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The Effect of Solvent on the Structure of the Transition State for the S_N2 Reaction between Cyanide Ion and Ethyl Chloride in DMSO and THF Probed with Six Different Kinetic Isotope Effects

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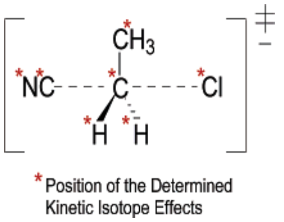
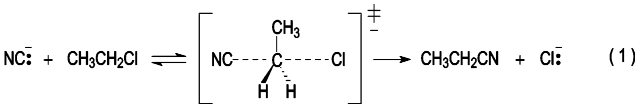


The secondary α- and β-deuterium, the α-carbon, the nucleophile carbon, the nucleophile nitrogen, and the chlorine leaving group kinetic isotope effects for the S_N2 reaction between cyanide ion and ethyl chloride were determined in the very slightly polar solvent THF at 30 °C. A comparison of these KIEs with those reported earlier for the same reaction in the polar solvent DMSO shows that the transition state in THF is only slightly tighter with very slightly shorter $NC-C_\alpha$ and $C_\alpha-Cl$ bonds. This minor change in transition state structure does not account for the different transition structures that were earlier suggested by interpreting the experimental KIEs and the gas-phase calculations, respectively. It therefore seems unlikely that the different transition states suggested by the two methods are due to the lack of appropriate solvent modeling in the theoretical calculations. Previously it was predicted that the transition state of S_N2 reactions where the nucleophile and the leaving group have the same charge would be unaffected by a change in solvent.[1] The experimental KIEs support this view.

Introduction

In a recent study,[2] six different kinetic isotope effects (KIEs) for the S_N2 reaction between ethyl chloride and cyanide ion in DMSO, eq 1, were determined experimentally and used to estimate the structure of the transition state for the reaction. The transition state structures and the KIEs calculated by a number of theoretical methods were also reported. Interpreting the experimental kinetic isotope effects by using the traditional (qualitative) relationships suggested the transition state for the reaction was product-like with a short $NC-C_\alpha$ bond and a long $C_\alpha-Cl$ bond. All of the theoretical methods, however, predicted a reactant-like transition structure with a long $NC-C_\alpha$ and a short $C_\alpha-Cl$ bond. This disagreement between theory and experiment for a small reaction system is troublesome because these are the two approaches used by chemists to obtain transition state structures.



$$\mathrm{NC{:}^- + CH_3CH_2Cl \rightleftharpoons \left[NC\text{----}\underset{H\ \ H}{\overset{CH_3}{C}}\text{-----}Cl \right]^{\ddagger -} \longrightarrow CH_3CH_2CN + Cl{:}^-} \qquad (1)$$

Unfortunately, the KIEs for this S_N2 reaction could not be determined in the gas phase because the reaction was too slow.[3] In addition, theory continues to have some difficulty making predictions for reactions involving highly energetic and strongly solvated states. To assess whether the lack of solvation in the

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TABLE 1. The 2° α-D_2 KIEs for the S_N2 Reaction between Tetrabutylammonium Cyanide and Ethyl Chloride in Anhydrous THF at 30.000 ± 0.002 °C

expt	10^4k_H [M^{-1} s^{-1}][a]	10^4k_D [M^{-1} s^{-1}][a]	$(k_H/k_D)_\alpha$
1	6.571	6.565	1.001
2	6.591	6.585	1.001
3	6.582	6.549	1.005
av			1.002 ± 0.003[b]

[a] The substrate and nucleophile concentrations in these experiments were approximately 0.04 and 0.08 M, respectively. [b] Standard deviation.

TABLE 2. The 2° β-D_3 KIEs for the S_N2 Reaction between Tetrabutylammonium Cyanide and Ethyl Chloride in Anhydrous THF at 30.000 ± 0.002 °C

expt	10^4k_H [M^{-1} s^{-1}][a]	10^4k_D [M^{-1} s^{-1}][a]	$(k_H/k_D)_\beta$
1	6.501	6.487	1.002
2	6.549	6.527	1.003
av	6.525	6.507	1.003 ± 0.005[b]

