iodide, and tosylate were measured in anhydrous DMSO at 20 °C to determine whether these KIEs could be used to estimate the relative lengths of the $NC-C_\alpha$ transition-state bonds in these reactions. The secondary α-deuterium KIEs were also measured for these reactions to try to define the transition-state structures in more detail.

The rate constants and experimental nucleophile $^{11}C/^{14}C$ KIEs and secondary α-deuterium KIEs for the S_N2 reactions between cyanide ion and ethyl chloride, bromide, iodide, and tosylate in anhydrous DMSO at 20 °C are given in Tables 1 and 2, respectively. The transition-state structures obtained at the RHF/6-31+G(d), the B3LYP/6-31+G(d), and the B3LYP/aug-cc-

TABLE 1: Rate Constants and Nucleophile $^{11}C/^{14}C$ KIEs for the S_N2 Reactions between Cyanide Ion and Ethyl Iodide, Bromide, Chloride, and Tosylate in Anhydrous DMSO at 20 °C

substrate	average k (M^{-1} s^{-1})[a]	k^{12}/k^{13}	k^{11}/k^{14} [b]
ethyl iodide	2.024×10^{-1}		1.0066 ± 0.0008[d] (6)[e]
ethyl bromide	3.576×10^{-2}		1.0028 ± 0.0015[c] (8)[e]
ethyl chloride[c]	4.232×10^{-4c}	1.0009 ± 0.0007[d] (18)[e]	1.0027[f]
ethyl tosylate	4.828×10^{-3}		1.0015 ± 0.0011[c] (6)[e]

[a] These rate constants are taken from Table 2. The individual rate constants were not required in these experiments. [b] The substrate and nucleophile concentrations in these experiments were approximately 0.08 and 0.1 M, respectively. [c] This data is taken from ref 16. The KIE was measured at 30 °C in anhydrous DMSO. [d] Standard deviation. [e] The number of separate evaluations of the KIE used to calculate the average KIE. [f] Estimated using the method in ref 24.

pVDZ levels of theory are presented in Table 3, and the corresponding nucleophile $^{11}C/^{14}C$ and secondary α-deuterium KIEs are given in Tables 4 and 5.

3.1. Experimental Nucleophile $^{11}C/^{14}C$ KIEs. With the exception of the KIE for the ethyl chloride reaction, the nucleophile $^{11}C/^{14}C$ KIEs for the S_N2 reactions between cyanide ion and ethyl chloride, bromide, iodide, and tosylate in anhydrous DMSO at 20 °C (Table 1) are smaller when a poorer leaving group is present. However, it is worth noting that the very small nucleophile $^{11}C/^{14}C$ KIE for the ethyl chloride reaction was estimated[24] from a $^{12}C/^{13}C$ KIE measured in an earlier study[16] and thus comparing it with the KIEs from this study is problematic. Even so, it is interesting that the $^{11}C/^{14}C$ KIE decreases when a poorer **halogen** leaving group is present in the substrate. Since current theory suggests that a smaller nucleophile $^{11}C/^{14}C$ KIE is indicative of a shorter $Nu-C_\alpha$ transition-state bond,[4,25] the nucleophile $^{11}C/^{14}C$ KIEs found in this investigation suggest that $NC-C_\alpha$ bond formation is more complete (i.e., the $NC-C_\alpha$ transition-state bond is shorter) in reactions with a poorer leaving group.

3.2. Experimental Secondary α-Deuterium KIEs. The secondary α-deuterium KIEs were also measured for the S_N2 reactions between ethyl chloride, bromide, iodide, and tosylate in an effort to determine the structure of the S_N2 transition states in more detail. The results (Table 2) show that the $(k_H/k_D)_\alpha$ decreases with leaving group ability within the **halogen** series of leaving groups but that the $(k_H/k_D)_\alpha$ for the ethyl tosylate reaction is much larger than expected based on leaving group ability.

The usual relationship between the magnitude of a secondary α-deuterium KIE and transition-state structure in S_N2 reactions is that a larger KIE is found when the nucleophile−leaving group distance in the transition state is greater, at least for S_N2 reactions with the same leaving group.[29,30] If the same relationship holds for the ethyl halide S_N2 reactions in this study, even though they have different leaving groups, one would conclude that the transition state is tighter with shorter $NC-C_\alpha$ and/or $C_\alpha-LG$ bonds when a poorer **halogen** leaving group is present. In this regard, it is important to note that the plot of the experimental $(k_H/k_D)_\alpha$ versus R_{TS} (the nucleophile−leaving group distance in the transition state;[31] Table 3) for the **ethyl halide** reactions is linear with a correlation coefficient of 0.991. This relationship with R_{TS} for a family of leaving groups is probably fortuitous because a significant portion of this trend is due to the change in the ground-state $C_\alpha-X$ bond (Table 3 footnote) and because the

TABLE 2: Secondary α-Deuterium KIEs for the SN2 Reactions between Cyanide Ion and Ethyl Iodide, Bromide, Chloride, and Tosylate in Anhydrous DMSO at 20 °C

substrate	average k_H (M^{-1} s^{-1})[a]	average k_D (M^{-1} s^{-1})[a]	$(k_H/k_D)_\alpha$
ethyl iodide[b]	$(2.024 \pm 0.004)^f \times 10^{-1}$	$(1.961 \pm 0.003)^f \times 10^{-1}$	1.0318 ± 0.0036^d
ethyl bromide[b]	$(3.576 \pm 0.001) \times 10^{-2}$	$(3.552 \pm 0.0008) \times 10^{-2}$	1.0065 ± 0.0005
ethyl chloride[c]	$(4.232 \pm 0.073) \times 10^{-4}$	$(4.274 \pm 0.077) \times 10^{-4}$	0.990 ± 0.004^e
ethyl tosylate[b]	$(4.828 \pm 0.002) \times 10^{-3}$	$(4.548 \pm 0.002) \times 10^{-3}$	1.0617 ± 0.0005

[a] The rate constants from three separate experiments were used in calculating the average rate constant. [b] The substrate and nucleophile concentrations in these experiments were approximately 0.003 and 0.005 M, respectively, for the ethyl iodide reactions, 0.0037 and 0.0073 M, respectively, for the ethyl bromide reactions, and 0.034 and 0.06 M, respectively, for the ethyl tosylate reactions. [c] This data is taken from ref 16. The KIE was measured at 30 °C in anhydrous DMSO. The temperature effect on these KIEs is very small[26–28] and can be ignored. [d] The error in the KIE is $1/k_D[(\Delta k_H)^2 + (k_H/k_D)^2 \times (\Delta k_D)^2]^{1/2}$, where Δk_H and Δk_D are the standard deviations for the average rate constants for the reactions of the undeuterated and deuterated substrates, respectively.[1] [e] This error is the standard deviation for four different measurements of the KIE. [f] Standard deviation.

