

The Effect of Inert Salts on the Structure of the Transition State in the S_N2 Reaction between Thiophenoxide Ion and Butyl Chloride

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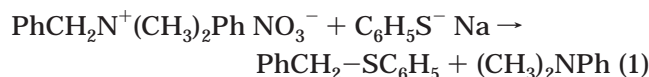
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The effect of inert salts on the structure of the transition state has been determined by measuring the secondary α deuterium and the chlorine leaving group kinetic isotope effects for the S_N2 reaction between *n*-butyl chloride and thiophenoxide ion in both methanol and DMSO. The smaller secondary α deuterium isotope effects and very slightly larger chlorine isotope effects found in both solvents when the inert salt is present suggests that the S_N2 transition state is tighter and more product-like, with a shorter S–C _{α} and very a slightly longer C _{α} –Cl bond when the added salt is present. The salt effect on the reaction in methanol where the reacting nucleophile is the solvent-separated ion-pair complex is much greater than the salt effect on the reaction in DMSO where the reacting nucleophile is the free ion. This greater change in transition-state structure found when the inert salt is present in methanol is consistent with the solvation rule for S_N2 reactions. The greater change in the S–C _{α} bond is predicted by the bond strength hypothesis. A rationale for the changes found in transition-state structure when the inert salt is present is suggested for both the free-ion and the ion-pair reactions.

Introduction

The effect of salts on reaction rates have been investigated in some detail.^{1–7} Although the added salts affected the rate constants for the reaction, they were not thought to affect the reaction or the structure its transition state. Recently, however, Pham and Westaway⁸ reported that the transition state for the S_N2 reaction between benzyldimethylphenylammonium nitrate and thiophenoxide in DMF at 0 °C, eq 1, was



strongly influenced by the addition of inert salts. In fact, the secondary α deuterium and the nitrogen leaving group kinetic isotope effects (KIEs), Table 1, were significantly larger and smaller, respectively, when the ionic strength of the solvent was increased from 0.64 to

TABLE 1. Effect of Ionic Strength on the Secondary α Deuterium and Nitrogen Leaving Group Kinetic Isotope Effects for the S_N2 Reaction between Benzyldimethylphenylammonium Nitrate and a Sodium Thiophenoxide Ion Pair in DMF at 0 °C

ionic strength (M)	$(k_{\text{H}}/k_{\text{D}})_{\alpha}$	k^{14}/k^{15}	rel transition state structure
0.90	1.215 ± 0.011^a	1.0166 ± 0.0004^b	$\delta^- \quad \delta^+$ S-----C _{α} -----N
0.64	1.179 ± 0.007	1.0200 ± 0.0007	$\delta\delta^- \quad \delta\delta^+$ S-----C _{α} -----N

^a The error in the KIE is $1/k_{\text{D}}[(\Delta k_{\text{H}})^2 + (k_{\text{H}}/k_{\text{D}})^2(\Delta k_{\text{D}})^2]^{1/2}$, 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.⁸ ^b Standard deviation on five different measurements of the KIE.

0.90 M by adding the inert salt, sodium nitrate, to the reaction mixture. The marked changes in both KIEs indicated that the transition state, Table 1, is significantly different when the ionic strength is changed in this reaction. These changes in transition-state structure were thought to arise because this was a type II S_N2 reaction where the incoming nucleophile and the leaving group have different charges,⁹ i.e., the thiophenoxide ion has a negative charge while the leaving group is neutral. The transition states for type II S_N2 reactions have been found to be very sensitive to a change in solvent.^{9,10} This

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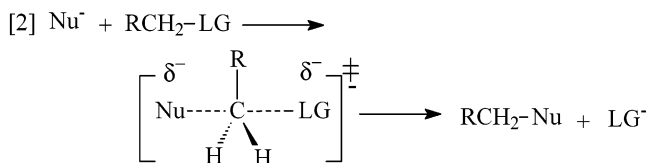
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presumably occurs because a change in solvent changes the solvation of the two (a neutral and a negatively charged) nucleophiles in the reaction differently. This changes the relative nucleophilicity of the two nucleophiles and, therefore, the structure of the transition state significantly.⁹ Since adding the inert salt changes the solvent making it more ionic,⁸ the structure of the type II S_N2 transition state is altered by the added salt.