[a] The substrate and nucleophile concentrations in these experiments were approximately 0.05 and 0.07 M, respectively. [b] The error was estimated from the errors in the individual rate constants.[2]

calculations is a major reason for the difference between the transition state structure predicted by theory in the gas phase and interpreting the experimental KIEs in DMSO, the six previously measured KIEs for the ethyl chloride−cyanide ion S_N2 reaction were determined in THF (dielectric constant (ϵ) = 7.3 as compared to DMSO which has $\epsilon = 49$).[4] Although THF is not close to the gas phase,[5] it was chosen because it is much less polar and would not solvate the anions and transition state significantly thereby approximating the gas phase ($\epsilon = 1.0$) as closely as one could experimentally.[6] Thus, the KIEs in THF should be closer to those expected in the gas phase, i.e., from theory. This experimental approach should suggest whether the absence of solvent in the calculations could be the cause of the difference in the structure of the transition state predicted by the two methods.

This study is also of interest because a few of the theoretical calculations[2] indicated that adding solvent with continuum models had little or no effect on the structure of the transition state. Also, the results will provide a test for the experimentally based "Solvation Rule for S_N2 Reactions"[1] that suggests the transition state for this reaction would not be affected significantly by a change in solvent.

Results and Discussion

Six different KIEs for the S_N2 reaction between cyanide ion[7] and ethyl chloride, eq 1, were measured in anhydrous THF to learn how a significant change in solvent affects the transition state structure of the reaction and to attempt to learn whether the lack of appropriate solvent modeling in the theoretical calculations was the reason that different transition states were suggested by interpreting the experimental KIEs and theory. The secondary α-deuterium (2° α-D_2) and β-deuterium (2° β-D_3), the α-carbon $^{11}C/^{14}C$, the nucleophile carbon $^{12}C/^{13}C$, the nucleophile nitrogen $^{14}N/^{15}N$, and the chlorine leaving group $^{35}Cl/^{37}Cl$ KIEs for the S_N2 reaction between ethyl chloride and tetrabutylammonium cyanide in anhydrous THF are presented in Tables 1−6. Then, the KIEs found previously in anhydrous DMSO are compared with those found in anhydrous THF, Table 7.

The 2° α-D_2 KIE. A small 2° α-D_2 KIE of 1.002 ± 0.003, Table 1, was found for the ethyl chloride−cyanide ion S_N2 reaction in THF. Although there is no completely accepted way of relating the magnitude of these KIEs to transition state structure, the best interpretation of these KIEs is that their magnitude is related to the nucleophile−leaving group distance in a symmetric S_N2 transition state[8−10] or to the length of the shorter of the nucleophile−α-carbon and α-carbon−leaving group bonds in an unsymmetric transition state[8,11] when only the solvent is changed. The vibrational contribution to these KIEs is the result of changes that occur in both the C_α−H stretching and the H−C_α−H bending vibrations when the reactant is converted into the transition state. The C_α−H stretching vibration is of higher energy in the transition state generating an inverse contribution to the KIE that is the same for all the S_N2 reactions with a particular substrate and leaving group.[9] The contribution due to the H−C_α−H bending vibrations is larger (in the absolute sense), i.e., less inverse or more normal for a looser transition state, i.e., one with longer nucleophile−α-carbon and/or α-carbon−leaving group bonds.[9] Therefore, a less inverse or more normal KIE is observed for a looser transition state. Although the 2° α-D KIE for the S_N2 reaction between ethyl chloride and tetrabutylammonium cyanide in THF, Table 7, is only very slightly larger (1.002 ± 0.003 versus 0.990 ± 0.004) than that in DMSO, the difference is very small considering the experimental errors in the measurements. In fact, the two KIEs are not significantly different at a 95% confidence level. Therefore, it appears that neither the nucleophile−α-carbon (NC−C_α) nor the α-carbon−leaving group (C_α−Cl) transition state bond is altered significantly even though there has been a large and significant change from the dipolar aprotic solvent DMSO where the cyanide ion and ionic transition state would be highly solvated to a low dielectric aprotic solvent THF where the cyanide ion and ionic transition state is very much less solvated.

The 2° β-D_3 KIE. The 2° β-D_3 KIE of 1.003 ± 0.005 found for the S_N2 reaction between cyanide ion and ethyl chloride in THF, Table 2, is also very small. Although the magnitude of a 2° β-D_3 KIE is affected slightly by steric crowding and the inductive effect of the deuteriums,[12] it is primarily determined by the amount of positive charge on the α-carbon in the transition state (hyperconjugation).[12] This means that large, normal 2° β-D_3 KIEs are observed when positive charge on

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(7) A conductivity study in our laboratories shows significant levels of cyanide ion pairs in both DMSO and THF. This suggests the reacting cyanide ion is the same in both solvents.

