Solvent effects on nucleophilic substitution reactions. III. The effect of adding an inert salt on the structure of the S_N 2 transition state

T.V. Pham and K.C. Westaway

Abstract: The nitrogen and secondary α -hydrogen-deuterium kinetic isotope effects found for the S_N2 reaction between thiophenoxide ion and benzyldimethylphenylammonium ion at different ionic strengths in DMF at 0°C indicate that the structure of the transition state changes markedly with the ionic strength of the reaction mixture. In fact, a more reactant-like, more ionic, transition state is found at the higher ionic strength. This presumably occurs because a more ionic transition state is more stable in the more ionic solvent.

Key words: transition state, ionic strength, secondary α deuterium kinetic isotope effects, nitrogen isotope effects, S_N2.

Résumé: On a déterminé les effets isotopiques cinétiques primaires de l'azote et secondaire des hydrogène/deutérium en α sur la réaction S_N2 des ions thiophénolate et benzyldiméthylphénylammonium, à diverses forces ioniques, dans le DMF, à 0°C; ils suggèrent que la structure de l'état de transition varie d'une façon importante avec la force ionique du mélange réactionnel. En fait, on observe que, à force ionique élevée, l'état de transition est plus ionique et qu'il ressemble aux réactifs. Cette situation existe probablement parce qu'un état de transition plus ionique est plus stable dans le solvant plus ionique.

Mots clés : état de transition, force ionique, effets isotopiques cinétiques secondaires des deutériums en α , effets isotopiques de l'azote, S_N2.

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Introduction

Inert salts are often added to organic reactions where ionic reactants are converted into neutral products so accurate rate constants can be measured. The problem arises because the rate constant "k" for a reaction between two ionic reactants varies with the ionic strength of the medium, eq. [1].

[1] $\log k = \log k_0 + Z_A Z_B c (\mu / D^3 T^3 \rho)^{1/2}$

where "log k_0 " is the rate constant at infinite dilution, " Z_A " and " Z_B " are the charges on the reacting ions, *c* is a constant, " $\mu = 1/2(\sum_i c_i Z_i^2)$ " is the ionic strength of the solution, " c_i " is the concentration of ion *i*, " Z_i " is the charge on ion *i*, "*D*" is the dielectric constant of the solvent, "*T*" is the absolute temperature, and " ρ " is the density of the solution (1). In a reaction where two ionic reactants are converted into neutral products (ions are consumed in the reaction), the ionic strength decreases throughout the reaction and the rate constant changes according to eq. [1]. This means that one cannot determine an accurate rate constant for the reaction and, therefore, cannot measure kinetic isotope effects, or any other mechanis-

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¹ Author to whom correspondence may be addressed. Telephone: (705) 675-1151, ext. 2105, Fax: (705) 675-4844. E-mail: kwestawa@nickel.laurentian.ca tic criteria based on kinetic data, to determine the reaction mechanism. In practice, a constant (accurate) rate constant can be obtained for these reactions if the rate constant is determined in solutions containing a high concentration of an inert salt. This is effective because the high concentration of inert salt maintains a high, and effectively constant, ionic strength throughout the reaction so the rate constant does not change significantly. In all the studies where this technique has been used, it is assumed that the added salt only keeps the ionic strength of the medium constant (maintains the rate constant) but does not have any effect on the reaction. The results of this study indicate that an added, inert, salt affects the structure of an S_N2 transition state significantly.

Results and Discussion

The S_N^2 reaction between thiophenoxide ion and benzyldimethylphenylammonium ion, eq. [2],

[2]
$$Z \longrightarrow S^- + C_6H_5CL_2 \longrightarrow \dot{N}(CH_3)_2C_6H_5$$

 $\xrightarrow{DMF} Z \longrightarrow S \longrightarrow CL_2C_6H_5 + (CH_3)_2NC_6H_5$
 $L = H, D$

has been investigated at 0°C in DMF containing a high concentration of the inert salt, sodium nitrate. The high concentration of sodium nitrate kept the ionic strength virtually constant throughout the reaction, making it possible to determine accurate rate constants.

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Table 1. The primary nitrogen (leaving group) and secondary α -hydrogen-deuterium kinetic isotope effects for the S_N2 reaction between sodium thiophenoxide and benzyldimethylphenyl-ammonium nitrate at different ionic strengths in DMF at 0°C.

Ionic strength (M)	k^{14}/k^{15}	$(k_{\rm H}/k_{\rm D})_{lpha}$
0.904	1.0166 ± 0.0004^{a}	1.215 ± 0.011^{t}
0.64	1.0200 ± 0.0007^{a}	1.179 ± 0.007^{t}

 ${}^{a}\mathrm{The}$ errors are the standard deviation of the mean of five different measurements.