TABLE 3: Calculated C_α–LG and NC–C_α Transition-State Bond Lengths for the SN2 Reactions between Cyanide Ion and Ethyl Iodide, Bromide, Chloride, and Tosylate at 25 °C using Three Different Levels of Theory

	$(C_\alpha$–LG$)^\ddagger$ bond length (Å)			$(NC–C_\alpha)^\ddagger$ bond length (Å)			$(C–C_\alpha + C_\alpha$–LG$)^\ddagger =$
substrate	RHF/ 6-31+G(d)	B3LYP/ 6-31+G(d)	B3LYP/ aug-cc-pVDZ	RHF/ 6-31+G(d)	B3LYP/ 6-31+G(d)	B3LYP/ faug-cc-pVDZ	R_{TS} (Å)
Et–I[a]	2.6841	2.6129	2.5966 (18.9%)[b]	2.4937	2.4452	2.4175 (65.7%)[c]	5.0141[d]
Et–Br	2.4709[e]	2.4048[e]	2.4183 (21.7%)	2.3724[e]	2.3379[e]	2.3969 (64.3%)	4.8152
Et–Cl	2.3623	2.2996	2.2910 (25.3%)	2.3708	2.3477	2.3417 (60.5%)	4.6327
Et–OTs	1.9313	1.8664	1.8710 (28.3%)	2.4425	2.4273	2.4048 (64.8%)	4.2758
leaving group effect (I–Cl)	0.3218	0.3133	0.3056 (−6.4%)	0.1229	0.0975	0.0758 (5.2%)	0.3814

[a] Huzinaga's double-ζ basis set[21] was used for iodine. [b] The % extension of the C_α–LG bond on going to the transition state = [(C_α–LG bond length in the transition state − C_α–LG bond length in the reactant)/C_α–LG bond length in the reactant]. The C_α–LG bond lengths in the reactant were C_α–I = 2.1834 Å, C_α–Br = 1.9878 Å, C_α–Cl = 1.8279 Å, and C_α–O = 1.4584 Å. [c] The % extension of the NC–C_α bond in the transition state = [(NC–C_α bond length in the transition state − NC–C_α bond length in the product)/NC–C_α bond length in the product]. The NC–C_α bond length in the product was 1.459 Å. [d] At the B3LYP/aug-cc-pVDZ level of theory. [e] These values were obtained using the BC6-31+G(d) basis set for bromine.

change in the magnitude of a $(k_H/k_D)_\alpha$ in an unsymmetric SN2 transition state is determined by the change in the length of the shortest transition-state bond only.[32,33] This is because any change in the bond to the more distant nucleophile in the transition state will occur too far away from the C_α to affect the C_α–H(D) bending vibrations that are mainly responsible for the magnitude of the KIE. In the **ethyl halide** reactions, theoretical calculations of the transition structure at the B3LYP/aug-cc-pVDZ level of theory (Table 3) indicate that the transition state is reactant-like with a long NC–C_α and significant, but not extensive, C_α–X bond rupture, that is, the percent extensions (eq 2)

% extension on going to the transition state =

$$\frac{\text{TS bond length} - \text{reactant (product) bond length} \times 100\%}{\text{reactant (product) bond length}} \quad (2)$$

of the NC–C_α and C_α–X bonds on going to the transition state are 63 ± 3 and 24 ± 5%, respectively (i.e., the calculations show that the transition states are all reactant-like with a long NC–C_α bond). Therefore, the change in the shorter C_α–X bond will determine the magnitude of these KIEs and the transition states with the shortest C_α–X bond will have the smallest KIE (i.e., the KIE and C_α–X bond distance in the transition state decrease when a poorer **halogen** leaving group is present in the substrate). Other support for this interpretation of the secondary α-deuterium KIEs is that the "bond strength hypothesis"[34] suggests that the weakest reacting bond will change more than the stronger bond in an SN2 transition state when the leaving group is altered. Thus, a greater change in the weaker C_α–X transition state bond is expected when the leaving group is changed. Since the change to a poorer leaving group is accompanied by a decrease in the KIE and a tighter transition

TABLE 4: Nucleophile ¹¹C/¹⁴C KIEs for the SN2 Reactions between Cyanide Ion and Ethyl Iodide, Bromide, Chloride, and Tosylate at 25 °C Using Three Different Levels of Theory

	k^{11}/k^{14}			
substrate	RHF/ 6-31+G(d)	B3LYP/ 6-31+G(d)	B3LYP/ aug-cc-pVDZ	expt
ethyl iodide[a]	0.9811	0.9869	0.9843	1.0066
ethyl bromide	0.9691[b]	0.9750[b]	0.9845	1.0028
	0.9767[c]	0.9828[c]		
ethyl chloride	0.9723	0.9793	0.9809	1.0027[d]
ethyl tosylate	0.9737	0.9793	0.9800	1.0015
leaving group effect (I–Cl)	0.0087	0.0076	0.0034	0.0039

[a] Huzinaga's double-ζ basis set[21] was used for iodine. [b] These values were obtained using the BC6-31+G(d) basis set for bromine. [c] Values obtained using the standard bromine 6-31+G(d) basis set. [d] Estimated using the method in ref 24 from the incoming nucleophile $k^{12}/k^{13} = 1.0009$[16].

state and the greatest change is in the C_α–X bond, the transition state with the poorer leaving group must have a shorter C_α–X bond.

The final problem, then, is how to interpret the much larger than expected $(k_H/k_D)_\alpha$ of 1.062 found for the ethyl tosylate reaction (i.e., the plot of the experimental $(k_H/k_D)_\alpha$ versus R_{TS} suggests the $(k_H/k_D)_\alpha$ should be 0.95 whereas it is 1.062). Unfortunately, the interpretation of the tosylate KIE is not straightforward. Much larger than expected secondary α-deuterium KIEs are observed when the leaving group is large (bulky) because the steric hindrance to the C_α–H(D) bending vibrations in the tetrahedral reactant (with a short bond to the bulky leaving group) is greater than the steric hindrance to these

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TABLE 5: Secondary α-Deuterium [$(k_H/k_D)_\alpha$] KIEs for the S_N2 Reactions between Cyanide Ion and Ethyl Iodide, Bromide, Chloride, and Tosylate at 25 °C Using Three Different Levels of Theory

	$(k_H/k_D)_\alpha$			
substrate	RHF/ 6-31+G(d)	B3LYP/ 6-31+G(d)	B3LYP/ aug-cc-pVDZ	expt
ethyl iodide[a]	0.9436	0.9723	0.9718	1.032
ethyl bromide	0.9474[b]	0.9734[b]	0.9762	1.0065
	0.9545[c]	0.9804[c]		
ethyl chloride	0.9655	0.9987	0.9899	0.990[d]
ethyl tosylate	1.0188	1.0206	1.0009	1.0617
leaving group effect (I−Cl)	−0.0220	−0.0265	−0.0182	0.0418

[a] Huzinaga's double-ζ basis set[21] was used for iodine. [b] These values were obtained using the BC6-31+G(d) basis set for bromine. [c] Values obtained using the standard bromine 6-31+G(d) basis set. [d] This value was measured in anhydrous DMSO at 30 °C.[16] The temperature effect on these KIEs is very small[26−28] and can be ignored.

