Secondary kinetic isotope effects in bimolecular nucleophilic substitutions. III. Deuterium effects in the Bunte salt reaction of methyl halides and sulfonates

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Secondary kinetic deuterium isotope effects have been measured for the reaction between thiosulfate ion and methyl- d_3 halides and sulfonates in 50% v/v ethanol-water. The results are used to extend the correlation of Seltzer of $k_{\rm H}/k_{\rm D}$ with the difference between the polarizabilities of the attacking nucleophile and the leaving group.

Dissociation constants for the $[NaS_2O_3]^-$ ion have been determined by conductivity measurements for the reaction conditions and used to calculate the concentration of free thiosulfate ions present in the reaction mixture. The activation parameters ΔH^{\pm} and ΔS^{\pm} , based on second order rate constants calculated with respect to the concentration of thiosulfate ion, are reported.

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Introduction

Secondary deuterium isotope effects in nonsolvolytic $S_N 2$ reactions, although generally smaller than analogous effects in $S_N 1$ or solvolytic $S_N 2$ reactions, are, nevertheless, large enough to warrant systematic study. An earlier paper (1) in this series showed that for the Bunte salt reaction

$$S_2O_3^{2-} + RBr \rightarrow RS_2O_3^{-} + Br^{-}$$

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of certain alkyl bromides in 50% v/v ethanolwater, α -deuterium isotope effects were normal $(k_{\rm H}/k_{\rm D} > 1)$ and could be as large as 7%. The direction of this effect was opposite to that expected from the solvolytic studies of Hartman and Robertson (2) and the magnitude was, at that time, greater than any previous measurements (3, 4). Since then several reports have confirmed the frequent occurrence of normal secondary deuterium isotope effects in $S_N 2$ reactions; e.g., Wu and Robertson (5) found normal effects for the attack of phenoxide and ethoxide ion on deuterated trimethylsulfonium ion, Östman (6) obtained ratios $(k_{\rm H}/k_{\rm D})$ between 1.05 and 1.09 for the chloride-36 exchange of α -deuterated benzyl chloride and both 2-thenyl and 3-thenyl chloride. Recently, Seltzer and Zavitsas (7) have measured the iodide-131 exchange of methyl- d_3 iodide $(k_{\rm H}/k_{\rm D} = 1.05$ in methanol and 1.10 in water) and also proposed a correlation of isotope effects with the polarizabilities of the attacking nucleophile and leaving group. For a given alkyl group the rate ratio was correlated with the difference between the

Edwards *E*-value (8-10) for the entering and leaving groups $(E_n - E_1)$.

This paper further explores the deuterium isotope effect in Bunte salt reactions and, in particular, tests Seltzer's correlation for this system in which the value of $(E_n - E_1)$ is large and positive, outside of the range of $(E_n - E_1)$ previously available.

Results and Discussion

Solutions of sodium thiosulfate in 50% v/v ethanol-water are not fully ionized (11) and it has been shown for the case of magnesium thiosulfate and *n*-propylbromide that the reaction takes place entirely via the thiosulfate ion (12). Thus the second order rate constant calculated with respect to the concentration of thiosulfate ion does not vary with the ionic concentration, whereas that calculated with respect to the stoichiometric sodium thiosulfate concentration does vary with the stoichiometric concentration. However, the latter rate constants may be used in isotopic studies since

$$k_{2(\text{ionic})} = \frac{k_{2(\text{stoich.})}}{\alpha}$$

where α is the fraction of thiosulfate present as $S_2O_3^{2^-}$ ions. All values of k quoted in this paper are second order rate constants calculated with respect to the stoichiometric sodium thiosulfate concentration.

Isotope Effects

Since extensive selective solvation takes place

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TABLE I

Secondary α -deuterium isotope effects for the reaction of sodium thiosulfate with ethyl-1,1 d_2 bromide at 25 °C

		N	$10^4 k_{ m H}$	$10^4 k_{\rm D}$	
(% v/v ethanol)	$\begin{bmatrix} Na_2S_2O_3 \end{bmatrix} \\ (M)$	NO. Of runs	$(1 \text{ mole}^{-1} \text{ s}^{-1})$		$k_{\rm H}/k_{\rm D} \pm {\rm Std. error}$
56 50 42 50 50	0.075 0.075 0.075 0.050 0.050	3 4 2 3 3	10.22 11.19 14.78 12.07 12.23	9.53 10.36 13.65 11.23 11.45	$1.07_{2} \pm 0.01$ $1.08_{0} \pm 0.01$ $1.08_{3} \pm 0.01$ $1.07_{5} \pm 0.01_{6}$ $1.06_{8} \pm 0.01_{6}$

*Reference (1).