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TABLE 3. The α-Carbon $^{11}C/^{14}C$ KIEs for the S_N2 Reaction between Tetrabutylammonium Cyanide and Ethyl Chloride[a] in Anhydrous THF at 30.0 °C

expt	sample[b]	fraction of reaction (f)	R_f/R_0[c]	$(k^{11}/k^{14})_\alpha$[d]	av per expt
1	1	0.2332	0.9486	1.2484	
	2	0.4080	0.9042	1.2376	
	3	0.5495	0.8646	1.2231	1.2364[e]
2	1	0.5800	0.8677	1.1955	
	2	0.7221	0.8029	1.2068	
	3	0.7906	0.7582	1.2151	1.2058
3	1	0.4668	0.8939	1.2169	
	2	0.6830	0.8351	1.1860	
	3	0.7756	0.7777	1.2032	
	4	0.8182	0.7642	1.1873	1.1982
total av					1.212 ± 0.021[f]

[a] The substrate and nucleophile concentrations in these experiments were approximately 0.05 and 0.05 M, respectively. [b] Several samples from each experiment were withdrawn and analyzed with regard to ethyl chloride. [c] R_f is the isotopic ratio of ethyl chloride at fraction of reaction f. R_0 is the isotopic ratio at 0% conversion. [d] The isotope effect is calculated by using the formula $k^{11}/k^{14} = \ln(1 - f)/[(1 - f)(R_f/R_0)]$. [e] Experiment performed without addition of unlabeled ethyl chloride. [f] Standard deviation.

TABLE 4. The Nucleophile Carbon $^{12}C/^{13}C$ KIE for the S_N2 Reaction between Tetrabutylammonium Cyanide and Ethyl Chloride in Anhydrous THF at 30.0 °C

sample	fraction of reaction (f)	$\delta^{13}C$	k^{12}/k^{13}
1	0.33	−25.56	
2	0.39	−24.88	
3	0.50	−24.89	
4	0.60	−25.24	
5	0.14	−24.61	
6	0.25	−24.64	
7	0.40	−24.75	
8	0.49	−24.95	
9	0.57	−24.95	
10	0.10	−27.16	
11	0.27	−26.34	
12	0.31	−25.52	
13	0.42	−26.54	
14	0.47	−25.70	
kinetic isotope effect			0.9990 ± 0.0007[a,b]

[a] Standard deviation. [b] The KIE was calculated from the slope of the linear plot of $\ln(1000 + \delta^{13}C)$ vs $\ln(1 - f)$. The $\delta^{13}C$ was measured against a Pee Bee Dolomite (PBD) standard.

TABLE 5. The Nucleophile 2° Nitrogen $^{14}N/^{15}N$ KIE for the S_N2 Reaction between Tetrabutylammonium Cyanide and Ethyl Chloride in Anhydrous THF at 30.0 °C

sample	fraction of reaction (f)	$\delta^{14}N$	k^{14}/k^{15}
1	0.00	0.92	
2	0.00	0.81	
3	0.00	0.76	
4	0.33	1.90	
5	0.39	1.90	
6	0.50	2.06	
7	0.60	2.16	
8	0.14	1.18	
9	0.25	0.85	
10	0.40	1.20	
11	0.49	1.33	
12	0.57	1.77	
13	0.10	0.81	
14	0.27	0.84	
15	0.31	1.00	
16	0.42	1.24	
17	0.47	2.04	
kinetic isotope effect			1.0014 ± 0.0003[a,b]

[a] Standard deviation. [b] The KIE was calculated from the slope of the linear $\ln(1000 + \delta^{13}N)$ vs $\ln(1 - f)$ plot. The $\delta^{15}N$ was measured against a home standard sample of nitrogen.

the α-carbon has increased significantly on going from the reactant to the transition state. Therefore, the small values for these KIEs in DMSO and in THF, Table 7, indicate that there is little or no positive charge on the α-carbon in the transition state of this reaction in either solvent, i.e., that the reaction is of the constant or increased total bonding type. The slightly larger KIE in anhydrous DMSO (1.014 ± 0.003 versus 1.003 ± 0.005 in THF) suggests there is slightly more positive charge on the α-carbon in the transition state in DMSO than there is in THF. This suggests the transition state in THF is slightly tighter with either a slightly shorter $NC{-}C_\alpha$ and/or $C_\alpha{-}Cl$ bond in the transition state.