vibrations in the pentacoordinate transition state where the bond to the leaving group is longer.[35,36] Support for this idea was provided by Abraham and McLennan,[37] who suggested that the lone pairs of electrons on the oxygens of arenesulfonate leaving groups cause steric hindrance for the C_α−H(D) bending vibrations in the ground state and increase the $(k_H/k_D)_\alpha$. This explanation for the larger than expected $(k_H/k_D)_\alpha$ of 1.062 for the tosylate reaction is reasonable because (1) the cyanide ion nucleophile is small and will not sterically hinder the bending vibrations of the C_α−H(D) bonds in the transition state, (2) theoretical calculations of the transition-state structure at the B3LYP/aug-cc-pVDZ level of theory (Table 3) indicate the transition state is reactant-like with a long NC−C_α and significant, but not extensive, C_α−O bond rupture (i.e., the percent extensions (eq 2) of the NC−C_α and C_α−O bonds on going to the transition state are 64.8 and 28.3%, respectively), and (3) since the NC−C_α and particularly the C_α−O % extensions are greater than those found for the ethyl halide reaction transition states, the steric explanation for the much larger α-deuterium KIE for the tosylate reaction is reasonable. Since this steric effect of the bulky leaving group is not present in the halide reactions, their $(k_H/k_D)_\alpha$'s show a clean trend with the smaller KIE and tighter transition state for the reactions with a poorer leaving group.

3.3. Effect of Changing the Leaving Group on the Structure of the S_N2 Transition State Predicted by Experiment. The nucleophile carbon KIEs suggest that the NC−C_α bonds are shorter in the transition states with a poorer leaving group. The secondary α-deuterium KIEs indicate that the transition states with a poorer *halogen* leaving group have a shorter C_α−X transition-state bond. Unfortunately, the secondary α-deuterium KIEs do not enable one to determine the change in the NC−C_α transition-state bond with leaving group since the magnitude of these KIEs is determined by only the shorter (the C_α−LG) transition-state bond.

3.4. Effect of Changing the Leaving Group Predicted by Theory. *Transition-State Structure.* The results in Table 3 show that, with one exception, the transition structures calculated at three different levels of theory have a shorter NC−C_α transition-state bond as one goes from a better to a poorer *halogen* leaving group. This is in agreement with the conclusion based on interpreting the experimental $^{11}C/^{14}C$ KIEs. The calculations at all three levels of theory also indicate that both the C_α−X transition-state bond and R_{TS} shorten when a poorer *halogen*

leaving group is used. These results are in total agreement with the predictions based on interpreting the experimental $^{11}C/^{14}C$ KIEs and the $(k_H/k_D)_\alpha$'s. Thus, the agreement between theory and experiment for the reactions with a *halogen* leaving group is excellent.

Another important observation is that the calculations indicate that the change in the C_α−X transition-state bond with leaving group is much larger than the change in the NC−C_α transition-state bond when a poorer *halogen* leaving group is used (i.e., the change in the NC−C_α transition-state bonds in going from I$^-$ (best leaving group) to Cl$^-$ (poorest leaving group) is only 0.08 Å at the B3LYP/aug-cc-pVDZ level of theory, whereas the corresponding change in the C_α−X transition-state bond is four times larger at 0.31 Å). This is consistent with interpretation of the secondary α-deuterium KIEs and the "bond strength hypothesis,"[34] which predicts that the greatest change in the transition-state structure with a change in leaving group will occur at the weakest reacting bond.

It is important to note that the transition-state structure for the ethyl tosylate reaction does not fit the trend in transition-state structure found for the reactions with the halogen leaving groups. The tosylate reaction has much larger bond extensions for the NC−C_α and C_α−O transition-state bonds than expected given its reactivity. This mirrors the predictions based on the experimental KIEs and again suggests that the tosylate reaction is very different from the ethyl halide reactions. Obviously, changing from a halogen to a tosylate leaving group alters the transition-state structure too much to hope the reaction fits the trends found for the halogen family of leaving groups.

The important conclusions, however, are that (1) one can use the nucleophile carbon KIEs to estimate the relative length of the NC−C_α transition-state bonds in a closely related series of S_N2 reactions (i.e., those with a *halogen* leaving group), (2) the usual interpretation of the $(k_H/k_D)_\alpha$'s predicts the change in the C_α−X transition-state bond with leaving group,[32,33] and (3) the transition state becomes tighter when a poorer *halogen* leaving group is present.

Experimental vs Calculated Nucleophile $^{11}C/^{14}C$ KIEs. The next consideration was to compare the calculated KIEs with the experimental values. The nucleophile $^{11}C/^{14}C$ KIEs calculated at three different levels of theory are presented along with the experimental values in Table 4. The results show that the $^{11}C/^{14}C$ KIE is only affected slightly by the level of theory (i.e., the nucleophile $^{11}C/^{14}C$ KIEs only vary by 1.5% with the level of theory). The agreement between the experimental and the calculated KIEs is satisfying although theory predicts nucleophile carbon KIEs approximately 2% smaller than the experimental KIEs at the B3LYP/aug-cc-pVDZ level of theory. However, at this level of theory, the change in the calculated $^{11}C/^{14}C$ KIE with leaving group is approximately 20% smaller than the change in the experimental KIEs (i.e., 0.34% by theory and 0.39% experimentally). At the B3LYP/aug-cc-pVDZ level of theory, the trends in the calculated $^{11}C/^{14}C$ KIE follow those found experimentally, except that the calculated $^{11}C/^{14}C$ KIE for the ethyl iodide reaction is slightly smaller than that for the ethyl bromide reaction. This may arise from using the Huzinaga basis set[21] for iodine and the aug-cc-pVDZ basis set for the other atoms. This is reasonable because the ethyl iodide $^{11}C/^{14}C$ KIE is larger than the ethyl bromide $^{11}C/^{14}C$ KIE using the other two levels of theory.

With one exception (vide supra), both the calculated and experimental $^{11}C/^{14}C$ KIEs and calculated transition structures indicate the NC−C_α transition-state bond is shorter when a poorer *halogen* leaving group is present. Thus, both the

TABLE 6: Calculated C_α−LG and NC−C_α Transition-State Bond Lengths for the S_N2 Reactions between Cyanide Ion and Ethyl Iodide, Bromide, Chloride, and Tosylate in DMSO at 25 °C using Three Different Levels of Theory

	$(C_\alpha-LG)^\ddagger$ bond length (Å)			$(NC-C_\alpha)^\ddagger$ bond length (Å)			$(C-C_\alpha + C_\alpha\text{-}LG)^\ddagger =$
substrate	RHF/ 6-31+G(d)	B3LYP/ 6-31+G(d)	B3LYP/ aug-cc-pVDZ	RHF/ 6-31+G(d)	B3LYP/ 6-31+G(d)	B3LYP/ aug-cc-pVDZ	R_{TS} (Å)
Et−I[a]	2.7819	2.6762	2.6557 (21.0%)[b]	2.5150	2.3806	2.3490 (60.2%)[c]	5.0047[d]
Et−Br	2.5384[e]	2.4405[e]	2.4654 (23.1%)	2.4115[e]	2.3107[e]	2.3650 (61.3%)	4.8304
Et−Cl	2.4271	2.3295	2.3227 (25.9%)	2.4481	2.3517	2.3387 (59.5%)	4.6614
Et−OTs	2.0270	1.9446	1.9453 (32.6%)	2.4268	2.3552	2.3320 (59.1%)	4.2773