TABLE II

Secondary deuterium isotope effect for the reaction of sodium thiosulfate with methyl esters in 50% v/v ethanol-water at 25 °C

Compound	No. runs	$10^4k_2 \pm \text{Std. error}$ (1 mole ⁻¹ s ⁻¹)	$k_{\rm H}/k_{\rm D} \pm {\rm Std. error}$
Methyl bromide Methyl- d_3 bromide	5 3	872 <u>+</u> 7 846 <u>+</u> 6	$1.03_1 \pm 0.01*$
Methyl iodide Methyl-d3 iodide	4 3	1078±5 1017±5	$1.05_8 \pm 0.01$
Methyl methanesulfonate Methyl-d ₃ methanesulfonate	5 4	$285.1 \pm 1.7 \\ 257.2 \pm 0.9$	1.11 ± 0.01
Methyl <i>p</i> -toluenesulfonate Methyl-d ₃ <i>p</i> -toluenesulfonate	3 3	$231.2 \pm 1.0 \\ 205.8 \pm 1.0$	1.12 ± 0.01

*Reference (1).

when sodium thiosulfate is dissolved in alcoholwater mixtures, it is necessary to be sure that no significant changes in isotopic rate ratio can be produced by variation of the solvent medium. Table I contains results obtained for several solvent mixtures and concentrations of sodium thiosulfate. Ethyl-1,1, d_2 bromide was used as the substrate as this compound was known to give an isotope effect of about 7% (1).

The experimental requirements preclude large variations in the medium, but it can be seen that no distinct changes in rate ratio occur, and that none is likely to occur from accidental variations in the medium or reagent concentration which is large compared to the experimental error.

The correlation of Seltzer and Zavitsas of $k_{\rm H}/k_{\rm D}$ with $(E_n - E_1)$ (7), although strictly valid only for solvent water, works well with the Bunte salt isotope effects previously reported (1).

Since E = 2.52 for thiosulfate, a large normal isotope effect would be expected for the Bunte salt reactions of alkyl sulfonates. Some results for a series of methyl compounds are shown in Table II.

Qualitatively, the sulfonate rate ratios are as predicted by the correlation. The plot $k_{\rm H}/k_{\rm D}$ versus $(E_n - E_1)$, including the results presented in Table II, is given in Fig. 1. Drawing a line with a slightly steeper gradient than that used by Seltzer gives a reasonably good correlation of the effect, except for a few points already discussed by Seltzer and Zavitsas (7).¹

In the above correlation the fact that the rate measurements were made at temperatures varying between 25° and 100 °C has been ignored. The justification for this is that a number of secondary deuterium isotope effects have been found to be independent of temperature (13, 14).²

However, none of the rate ratios included in the above plot has been tested experimentally because of the difficulty of determining the temperature dependence of a small effect over the experimentally accessible range of tempera-

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¹Another anomalous result has been found for the attack of cyanide ion on methyl- d_3 iodide in aqueous solution by A. Willi (private communication). For this reaction $k_{\rm H}/k_{\rm D} = 0.926$. ²R. E. Robertson. Private communication.

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FIG. 1. Correlation of the isotopic rate ratio with the difference between the polarizabilities of the attacking nucleophile and the leaving group. Open circles—This work; closed circles—earlier work. Circles refer to: Solvolysis in water of: 1, CH₃L; 2, CH₃Br; 3, CH₃CI; 4, CH₃ONO₂; 5, CH₃OSO₂CH₃; 6, CH₃OSO₂C₆H₄CH₃; 7, (CH₃O)₂SO₂; 8, CH₃I + C₅H₅N in C₆H₆ solvent; attack of $S_2O_3^{-2}$ in 50% v/v ethanol-water on 9, CH₃Br; 10, CH₃I; 11, CH₃OSO₂C₆H₄CH₃; 12, CH₃OSO₂CH₃.

ture, although a closely related reaction to No. 8 of Fig. 1 has been investigated (14). As the 12%effect found with methyl- d_3 p-toluensulfonate is the largest of this type observed to date, an attempt to determine its temperature dependence was made. The results are given in Table III. Although the rate ratios are not precise enough to separate the isotope effect into its enthalpic and entropic contributions, it is clear that the rate ratio is not markedly dependent on temperature so that no serious error in the correlation plot is likely to arise from this source. Robertson et al. (15) have suggested that the relation between these secondary isotope effects and temperature may be a further means of distinguishing between $S_N 1$ and $S_N 2$ mechanisms. Arguing from the theoretical treatment of Wolfsberg and Stern (16), they suggested that temperature-independent isotope effects are more likely to occur in an S_N2 reaction than in an S_N reaction. As far as the results in Table III show no clear change with temperature, they agree with Robertson's proposal.