^{*b*}The error in the isotope effect = $(1/k_D)[(\Delta k_H)^2 + (k_H/k_D)^2 \times (\Delta k_D)^2]^{1/2}$ where Δk_H and Δk_D are the standard deviations for the rate constants for the undeuterated and deuterated substrates, respectively. The Δk_H and Δk_D values were obtained from three rate constants for the undeuterated and three rate constants for the deuterated substrates, respectively, that were measured simultaneously.

'This isotope effect was determined by whole-molecule mass spectrometry. The error is the standard deviation for four separate determinations (2).

The nitrogen (leaving group) and the secondary α -hydrogen-deuterium kinetic isotope effects were measured for this S_N2 reaction at two different ionic strengths to learn whether the added, inert, salt affects the reaction and the structure of its transition state. An examination of the nitrogen (leaving group) and secondary α -hydrogen-deuterium kinetic isotope effects, Table 1, shows that the isotope effects are very different when the reaction is carried out at different ionic strengths. For instance, the nitrogen kinetic isotope effect found at the higher ionic strength $(k^{14}/k^{15} = 1.0166 \pm 0.0004)$ is significantly smaller than the $k^{14}/k^{15} = 1.0200 \pm 0.0007$ found for this reaction at the lower ionic strength of 0.64 M (2). The magnitude of a heavy atom (nitrogen (leaving group)) kinetic isotope effect increases linearly with the percent of α -carbonnitrogen (C_{α} - -N) bond rupture in the transition state (2, 3). Therefore, the smaller nitrogen isotope effect found for the reaction at the higher ionic strength indicates that the C_{α} - - N bond rupture is much less advanced in the transition state of the high ionic strength reaction.

Recent work has shown that the magnitude of a secondary α -hydrogen-deuterium kinetic isotope effect is determined by the changes that occur in both the C_{α} —H(D) stretching and the out-of-plane bending vibrations when the reactant is converted into the transition state (4, 5). However, a comparison of the secondary α -hydrogen-deuterium kinetic isotope effects for a series of S_N2 reactions between methyl or ethyl chlorides and fluorides with several different nucleophiles (5) has shown that the magnitude of the isotope effect for a series of S_N2 reactions with the same leaving group is determined by the changes that occur in the out-of-plane bending vibrations when the reactant is converted into the transition state (5). This means the magnitude of the secondary α -hydrogendeuterium kinetic isotope effect for a series of S_N^2 reactions with the same leaving group is determined by the nucleophile - leaving group distance (the tightness) of the S_N2 transition state (5-7).

The secondary α -hydrogen-deuterium kinetic isotope effect found at the high ionic strength ($(k_{\rm H}/k_{\rm D})_{\alpha} = 1.22 \pm 0.01$) is significantly larger than the $(k_{\rm H}/k_{\rm D})_{\alpha} = 1.179 \pm 0.007$ (2) found at an ionic strength of 0.64 M, Table 1. Since the magnitude of a

Fig. 1. The relative transition state structures for the S_N^2 reactions between sodium thiophenoxide and benzyldimethylphenyl-ammonium nitrate at different ionic strengths in DMF at 0°C.

$$\mu = 0.90 \text{ M} \qquad \begin{array}{c} \delta^{-} & \delta^{+} \\ S^{-} & C_{\alpha}^{-} & N \end{array}$$

$$\mu = 0.64 \text{ M} \qquad \begin{array}{c} \delta \delta^{-} & \delta \delta^{+} \\ S^{-} & C_{\alpha}^{-} & N \end{array}$$

secondary α -hydrogen-deuterium kinetic isotope effect is related to the nucleophile – leaving group distance in the S_N2 transition state (5–7), the larger isotope effect found for the higher ionic strength reaction indicates that the high ionic strength transition state is looser with a greater nucleophile – leaving group distance than the lower ionic strength transition state. If the high ionic strength transition state has a greater nucleophile – leaving group distance but a shorter C_{α}- - -N bond (vide supra), then the S- - -C_{α} transition state bond in the high ionic strength reaction must be much longer than the S- - -C_{α} bond in the transition state of the low ionic strength reaction, Fig. 1.