[a] Huzinaga's double-ζ basis set[21] was used for iodine. [b] The % extension of the C_α−LG bond on going to the transition state = [(C_α−LG bond length in the transition state − C_α−LG bond length in the reactant)/C_α−LG bond length in the reactant]. The C_α−LG bond lengths in the reactant were C_α−I = 2.1949 Å, C_α−Br = 2.0033 Å, C_α−Cl = 1.8444 Å, and C−O = 1.4584 Å. [c] The % extension of the NC−C_α bond in the transition state = [(NC−C_α bond length in the transition state − NC−C_α bond length in the product)/NC−C_α bond length in the product]. The NC−C_α bond length in the product was 1.4660 Å. [d] At the B3LYP/aug-cc-pVDZ level of theory. [e] These values were obtained using the BC6-31+G(d) basis set for bromine.

transition structures and the KIEs predicted by theory agree with the change in the NC−C_α transition-state bond predicted by interpreting the experimental ^{11}C/^{14}C KIEs. The calculated ^{11}C/^{14}C KIE for the tosylate reaction is, however, smaller than expected based on its leaving group ability.

Experimental vs Calculated $(k_H/k_D)_\alpha$'s. The agreement between the experimental and the calculated secondary α-deuterium KIEs (Table 5) is less satisfying. Although the $(k_H/k_D)_\alpha$'s only change by $\leq 3.0\%$ using different levels of theory, the difference between the B3LYP/aug-cc-pVDZ and experimental $(k_H/k_D)_\alpha$'s is larger (i.e., they differ by 3.0% for the ethyl bromide reaction and by 6.0 and 6.1% for the ethyl iodide and tosylate reactions, respectively). In fact, the calculated and experimental $(k_H/k_D)_\alpha$ is only identical for the ethyl chloride reaction. More importantly, the trend in the calculated $(k_H/k_D)_\alpha$ for the reactions with the ***halogen*** leaving groups is opposite that found using the experimental values. The experimental values decrease with leaving group ability, suggesting the transition state becomes tighter with a shorter C_α−LG bond when a poorer leaving group is used, whereas the calculated $(k_H/k_D)_\alpha$ increases very slightly when a poorer leaving group is present. Since the change in the calculated C_α−X bond is greater than the change in the NC−C_α bond when a poorer leaving group is used (vide supra), the increase in the calculated $(k_H/k_D)_\alpha$ with a poorer leaving group suggests the transition state C_α−X bond lengthens when a poorer leaving group is present. This is clearly opposite the change in transition structure with leaving group predicted by interpreting the experimental $(k_H/k_D)_\alpha$ and the change in the transition structures calculated for these reactions!

Although the change in the experimental nucleophile carbon KIEs for the reactions with the ***halogen*** leaving groups is slightly larger than the change found theoretically (0.39 vs 0.34%; Table 4), the change in the experimental α-deuterium KIEs with leaving group is opposite (+4.2 vs −1.8%; Table 5) that found theoretically at all three levels of theory. Moreover, the magnitude of these KIEs is significantly lower than the experimental values for these KIEs.

Finally, it is interesting that both the calculated and experimental $(k_H/k_D)_\alpha$'s for the ethyl tosylate reaction are larger than those for the ethyl halide reactions as would be expected for a reaction with a bulky leaving group.[35−37]

3.5. Effect of Solvent. Since the calculations were done in the gas phase and the experimental results are from solution, solvent was added to the calculations to learn whether this would make the trend in the calculated $(k_H/k_D)_\alpha$'s with leaving group and the magnitude of these KIEs match the experimental values. The calculations in DMSO were performed using PCM.

Transition-State Structure. A comparison of the B3LYP/aug-cc-pVDZ results in Tables 3 and 6 shows that all the transition states become more productlike with a shorter NC−C_α and a longer C_α−LG bond when solvent is added to the calculations. It is interesting that adding DMSO to the calculations at the B3LYP/aug-cc-pVDZ level of theory changes the NC−C_α transition-state bond more than the C_α−LG transition-state bond (i.e., the changes in the % extension of the NC−C_α transition-state bond on adding solvent vary from 5.5 to 1.0%, whereas the corresponding changes for the C_α−X bonds vary only from 2.1 to 0.6%). It is also worth noting that, as one might expect, adding solvent in the *ethyl halide* reactions has the largest effect on the transition structure of the reactions with the loosest transition state (i.e., with the largest R_{TS} and the greatest negative charges on the nucleophilic atoms in the transition state). For instance, the total change in the % extension of the reacting bonds = [(% extension C_α−X_{DMSO} − % extension C_α−X_{gas}) − (% extension NC−$C_{\alpha DMSO}$ − % extension NC−$C_{\alpha gas}$)] = −3.4% for the ethyl iodide reaction, which has the loosest transition state, −1.6% for the ethyl bromide reaction, and only −0.4% for the ethyl chloride reaction, which has the tightest S_N2 transition state and smallest R_{TS}.

Unfortunately, the NC−C_α transition-state bond in DMSO does not change regularly with ***halogen*** leaving group at any of the levels of theory tested. It is worth noting that this problem does not arise in the gas-phase calculations. Finally, although there is a problem with the trends in the NC−C_α bond length, the C_α−X transition-state bonds are shorter when a poorer leaving group is used in the ***ethyl halide*** reactions.

Nucleophile ^{11}C/^{14}C KIEs. A comparison of the nucleophile carbon KIEs calculated at the B3LYP/aug-cc-pVDZ level of theory (Tables 4 and 7) shows that adding solvent to the calculation leads to a slightly more inverse KIE for all the reactions. This trend in the KIE with leaving group is expected because the NC−C_α transition-state bond is shorter when the solvent is present. However, the change in the KIE with leaving group ability at the B3LYP/aug-cc-pVDZ level of theory does not match the trend in the KIE with the ***halogen*** leaving groups found experimentally or in the calculations at the RHF/6-31+G(d) and B3LYP/6-31+G(d) levels of theory. The reason the calculated ^{11}C/^{14}C KIEs at the B3LYP/aug-cc-pVDZ level of theory do not decrease with a poorer ***halogen*** leaving group, like the calculated NC−C_α transition-state bond and experiment suggest, may be due to using Huzinaga's basis set at the B3LYP/aug-cc-pVDZ level of theory for the ethyl iodide calculation. This is because the ^{11}C/^{14}C KIEs in DMSO and in the gas phase at the RHF/6-31+G(d) and B3LYP/6-31+G(d) levels of theory do become more inverse when a poorer ***halogen*** leaving group

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TABLE 7: Nucleophile $^{11}C/^{14}C$ KIEs for the S_N2 Reactions between Cyanide Ion and Ethyl Iodide, Bromide, Chloride, and Tosylate in DMSO at 25 °C Using Three Different Levels of Theory

| | k^{11}/k^{14} | | | |
| | RHF/ 6-31+G(d) | B3LYP/ 6-31+G(d) | B3LYP/ aug-cc-pVDZ | |
substrate				expt
ethyl iodide[a]	0.9878	0.9850	0.9787	1.0066
ethyl bromide	0.9758[b]	0.9751[b]	0.9820	1.0028
	0.9841[c]	0.9826[c]		
ethyl chloride	0.9523	0.9749	0.9793	1.0027[d]
ethyl tosylate	0.9778	0.9778	0.9778	1.0015
leaving group effect (I−Cl)	0.0355	0.0101	−0.0006	0.0039

^{a} Huzinaga's double-ζ basis set[21] was used for iodine. ^{b} These values were obtained using the BC6-31+G(d) basis set for bromine. ^{c} Values obtained using the standard bromine 6-31+G(d) basis set. ^{d} Estimated using the method in ref 24 from the nucleophile k^{12}/k^{13} = 1.0009[16].

