Ethanolysis of (4,4′,4″-Trimethoxytriphenyl)methyl Ethyl Sulfide[1]

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Ethanolysis of (4,4′4″-trimethoxytriphenyl)methyl ethyl sulfide (1) was carried out under basic conditions in absolute ethanol at 100, 110, and 120 °C. Evidence is consistent with an S_N1 mechanism. Extrapolation to 25 °C gave a rate constant of about $2.6 \times 10^{-9}\ s^{-1}$. Comparison with an estimated value derived from literature data indicates that the thioethoxy group undergoes ionization at a rate about 10^{-14} that of chloride. Therefore, a general basis is provided for comparison of related solvolyses involving highly stabilized carbonium ion intermediates. This report comprises the first quantitative investigation of sulfide solvolysis in a nonacidic medium.

Although acidic solvolyses of thioethers and ethers are well known,[3] thioalkoxide and alkoxide anions are poor leaving groups in elimination or S_N reactions. There are a few literature examples[4] of cleavage or decomposition processes in sulfide chemistry, but as far as we are aware, no S_N1 solvolysis has been reported in which thioalkoxide is a leaving group. In connection with other work,[5] we have been interested in solvolytic displacement reactions of substrates which should form highly stabilized carbonium ions by departure of a relatively poor leaving group. This report comprises a study of the ethanolysis of (4,4′,4″-trimethoxytriphenyl)methyl ethyl sulfide (1) and a comparison of its rate with that of the corresponding chloride 6.

$(4\text{-}CH_3OC_6H_4)_3C\text{–}X$
1, $X = SC_2H_5$
2, $X = OH$
3, $X = OC_2H_5$
4, $X = SC_3H_7$
5, $X = H$
6, $X = Cl$

Results and Discussion

The substrate 1 was prepared by acid-catalyzed reaction of the corresponding triarylcarbinol (2) with ethanethiol and was characterized by spectroscopic and elemental analysis. Solvolysis in absolute ethanol could be monitored by integration of the methylene resonances in the NMR spectrum of ether–thioether mixtures isolated from reaction aliquots.

Early studies indicated the likelihood of complications arising from catalysis by traces of acid under the rather severe reaction conditions employed. Very erratic results were obtained in an attempted solvolysis of trityl ethyl sulfide in neutral ethanol, and no reaction occurred in basic solvent.[6] In preliminary "one point kinetics" runs with substrate 1, behavior in the absence of added base again appeared to be somewhat erratic. The extent of reaction increased with increasing sodium ethoxide concentration and leveled off to a constant percentage above 0.7 M base. (For example, after 21.5 h at 120 °C, the extents of the reactions found for solutions 0.0, 0.16, 0.25, 0.67, and 1.00 M in sodium ethoxide were 28.6, 32.9, 37.9, 55.5, and 56.0%.) The behavior observed is consistent with the reactions of Scheme I. In basic solution, the strongly nucleophilic thioethoxide ion accumulates as a reaction product. This should compete effectively with solvent in trapping a carbonium ion intermediate and returning it to starting material. At high base concentrations, essentially all of the carbonium ions formed will react with ethoxide to form product. Undoubtedly, a salt effect should also contribute to this rate enhancement by sodium ethoxide, and it is conceivable that the entire effect of base could be simply a salt effect. It is also possible that the ethoxide ion may affect the partitioning of an intermediate ion pair between product and starting material. We consider the latter two possibilities less likely. Salt effects by alkoxide are notably small.[7] We have found that another thioether substrate of similar reactivity, namely, 3-(thioethoxy)-*N*-methyl-4-azahomoadamantane, solvolyzes at a constant rate above 0.1 M base.[5] The carbonium ion from the latter system should have a more localized charge and so might reasonably be more subject to the salt and ion-pairing effects but less selective toward the softer nucleophile thioethoxide. In any event, the observed solvolysis rate at high base concentration should reflect the rate of ionization in that medium. Therefore, in order to avoid complications arising from either inadvertent acid catalysis or the expected complex kinetic form at intermediate base concentrations, subsequent kinetics were followed in solutions containing 0.8 to 1.0 M sodium ethoxide.

