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Sulfur Isotope Effects in Substitution Reactions of Trimethylsulfonium Ion[1]

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Abstract: Sulfur isotope effects were determined for the S_N2 reactions in ethanol at 60 °C of trimethylsulfonium ion with bromide, thiophenoxide, ethoxide, and phenoxide. The effects were 1.36, 1.20, 0.96, and 0.96%, respectively. The isotope effect with ethoxide in ethanol decreased upon addition of dimethyl sulfoxide. The decrease was almost linear with mole percent dimethyl sulfoxide, reaching a value of 0.35% at 65% dimethyl sulfoxide. These results suggest that the basicity of the attacking nucleophile is the most important factor in determining the extent of carbon–sulfur cleavage in the transition state.

The effect on transition-state structure of changes in reactant structure or reaction conditions is one of the central problems of physical organic chemistry. Two main theoretical approaches to this problem are currently in use: the Hammond postulate,[2] which is based on the idea that species of similar energy should have similar electronic structures, and the Swain–Thornton rule,[3] which considers the effects of perturbations on the normal modes of the transition state. Both theories predict that changing to a more reactive nucleophile in an S_N2 reaction will give a more reactant-like transition state.

Difficulty in making unambiguous predictions arises

Table I. Sulfur Isotope Effects in the Reactions of Various Nucleophiles with Trimethylsulfonium Ion in Ethanol at 59.8 °C[a]

Nucleophile	No. of runs	$(k_{32}/k_{34} - 1) \times 100$[b]	95% conf limit
Br^-	5	1.36 ± 0.03	0.08
PhS^-	3	1.20 ± 0.01	0.06
PhO^-	3	1.04 ± 0.03 (0.96[c])	0.14
EtO^-	4	0.96 ± 0.02	0.06

[a] ±0.1 °C. [b] % sulfur isotope effect, with standard deviation of the mean. [c] Corrected for 20% reaction with bromide ion, assuming $1.04 = 0.20\,(1.36) + 0.80x$, where x is the true isotope effect for reaction with phenoxide.

Table II. The Rates of Reaction of Trimethylsulfonium Ion with Sodium Ethoxide in Mixtures of Dimethyl Sulfoxide and Ethanol at 60 °C[a]

Mol % DMSO	$k_2 \times 10^3$, $M^{-1}\,s^{-1}$	Mol % DMSO	$k_2 \times 10^3$, $M^{-1}\,s^{-1}$
0	2.90 ± 0.12[b]	55	9.73 ± 0.55
17	4.38 ± 0.10	65	14.8 ± 0.1[c]
35	5.67 ± 0.23	77	31.1 ± 0.5

[a] Temperature control to ±0.1 °C. [b] Each figure is the mean of three or four runs, with standard deviation of the mean. [c] Two runs only.

from uncertainty over the meaning of "more reactive nucleophile". Nucleophilicities, as measured by rates, are not invariant with substrate structure and solvent. Thornton suggests that the electron-releasing ability of the nucleophile, as measured by its basicity, is the appropriate quantity,[3] while Swain, Kuhn, and Schowen[4] consider that electron-releasing ability should vary inversely with ability as a leaving group. The present work was undertaken to examine the effects of nucleophilicity and basicity on transition-state structure in SN2 reactions of trimethylsulfonium ion.

Secondary α-deuterium isotope effects for the reaction of trimethylsulfonium ion with three nucleophiles have been reported by Robertson and Wu.[5] The effects run phenoxide > ethoxide > thiophenoxide, the last of the nucleophiles giving an inverse effect of $k_H/k_D = 0.91$. Interpretation of this order is rendered uncertain by the fact that another secondary isotope effect, that from the deuterium in the departing dimethylsulfonium group, may also contribute to the observed effect.

Our initial effort involved determination of the $^{32}S/^{34}S$ isotope effects for reaction of trimethylsulfonium ion with the same three nucleophiles as Robertson and Wu used, plus bromide ion. Rough kinetic studies were done to determine the proper reaction time for 5% or less of reaction, and the isotope effect determined by comparing the isotope ratios of the evolved dimethyl sulfide from 5 to 100% reaction. The thiophenoxide reaction was too fast for this technique, so that a nucleophile concentration 5% of that of the sulfonium salt was used to stop the reaction at the desired degree of completion. The results are shown in Table I.

