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AN UNUSUALLY LARGE α-SECONDARY DEUTERIUM KINETIC ISOTOPE EFFECT.

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The magnitude of α-secondary deuterium kinetic isotope effects has been used widely as a criterion of mechanism for nucleophilic substitution reactions at saturated carbon (1,2). Although the magnitude of the isotope effect clearly varies with leaving group (3,4), Table 1, a large isotope effect (for example, $k_H/k_D \geqslant 1.07$ per α-D for primary alkyl iodides) is normally accepted as sufficient evidence for a carbonium ion mechanism whereas a very small or inverse isotope effect ($k_H/k_D \leqslant 1.04$ per α-D (4)) is taken as positive evidence for an S_N2 mechanism (5).

Table 1. Alpha-Deuterium Isotope Effects for Different Leaving Groups in Carbonium Ion Reactions.

Leaving Group	Maximum k_H/k_D per α-D	k_H/k_D per α-D if ionization is rate determining (6)
OTs, OBs	1.23	1.17
F	1.22	1.16
Cl	1.13	1.11
Br	1.125	1.09
I	1.09	1.07

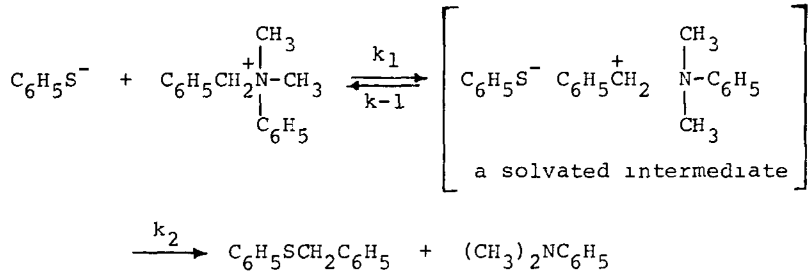
A recent investigation (7) of the nucleophilic substitution reaction of benzyldimethylphenylammonium nitrate with thiophenoxide ion in N,N-dimethylformamide at 0°C, eq. [1],

$$[1] \quad C_6H_5\overset{-}{S} + C_6H_5CH_2\overset{+}{N}(CH_3)_2C_6H_5 \xrightarrow[0^{\circ}C\ NaNO_3]{D.M.F} C_6H_5SCH_2C_6H_5 + (CH_3)_2NC_6H_5$$

has shown that this reaction is first order in both thiophenoxide ion and the substrate. The rate dependence on thiophenoxide ion is clearly consistent with carbon-sulfur bond formation in the slow step of the reaction. A small positive Hammett ρ value of +2.04 for substitution in the N-phenyl group, and a large nitrogen kinetic isotope effect of 1.0200 eliminate any ion-pair mechanisms involving a pre-equilibrium carbon-nitrogen bond rupture and prove that the carbon-nitrogen bond is broken in the rate-determining step of the reaction (7).

Only two substitution mechanisms require a rate dependence on thiophenoxide ion and a rate-determining carbon-nitrogen bond rupture. They are an S_N2 mechanism where carbon-sulfur bond formation and carbon-nitrogen bond rupture occur simultaneously, and Bordwell's ion-sandwich mechanism (8) provided that the first step is fully rate-determining, eq. [2].

[2]

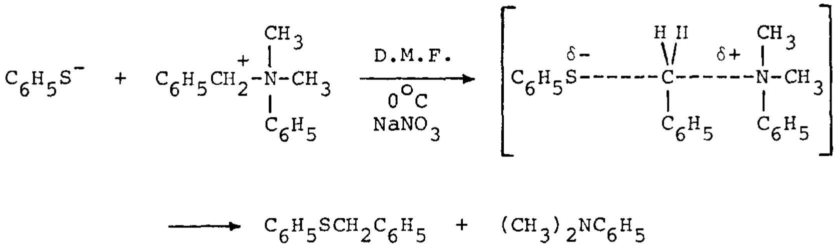


$$C_6H_5S^- + C_6H_5CH_2\overset{\overset{CH_3}{+|}}{\underset{\underset{C_6H_5}{|}}{N}}-CH_3 \underset{k-1}{\overset{k_1}{\rightleftharpoons}} \left[\begin{array}{c} C_6H_5S^-\quad \overset{+}{C_6H_5CH_2}\quad \overset{\overset{CH_3}{|}}{\underset{\underset{CH_3}{|}}{N}}-C_6H_5 \\ \text{a solvated intermediate} \end{array}\right]$$