The $^{11}C/^{14}C$ α-Carbon KIE. A large, normal $^{11}C/^{14}C$ α-carbon KIE = 1.212 ± 0.021 was found for the ethyl chloride−cyanide ion S_N2 reaction in THF, Table 3. The magnitude of α-carbon KIEs is large for S_N2 reactions and small for a carbenium ion (S_N1) reaction.[13] Thus, the large $^{11}C/^{14}C$ α-carbon KIEs observed in both DMSO and THF (1.208 ± 0.019 in DMSO and 1.212 ± 0.021 in THF), Table 7, confirm the S_N2 mechanism for the reaction in both solvents. The relationship between the magnitude of these KIEs and transition state structure for S_N2 reactions has been interpreted by using the Melander−Westheimer relationship.[14] However, a recent publication[13] has suggested that near maximum α-carbon KIEs will be observed for S_N2 reactions with a wide range of transition structures. As Matsson et al.[13] predicted, the large, and identical, α-carbon $^{11}C/^{14}C$ KIEs in the two solvents, 1.208 ± 0.019 in DMSO and 1.212 ± 0.021 in THF, are near the experimental maximum KIE found for S_N2 reactions. Since the KIEs in the two solvents are identical, no change in transition-state structure can be deduced from these KIEs.

The Nucleophile Carbon $^{12}C/^{13}C$ KIE. An inverse nucleophile carbon KIE of $k^{12}/k^{13} = 0.9990 \pm 0.0007$, Table 4, was found for the ethyl chloride−cyanide ion S_N2 reaction. The nucleophile carbon $^{12}C/^{13}C$ KIE becomes more inverse as the amount of bonding between the nucleophile and the α-carbon increases in the transition state[15,16] Thus, the slightly smaller nucleophile carbon $^{12}C/^{13}C$ KIE found in THF, i.e., 0.9990 ± 0.0007 versus 1.0009 ± 0.0007 in DMSO, Table 7, suggests that the $NC{-}C_\alpha$ transition-state bond is slightly shorter in THF than it is in DMSO.

The Nucleophile Nitrogen $^{14}N/^{15}N$ KIE. A very small nucleophile nitrogen KIE of $k^{14}/k^{15} = 1.0014 \pm 0.0003$ was found for the ethyl chloride−cyanide ion S_N2 reaction in THF, Table 5. This indicates there is very little change in the bonding to the cyanide nitrogen in going from the reactant to the transition state for the reaction. The KIE in THF is slightly larger (1.0014 ± 0.0003 versus 1.0002 ± 0.0006) than that in DMSO, Table 7. However, the difference between the two very small

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TABLE 6. The $^{35}Cl/^{37}Cl$ Chlorine (Leaving Group) Kinetic Isotope Effect for the S_N2 Reaction between Tetrabutylammonium Cyanide and Ethyl Chloride[a] in Anhydrous THF at 30.000 ± 0.002 °C

sample	δ value	av f	R_0/R_f[b]	k^{35}/k^{37}
1	−10.956	0.1197	0.993696	1.006766[c]
2	−10.626	0.1469	0.994021	1.006519
3	−10.612	0.1841	0.994035	1.006655
4	−10.351	0.2138	0.994291	1.006491
5	−10.228	0.2460	0.994412	1.006492
av				1.00659 ± 0.00012[d]

[a] The substrate and nucleophile concentrations in these experiments were approximately 0.05 and 0.08 M, respectively. [b] The average R_0 from five different samples was 3.13046 relative to a standard methyl chloride sample. The R_f values were obtained from $R_f = R_r(1 - \delta/1000)$, where R_r is the $^{35}Cl/^{37}Cl$ ratio of the standard methyl chloride sample. [c] The isotope effect is calculated with the formula $k^{35}/k^{37} = \ln(1 - f)/\ln(1 - (R_0/R_f)f)$, where f is the fraction of reaction, R_f is the $^{35}Cl/^{37}Cl$ ratio in the chloride ion isolated after the fraction of reaction f, and R_0 is the $^{35}Cl/^{37}Cl$ ratio of the chlorine in the starting material. [d] Standard deviation.