The isotope effects are of a reasonable size compared with literature values for related reactions. The SN2 reactions of substituted benzyldimethylsulfonium ions with hydroxide ion give sulfur isotope effects in the range of 0.82–0.96%,[6] while SN1 solvolysis of *tert*-butyldimethylsulfonium ion occurs with sulfur isotope effects of 1.8% in water[7] and 1.0% in ethanol.[8a]

The source of the trends in Table I is not immediately obvious. The isotope effects increase roughly with increasing nucleophilicity or decreasing basicity. Decreasing the reactivity of the reagent is expected to give a more productlike transition state.[2,3]

The mass of the nucleophile could also influence the isotope effect. The heavier the nucleophile, the more the mass of sulfur will contribute to the reduced mass for the symmetric stretch. The resulting increase in isotopic sensitivity of the symmetric stretch would, however, *decrease* the isotope effect, by canceling out a greater fraction of the zero-point energy difference between the isotopic reactants. Such a trend is contrary to the facts, and cannot be a controlling factor. It is highly unlikely that bending modes of the transition state would contribute significantly, for the X–C–S bend will be of very low frequency, and the H–C–S bends will be virtually insensitive to isotopic substitution in sulfur. Model calculations on elimination reactions of sulfonium salts show the sulfur isotope effect to be unchanged by changes in H–C–S bending force constants.[8b]

Finally, the strength of the full carbon–nucleophile bond is relevant. If a given fractional decrease in the carbon–sulfur bond strength is accompanied by a proportionate increase in the carbon–nucleophile bond strength, then a nucleophile capable of forming stronger bonds will give a tighter transition state with a larger isotopic zero point energy difference for a given degree of carbon–sulfur bond cleavage. By the same line of reasoning as above, this leads to the prediction that the isotope effects should run $Br > PhS^- > EtO^- \sim PhO^-$ (the order of increasing C–X bond strength), which is in accord with the facts.

The two explanations consistent with the facts, then, are that decreasing basicity of the reagent leads to more C–S bond rupture, or that decreasing strength of the C–X bond results in a looser transition state and a higher isotope effect even in the absence of changes in the C–S bond strength. In order to distinguish between these two factors, we chose to vary the basicity of the nucleophile while keeping the nucleophilic atom constant. The basicities of hydroxide ion in water and alkoxide ions in alcohols are known to be increased by the addition of dimethyl sulfoxide,[9,10] and this fact has been used to vary systematically the basicity of the reagent in elimination reactions of 2-phenylethyldimethylsulfonium ion with hydroxide ion in mixtures of water and dimethyl sulfoxide.[11,12] In that case the rate increased, the sulfur isotope effect decreased, and the β-deuterium isotope effect went through a maximum as the concentration of dimethyl sulfoxide increased. These results were interpreted as indicating more reactantlike transition states in the more basic media.

The reaction of trimethylsulfonium ion with ethoxide ion in ethanol is likewise accelerated by the addition of dimethyl sulfoxide, though to a relatively modest extent, as shown by the rate constants in Table II. Sulfur isotope effects for this reaction were determined by combusting to sulfur dioxide the dimethyl sulfide from a known extent of reaction. The sulfur isotope ratio for this sulfur dioxide was then compared to that of sulfur dioxide from combustion of the original sulfonium salt, and the Stevens–Attree[13] formula used to calculate the isotope effects when the extent of reaction exceeded 5%. The results are given in Table III.

First, the difference in the technique for determining the isotope effects seems to occasion no systematic differences in results, for the isotope effect in pure ethanol is the same, well within experimental error, as that obtained by determining isotope ratios on dimethyl sulfide (Table I). Second, the sulfur isotope effect clearly decreases as the concentration of dimethyl sulfoxide in the medium increases.