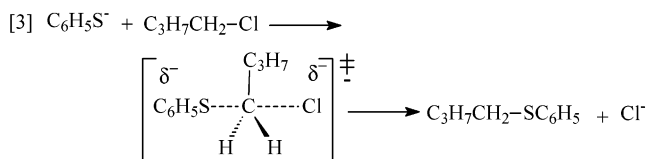
This study was undertaken to find out whether a change in the ionic strength resulting from the addition of an inert salt would also affect the transition state of a type I S_N2 reaction that has a negatively charged nucleophile and a negatively charged leaving group, eq 2.



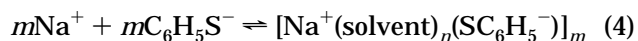
An investigation of the salt effect on a type I S_N2 reaction was of interest because these reactions do not seem to be affected significantly by a change in solvent.^{9,11,12} This presumably occurs because the change in solvent changes the solvation of the two reacting nucleophiles in the transition state in the same way. As a result, one would not expect the relative nucleophilicity of the nucleophile and leaving group or the structure of the transition state to change significantly with solvent.⁹ If the addition of an inert salt can be considered as a change in solvent as has been suggested,⁸ one would expect the added inert salt to have little or no effect on the structure of a type I S_N2 transition state.

Results and Discussion

The effect of adding an inert salt on the transition-state structure of a type I S_N2 reaction was determined by measuring the secondary α deuterium and the chlorine leaving group KIEs for the S_N2 reaction between *n*-butyl chloride and sodium thiophenoxide, eq 3, in the presence and absence of the inert salt, sodium nitrate, in two solvents, DMSO and methanol. This type I S_N2 reaction was chosen for this study because it has been studied extensively.^{11–13}



The Form of the Reacting Nucleophile. One discovery resulting from our investigation of the S_N2 reaction between *n*-butyl chloride and thiophenoxide ion was that the nucleophile, thiophenoxide ion, can react as a free ion or as a solvent-separated ion-pair complex, eq 4, in DMSO and in methanol.^{12,13}



Another discovery was that the concentration where ion pairing begins is different in DMSO and in methanol. For instance, sodium thiophenoxide exists as a solvent-separated ion-pair complex at concentrations greater than 2×10^{-2} M in DMSO and at concentrations greater than 1×10^{-4} M in methanol, which has a smaller dielectric constant.¹³ Since sodium thiophenoxide only exists as the solvent-separated ion pair complex at concentrations greater than 2×10^{-2} M in DMSO and the maximum (initial) sodium thiophenoxide concentration in the DMSO study was 2.3×10^{-3} M or 10 times smaller than the concentration where ion pairing begins, the reacting nucleophile in the DMSO reaction must be the free thiophenoxide ion. In methanol, on the other hand, the sodium thiophenoxide concentration was 1.8×10^{-1} M or 3 orders of magnitude greater than the 1×10^{-4} M concentration where ion pairing begins. As a result, the reacting nucleophile in methanol is the sodium thiophenoxide solvent-separated ion-pair complex.

The obvious question, however, is whether the inert salt, sodium nitrate, affects the form of the reacting nucleophile in DMSO and methanol. This was investigated by adding large amounts (enough to make the sodium nitrate approximately 1.0 M in DMSO and 0.21 M in methanol¹⁴) of sodium nitrate to the 2×10^{-3} and 1.8×10^{-1} M sodium thiophenoxide solutions in DMSO and in methanol, respectively. In both solvents, the absorption of the sodium thiophenoxide solvent-separated ion-pair complex ion was not affected by the addition of the sodium nitrate. This clearly indicates that the added salt does not affect the form of the reacting thiophenoxide ion (the amount of ion pairing). This presumably occurs because the solvent preferentially solvates the sodium nitrate rather than the sodium thiophenoxide; i.e., the solvation energy must be greater for the nitrate ion than for the thiophenoxide ion in both these solvents. Because the sodium nitrate does not affect the form of the reacting thiophenoxide ion significantly, the reacting nucleophile is the free thiophenoxide ion in DMSO and a solvent-separated sodium thiophenoxide ion-pair complex in methanol in both the presence and absence of the inert salt.

Secondary α Deuterium Kinetic Isotope Effects.