Activation Parameters

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Calculation of activation parameters from the rate constants would yield values which were correct only for one particular sodium thiosulfate concentration. To obtain true parameters, it is necessary to use k_2/α . Conductivity measurements were carried out using the procedure

TABLE III	
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Secondary deuterium isotope effect for the reaction of sodium thiosulfate with methyl *p*-toluenesulfate in 50% v/v ethanol-water

		$10^4 k_{\rm H}$	$10^{4}k_{\rm p}$	
Temperature (°C)	No. runs	(1 mole	$k_{\rm H}/k_{\rm D}*$	
14.95	3	92.7	84.7	1.095
19.98	3	150.3	138.2	1.09
25.00	3	231.2	205.8	1.12
29.98	3	364.7	325.1	1.12
35.02	3	562.1	512.4	1.10
40.02	4	812.3	743.2	1.09

*Standard error in each ratio is 0.01.

described by Bevan and Monk (11) to determine the fraction of sodium thiosulfate, α , which was present in the 50% ethanol-water solution as free thiosulfate ion at temperatures between 20° and 40 °C.

For the system

$$NaS_2O_3]^- \rightleftharpoons Na^+ + [S_2O_3]^2^-$$

the dissociation constant K_{diss} is related to α by the expression

$$K_{\rm diss} = \frac{\alpha^2 C \cdot f_{\rm S_2O_3}^{2-1}}{(1-\alpha)}$$

where C is the stoichiometric sodium thiosulfate concentration and $f_{[5_2O_3]}^{2-}$ is the activity coefficient of the thiosulfate ion. Table IV shows the average values of K_{diss} obtained at the various temperatures using solutions of concentration less than $10^{-3} M$, together with those of α calculated for the actual reaction conditions of the rates quoted in Table III. Bevan and Monk (11) measured K_{diss} for sodium thiosulfate at 25 °C and obtained a value of 1.45×10^{-2} , about 10% lower than our result.

When the apparent rate constants are divided by α , the true second order rate constants, i.e.,

TABLE IV

C _{diss}	values	and	α	tor	the	reaction	conditions

$10^2 K_{d iss}(mole l^{-1})$	α
4.46 3.59 2.21 1.62 1.305	0.847 0.818 0.736 0.673 0.625
	$ \begin{array}{r} 10^2 K_{diss}(molel^{-1}) \\ 4.46 \\ 3.59 \\ 2.21 \\ 1.62 \\ 1.305 \\ \\ \end{array} $

*Obtained by extrapolation.

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-1.0

-1.1

-1.2

those which do not change with change of the sodium thiosulfate concentration, are obtained. Figure 2 shows plots of $k_{\rm H}/\alpha$ and $k_{\rm D}/\alpha$ vs. $10^3/T$, for methyl and methyl- d_3 *p*-toluenesulfonate: from which the following true activation parameters were obtained by least squares computations:

$$CH_3OTs \Delta H_H^{\ddagger} = 12.6_5 \pm 0.07 \text{ kcal} \cdot \text{mole}^{-1}$$

$$\Delta S_{\rm H}^{*} = -22.7_6 \pm 0.25 \, {\rm cal \cdot mole^{-1}}$$

$$\cdot deg^{-1}$$

$$CD_3OTs \Delta H_D^{\pm} = 12.6_4 \pm 0.13 \text{ kcal} \cdot \text{mole}^{-1}$$

 $\Delta S_D^{\pm} = -23.02 \pm 0.4_4 \text{ cal} \cdot \text{mole}^{-1}$

Hammett et al. (17, 18) determined apparent activation parameters for several Bunte salt reactions, one of which was re-determined by Bevan and Monk (11) with magnesium thiosulfate as reagent, from which true activation parameters were calculated using k_2/α values. It is now possible to recalculate Hammett's results (17, 18) with k_2/α values using our conductivity measurements to calculate the values of α for the reaction conditions used by Hammett. These revised activation parameters, recorded in Table V, were obtained graphically since rate constants are available at only three temperatures in most cases. The temperature range 12.5° to 37.5° was used, except for methyl bromide for which two, at 10° and 20° were used.