The results show that increasing the basicity of the nucleophile leads to a more reactantlike transition state. The strength of the carbon–nucleophile bond in the product can-

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Table III. Sulfur Isotope Effects in the Reactions of Ethoxide Ion with Trimethylsulfonium Bromide in Mixtures of Ethanol and Dimethyl Sulfoxide at 60 °C[a]

Mol % DMSO	No. of runs	$(k_{32}/k_{34} - 1) \times 100^{b}$	95% conf limit
0	9^{c}	0.95 ± 0.03	0.07
17	4^{d}	0.75 ± 0.04	0.13
25	4^{e}	0.71 ± 0.08	0.25
35	2^{f}	0.66 ± 0.08^{i}	
55	3^{g}	0.40 ± 0.03	0.13
65	2^{h}	0.35 ± 0.04^{i}	

[a] ±0.1 °C. [b] % sulfur isotope effect, with standard deviation of the mean. [c] Runs of 5, 10, and 20% completion. Four runs utilized multiple scanning of m/e 64 and 66, rather than dual collection. [d] Runs of 5, 10, and 20% completion. [e] Runs of 5 and 10% completion. [f] Runs of 5 and 20% completion. [g] Runs of 5% completion only. [h] Runs of 10 and 20% completion. [i] Average deviation.

not be a major factor, for the product is identical in all of the solvent mixtures. The results are in agreement with predictions of the Hammond postulate[2] and the Swain–Thornton rule,[3] and support Thornton's contention that basicity is the most appropriate measure of the electron-releasing ability of a nucleophile.[3]

From the results with bromide and thiophenoxide ions vs. oxygen anions, it is evident that basicity is more important than nucleophilic reactivity in discussing effects on transition-state structure. A similar observation was made by Grimsrud and Taylor,[14] who found that sulfur nucleophiles gave larger chlorine isotope effects than oxygen nucleophiles in SN2 reactions of *p*-nitrobenzyl and *n*-butyl chlorides. They argued that the sulfur nucleophiles react faster because they are more easily desolvated but that, once desolvation is accomplished, the oxygen nucleophiles are actually more strongly nucleophilic. This hypothesis is entirely consistent with the dependence of transition-state structure on the basicity of the nucleophile. Ease of desolvation of the base should not be a significant factor in either kinetic or equilibrium basicity, since the proton which neutralizes the base comes from the solvation shell of the base when the neutralization occurs in a protic solvent.

Against a simple dependence on equilibrium basicity stands the fact that the sulfur isotope effects with ethoxide and phenoxide are the same within experimental error (Table I). We must remember, however, that the effect of the nucleophile on transition-state structure is being exerted in a transition state having a partly formed nucleophile–carbon bond. Under such circumstances, the charge of the phenoxide ion may be so localized on oxygen that its effective basicity approaches that of ethoxide ion.

Experimental Section[15]

Trimethylsulfonium bromide was prepared by adding methyl bromide to a cold (0 °C) solution of dimethyl sulfide in absolute ethanol containing a little ether. After several hours at 0 °C, a solid separated. It was collected by suction filtration and recrystallized from absolute ethanol to give white crystals of mp 170–171 °C dec, lit.[16] 172 °C.

Solvents. Commercial absolute ethanol was further dried by refluxing over magnesium and a trace of iodine for 24 h, followed by fractionation.[17] The first 10% was discarded and the remainder tested for water content as described by Vogel.[17] Only batches containing less than 0.5% water were used. Dimethyl sulfoxide (Fisher A.R.) was allowed to stand over grade 5A Molecular Sieves (Linde) for several days and distilled from calcium hydride at reduced pressure. The distillate had mp 18–18.5 °C (lit.[18] 18.5 °C). Mixtures of ethanol and dimethyl sulfoxide were prepared by volume.

Base Solutions. Sodium metal was cleaned of surface oxide in xylene or hexane, washed in dry ethanol, and quickly transferred to a flask containing ethanol under dry nitrogen. The stock solution, made to be ca. 0.9 M, was standardized by titration with hydrochloric acid. The solution could be stored in the refrigerator under nitrogen in a flask sealed with a rubber serum cap for up to 2 weeks. Solutions for kinetic runs were prepared by diluting the stock solution with ethanol or ethanol and dimethyl sulfoxide. Phenoxide solutions were prepared by adding recrystallized (hexane–benzene) and sublimed phenol (two to three times the amount of ethoxide) to ethoxide solution of the desired concentrations. Thiophenoxide solutions were prepared in the same manner from redistilled thiophenol.

Kinetics. Concentrations were used such that the final solution would be 0.04 M in trimethylsulfonium bromide and 0.05–0.08 M in base. The sulfonium salt in ethanol or ethanol plus an appropriate volume of dimethyl sulfoxide and the base solution in ethanol were equilibrated separately in a constant-temperature bath. The solutions were then thoroughly mixed and the reaction flask was closed by a rubber septum. An aliquot was taken immediately with a calibrated syringe, and subsequent aliquots were taken at appropriate intervals so as to give about a dozen points covering 60–80% reaction. Titration was performed by quenching the aliquot in a 10–15-fold excess of water and titrating with hydrochloric acid, using methyl red, phenolphthalein, or bromocresol green (the latter for the thiophenoxide reactions) as indicators.