TABLE 8: Secondary α-Deuterium $(k_H/k_D)_\alpha$ KIEs for the S_N2 Reactions between Cyanide Ion and Ethyl Iodide, Bromide, Chloride, and Tosylate in DMSO at 25 °C Using Three Different Levels of Theory

| | $(k_H/k_D)_\alpha$ | | | |
| | RHF/ 6-31+G(d) | B3LYP/ 6-31+G(d) | B3LYP/ aug-cc-pVDZ | |
substrate				expt
ethyl iodide[a]	1.0067	0.9611	0.9517	1.032
ethyl bromide	1.0128[b]	0.9722[b]	0.9722	1.0065
	1.0332[c]	0.9818[c]		
ethyl chloride	1.0540	1.0090	0.9920	0.990[d]
ethyl tosylate	1.0923	1.0043	0.9892	1.0617
leaving group effect (I−Cl)	−0.0473	−0.0479	−0.0402	0.0418

^{a} Huzinaga's double-ζ basis set[21] was used for iodine. ^{b} These values were obtained using the BC6-31+G(d) basis set for bromine. ^{c} Value obtained using the standard bromine 6-31+G(d) basis set. ^{d} This value was measured in anhydrous DMSO at 30 °C.[16] The temperature effect on these KIEs is very small[26-28] and can be ignored.

is used and the NC−C_α transition-state bond is shorter. Finally, it is interesting that the change in the experimental nucleophile carbon KIE with leaving group is larger than the change in the calculated KIEs in DMSO, just as it was for the gas-phase reactions (i.e., the calculated change in the KIE with leaving group is 0.0034 in the gas phase and −0.0006 in DMSO whereas it is 0.0039 experimentally). More important, the change in the calculated KIE with the *halogen* leaving group in DMSO is significantly different than that found experimentally and in the gas-phase calculations.

Secondary α-Deuterium KIEs. The comparison of the B3LYP/aug-cc-pVDZ $(k_H/k_D)_\alpha$s in the gas phase and in solution (Tables 5 and 8, respectively) shows that two of the three KIEs for the **ethyl halide** reactions are smaller in solution, suggesting the transition-state structures are tighter in solution. However, the R_{TS} values in Tables 3 and 6 indicate that, except for the ethyl iodide reaction, the calculated transition-state structures are looser in solution. Thus, the trend in the calculated KIE does not agree with the change in the calculated transition-state structure for these reactions. Also, the agreement between experiment and theory is not good. The experimental $(k_H/k_D)_\alpha$ decrease, suggesting the transition structures for these reactions become tighter when a poorer leaving group is used, whereas the calculated KIEs in Table 8 increase when a poorer leaving group is used. This is best illustrated by the fact that the change

TABLE 9: Calculated and Experimental Free Energies of Activation for the S_N2 Reactions between Cyanide Ion and Ethyl Iodide, Bromide, Chloride, and Tosylate in DMSO at 25 °C

| | $\Delta G^{\ddagger}$ (kJ mol^{-1}) | | | | |
| | gas phase | | DMSO | | |
	B3LYP/ 6-31+G(d)	B3LYP/ aug-cc-pVDZ	B3LYP/ 6-31+G(d)	B3LYP/ aug-cc-pVDZ	expt[a]
ethyl iodide[b]	12.4	6.7	91.2	87.7	77.0
ethyl bromide	21.4[c]	19.1	93.2[c]	91.6	81.3
ethyl chloride	39.4	34.7	102.4	99.8	92.3[d]
ethyl tosylate	36.8	36.0	122.9	131.1	86.2

^{a} Calculated from the average experimental rate constants in Table 2. Given the errors in rate constants, the experimental $\Delta G^{\ddagger}$ is accurate to one decimal place. ^{b} Huzinaga's double-ζ basis set[21] was used for iodine. ^{c} These values were obtained using the BC6-31+G(d) basis set for bromine. ^{d} Value obtained from the experimental rate constant measured at 30 °C.

in the experimental KIE on going from the best to the poorest *halogen* leaving group (4.2%) is effectively equal, but opposite (−4.0%) the change calculated in solution and larger and opposite that found for the calculated KIEs (−1.8%) in the gas phase.

Although R_{TS} for ethyl tosylate is greater in DMSO than in gas phase, the $(k_H/k_D)_\alpha$ in DMSO is smaller than that in gas phase. Thus, the change in transition-state structure and in the KIE on adding solvent are opposite to that expected.

Finally, using other levels of theory does not give better results. In some cases, adding solvent to the calculation increases the KIE while it decreases the KIE in other reactions.

Overall, adding solvent to the calculations does not lead to better results for these KIEs. This may occur because the continuum model cannot account for the complex changes that occur in the solvent during a reaction.[38-40]

3.6. Effect of Changing the Leaving Group on the Free Energy of Activation. The free energies of activation calculated at two levels of theory and from the experimental rate constants using $\Delta G^{\ddagger} = -RT \ln(k_r h/k_B T)$, where k_r is the experimental rate constant, are given in Table 9. The $\Delta G^{\ddagger}$ values calculated from structures optimized at the B3LYP/aug-cc-pVDZ level of theory in DMSO are in very good agreement with the $\Delta G^{\ddagger}$ values determined from the experimental rate constants for the **alkyl halide** reactions, differing by no more than 11 kJ mol^{-1}. The $\Delta G^{\ddagger}$ values for the alkyl halide reactions also increase with a poorer *halogen* leaving group, in agreement with experiment. However, for ethyl tosylate, the difference in $\Delta G^{\ddagger}$ is significantly larger (i.e., the B3LYP/aug-cc-pVDZ $\Delta G^{\ddagger}$ is 45 kJ mol^{-1} higher than the experimental value). In fact, the computed and experimental $\Delta G^{\ddagger}$ values for all the reactions are only in the same order at the B3LYP/6-31G(d) level of theory in the gas phase. Unlike experiment, the $\Delta G^{\ddagger}$ values for the tosylate reaction are larger than those for ethyl chloride at both the B3LYP/6-31G(d) and the BLYP/aug-cc-pVDZ levels in DMSO. The failure to observe the experimental trend in $\Delta G^{\ddagger}$ with the ethyl tosylate suggests again that the transition state for this reaction must be very different from those for the ethyl halide reactions.