TABLE 7. The 2° α-D_2, the 2° β-D_3, the α-Carbon $^{11}C/^{14}C$, the Nucleophile Carbon $^{12}C/^{13}C$, the Nucleophile Nitrogen $^{14}N/^{15}N$, and the Chlorine $^{35}Cl/^{37}Cl$ Leaving Group KIEs and the Rate Constants Found for the S_N2 Reaction between Ethyl Chloride and Tetrabutylammonium Cyanide in Anhydrous DMSO and THF at 30 °C and the Best Set of KIEs Calculated by Theory

KIE	DMSO	THF	KIE theory[a]
$(k_H/k_D)_\alpha$	0.990 ± 0.004	1.002 ± 0.004	0.994
$(k_H/k_D)_\beta$	1.014 ± 0.003	1.003 ± 0.005	1.005
$(k^{11}/k^{14})_\alpha$	1.208 ± 0.019	1.212 ± 0.021	1.17
$(k^{12}/k^{13})_{Nuc}$	1.0009 ± 0.0007	0.9990 ± 0.0007	0.993
$(k^{14}/k^{15})_{Nuc}$	1.0002 ± 0.0006	1.0014 ± 0.0003	1.0003
k^{35}/k^{37}	1.00699 ± 0.00026	1.00659 ± 0.00012	1.0070
10^4k_H (M^{-1} s^{-1})	4.22	6.58	

[a] The KIEs quoted were calculated at the B3LYP/aug-cc-pVDZ level of theory. They represent the best set of calculated KIEs based on the absolute value of ($KIE_{DMSO} - KIE_{calc}$) for all six KIEs.[2]

KIEs is very small (ca. 0.001). Therefore, the best interpretation of these KIEs is that the N≡C bond has not been altered significantly by the change in solvent.

The Chlorine Leaving Group KIE. A chlorine leaving group KIE of 1.00659 ± 0.00012 was found for the ethyl chloride−cyanide ion S_N2 reaction in THF, Table 6. Although a recent publication[17] has questioned the usual relationship between the magnitude of an observed chlorine leaving group KIE and transition state structure, it is believed that chlorine leaving group KIEs measured for the same reaction in different solvents will follow the usual relationship, i.e., that a larger KIE will be observed when there is more C_α−Cl bond rupture in the transition state. Since a smaller chlorine KIE was found in THF (1.00659 ± 0.00012 versus 1.00699 ± 0.00026 in DMSO), Table 7, the transition state in THF must have a slightly shorter C_α−Cl transition state bond.

The Effect of Changing the Solvent from DMSO to THF on the Structure of the S_N2 Transition State. An examination of the KIEs in Table 7 shows that only two of the KIEs, the nucleophile carbon and the chlorine leaving group KIEs, change significantly when the solvent is changed from DMSO to THF. The nucleophile carbon KIE becomes inverse on going to THF signaling that NC−C_α bond formation is more advanced in the transition state.[15,16] The leaving group chlorine KIE decreases on going to THF indicating there is less C_α−Cl bond rupture in the transition state in THF. Both these changes indicate there is a slightly tighter transition state in THF. The change in the NC−C_α and C_α−Cl transition state bonds can be estimated by comparing the observed change in the KIE with the maximum possible change in the KIE. For the NC−C_α bond, the change in the KIE on going from DMSO to THF is (0.19/5.3) × 100% or only 3.6%[18−20] while the corresponding change in the C_α−Cl bond is only (0.040/1.90) × 100% or 2.1%.[17,21] Thus, the changes in the nucleophile carbon and the chlorine leaving group KIEs in THF suggest that the transition state is only very slightly tighter in THF. This conclusion is consistent with the slightly smaller 2° β-D_3 KIE found for the reaction in THF. Only the change in the 2° α-D_2 KIE and in the nucleophile nitrogen $^{14}N/^{15}N$ KIE with solvent is inconsistent with this interpretation. The 2° α-D_2 KIE would be expected to be smaller in THF where the transition state is tighter. However, although the KIE is larger in THF than in DMSO, the KIEs in THF and in DMSO are the same considering the experimental errors in the measurements and it appears that this KIE is not sensitive enough to detect the small change in transition state structure that occurred when the solvent was changed.