Scheme I

$$1 \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} (4\text{-}CH_3OC_6H_4)_3C^+ + {}^-SC_2H_5$$

$$(4\text{-}CH_3OC_6H_4)_3C^+ + {}^-OC_2H_5 \xrightarrow{k_2} 3$$

$$(4\text{-}CH_3OC_6H_4)_3C^+ + HOC_2H_5 \xrightarrow{k_3} 3 + H^+$$

$${}^-SC_2H_5 + H^+ \rightleftharpoons HSC_2H_5$$

Several lines of evidence confirm that the ethanolysis of 1 is indeed an S_N1 process. The kinetics runs, involving between five and eleven points over the first 1–3 half-lives at 100, 110, and 120 °C, followed satisfactory first-order kinetics. First-order dependence on substrate was confirmed by "one-point" experiments at 0.033 and 0.066 M substrate concentration; the extent of reaction in the two runs was identical (56.0 and 56.6%). It is clear from the preliminary solvolytic attempts with trityl ethyl sulfide that the reaction is subject to a large substituent effect, favored by electron release from the *p*-methoxy groups of 1. The behavior of the reaction with varied base concentration, as discussed above, is consistent with the S_N1 scheme shown, although a detailed kinetic study of the base dependence was not undertaken. The rate was also found to be sensitive to the ionizing power of the solvent. In methanol (ca. 1 M in $NaOCH_3$ at 100 °C), reaction occurred about 8.5 times as rapidly as in ethanol. The solvent effect corresponds to an *m* value of about unity.[8,9]

In an additional experiment supporting Scheme I, ethanolysis of 1 was run in the presence of 0.8 M sodium ethoxide and 0.03 M propanethiol (present in solution as $C_3H_7S^-$). The reaction mixture after 200 min contained reactant 1 (77.4%), ethyl ether 3 (8.3%), and propyl thioether 4 (14.3%). In a parallel experiment without propanethiol, 1 (80.0%) and 3 (20.0%) were present. Thus, the thiopropoxide anion diverted the course of the reaction by intercepting the intermediate carbonium ion without affecting the overall rate. An approximate competition factor k_{-1}/k_2 of about 30 may be derived from this experiment.

An S_N2 mechanism must be considered as an alternative possibility in light of the evidence of Fava and Miotti[11] that

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this course is followed in the reaction of (4,4′,4″-trinitrotriphenyl)methyl chloride with radiochloride and azide. An S_N2 mechanism appears to be inconsistent with either the limiting rate at higher ethoxide concentrations or the trapping observed with thiopropoxide. It also appears inconsistent with the substituent effect, since Fava and Miotti found that the S_N2 pathway was strongly favored by electron-withdrawing nitro substituents, whereas the present reaction requires the electron-releasing methoxy groups.

At long reaction times, small amounts of (4,4′,4″-trimethoxytriphenyl)methane (**5**) were found. This product may have been formed by hydride abstraction[12] by carbonium ion from ethanol or ethoxide ion or by a minor side reaction entailing homolytic cleavage.[13] The latter reaction course should not produce the major product **3**.

Observed rate constants are listed in Table I. Extrapolation to 25 °C gave a rate constant of 2.6×10^{-9} s^{-1}. Because of the lengthy extrapolation, the result is only approximate; a range of extrapolated rate constants from 1.0 to 8.2×10^{-9} s^{-1}, was found using values at the extremes of ±10% error limits at 100 and 120 °C. Nevertheless, the rate comparison below reveals such large differences that errors in the extrapolation or in the estimate given in the next paragraph become relatively unimportant.

Table I. Kinetic Results for Ethanolysis of $(4\text{-}CH_3OC_6H_4)_3CSC_2H_5$ (1)[a,b]

T, °C	rate,[c] s^{-1}
120	$11.6 \pm 0.55 \times 10^{-6}$
110	$5.46 \pm 0.36 \times 10^{-6}$
100	$2.84 \pm 0.26 \times 10^{-6}$
25[d]	2.6×10^{-9} [e]

[a] 0.8–1.0 M ethanolic $NaOC_2H_5$; 0.033 M substrate. [b] $\Delta H^{\ddagger} = 19.9 \pm 1.2$ kcal/mol; $\Delta S^{\ddagger} = -30.8 \pm 4.2$ eu. [c] Error units are standard deviations. [d] Extrapolated from runs at 100, 110, and 120 °C. [e] Error range $1.0\text{–}8.2 \times 10^{-9}$.