The secondary α deuterium KIEs for the reactions with and without the inert salt in DMSO and in methanol are presented in Table 2. In both solvents, the KIE is smaller in the reaction with the inert salt, i.e., by 3.8% in DMSO and by 10.3% in methanol. Since a smaller secondary α deuterium KIE is found when the S_N2 transition state is tighter, i.e., with a shorter nucleophile–leaving group distance in the transition state,^{15,16} the smaller secondary α deuterium KIEs found in the reactions with the sodium nitrate indicate that the S_N2 transition state is tighter with shorter S–C_α and/or C_α–Cl transition-state bonds when sodium nitrate is present in both DMSO and methanol.

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TABLE 2. Secondary α Deuterium Kinetic Isotope Effects for the S_N2 Reaction between *n*-Butyl Chloride and Sodium Thiophenoxide in DMSO and in Methanol at 20.000 ± 0.002 °C with and without Added Sodium Nitrate

$k_H \times 10^2$ (L/M·s)	$k_D \times 10^2$ (L/M·s)	$(k_H/k_D)_\alpha$
	DMSO, No Salt Added	
$2.576^a \pm 0.038^b$	$2.335^a \pm 0.033^b$	1.103 ± 0.023^c
	DMSO + 1.073 M NaNO ₃	
2.622 ± 0.014	2.462 ± 0.010	1.065 ± 0.007
	MeOH, No Salt Added	
2.321 ± 0.004	2.195 ± 0.015	1.057 ± 0.007
	MeOH + 0.2074 M NaNO ₃	
1.892 ± 0.014	1.983 ± 0.007	0.954 ± 0.008

^a Average of three different rate constants measured on different days. ^b Standard deviation. ^c The error in the KIE is $1/k_D[(\Delta k_H)^2 + (k_H/k_D)^2(\Delta k_D)^2]^{1/2}$, 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.⁸

Chlorine (Leaving Group) Kinetic Isotope Effects. Although the chlorine KIEs in the reactions with and without the added salt, Table 3, are identical considering the experimental errors, the average KIE is slightly larger when the inert salt is present in both solvents. Because a larger chlorine (leaving group) KIE is observed when the amount of C_α-Cl bond rupture in the transition state is greater,^{17,18} the chlorine KIEs indicate that the C_α-Cl bond is the same or very slightly longer when sodium nitrate is present in both DMSO and methanol.

Effect of the Inert Salt (Ionic Strength) on the Structure of the S_N2 Transition State. The smaller secondary α deuterium KIE found in the presence of the inert salt in both solvents indicates that the S_N2 transition state is tighter, i.e., has a shorter nucleophile-leaving group distance when the inert salt is present. The chlorine leaving group KIEs on the other hand, are identical or very slightly larger in both solvents when the inert salt is present. This indicates that the C_α-Cl transition-state bond is the same or very slightly longer when sodium nitrate is present in both solvents (vide supra). If the C_α-Cl transition-state bond is the same or very slightly longer and the nucleophile-leaving group distance is shorter, the S_N2 transition state must be tighter when the inert salt is present in both solvents; i.e., adding the inert salt must lead to an S_N2 transition state with a much shorter S-C_α bond and an equal or very slightly longer C_α-Cl bond whether the reacting nucleophile is the solvent-separated ion-pair complex in methanol or the free thiophenoxide ion in DMSO.

It is worth noting that the change in transition-state structure found when the sodium nitrate is added to the solvent for both the free-ion reaction in DMSO and the solvent-separated ion-pair complex reaction in methanol is predicted by the bond strength hypothesis.¹⁹ The bond strength hypothesis suggests that changing a substituent in the nucleophile, the substrate, or the leaving group of an S_N2 reaction will cause a significant change in the

TABLE 3. Chlorine (Leaving Group) KIEs for the S_N2 Reactions of Sodium Thiophenoxide and Butyl Chloride in DMSO and in Methanol at 20.000 ± 0.002 °C