The very small nitrogen KIE, i.e., only approximately 0.1%, is slightly larger in THF rather than smaller as one would expect.[22] However, the change in the nitrogen KIE of approximately 0.1% is very small and probably does not represent a significant change in the KIE and transition state structure at the nitrogen. Thus, the best interpretation of the small changes in the KIEs in the two solvents is that the transition state is very slightly tighter in THF. The direction of this change in transition state structure is expected on going from the highly polar solvent DMSO ($\epsilon = 49$) to the less solvating THF ($\epsilon = 7.3$).[4] A tighter, less ionic, transition state would be expected when the solvent's ability to stabilize the ionic transition state is decreased.

The transition-state structure of the ethyl chloride−cyanide ion S_N2 reaction in DMSO has recently been estimated by interpreting experimental KIEs, using the traditional qualitative relationships and by theoretical calculations.[2] The calculations predicted an early transition state with a long NC−C_α bond and a short C_α−Cl bond whereas the experimental KIEs implied

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(18) The maximum change in the nucleophile $^{12}C/^{13}C$ KIE has been estimated by adjusting the nucleophile $^{11}C/^{14}C$ KIE calculated by Matsson et al.[15] for the different masses of the isotopes to be 5.0%. This agrees very well with the maximum $^{12}C/^{13}C$ KIE of 5.5% and 5.4% suggested by Maccoll[19] and Buddenbaum and Shiner,[20] respectively. The average of these values (5.3%) was used in calculating the change in the nucleophile carbon KIE with solvent.

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(22) Because the vibrational frequency of the C≡N bond increases from 2057 cm^{-1} in cyanide ion to 2250 cm^{-1} in the product of this reaction in DMF,[23] this KIE behaves like the nucleophile carbon KIE,[15,16] and should decrease with more NC−C_α bond formation in the transition state. Since the NC−C bond is very slightly shorter in THF than in DMSO and since the vibrational energy of the N≡C bond increases on going to the product, one would have expected that shortening the NC−C_α bond in the transition state would also lead to some shortening of the N≡C bond and a smaller, not the larger, KIE that is observed in THF. However, the change in the very small secondary nitrogen KIE of approximately 0.1% is very small and probably does not represent a significant change in the KIE and transition state structure at the nitrogen.

a late transition state with a short NC$-$C$_\alpha$ bond and significant C$_\alpha$$-$Cl bond rupture. It is important to note, however, that changing the solvent only causes a slight tightening of the S$_N$2 transition state, but does not cause the large shift required to change the transition state from product-like in DMSO to reactant-like in THF even though THF bridges the gap between the reaction in DMSO and the gas phase to as large an extent as possible experimentally. Even though the solvation in THF is far from that in the gas phase,[5] the great difference in the polarity of the two solvents should show a trend toward an early transition state if it is mainly the absence of solvent in the gas phase calculations that is responsible for the difference in the transition states predicted by the two methods. Therefore, it is highly unlikely that the absence of solvent in the gas-phase calculations is responsible for the very different transition states that were predicted by interpreting the experimental KIEs found in DMSO and by the gas-phase calculations.

Apart from the minor variations in transition structures, every level of theory that was investigated predicted the transition state was reactant-like. In fact, it now appears likely that the theoretical calculations, even in the absence of solvent modeling, give the most accurate transition state structure. The following arguments appear to support this view: First, a recent theoretical investigation has demonstrated that the observed chlorine leaving group KIE for a particular S$_N$2 reaction cannot be simply related to the amount of C$_\alpha$$-$Cl bond rupture in the transition state[17] as had been previously believed. In fact, the product-like transition state for the reaction between cyanide ion and ethyl chloride was suggested originally because the chlorine KIE was large suggesting there was significant C$_\alpha$$-$Cl bond rupture in the transition state. It is worth noting that the experimental α-deuterium, the β-deuterium, the α-carbon, the nucleophile carbon, and the nucleophile nitrogen KIEs are all consistent with a reactant-like transition state and since the chlorine KIE of 1.0070 could be found for a reactant-like transition state, there is no good reason to conclude that the transition state is product-like.