3.7. Effect of Scaling Factors for the Vibrational Frequencies on $(k_H/k_D)_\alpha$'s. Normally, calculated vibrational frequencies obtained by different levels of theory are scaled to match experimental frequencies. Scott and Radom[41] compared a total of 1066 calculated harmonic frequencies with experi-

TABLE 10: Scale Factors Used for Frequencies Lower Than 750 cm⁻¹ in Calculating $(k_H/k_D)_\alpha$ for the S_N2 Reactions between Cyanide Ion and Ethyl Iodide, Bromide, and Chloride at 25 °C in the Gas Phase and in DMSO at the B3LYP/aug-cc-pVDZ Level of Theory

substrate	low frequency scale factors in the gas phase[a]	$(k_H/k_D)_\alpha$ in the gas phase (using the scale factors)	low frequency scale factors in DMSO[a]	$(k_H/k_D)_\alpha$ in DMSO (using the scale factors)	exptl $(k_H/k_D)_\alpha$
Et−I	0.9953	1.0318	1.0023	1.0319	1.032
Et−Br	0.9902	1.0065	0.9915	1.0065	1.0065
Et−Cl	0.9709	0.9901	0.9692	0.9900	0.990

[a] Frequencies higher than 750 cm⁻¹ are scaled by the recommended frequency scaling factor of 0.97 for B3LYP/aug-cc-pVDZ.[41,42]

TABLE 11: Individual Contributions to the Calculated Nucleophile ¹¹C/¹⁴C KIEs for the S_N2 Reactions between Cyanide Ion and Ethyl Iodide, Bromide, Chloride, and Tosylate at 25 °C in the Gas Phase at the B3LYP/aug-cc-pVDZ Level of Theory

substrate	TDF_R	KIE_T	$TIF^\ddagger$	$KIE_T \times TIF^\ddagger$	$TDF^\ddagger$	$KIE^\ddagger = \{KIE_T \cdot TIF^\ddagger \cdot TDF^\ddagger\}$	total k^{11}/k^{14}	% $(KIE_T \times TIF^\ddagger)/k^{11}/k^{14}$
ethyl iodide	1.2964	1.0021	1.0102	1.0123	0.7501	0.7593	0.9843	78.3
ethyl bromide	1.2964	1.0022	1.0094	1.0116	0.7507	0.7594	0.9845	74.8
ethyl chloride	1.2964	1.0025	1.0089	1.0115	0.7481	0.7566	0.9809	60.2
ethyl tosylate	1.2964	1.0025	1.0071	1.0096	0.7488	0.7560	0.9800	48.0
leaving group effect (I−Cl)	0.0000	−0.0004	0.0013	0.0008	0.0020	0.0027	0.0034	18.1

mental frequencies and found that the vibrational frequencies require different scaling factors depending on the level of theory, the basis set, and whether they are high or low energy vibrations. For the cyanide ion−ethyl halide reactions, the vibrational frequencies range from as low as 55 cm⁻¹ to as high as 3400 cm⁻¹. Since both the high energy modes (C_α−H stretch) and low energy modes (C_α−H bending) play an important role in determining the magnitude of a $(k_H/k_D)_\alpha$ and will be affected by isotopic substitution, it was expected that scaling might play a critical role in calculating a $(k_H/k_D)_\alpha$. The recommended scaling factor for all vibrational modes is 0.97 at the B3LYP/aug-cc-pVDZ level of theory.[42] All the frequencies greater than 750 cm⁻¹ were scaled by 0.97. The scaling factor for low energy frequencies at this level of theory is not known so the scaling factor for the low energy vibrations was varied until the calculated $(k_H/k_D)_\alpha$ matched the experimental $(k_H/k_D)_\alpha$. The scale factors for the lower frequency modes in both the gas phase and in DMSO that gave the experimental $(k_H/k_D)_\alpha$'s for the ethyl chloride, bromide, and iodide reactions are given in Table 10. For ethyl chloride, the scale factors for both low and high frequencies are very close to 0.97. However, for ethyl bromide and iodide, the scaling factors for the lower energy frequencies are closer to unity as Scott and Radom suggested.[41] It is evident that proper scaling of the low and high energy frequencies is an important factor in being able to calculate both the value and the trend in $(k_H/k_D)_\alpha$.

3.8. Implications of the Theoretical Study on Using Nucleophile Carbon KIEs To Determine the Transition States of S_N2 Reactions. The nucleophile carbon KIE can be expressed as

$$KIE = TDF_R \times KIE_T \times TIF^\ddagger \times TDF^\ddagger = TDF_R \times KIE^\ddagger \quad (3)$$

where the transition-state contribution to the total KIE ($KIE^\ddagger$) is the product of the tunneling KIE (KIE_T), the imaginary frequency ratio for the reactions with the ¹¹C and ¹⁴C isotopes ($TIF^\ddagger$), and the isotope effect on the vibrational energy of the transition state ($TDF^\ddagger$). TDF_R represents the isotope effect on

the vibrational energy of the cyanide ion (reactant). TDF_R and $TDF^\ddagger$ can be calculated[43] from

$$TDF_R = \prod_i^{3N-6} [\mu_{iH}^R \sinh(\mu_{iL}^R/2)/\mu_{iL}^R \sinh(\mu_{iH}^R/2)] \quad (4)$$

$$TDF^\ddagger = \prod_i^{3N^\ddagger-7} [\mu_{iL}^\ddagger \sinh(\mu_{iH}^\ddagger/2)/\mu_{iH}^\ddagger \sinh(\mu_{iL}^\ddagger/2)] \quad (5)$$

respectively, where R represents the substrate, ‡ indicates the transition state, $\mu_i = h\nu_i/k_BT$ where the ν_i is the vibrational frequency, and L and H represent the ¹¹C and ¹⁴C isotopes, respectively. KIE_T was calculated using the Wigner approximation.[22]

The individual contributions to the nucleophile carbon KIEs calculated at the B3LYP/aug-cc-pVDZ level of theory (Table 11) sheds light on the origin of these KIEs. All the terms except for TDF_R vary with leaving group. TDF_R is constant because there is no bonding between the carbon isotope in the cyanide ion and C_α in the reactant. TDF_R is large because of the strong C≡N bond in the ground state. Since the strong C≡N bond is also present in the transition state, the $TDF^\ddagger$ terms are also large. However, the inverse $TDF^\ddagger$ is larger than the normal TDF_R because the new NC−C_α bond being formed in the transition state increases the vibrational energy of the carbon isotope.[44] As a result, the $TDF^\ddagger$ is the major factor in determining the leaving group effect on the vibrational component of the nucleophile KIE and is primarily responsible for the decrease in the KIE when the leaving group changes. This is for two reasons: (1) both KIE_T and $TIF^\ddagger$ are small because there is very little bonding between the cyanide carbon and C_α in the reactant-like transition states of all the reactions in this study (Table 3) and (2) the KIE_T and $TIF^\ddagger$ vary in opposite directions with the change in leaving group (i.e., KIE_T increases while $TIF^\ddagger$ decreases with leaving group ability). However, since KIE_T is only about one-third the magnitude of the $TIF^\ddagger$, the [$KIE_T \times TIF^\ddagger$] decreases with a poorer leaving group. Since the $TDF^\ddagger$ also decreases when a poorer leaving group is used and changes more with leaving group than the other terms, $KIE^\ddagger$ decreases with the leaving group ability. As a result, the total KIE decreases when the length of the NC−C_α transition-state bond shortens in the transition state as the simple theory suggests.