ionic strength NaNO ₃ (M)	δ	average f	R_o/R_f^a	k^{35}/k^{37} ^b
	DMSO, No Salt Added			
0.000	-12.19	0.1334	0.992655	1.00796
	-11.59	0.1530	0.993243	1.00740
	-11.52	0.1667	0.993312	1.00739
	-11.89	0.1858	0.992949	1.00788
	-11.94	0.2268	0.992900	1.00816
average				1.00776 ± 0.00035^c
	DMSO + 1.00 M NaNO ₃			
1.00	-12.44	0.1451	0.992409	1.00828
	-11.68	0.1531	0.003155	1.00750
	-11.94	0.1792	0.992900	1.00791
	-11.11	0.2199	0.993715	1.00718
	-12.04	0.2240	0.992802	1.00825
average				1.00782 ± 0.00048
	Methanol, No Salt Added			
0.000	-12.39	0.1273	0.992212	1.00841
	-12.05	0.1459	0.992546	1.00814
	-11.78	0.1933	0.992811	1.00808
	-11.97	0.2159	0.992624	1.00841
	average			
	Methanol + 0.212 M NaNO ₃			
0.212	-12.09	0.1165	0.992507	1.00804
	-12.25	0.1612	0.992350	1.00843
	-12.22	0.1898	0.992379	1.00855
	-12.30	0.2226	0.992301	1.00882
	-11.72	0.2491	0.992870	1.00832
average				1.00843 ± 0.00029

^a The average R_o from five different samples was 3.13046 relative to a standard methyl chloride sample. The R_f values were obtained from $R_f = R_o(1 - \delta/1000)$ where R_f is the ³⁵Cl/³⁷Cl ratio of the standard methyl chloride sample. ^b The isotope effect is calculated using the formula $k^{35}/k^{37} = \ln(1 - f)/\ln(1 - (R_o/R_f) f)$ where f is the fraction of reaction, R_f is the ³⁵Cl/³⁷Cl ratio in the chloride ion isolated after the fraction of reaction f , and R_o is the ³⁵Cl/³⁷Cl ratio of the chlorine in the starting material. ^c Standard deviation.

weaker reacting bond and little or no change in the stronger reacting bond in the S_N2 transition state. Although adding the sodium nitrate to the solvent is not a change in substituent, it leads to the predicted change in transition-state structure, i.e., the weaker S-C_α bond shortens significantly while there is only a small or zero change in the stronger C_α-Cl bond. Thus, the results demonstrate that the strength of the reacting bonds plays a significant role in predicting how the bonds to the nucleophile and the leaving group will be altered in these S_N2 reactions. Unfortunately, the bond strength hypothesis does not indicate how each reacting bond will change in a reaction.

Although the changes in transition-state structure on the addition of the inert salt in both the ion-pair and free-ion reactions are in accordance with the bond strength hypothesis and are also in the same direction, i.e., a tighter, more product-like, transition state is found when the sodium nitrate is present, they are of a different magnitude. The changes found in the secondary α deuterium and the chlorine KIEs when sodium nitrate is added to the ion-pair reaction in methanol are approximately three times larger than those found in the free-ion reaction in DMSO; i.e., the secondary α deuterium KIE decreases by 10.3% in the ion-pair reaction in

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methanol whereas it only decreases by 3.8% in the free-ion reaction in DMSO. The change in the chlorine KIE upon addition of the sodium nitrate is also three times larger in methanol; i.e., it increases by 0.00017 in methanol whereas it only increases by 0.00006 in DMSO.

This much larger salt effect on the ion-pair reaction in methanol was expected. Several studies have shown that the structure of a type I S_N2 transition state is not affected significantly by a change in solvent. For instance, Graczyk et al.¹¹ found identical chlorine leaving group KIEs (the average KIE was 1.00944 ± 0.00012) for the S_N2 reaction between thiophenoxide ion and *n*-butyl chloride in several solvents ranging from the dipolar aprotic solvents DMSO and DMF, to the aprotic solvents tetraglyme and diglyme, to the protic solvents propanol and methanol. It is worth noting that the rate constant for the reaction changed by over 3 orders of magnitude over this range of solvents. In another study, Westaway and Lai¹² found that the secondary α deuterium KIE was 1.125 ± 0.008 for this type I S_N2 reaction when the solvent was DMSO, DMF, or methanol and the free thiophenoxide ion was the reacting nucleophile. Since neither the α carbon–chlorine nor the total nucleophile-leaving group distance (the magnitude of the secondary α deuterium KIE) change when the solvent is altered and the rate constant changes drastically, the structure of the transition state of this type I S_N2 reaction is not altered by a change in solvent.

Very different results were found for the same reaction, however, when the solvent was changed in the reactions where the nucleophile was the solvent-separated ion-pair complex. Here, the secondary α deuterium KIEs for the thiophenoxide ion and *n*-butyl chloride S_N2 reaction changed from 1.034 to 1.084 to 1.110 to 1.141 when the solvent was changed from DMSO to DMF to methanol to diglyme. It is worth noting that the rate constants for the ion-pair complex reactions also changed by 3 orders of magnitude when the solvent was changed. These results demonstrate that the ion-pair reaction is very susceptible to a change in solvent.