Comparable data are not available for solvolysis of (4,4′,4″-trimethoxytriphenyl)methyl derivatives with more traditional leaving groups. However, an estimate of the solvolysis rate for the chloride (**6**) may be made as follows. Reasonable linear free-energy correlations may be made between data for solvolysis of substituted trityl and other arylmethyl chlorides in 60% ether–40% ethanol[14] and $pK_R{}^+$ values for the corresponding carbonium ions.[15] The correlation is most consistent with a rate constant of about 900 s^{-1} for **6** at 25 °C in that solvent mixture. Trityl chloride solvolyzes about 350 times as fast in ethanol (extrapolated from lower temperatures[16]) as in the mixed solvent.[14] If a similar solvent effect applies to chloride **6**, we obtain an estimated rate constant of about 3×10^5 s^{-1} at 25 °C in ethanol. A similar correlation between solvolysis rates of substituted benzhydryl chlorides in ethanol[17] and $pK_R{}^+$ of the corresponding carbonium ions[15] predicts a solvolysis rate for **6** about 500-fold higher. Although it does not require estimation of a solvent effect, the latter figure may be less reliable, since it also overestimated the solvolysis rate of trityl chloride by a factor of 10.

Combination of the rate constant extrapolation from our data for sulfide **1** with that estimated for chloride **6** under similar conditions yields a sulfide to chloride rate ratio of roughly 1:10^{14} (or possibly as great as 10^{17}!). Although combined errors in this ratio are sizable, it nevertheless illustrates a great difference in reactivity and may serve as a useful semiquantitative estimate for sulfide–chloride rate comparisons.[5] Solvolysis of sulfides opens new possibilities for investigation of very readily formed cations by conventional methods.

Experimental Section

Commercial materials were used without purification except for ethanol (see kinetic procedures). Infrared spectra were obtained on a Beckman IR8 spectrophotometer and NMR spectra on a Varian T60-A instrument in $CDCl_3$. Elemental analyses were performed by Microtech Laboratories, Skokie, Ill., and Galbraith Laboratories Inc., Knoxville, Tenn. Melting points are uncorrected.

(4,4′,4″-Trimethoxytriphenyl)methanol (2). The synthesis reported by Deno[15a] et al. as modified by Mueller[12a] was employed. Magnesium metal (15.0 g, 0.62 mol) was added to a solution of *p*-bromoanisole (114.2 g, 0.61 mol) dissolved in THF (150 mL) (distilled from $LiAlH_4$). The mixture was stirred at reflux under N_2 for 3 h. Methyl anisate (35 g, 0.21 mol) in THF (70 mL) was added with stirring over 10 min without heating. After reflux was continued overnight, saturated ammonium chloride solution (100 mL) was added dropwise, followed by water (200 mL). Stirring was continued for another 40 min. After the layers were separated, the aqueous solution was extracted with ether. The combined organic portion was washed in succession with 5% HCl, 10% $NaHCO_3$, and water. Evaporation of the dried (Na_2SO_4) solution under reduced pressure produced a red oil which was crystallized from 90% ethanol. The solid was washed with hexane and dried: mp 76–78 °C (lit. mp 83.5–84 °C,[18] 81–82 °C[15a]); yield 48% (lit. yields 25%;[15a] 71%[12a]); IR ($CDCl_3$) 3600, 2700, 1610, 1500, 1295, 1245, 1030, 820 cm^{-1}; NMR δ 7.00 (aromatic, 12 H), 3.80 (s, OCH_3, 9 H), 2.85 (s, OH, 1 H).