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The last column of Table 11, which gives [$KIE_T \times TIF^{\ddagger}$] as a percentage of the nucleophile carbon KIEs, shows that [$KIE_T \times TIF^{\ddagger}$] represents a significant portion (48−78%) of the nucleophile carbon KIE and that [$KIE_T \times TIF^{\ddagger}$] contribution to the total KIE decreases with a poorer leaving group (i.e., from a high of 78.3% to a low of 48% of the nucleophile carbon KIE). This significant contribution of the [$KIE_T \times TIF^{\ddagger}$] to the KIE was reported previously.[13] Another observation is that the [$KIE_T \times TIF^{\ddagger}$] decreases as the NC−$C_{\alpha}$ bond in the transition state shortens. Because the [$KIE_T \times TIF^{\ddagger}$] varies with transition-state structure in the same way as the $TDF^{\ddagger}$, the change in the KIE on changing to a poorer leaving group is that predicted from the experimental KIEs and the theoretical calculations (i.e., a shorter NC−C_{α} bond is found in the transition state with a poorer leaving group).

4. Conclusions

Interpreting the experimental nucleophile $^{11}C/^{14}C$ and secondary α-deuterium KIEs in the usual fashion suggests that changing to a poorer *halogen* leaving group leads to a tighter transition state with a slightly shorter Nu−C_{α} bond and a much shorter C_{α}−LG bond. It is important to note that this is exactly the change in transition-state structure predicted in both the gas phase and in solution by theory. The results also confirm that nucleophile $^{11}C/^{14}C$ KIEs can be used to determine transition-state structure in different reactions and that the usual method of interpreting these KIEs is correct. For the secondary α-deuterium KIEs, the results also show that the experimental KIE and the Nu−LG transition-state distance decreases when a poorer *halogen* leaving group is used. Also, the experimental KIEs decrease with R_{TS} (Nu−LG distance) in the S_N2 transition state for the reactions with a *halogen* leaving group. Unfortunately, the change in the experimental and theoretical $(k_H/k_D)_{\alpha}$s with leaving group ability is in opposite directions unless the low energy vibrations are scaled differently from the high energy vibrations. The effect of adding solvent to the calculations using PCM depends on the level of theory used and does not improve the results significantly. This presumably occurs because the continuum model cannot account for the complex changes that occur in the solvent during a reaction. Finally, neither the experimental nor the theoretical secondary α-deuterium KIEs for the ethyl tosylate reaction fit the trend found for the reactions with a halogen leaving group. This presumably is found because of the bulky (sterically hindered) leaving group in the tosylate reaction. From every perspective, the tosylate reaction is too different from the halogen reactions to be compared.

5. Experimental Section

5.1. Nucleophile $^{11}C/^{14}C$ KIEs. *Reagents.* The ethyl chloride, bromide, and iodide were used as received. The ethyl tosylate was distilled under reduced pressure before use. The anhydrous DMSO (Aldrich 99.9 +%, <0.005% water cont.) was used as received and stored under extra-dry nitrogen. The tetrabutylammonium cyanide (TBACN) was stored in a desiccator over P_2O_5. To avoid buildup of [^{14}C]formic acid, small aliquots of the solid [^{14}C]potassium cyanide (2.04 GBq/mmol, American Radiolabeled Chemicals, Inc.) were withdrawn and dissolved in distilled water on the day of a kinetic run. The preparation and purification of the H[^{11}C]N is described elsewhere,[43] the only difference being that the labeled hydrogen cyanides were trapped in 0.9 mL of anhydrous DMSO instead of 1.0 mL of THF. Transfer of the labeled HCN solution to a capped vial with TBACN in anhydrous DMSO (1.0 M, 0.1 mL) resulted in a 0.1 M solution of cyanide ion. The obtained

radioactivity was usually between 30 and 300 MBq after 7 min of distillation.

Kinetic Procedure. Two portions (600 and 150 μL) were withdrawn from the labeled cyanide solution and transferred to septum-capped 1.5-mL vials. A 10-μL aliquot was injected into an HPLC system equipped with a β^+-flow detector. A C18 column (Phenomenex, Synergy 4 μ Hydro-RP 80 Å, 150 × 4.60 mm) was used with a flow of 1 mL/min. The mobile-phase system consisted of ammonium formate, 50 mM at pH 3.5 (A), and acetonitrile (B). The gradient system used was from 0 to 2 min: 7% B, from 2 to 3 min: 7 to 80% B, 3−8 min: 80% B, 8−9 min: 80 to 7% B, 9−16 min: 7% B. The product fraction, 5.0−6.5 min, was collected to serve as a correction for ^{14}C-impurities (see below). For this reason, 70 μL of reaction medium was put aside to enable further injections at a later stage. To achieve flexible and clean collection, a manual procedure was employed. The outlet from the β^+-detector was elongated by Teflon tubing so that it could be directly immersed into a polyethylene scintillation vial containing 14 mL of Zinsser Analytic QUICKSAFE A scintillation cocktail. A lid was threaded over the tubing, capping the vial during collection. Immediately after collection, the outlet was withdrawn, and the vial was recapped and vigorously shaken.

An adjusted (vide infra) quantity of substrate dissolved in anhydrous DMSO was introduced to the 600-μL portion of cyanide solution. After vortex mixing, the vial was placed in an autoinjector rack connected to a temperature bath at 20.00 ± 0.01 °C. Aluminum foil was used to screen the reaction vial from light. Every 20 min an aliquot of 10−30 μL was injected and the product fraction was collected as described above. Care was taken to reseal the reaction vial with parafilm after each injection as the septum became increasingly pierced. The intent was to achieve a spread of cyanide conversion (30−60%) within one experimental run. For the slowly reacting ethyl tosylate, one addition (10 mg in 25 μL of DMSO) sufficed. The ethyl halides however, required addition in a cumulative fashion. For example, 7 min after a first addition of ethyl iodide (7 μL, 20 v/v% in DMSO) 30% of the cyanide ion had been consumed. After this sample had been analyzed, more substrate was added and the reaction continued.

To ensure complete reaction with respect to cyanide ion, 20 μL of neat ethyl chloride was introduced to the 150-μL portion of cyanide ion solution at the beginning of the experiment. At the end of the experiment, a 25-μL aliquot of the reaction mixture was withdrawn and injected into the HPLC. The product fraction was collected as described above.

The procedure used to determine the radioactivity of the samples and calculate the kinetic isotope effect is described in ref 43.