The greater sensitivity to the added salt found in the ion-pair complex reaction can be rationalized by an extension of the solvation rule for S_N2 reactions¹² if one assumes adding the inert salt only changes the solvent by increasing its dielectric constant. The S_N2 transition states for the free-ion and ion-pair complex reactions, Figure 1, are very different from the point of view of solvation. The S_N2 transition state for the free-ion reaction will be mainly, if not exclusively, solvated at the two negatively charged nucleophiles. As a result, the relative nucleophilicity of the two nucleophiles will not be changed significantly by a change in solvent and the transition-state structure and KIEs will not be altered.⁹ In the ion-pair complex reactions where the nucleophile is a tight solvent-separated ion pair,¹² Figure 1b, the solvation will be mainly at the sodium ion, which has a full positive charge and blocks the normal solvation of the partially charged sulfur anion, and the developing chloride ion which has a partial negative charge. As a result, changing from the protic solvent, methanol, to the dipolar aprotic solvent, DMSO, changes the solvation from hydrogen bonding to an ion–dipole interaction at the negatively charged chloride ion. Since hydrogen bonding lowers the electron density of an anion, the loss

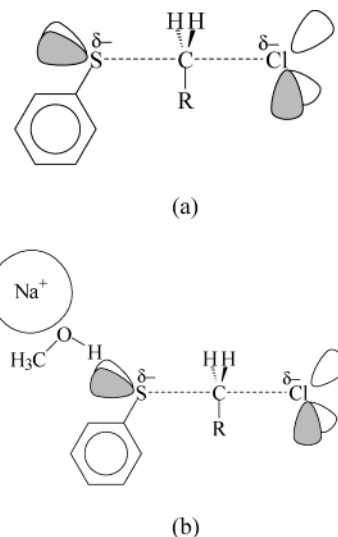


FIGURE 1. S_N2 transition states for the reaction between *n*-butyl chloride and (a) the free thiophenoxide ion and (b) the solvent-separated sodium thiophenoxide ion-pair complex.

of hydrogen bonding to the developing chloride ion will increase the electron density (the nucleophilicity) of the chloride ion. The methanol molecule(s) in a tight solvent-separated ion-pair complex cannot hydrogen bond to the sulfur anion in the S_N2 transition state because the distance between the sodium and sulfur ions is too small to form linear hydrogen bonds to methanol. Thus, no hydrogen bonding is lost at sulfur when the solvent changes, i.e., the change in solvent from methanol to DMSO only changes one dipole–ion interaction for another at the sulfur ion. As a result, the electron density (the nucleophilicity) of the sulfur anion is not markedly affected by the change in solvent. Since the solvent change alters the electron density on the chloride anion much more than that on the sulfur ion, the *relative* nucleophilicity of the chloride and sulfur anions is altered significantly by a change in solvent (adding the inert salt). As a result, the ion-pair S_N2 transition state behaves like a type II system,⁹ and the transition-state structure and the secondary α -deuterium KIE is altered markedly by a change in solvent. It is worth noting that this effect has been reported previously.¹² However, the important observation is that the changes in the KIEs (transition-state structure) caused by adding the inert salt to the free-ion reaction in DMSO were significantly smaller than (approximately one-third) those found when the salt was added to the ion-pair complex reaction in methanol.

The Role of the Inert Salt. Although the greater change in the S–C _{α} bond and in transition-state structure on the addition of the sodium nitrate in the ion-pair reaction has been rationalized, it is important to try to understand why adding an inert salt leads to a tighter, more product-like S_N2 transition state in both the ion-pair and the free-ion reactions. One possibility is that the sodium nitrate simply changes the solvent by increasing its dielectric constant. In Westaway and Lai's earlier study of the *n*-butyl chloride–sodium thiophenoxide S_N2 reaction where the nucleophile was the ion-pair complex,¹² a smaller secondary α deuterium KIE and tighter transition state was found in the solvent with the

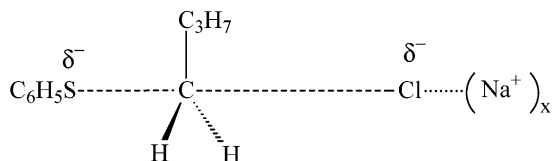


FIGURE 2. Interaction of the cation in the added salt with the developing chloride ion leaving group in the S_N2 reaction between *n*-butyl chloride and thiophenoxide ion in DMSO.