Reactions for Isotope Effect Determinations. Trimethylsulfonium bromide solutions and base solutions were prepared and mixed as in the kinetic runs. The final solution (50 ml total except for the runs in ethanol–dimethyl sulfoxide, where it was 160 ml total) was 0.04 M in sulfonium salt. The solution was 0.05–0.08 M in base except in the thiophenoxide runs, where an insufficiency of base (<5% of the molar amount of sulfonium salt) was used. One neck of the reaction flask was fitted with a fritted glass bubbler connected to a nitrogen tank, and another neck was fitted with a water-cooled condenser. The condenser was connected to an ice–salt trap (only for the runs in ethanol–dimethyl sulfoxide) and a calcium chloride drying tube. To the outlet of the drying tube was connected a coil trap immersed in liquid nitrogen. After mixing of the base and sulfonium–salt solutions, the reaction was allowed to run to <5% completion. It was then quenched with 70 ml of cold water, and a stream of nitrogen was bubbled through the flask for 2 h to carry the dimethyl sulfide into the liquid nitrogen trap.

A similar procedure was used to collect the dimethyl sulfide from 100% reaction. About 25 ml of reaction mixture with base in fivefold excess over sulfonium salt was heated for at least 10 half-lives at 70 °C and the dimethyl sulfide isolated as above.

Purification of Dimethyl Sulfide and Sulfur Dioxide. The sample in the collection trap was transferred to a vacuum line and pumped cautiously to remove liquid oxygen. The line was then evacuated to diffusion-pump pressure and the sample distilled into a liquid-nitrogen-cooled U-tube trap fitted with three-way stopcocks at each end. The stopcocks were closed and one end of the U tube connected to a helium tank and the other end to the inlet of a Varian-Aerograph A-90 gas chromatograph fitted with a 10-ft × 0.25-in. column of 20% Ucon HB 5100 on 60–80 mesh Chromosorb P at room temperature. The helium pressure was set to 14 psi and the stopcocks opened so as to sweep the sample onto the column. It was collected in a trap cooled with liquid nitrogen at the exit port.

Combustion of Trimethylsulfonium Bromide and Dimethyl Sulfide to Sulfur Dioxide. The apparatus was adapted from that described by Beuerman and Meloan.[19] A combustion tube of 15-in. × 1.25-in. stainless steel with fittings at each end connected to glass-to-metal seals was placed in a cylindrical Hoskins Electric Furnace type FD 303 A. A water cooling coil was placed just before the entrance to the furnace. The Pyrex end of the entry tube was sealed with a rubber septum. Several centimeters before the end was a T-joint for introduction of oxygen and the gaseous dimethyl sulfide samples. It contained a piece of tightly coiled wire gauze to prevent flashback during combustion[20] and was connected to a drying tube containing Ascarite. The Pyrex exit tube from the furnace was connected to a calcium chloride drying tube, a coil trap, a water-vapor trap cooled by liquid nitrogen, and an aspirator pump.

The furnace was switched on and allowed to reach operating temperature of 900–950 °C (ca. 45 min) with water flowing through the cooling coils. The sulfonium salt (ca. 0.3 mmol) was placed in a porcelain boat which was inserted in the entry tube at the end covered by the rubber septum. A steel wire through the septum permitted subsequent positioning of the boat. The aspirator was started and the system flushed for 15 min with oxygen at a rate of 15 ml/min. The traps were filled with liquid nitrogen and the sample boat pushed near and eventually into the furnace entrance. The water in the cooling coil was turned off to permit gradual heating of the sample. After 15 min the system was turned off and the sulfur dioxide trap removed.

Dimethyl sulfide was combusted in essentially the same way. The sample was contained in a liquid-nitrogen-cooled U-tube trap with a bypass which was inserted just after the Ascarite trap in the oxygen line. When the furnace reached operating temperature the liquid nitrogen was removed from the trap and the stopcocks turned so that the oxygen stream would pass through the trap and slowly carry the dimethyl sulfide into the furnace as the trap warmed up.