5.2. Secondary α-Deuterium KIEs. *Reagents.* The preparation of the [1,1-$^2H_2$]ethyl chloride is described in ref 16. The [1,1-$^2H_2$]ethyl bromide and [1,1-$^2H_2$]ethyl iodide were used as received from Sigma-Aldrich. The [1,1-$^2H_2$]ethyl tosylate was prepared by adding 5 g of [1,1-$^2H_2$]ethyl alcohol dropwise to a solution of 22 g of tosyl chloride in 88 mL of dry pyridine at −10 °C. The temperature rose to −6 °C after 2 min and then fell to −10 °C. After the mixture was stirred at −10 °C for 30 min, 250 mL of 5 N sulfuric acid cooled to 0 °C was added rapidly. On cooling, the product crystallized out. It was filtered, washed with water, and dried overnight in a vacuum desiccator. The crude tosylate (14 g) was distilled at 135 °C/1.5 mmHg before use.

Kinetic Procedure. *Ethyl Chloride Reaction.* The following solutions were prepared under an extra-dry nitrogen atmosphere

in an I²R glovebag. One gram of tetrabutylammonium cyanide was dissolved in 15 mL of anhydrous DMSO, giving a 0.25 M solution, and 400 μL of ethyl chloride was injected with a 500-μL syringe that had been cooled in a deep freeze, into a sample vial containing 15 mL of DMSO, giving a 0.12 M ethyl chloride stock solution. The free space above the solvent in the vial was kept to less than 1 mL to reduce the risk of evaporation of the ethyl chloride. The amount of ethyl chloride added to the vial was determined by accurately weighing the vial before and after the ethyl chloride was added.

After these solutions had been temperature-equilibrated in a constant temperature bath at 30.000 ± 0.002 °C for 1 h, the reaction was started by injecting 5 mL of the ethyl chloride stock solution into the tetrabutylammonium cyanide solution. One-milliliter aliquots of the reaction mixture were taken and injected into 30 mL of 0.013 M nitric acid. This quenched the reaction by protonating the nucleophile and making it unreactive. **The acidic solution containing HCN from the unreacted cyanide ion was stirred in the fume hood for at least an hour so the hydrogen cyanide was completely removed.** Finally, the concentration of chloride ion was determined using a potentiometric titration and a standard 0.005 M silver nitrate solution.

Ethyl Bromide Reaction. The procedure used for the ethyl chloride reaction was used to measure the rate constants for the ethyl bromide reaction. The only difference was that the stock solutions had different concentrations. A 0.018 M stock solution of ethyl bromide was prepared by injecting 10 μL of ethyl bromide into a sample vial containing 7.00 mL of anhydrous DMSO, and a 0.009 M tetrabutylammonium cyanide stock solution was prepared by dissolving approximately 0.126 g of tetrabutylammonium cyanide (accurately weighed) in 50.00 mL of anhydrous DMSO. Finally, 20.00 mL of the tetrabutylammonium cyanide solution was transferred into a reaction flask fitted with a serum cap.

After both stock solutions had been temperature-equilibrated at 20.000 ± 0.002 °C for 1 h, the reaction was started by injecting 5.00 mL of the ethyl bromide stock solution into the reaction flask. Finally, the bromide ion in the sample was determined via a potentiometric titration using a standard 0.0005 M silver nitrate solution.

Ethyl Iodide Reaction. The procedure used for the ethyl chloride reaction was used to measure the rate constants for the ethyl iodide reaction. The only difference was that the stock solutions had different concentrations. A 0.011 M ethyl iodide stock solution was prepared by injecting 10 μL of ethyl iodide into a sample vial containing 10.00 mL of anhydrous DMSO, and a 0.006 M tetrabutylammonium cyanide stock solution was prepared by dissolving approximately 0.088 g of tetrabutylammonium cyanide (accurately weighed) in 50.00 mL of anhydrous DMSO. Finally, 20.00 mL of the tetrabutylammonium cyanide solution was transferred into a reaction flask fitted with a serum cap.

After the stock solutions had temperature-equilibrated at 20.000 ± 0.002 °C for 1 h, the reaction was started by injecting 5 mL of the ethyl iodide stock solution into the reaction flask. The iodide ion in the sample was analyzed using a potentiometric titration and a 0.0005 M silver nitrate solution.

Ethyl p-Toluenesulfonate Reaction. The procedure used for the ethyl chloride reaction was used to measure the rate constants for the ethyl tosylate reaction. The only difference was that the stock solutions had different concentrations. A 0.17 M ethyl p-toluenesulfonate stock solution was prepared by dissolving approximately 0.24 g of ethyl p-toluenesulfonate (accurately

weighed) in 7.00 mL of anhydrous DMSO, and a 0.08 M tetrabutylammonium cyanide stock solution was prepared by dissolving approximately 1.12 g of tetrabutylammonium cyanide (accurately weighed) in 50.00 mL of anhydrous DMSO. Finally, 20.00 mL of the tetrabutylammonium cyanide solution was transferred into a reaction flask fitted with a serum cap.

After the reaction flask and the ethyl p-toluenesulfonate stock solution had been temperature-equilibrated at 20.000 ± 0.002 °C for 1 h, the reaction was started by injecting 5 mL of the ethyl p-toluenesulfonate stock solution into the reaction flask. Then, 1.00 mL aliquots of the reaction solution were taken and quenched in 3 mL of a methanol solution that was 0.0045 M in the internal standard, methyl benzoate. Five microliters of this solution was injected into the Waters HPLC *immediately*, and the concentration of the unreacted ethyl p-toluenesulfonate was determined from the peak areas using a calibration curve. The HPLC analyses were done using a 83% methanol−17% water mixture as the eluant at a flow rate of 1 mL/min. The UV detector was set at 254 nm.

Product Analysis. The potentiometric titrations used to analyze the ethyl halide reactions indicated that the yield of halide ion was 100% in each reaction. Although it was reported that primary alkyl halides do not give E2 products when reacted with weak bases in dipolar aprotic solvents,[45] it is theoretically possible that S_N2 and E2 reactions, both of which produce a halide ion, could be competing in the ethyl halide reactions. This possibility was investigated in two ways for both the ethyl iodide and the ethyl bromide reactions. The ethyl iodide reaction was carried out by reacting 53 mg of tetrabutylammonium cyanide with 16 mg of ethyl iodide in 3.0 mL of anhydrous DMSO at 23 °C, while the ethyl bromide reaction was carried out by reacting 65 mg of tetrabutylammonium cyanide with 17 mg of ethyl bromide in 3.0 mL of anhydrous DMSO at 23 °C. The products from both reactions were examined by gas chromatography using a Varian CP 3800 gas chromatograph fitted with a 30 m × 2.5 μm Restek Rtx-5 column and a flame ionization detector. No ethene, the product of the E2 reaction, was detected in either the vapor or the reaction mixture from either the ethyl iodide or the ethyl bromide reaction. The absence of ethene in the product was confirmed when the color due to bromine did not disappear when two drops of a 2% solution of bromine in carbon tetrachloride were added to the ethyl iodide and ethyl bromide reactions at the end of the reaction. (The brown color of bromine would have disappeared if any ethene had been present in the reaction mixture.) Thus, neither the ethyl iodide nor the ethyl bromide gave any E2 product.

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