Another piece of evidence that suggests the S- - $-C_{\alpha}$ transition state bond is longer in the higher ionic strength reaction is the Hammett p value found by changing the para substituent on the nucleophile. A Hammett $\rho = -1.62 \pm 0.01$, Table 2, was observed for the high ionic strength reaction whereas a larger Hammett ρ value of -1.76 ± 0.19 was found for the reaction at an ionic strength of 0.64 M. Since a larger p value is observed when the change in charge on going from the reactants to the transition state is larger, i.e., when there is more nucleophile– α -carbon bond formation in the transition state, the reaction at the higher ionic strength (with the larger $(k_{\rm H}/k_{\rm D})_{\alpha}$) must have the longer S- - -C_{\alpha} transition state bond.² Thus, the p values support the conclusion based on the magnitude of the secondary α -hydrogen-deuterium kinetic isotope effects, i.e., that the transition state for the higher ionic strength reaction is looser with a much longer S- - $-C_{\alpha}$ bond than the transition state for the lower ionic strength reaction. Combining the information obtained from the nitrogen and the secondary α -hydrogen-deuterium kinetic isotope effects with that from the Hammett ρ value suggests that the high ionic strength transition state is earlier (more reactant-like) with a much longer S- - -C_{α} and a shorter C_{α}- - -N bond, Fig. 1.

Finally, it is interesting to speculate on why a more reactant-like transition state is found at a higher ionic strength. The earlier transition state in the high ionic strength reaction has both a greater negative and a greater positive charge on the

² Hoz et al. (8) used the results of theoretical calculations on homolytic cleavage reactions to question the validity of using Hammett ρ values to determine transition state structure. However, many workers currently use linear free energy relationships such as ρ values to indicate differences in transition state structure (9, 10) and there is no experimental evidence to show which position is correct. The authors believe that ρ values found in closely related systems can be used to indicate transition state structure. Support for this position is that the changes in the structure of the S_N2 transition state suggested by ρ values have been confirmed by isotope effect data (2, 11, 12).

Table 2. The rate constants and Hammett ρ values for the reactions between *para*-substituted sodium thiophenoxides and benzyldimethylphenylammonium nitrate at different ionic strengths in DMF at 0°C.

	Rate constant $\times 10^3$ (L M ⁻¹ s ⁻¹)	
on the thiophenoxide ion	Ionic strength $\mu = 0.904 \text{ M}$	Ionic strength $\mu = 0.64 \text{ M}$
сн ₃ о	30.1 ± 0.8^{a}	46.2 ± 3.3^{a}
Н	10.9 ± 0.3	12.8 ± 1.0
Cl	4.67 ± 0.07	6.13 ± 0.65
ρ	-1.62 ± 0.01	-1.76 ± 0.19
Correlation coefficient	1.00	0.994

"The errors are the standard deviation of the mean of at least three different measurements.

nucleophilic sulfur and nitrogen atoms, respectively. This means the transition state in the higher ionic strength solvent is more ionic. It is proposed that the more ionic transition state is found at high ionic strength because it is more stable (more highly solvated) in the more ionic solvent.

The significant observation, however, is that inert salts that are used to increase the ionic strength in reactions so that accurate rate constants can be measured, change the structure of the transition state markedly. This is an important discovery because it shows that adding even inert salts changes the reaction from a mechanistic point of view, i.e., the values obtained for any mechanistic criterion will not be for the reaction of interest.

Experimental

Nitrogen kinetic isotope effects for the S_N2 reactions between sodium thiophenoxide and benzyldimethylphenylammonium ion in DMF at 0°C

The procedure used to synthesize the benzyldimethylphenylammonium nitrate and measure the nitrogen kinetic isotope effect has been described (2). The only difference in the two isotope effects was that one was measured at a higher ionic strength. In both experiments, the ionic strength was adjusted by adding sodium nitrate to the solvent.

The secondary α -hydrogen-deuterium kinetic isotope effects for the S_N^2 reactions between sodium thiophenoxide and benzyldimethylphenylammonium ion in DMF at 0°C

The preparation of the benzyl-1,1- d_2 -dimethylphenylammonium nitrate has been described (2). The procedure used to measure the secondary α -hydrogen-deuterium kinetic isotope effect at the lower ionic strength using whole-molecule mass spectrometry is also described in ref. 2. The secondary α hydrogen-deuterium kinetic isotope effects at the high ionic strength were obtained by dividing the average second-order rate constant (from three separate kinetic runs done using the same stock solutions and at the same time) for the reaction of the undeuterated substrate with that for the reaction of the deuterated substrate. The least-squares kinetic plots had correlation coefficients of at least 0.999 and the reactions were followed to at least 67% of completion. The procedure used to measure these rate constants is given in refs. 12 and 13. The isotope effects measured with different batches of solvent on different days were identical.

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