largest dielectric constant (vide supra). If one assumes that the added salt simply increases the dielectric constant of the solvent, the transition state for the ion-pair reaction in methanol should be tighter when the salt is present. This is what is observed in methanol where the reacting nucleophile is the ion pair, i.e., the very slightly larger chlorine leaving group KIE and markedly smaller secondary α deuterium KIE indicate the transition state is tighter, and more product-like, when the salt is present. This means that the tighter transition state is found in the reaction with the solvent with the higher dielectric constant as Westaway and Lai observed.

While this explanation is acceptable for the ion-pair reaction in methanol, it is important to note that a change in the solvent does not explain why the salt affects the structure of the transition state in the free-ion reaction. The identical secondary α deuterium and chlorine leaving group effects found in several very different solvents by Westaway and Lai and by Grazyk et al. (vide supra) for this reaction indicate that changing the solvent does not alter the transition-state structure of the type I S_N2 reaction between *n*-butyl chloride and the free thiophenoxide ion significantly. This means the inert salt must play another role in the free-ion reaction.

One possibility is that the inert salt provides electrophilic catalysis for the reaction by bonding to the partial negative charge on the developing chloride ion in the S_N2 transition state, Figure 2. It is worth noting that this type of catalysis to a chloride ion leaving group using hydrogen bonding to protic solvents in S_N reactions has been suggested by Thornton and Gajewski.^{20,21} Electrophilic catalysis for the removal of a chloride ion leaving group by metal ions in E2 elimination reactions of alkyl chlorides was suggested by Smith et al.²² and by Zavada and co-workers.^{23,24} If this type of catalysis occurred, it would stabilize the developing chloride ion making it a better leaving group. A tighter, more product-like, transition state would be expected because Westaway and Ali²⁵ found that changing to a better leaving group in the S_N2 reactions between benzyldimethyl-para-substituted phenylammonium ions and thiophenoxide ion in DMF, eq 5, led to a change in transition-state structure where the length of the stronger C_α -N bond to the leaving group increased slightly while the weaker S- C_α nucleophile- α carbon transition-state bond shortened markedly.

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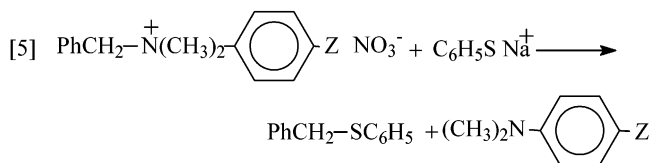
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This is precisely the effect that is observed in both the free-ion and ion-pair reactions when the inert salt is added, i.e., the stronger C_α -Cl bond lengthens very slightly while the weaker S- C_α bond shortens significantly.



This action of the sodium nitrate would, therefore, account for the change in transition-state structure found in the free-ion reaction. It would presumably also have an effect on the ion-pair reaction as well. Thus, the free-ion reaction would not be affected by the change in the solvent caused by adding the inert salt, but only by the electrophilic catalysis by the added sodium nitrate. The ion-pair reaction, on the other hand, is presumably affected by both the change in solvent and by the electrophilic catalysis of the sodium nitrate.

Conclusions

The important discovery is that adding an inert salt to an S_N reaction affects the structure of the S_N2 transition state whether the reaction is a type I or a type II S_N2 reaction. The results also show that the transition state is tighter, and more product-like, with the same or very slightly longer α carbon-leaving group (C_α -Cl) bond and a much shorter nucleophile- α carbon (S- C_α) bond when the inert salt is present whether the nucleophile is the free ion or a solvent-separated ion-pair complex. The much greater salt effect on transition-state structure found when the nucleophile is a solvent-separated ion-pair complex rather than a free ion can be rationalized by the solvation rule for S_N2 reactions.¹² The major change in transition-state structure is at the weaker reacting bond in the S_N2 transition states as the bond strength hypothesis¹⁹ suggests. It is suggested that the change in transition-state structure caused by the added salt is due to electrophilic catalysis by the cation of the added salt to the developing anion of the leaving group in a type I S_N2 reaction where the nucleophile is a free ion and is probably due to a change in the ionizing power of the solvent **and** the electrophilic catalysis to the leaving group in a type I S_N2 reaction where the nucleophile is a solvent-separated ion-pair complex.