(4,4′,4″-Trimethoxytriphenyl)methyl Ethyl Sulfide (1). Ethyl mercaptan (10 mL, 0.15 mol) and sulfuric acid (2 mL, 96%) were added to a solution of **2** (25 g, 0.071 mol) in anhydrous ether (120 mL). The mixture was stirred for about 1.5 days until the red color of the carbonium ion faded. Addition of 1 N NaOH (100 mL) followed by separation of layers, extraction of the aqueous layer with CH_2Cl_2, drying of the combined organic fraction (Na_2SO_4), and evaporation of solvent afforded a red solid. Recrystallization from 95% ethanol gave white crystals: mp 100.5–101 °C; yield 26.2 g (94%); IR (KBr) 2940, 2840, 1600, 1495, 1240, 1170, 1030, 810 cm^{-1}; NMR δ 7.1 (aromatic, 12 H), 3.75 (s, OCH_3), 2.17 (q, J = 7.3 Hz, SCH_2), 1.20 (t, J = 7.3 Hz, CH_3). Anal. Calcd for $C_{24}H_{26}O_3S$: C, 73.06; H, 6.64; S, 8.13. Found: C, 72.95; H, 6.73; S, 8.40.

(4,4′,4″-Trimethoxytriphenyl)methyl Ethyl Ether (3). Compound **2** (1.75 g, 0.005 mol) and one drop of concentrated H_2SO_4 were added to absolute ethanol (40 mL). After the orange solution was stirred for 1 day, ethanolic sodium ethoxide (10 mL, 0.9 M) was introduced. Ethanol was evaporated under reduced pressure followed by addition of water (50 mL). Repeated extraction with CH_2Cl_2, drying (Na_2SO_4), and evaporation of solvent produced a yellow oil (1.7 g, 90%). Chromatography on basic alumina with toluene afforded colorless oil which could only be crystallized readily by seeding with material which solidifed spontaneously about 1 year after isolation. Two recrystallizations from absolute ethanol afforded an analytical sample: mp 94–95 °C; IR (KBr) 2980, 2870, 1610, 1510, 1300, 1240, 1170, 1030, 810 cm^{-1}; NMR δ 7.1 (aromatic, 12 H), 3.70 (s, OCH_3), 3.13 (q, J = 7.0 Hz, OCH_2), 1.18 (t, J = 7.0 Hz, CH_3). Anal. Calcd for $C_{24}H_{26}O_4$: C, 76.16; H, 6.93. Found: C, 76.16; H, 7.13.

(4,4′,4″-Trimethoxytriphenyl)methyl *n*-Propyl Sulfide (4). Compound **2** (1.20 g; 0.0034 mol), *n*-propanethiol (2 mL) and 1 drop of concentrated H_2SO_4 were stirred for 2 h at room temperature. Aqueous sodium hydroxide (1 M, 20 mL) was added, and the layers were separated. Extraction of the inorganic layer with ether, followed by drying of the combined organic fraction (Na_2SO_4) and evaporation of solvent under vacuum, afforded yellow oil (1.4 g, 100%). Chromatography on basic alumina with toluene gave a colorless oil: NMR δ 7.1 (aromatic, 12 H), 2.5 (t, J = 7.0 Hz, SCH_2), 1.45 (m, CH_2), 0.85 (t, J = 7.0 Hz, CH_3).

Kinetic Procedure. Ethanol was purified according to Perrin[19] by refluxing with magnesium for several days and then distilling. Kinetic samples were prepared by placing the compound (typically 130 mg, 3.3×10^{-4} mol) in a pyrolysis tube and adding a titrated solution of fresh sodium ethoxide in ethanol (10 mL, ~0.8 N) under nitrogen to give a substrate concentration of 0.033 M. The reaction mixture was frozen in liquid nitrogen and sealed under vacuum. Kinetic runs under 100 °C were done in a glycerol bath and above 100 °C in a GLC oven. Workup involved adding the contents of the pyrolysis tube to 30 mL of water and extracting with CH_2Cl_2 (2 × 15 mL) and ether (2 × 15 mL). The combined organic layer was washed with saturated NaCl solution (1 × 15 mL) and dried with Na_2SO_4 (4 g) and $MgSO_4$ (4 g). After evaporation of solvent and removal of all volatile material by subjecting the sample to high vacuum for 24 h, the NMR spectrum was obtained in $CDCl_3$. Integrals of the methylene groups adjacent to sulfur and oxygen were used to calculate the extent of reaction.

Samples containing propyl mercaptan (25 mg; 3.3×10^{-4} mol) were worked up as above. The calculations were based on the middle methylene in the propyl group.