The changes in enthalpy and entropy of activation with change in alkyl group remain almost the same as those originally reported by Hammett et al. (17, 18), but the absolute



constants for the reactions between methyl p-toluenesulfonate (1) and methyl- d_3 p-toluenesulfonate (2) and thiosulfate ions in 50% v/v ethanol-water solvent.

values are markedly different (compare with the figures quoted by Streitwieser (19)). These reactions are now seen to be characterized by low enthalpies of activation which are balanced by large negative entropies of activation. The recalculated values are qualitatively very similar to those for Menschutkin reactions in nitro-

TABLE V

Activation parameters for the attack of thiosulfate ion on alkyl esters in 50% v/v ethanol-water solvent*

Compound	ΔH^{\ddagger} (kcal·mole ⁻¹)	ΔS^{\ddagger} (cal·mole ⁻¹ ·deg ⁻¹)
CH ₃ Br	8.5 ± 1	-39 ± 3
C_2H_5Br	11.6	- 32
n-C ₃ H ₇ Br	11.1	- 35
n-C ₃ H ₇ Br [†]	17.5	14
iso-C ₃ H ₇ Br	13.0	- 34
iso-C ₄ H ₉ Br	13.4	34
CH ₃ OSO ₂ C ₆ H ₄ CH ₃ ‡	12.6	-22.8

*Original data from Hammett (17, 18), except as noted. Errors are probably less than one unit in ΔH^+ and two units in ΔS^+ , except for methyl bromide. †Using MgS₂O₃ (12), ‡This work.

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[•]deg⁻¹

benzene and benzene solvent (19). The low enthalpies of activation are to be expected from a large polarizable nucleophile such as the thiosulfate ion, since the energy required to place the electrons into a bond forming position would be small. Negative entropies of activation are characteristic of S_N2 reactions where two entities in the initial stage are merging into one in the transition state. However, the size of the parameters in these Bunte salt reactions requires further discussion. The doubly charged thiosulfate ion is strongly and preferentially solvated by water molecules when dissolved in 50% aqueous ethanol. Concentrated solutions separate into two immiscible layers. On the other hand alkyl compounds will not be expected to be nearly as efficient in solvent sorting until the bromine takes on a fractional negative charge in the transition state. This fractional negative charge has been transferred from the thiosulfate ion which still carries more than one unit of negative charge. Thus, the amount of solvent sorting may well be increased in the transition state relative to the initial state, which would introduce another negative contribution to the entropy of activation.

Experimental

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Materials Ethyl-1,1,d₂ bromide (99.5% isotopic purity) was supplied by Merck, Sharp and Dohme Ltd., and methyl-d3 iodide (99.5%) by Stohler Isotope Chemicals. The normal compounds were reagent grade chemicals which were dried and fractionally distilled before use.

Methyl- d_3 methanesulfonate was prepared by reaction of silver methanesulfonate (1 g) in pure acetonitrile (40 ml) with methyl- d_3 iodide (0.31 ml) at 50° for 8 h. The suspension was filtered to remove silver iodide and the solvent was removed under vacuum. Recovery of the silver iodide showed that the reaction had gone to completion. The product, after purification by distillation under reduced pressure, was obtained in about 75% yield.

Methyl- d_3 p-toluenesulfonate was prepared by a similar procedure. The protium analogues were purchased from Eastman Organic Chemicals.

The solvent was prepared and analyzed as described previously (1).

Kinetic Methods

The method used was that described in Part I of this series (1). The initial concentration of the ethyl bromides was 0.020-0.025 M. For the ethyl compounds the thiosulfate concentration was initially about 0.05 M (except for the runs quoted in Table I) and for the methyl compounds about 0.02 M.

Conductance Measurements

The conductance measurements were made with a Wayne Kerr Universal Bridge B221 and stirred cells, which were the cells used by Robertson et al. (15) for ethanol-water mixtures. The dissociation constants of the ion pair (K) and the degrees of dissociation (α) were calculated by the method described by Bevan and Monk (11, 12).

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