$$\xrightarrow{k_2} C_6H_5SCH_2C_6H_5 + (CH_3)_2NC_6H_5$$

The ion-sandwich mechanism has been eliminated because (i) the formation of the charged ion-sandwich intermediate seems highly unlikely in the dipolar aprotic solvent, D.M.F., which does not solvate anions to any appreciable degree, (ii) the removal of the poor leaving group (N,N-dimethylaniline) would require a strong push from the nucleophile and (iii) a benzyl carbonium ion does not form during the reaction.[1] Thus it was concluded that this nucleophilic substitution reaction must proceed by way of the simple one-step S_N2 mechanism, eq. [3].

[3]



$$C_6H_5S^- + C_6H_5CH_2-\overset{\overset{CH_3}{+|}}{\underset{\underset{C_6H_5}{|}}{N}}-CH_3 \xrightarrow[\substack{0^\circ C \\ NaNO_3}]{D.M.F.} \left[C_6H_5\overset{\delta-}{S}\text{------}\overset{\overset{H\ H}{\vee}}{\underset{\underset{C_6H_5}{|}}{C}}\text{------}\overset{\overset{CH_3}{\delta+\ |}}{\underset{\underset{C_6H_5}{|}}{N}}-CH_3 \right]$$

$$\longrightarrow C_6H_5SCH_2C_6H_5 + (CH_3)_2NC_6H_5$$

The alpha-secondary deuterium kinetic isotope effect for this reaction was measured by the competitive technique (7). The ratio of the undeuterated/dideuterated starting material was determined by the weight of each reactant while the isotopic ratio of the product, undeuterated/dideuterated

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[1] Ref. 7 and unpublished results.

benzylphenyl sulfide, was determined by mass spectrometry. The percent reaction was determined in a gas chromatographic analysis of the product (9). Extensive control experiments and the fact that the isotope effect remains constant for several very different extents of reaction have shown that this method leads to an accurate value of the isotope effect.

The α-secondary deuterium kinetic isotope effect for this S_N2 reaction was found to be extremely large, ie. k_H/k_D = 1 19 ± 0.01 or 1.09 per α-deuterium This isotope effect is much larger than the maximum value predicted for an S_N2 reaction (4). In fact, the magnitude of this isotope effect places it in the range expected for carbonium ion reactions of primary alkyl iodides and bromides and in what is called the "borderline region" (5) for reactions of primary alkyl chlorides, arylsulfonates and fluorides, Table 1.

The extremely large α-secondary deuterium isotope effect in this S_N2 reaction clearly demonstrates

a) that S_N2 reactions can have isotope effects greater than 1 04 per α-deuterium,

b) that the magnitude of an α-secondary deuterium kinetic isotope effect cannot be used to identify an S_N2 reaction and suggests

c) that other reactions with α-deuterium isotope effects in the "borderline region" might also react by simple S_N2 mechanisms.

The large α-deuterium isotope effect in this reaction is attributed to the large and bulky leaving group, N,N-dimethylaniline. Several workers have shown that the magnitude of an α-secondary deuterium isotope effect is primarily determined by the C_α-H out-of-plane bending vibrations (2,10,11). In this reaction the large bulky leaving group, which is significantly larger than a t-butyl group, places the α-carbon and thus the C_α-H bonds in an extremely crowded environment. It follows that the C_α-H out-of-plane bending vibrations in the reactant will be very difficult (high frequency) and thus that the zero-point energy difference for the deuterated and undeuterated reactants will be very large. It is thought that the zero-point energy difference will be smaller in the pentavalent S_N2 transition state because breaking the carbon-nitrogen bond and removing the extremely large leaving group will decrease the crowding around the central carbon to such a great extent that even the additional crowding resulting from the incoming nucleophile would not be enough to make the C_α-H bending vibrations as difficult as in the reactants. This would lead to a smaller zero-point energy difference in the transition state and a larger isotope effect than those normally found for S_N2 reactions with small leaving groups and an increased crowding in the transition state.

In conclusion, this isotope effect illustrates that very large values of the α-secondary deuterium kinetic isotope effect are observed in S_N2 reactions when the leaving group is N,N-dimethylaniline and suggests that the actual size of the leaving group is very important in determining the magnitude of these isotope effects.

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