Experimental Section

Preparation of Reagents. The synthesis of butyl-1,1- d_2 chloride and sodium thiophenoxide have been described previously.¹³ NMR analysis indicated that the deuterated substrate was at least 99% deuterated at the α carbon. The sodium nitrate was dried at 110 °C overnight and then stored in a vacuum desiccator until it was used. The anhydrous dimethyl sulfoxide was used as purchased. The reagent-grade methanol was distilled before use.

Kinetics. In Anhydrous Dimethyl Sulfoxide. Extra dry nitrogen was bubbled through the anhydrous DMSO or freshly distilled methanol for 0.5 h to remove any oxygen. Then, all the required glassware that had been dried overnight in an oven at 110 °C and stored in a desiccator, the solvent, the sodium thiophenoxide, and the sodium nitrate were trans-

ferred to an I²R glovebag. After the glovebag had been filled, emptied, and refilled with extra-dry nitrogen, two stock solutions were prepared. One stock solution was prepared by dissolving approximately 0.05 g of accurately weighed sodium thiophenoxide in 150 mL of anhydrous DMSO. The other stock solution was prepared by adding approximately 0.08 g (accurately weighed in a gastight syringe with the end of the needle sealed by a rubber septum) of butyl chloride or butyl-1,1-*d*₂ chloride to 15 mL of anhydrous DMSO. Then, 50 mL of the sodium thiophenoxide stock solution was pipetted into each reaction flask and the reaction flask was sealed with a serum cap fitted on a ground glass adapter. Each reaction flask and the butyl chloride stock solutions were placed in the constant-temperature bath at 20.000 ± 0.002 °C for 1 h. In the reactions where sodium nitrate was present, the appropriate amount of dry sodium nitrate (vide supra) was added to the sodium thiophenoxide stock solution. The reaction was started by injecting 1.00 mL of the butyl chloride stock solution to the reaction flask. One milliliter samples of the reaction mixture were removed at various times throughout the reaction and quenched by injecting the sample into 2.5 mL of cold methanol containing a known amount (accurately weighed) of the internal standard, butyl phenyl ether. Each sample was diluted to 5 mL with methanol, and 10 μL of the 5 mL solution was injected onto a Zorbax ODS 4.6 mm × 15 cm HPLC column, and the concentration of the product, butyl phenyl sulfide, was determined from the [area ratio (internal standard/butyl phenyl sulfide)] versus the [mole ratio (internal standard/butyl phenyl sulfide)] calibration curve.²⁶ The HPLC separation was carried out using 85% methanol–15% water as the eluant at a flow rate of 1 mL/min. The UV detector was set at 250 nm.

In Methanol. The same general procedure was used for the reactions in methanol. The only changes were that the stock solution containing the sodium thiophenoxide and the

substrate were prepared by dissolving approximately 10.1 g of accurately weighed sodium thiophenoxide in 400 mL of purified methanol. The other stock solution was prepared by adding approximately 2.4 g (accurately weighed in a gastight syringe with the end of the needle sealed by a rubber septum) of butyl chloride or butyl-1,1-*d*₂ chloride to 10 mL of purified methanol. Then, 50 mL of the sodium thiophenoxide stock solution was pipetted into each reaction flask, and the reaction flask was sealed with a serum cap fitted on a ground glass adapter. Each reaction flask and the butyl chloride stock solutions were placed in the constant-temperature bath at 20.000 ± 0.002 °C for 1 h. In the reactions where sodium nitrate was present, the appropriate amount of sodium nitrate was added to the sodium thiophenoxide stock solution. The reaction was started by injecting 1.00 mL of the butyl chloride stock solution into 50 mL of the sodium thiophenoxide stock solution. The individual kinetic points and the analyses were done using the procedure described above.

Chlorine KIEs. These KIEs were measured by starting the reactions as described above. Then, the partial reactions were quenched by pouring the reaction mixture into 30 mL of methanol containing 4 drops of a 1:4 nitric acid solution after various extents of reaction ranging from 11% to 25% of completion, Table 3. The complete reaction was started as described, but it was allowed to react for over 10 half-lives before it was quenched and the chloride ion recovered. The procedures used for the analysis of the chloride ion, the recovery of the silver chloride, and its conversion into methyl chloride for isotope ratio mass spectrometry are described in ref 27.

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