Isotope Ratio Determinations were performed on an Atlas CH-4 mass spectrometer equipped with dual Faraday cup collectors. The amplifier for the signal from the less-abundant isotope was a vibrating-reed electrometer. Samples from a given extent of reaction and from 100% reaction (in the case of sulfur dioxide, the 100% sample was from combustion of the original sulfonium salt) were introduced into the dual inlet system and the sample sizes adjusted to be the same within ±2%. In the earlier work (A. M. Katz) on the isotope effects with bromide, thiophenoxide, ethoxide, and phenoxide, the samples were measured as dimethyl sulfide (*m/e* 62 and 64). In the later work (R. Hargreaves) on the isotope effects with ethoxide in mixtures of ethanol and dimethyl sulfoxide, the samples were measured as sulfur dioxide (*m/e* 64 and 66). The 100% and *X*% samples were compared four or five times and the average taken for each isotope effect determination.

Control Experiments. In the reactions of trimethylsulfonium bromide with thiophenoxide and ethoxide <5% of the trimethylsulfonium ion reacted with bromide ion to give methyl bromide. In the reaction with phenoxide, however, methyl bromide constituted approximately 20% of the product. The observed isotope effect ($\mathrm{IE}_{\mathrm{obsd}}$) was then corrected by means of the relation $\mathrm{IE}_{\mathrm{obsd}} = 0.80\,(\mathrm{IE}_{\mathrm{corr}}) + 0.20\,(\mathrm{IE}_{\mathrm{Br^-\,reaction}})$. Trimethylsulfonium bromide and thiophenol do not react under the conditions employed for reaction with thiophenoxide. The mass spectra of all samples were scanned and any samples containing significant impurities in the *m/e* 12–98 region were rejected.

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Alkaloids of *Delphinium staphisagria*. The Structure and Stereochemistry of Delphisine, Neoline, Chasmanine, and Homochasmanine

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Abstract: A new alkaloid, delphisine, has been isolated from the seeds of *Delphinium staphisagria* by a combination of pH extractions and chromatographic techniques. Chemical and spectral studies have suggested that it is a member of the aconitine-type alkaloids. An x-ray crystal structure determination of its hydrochloride confirmed it to be an aconitine-type alkaloid, with 1α-hydroxyl, 6α-methoxyl, 8β-acetate, 14α-acetate, 16β-methoxyl, 18-methoxyl, and *N*-ethyl substituents. The space group is $P2_12_12_1$, $a = 13.866$ (1), $b = 22.27$ (1), $c = 9.098$ (1) Å. The final agreement residuals are $R = 0.0351$ and $R_w = 0.0400$, based on 2875 observed reflections. The absolute configuration of delphisine is shown to be 1*S*, 4*S*, 5*R*, 6*R*, 7*R*, 8*R*, 9*R*, 10*R*, 11*S*, 13*R*, 14*S*, 16*S*, 17*R*. Ring A was found to exist in the boat conformation, stabilized by intramolecular hydrogen bonding. Spectral studies showed that this conformation exists in solution as well, and suggested that the previously published structure of neoline is in error. Neoline was prepared from delphisine by several routes. Comparison of both neoline and delphisine with their 1-epimers showed that neoline must have a 1α-hydroxyl group. On the basis of other well-established chemical correlations, the structures of chasmanine and homochasmanine must also be revised to show a 1α substituent.

The seeds of *Delphinium staphisagria L.* on extraction with ligroin yield a substantial alkaloid fraction of which delphinine (**1**) is the major component.[1] Accompanying delphinine are smaller amounts of the dimeric alkaloid staphisine (**2**).[2,3] A careful reexamination of the amorphous fraction accumulated during the isolation of a large quantity of delphinine led to the isolation of a new diterpene alkaloid named delphisine (**3**);[4] mp 122–123 °C, $[\alpha]^{26}\mathrm{D}$ 7.1° (*c* 4.0, ethanol). In this paper we present the details of our chemical studies of this alkaloid[5] and its correlation with neoline.[6]

Isolation of Delphisine. The separation of the alkaloids present in the amorphous fraction depended primarily on differences in basicity. Staphisine (**2**), which is the major constituent of the amorphous fraction (~40%, after the removal of delphinine (**1**)), is very sensitive to heat and light. Long treatment (1 week or more) of staphisine on an active

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