Second, another finding which suggests that the theory gives a good model for the transition state is that the experimental $\Delta H^\ddagger$ (18.7 kcal mol^{-1}) for the reaction in DMSO was very well reproduced with use of several continuum solvent models.[2] For example, SM5.42/HF/6-31G(d) calculated the $\Delta H^\ddagger$ exactly, while COSMO/PM3 calculated it within 0.4 kcal/mol, and several others gave values that were within 4 kcal/mol of the experimental value. It is worth noting that Almerindo and Pliego[24] calculated a $\Delta G^\ddagger$ in DMSO with the geometry optimized at the B3LYP/6-31G(d) level and the activation energy calculated at the MP2/6-311+G(2df,2p) level with the PCM continuum solvent model, that is within 1.5 kcal/mol of the experimental $\Delta G^\ddagger$ if one uses the experimental $\Delta S^\ddagger$.[2] Also the transition state found by Almerindo and Pliego and that in our 2003 paper using different levels of theory were similar, i.e., the NC$-$C$_\alpha$ transition state bonds were 2.156 and 2.392 Å and the C$_\alpha$$-$Cl transition state bonds were 2.332 and 2.134 Å, respectively.

Another reason for favoring the transition state found by theoretical calculations rather than the one suggested by interpreting the experimental KIEs in the traditional manner is that the KIEs calculated by theory for several S$_N$2 reactions have been close to the KIEs found experimentally.[25]

A fourth reason for suggesting the transition state predicted by theory is correct is that the difference between the best set of KIEs calculated from the transition structures and the experimental values, although outside experimental error, are small,[2] i.e., the Δ(KIE$_{calc}$ $-$ KIE$_{exp}$) are 0.004 (α-D$_2$), 0.009 (β-D$_3$), 0.04 (α-C), 0.008 (nucleophile C), 0.0001 (nucleophile N), and 0.0000 (leaving group Cl). This means theory, without solvent modeling, reproduces the experimental KIEs quite well. Also, finding that the transition state structure and the KIEs calculated with the solvent continuum model were close to those obtained in the gas-phase calculations[2] suggests that solvent does not affect transition state structure significantly. This is not surprising since the results of this study suggest the transition state is not affected significantly by solvent.

Finally, it is worth noting that this lack of change in transition state structure with solvation found in this experimental study is supported by theoretical calculations. For instance, Yamataka and Aida[26] showed that adding 10 more water molecules to the S$_N$2 reaction between water and methyl chloride, i.e., changing the solvating water molecules from 3 to 13 and changing the $\Delta G^\ddagger$ by 13.5 kcal/mol, did not change the transition structure significantly, i.e., the change in the C$_\alpha$$-$O transition state bond was only 0.18 Å while that in the C$_\alpha$$-$Cl transition state bond was only 0.074 Å. This very small change in transition state structure with the change in solvation is surprising because this is a Type II (the charges on the nucleophile and leaving group are different) S$_N$2 reaction where Saunders and co-workers[27] and Westaway and Jiang[28] found the transition state was altered significantly by a change in solvent. In another study of the S$_N$2 reaction between chloride ion and methyl chloride, Mohamed and Jensen[29] found that microsolvation by four water molecules did not affect the transition state structure significantly although they changed the rate constant (the $\Delta G^\ddagger$) for the reaction by approximately 16 kcal/mol. The results from our study show experimentally that a significant change in solvation does, indeed, not alter transition state structure significantly and gives some assurance that transition state predicted by theory is also correct. It is worth noting that both the above theoretical results and our experimental results suggest that the lack of solvent modeling is not the reason the transition state structure predicted by theory and by interpreting the experimental KIEs using the traditional method differ.

Finally, it is interesting that the rate constant for the reaction is not very sensitive (it only changes from 4.2×10^{-4} to 6.58×10^{-4} M^{-1} s^{-1}, see Table 7) to the significant change in solvent from DMSO to THF. The larger rate constant in THF indicates the change in solvation is greater at the cyanide ion than at the S$_N$2 transition state. This is what one would expect because the cyanide ion has a greater negative charge density than the charge dispersed transition state.

A discussion of the lack of change in transition state structure with a significant change in solvent is warranted. Several investigations of the effect of changing the solvent on transition

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state structure have been done with S_N2 reactions.[1,27,28,30,31] Two different effects of a change in solvent have been reported. In one study, Saunders and co-workers[27] found that the transition state of the S_N2 reaction between trimethylsulfonium ion and ethoxide ion in several ethanol−DMSO mixtures was very strongly affected by the solvent. In fact, the sulfur leaving group kinetic isotope effect for the reaction decreased regularly from 1.0095 to 1.0035 as the mole percent DMSO in the solvent (EtOH−DMSO) was increased from 0% to 65%. The rate constant for the reaction, however, only increased by five times over this range of solvents.

In another study, Taylor and co-workers[30] found that the chlorine leaving group KIEs for the S_N2 reaction between *n*-butyl chloride and thiophenoxide ion (ranging from 1.0096 to 1.0093 with an average of 1.00944 ± 0.00012, or less than the experimental error in the individual KIEs) were independent of the solvent even though the solvent was varied from dipolar aprotic solvents, to aprotic solvents, to protic solvents and the rate constant changed by over 3 orders of magnitude. Their conclusion that the transition state structure was not affected by a change in solvent was later confirmed by Westaway and Lai,[31] who found that the 2° α-D_2 KIEs for this S_N2 reaction (1.12 ± 0.01) did not change significantly when the solvent was varied over the same range of solvents.

The two different types of behavior found when the solvent was changed in the S_N2 reactions studied by Saunders and Taylor were first rationalized by Westaway.[1] It was suggested that there were two types of S_N2 reactions, a Type I S_N2 reaction where the leaving group and the nucleophile have the same charge and a Type II S_N2 reaction where the charges on the nucleophile and leaving group are different, and that the effect of changing the solvent should be different for Type I and Type II S_N2 reactions. A "Solvation Rule for S_N2 Reactions" stating that a change in solvent will not affect the structure of the transition state of a Type I S_N2 reaction significantly but will have a marked effect on the structure of the transition state of a Type II S_N2 reaction was proposed. The results from this study of the Type I S_N2 reaction between ethyl chloride and cyanide ion are consistent with this idea because changing the solvent from DMSO to THF does not change the transition state structure significantly, i.e., the change in the two reacting bonds is $<4\%$ when the solvent is altered drastically. It is interesting that the change in solvent has so little effect on the transition state for this reaction because when the "Solvation Rule" was proposed,[1] it was suggested that Type I transition states with very different nucleophiles, e.g., the S_N2 reaction between fluoride ion and methyl iodide, might indeed be sensitive to change in solvent. This was because the solvation of the two nucleophiles in the transition state would be very different, so a change in solvent would result in a very different effect on the solvation energy of each nucleophile. This would change the relative nucleophilicity of the nucleophiles and lead to a shift in transition state structure. The cyanide ion−ethyl chloride reaction with its very small cyanide ion carbon and the, in comparison, larger and more diffuse charge on the chloride ion in the transition state might be expected to be susceptible to the change of solvent from DMSO to THF. However, this is not observed.

Conclusions

A comparison of the six KIEs measured for the ethyl chloride−cyanide ion S_N2 reaction in DMSO and THF has indicated that the transition state is effectively the same in these solvents, but with very slightly shorter NC−C_α and C_α−Cl bonds in THF.

One reason for undertaking this study was to learn whether the lack of solvent in the theoretical calculations could account for the very different transition state structures predicted by theory and by using the traditional qualitative relationships to estimate transition state structure.[2] The results strongly suggest that the lack of solvation in the calculations is not responsible for the discrepancy between the transition-state structures predicted by the calculations and interpreting the experimental KIEs in DMSO. These conclusions further suggest that the transition state structure calculated by theory is correct and that there are problems in determining transition state structure from interpreting the experimental KIEs with use of the traditional qualitative relationships. Despite this it is believed that experimental KIEs are still the best method of determining the change in transition state structure caused by a change in solvent or substituent. Although this study appears to have resolved the source of the different transition state structures predicted by theory and interpreting the experimental KIEs for the ethyl chloride−cyanide ion S_N2 reaction, these two approaches to transition state structure have only been compared in this one system. Obviously, these two methods of obtaining transition state structure must be tested on other reactions and reaction types. Also, a more complete investigation of the effect of solvent on transition state structure by theory is required. Finally, the failure to detect any pronounced change in transition state structure upon changing the solvent is in accordance with the "Solvation Rule for S_N2 Reactions".

Experimental Section

Materials. THF was distilled over sodium and benzophenone. Zinc chloride was dried at 130 °C overnight, then stored in a desiccator over P_2O_5. The tetrabutylammonium cyanide was also stored in a desiccator over P_2O_5 once it had been opened.

The procedures used to synthesize the labeled substrates and measure the isotope effects reported in this paper are given in ref 2. The precursor for the [1-^{11}C]ethyl chloride was produced as previously described,[32] but with a modification: hydrogen gas was used instead of water in the carbonylation process.

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