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Registry No.—**1**, 69897-69-4; **2**, 3010-81-9; **3**, 69897-70-7; **4**, 69897-71-8; **6**, 49757-42-8; *p*-bromoanisole, 104-92-7; methyl *p*-anisate, 121-98-2; ethyl mercaptan, 75-08-1; sodium ethoxide, 141-52-6; *n*-propanethiol, 107-03-9.

References and Notes

(1) Presented at the 175th National Meeting of the American Chemical Society, Anaheim, Calif., 1978, ORGN-166.

(2) From the Ph.D. Thesis of P.M.S., 1978.

(3) D. S. Tarbell and D. P. Harnish, *Chem. Rev.*, **49**, 1 (1951); G. A. Olah, D. H. O'Brien, and C. U. Pittman, *J. Am. Chem. Soc.*, **89**, 2996 (1967).

(4) T. J. Wallace, J. E. Hofmann, and A. Schriesheim, *J. Am. Chem. Soc.*, **85**, 2739 (1963).

(5) P. M. Starewicz, G. Breitweiser, E. A. Hill, and P. Kovacic, *Tetrahedron*, in press.

(6) In one run, 40% conversion to product was found within 6 days, but the extent of reaction increased to only 53% after 23 days. In another run, reaction to an extent varying between 23 and 52% was observed for samples heated for 4 days at 123 °C; no reaction was detected in the presence of either 0.03 or 0.6 M sodium ethoxide.

(7) C. A. Bunton, T. W. Del Pesco, A. M. Dunlop, and K.-U. Yang, *J. Org. Chem.*, **36**, 887 (1971).

(8) We acknowledge the assistance of Mr. Michael Markgraf in performing this experiment.

(9) An attempt was made to determine the solvent effect in aqueous ethanol. However, the substrate was not sufficiently soluble in 80% ethanol. The rate of reaction in 90% ethanol was very similar to that in absolute ethanol. We believe this is an example of a "drying" effect of the electrolyte on the mixed solvent;[8,10] selective solvation of ions by water effectively removes the water from the bulk of the solvent, leaving a medium comparable to the absolute ethanolic sodium ethoxide in ionizing power.

(10) G. R. Lucas and L. P. Hammett, *J. Am. Chem. Soc.*, **64**, 1928 (1942).

(11) U. Miotti and A. Fava, *J. Am. Chem. Soc.*, **88**, 4274 (1966).

(12) (a) W. J. Mueller, M. Sc. Thesis, University of Minnesota, 1966; (b) E. A. Hill and W. J. Mueller, *Tetrahedron Lett.*, 2565 (1968).

(13) M. H. Back and A. H. Sehon, *Can. J. Chem.*, **38**, 1076 (1960).

(14) A. C. Nixon and G. E. K. Branch, *J. Am. Chem. Soc.*, **58**, 492 (1936).

(15) (a) N. C. Deno, J. J. Jaruzelski, and A. Schriesheim, *J. Am. Chem. Soc.*, **77**, 3044 (1955); (b) N. C. Deno and A. Schriesheim, *ibid.*, **77**, 3051 (1955); (c) E. M. Arnett and R. D. Bushick, *ibid.*, **86**, 1564 (1964).

(16) C. G. Swain and A. Maclachlan, *J. Am. Chem. Soc.*, **82**, 6095 (1960).

(17) J. F. Norris and C. Banta, *J. Am. Chem. Soc.*, **50**, 1804 (1928); J. F. Norris and J. T. Blake, *ibid.*, **50**, 1808 (1928); E. D. Hughes, C. K. Ingold, and N. A. Taher, *J. Chem. Soc.*, 949 (1940).

(18) A. Baeyer and V. Villiger, *Chem. Ber.*, **35**, 1189 (1902).

(19) D. D. Perrin, W. L. Farmarego, and D. R. Perrin, "Purification of Laboratory Chemicals", Pergamon Press, London, 1966, p 156.

Multiparameter Optimization Procedure for the Analysis of Reaction Mechanistic Schemes. Solvolyses of Cyclopentyl *p*-Bromobenzenesulfonate

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Through the use of steady-state equations, the isotope rate effects and product yields for the solvolysis of cyclopentyl *p*-bromobenzenesulfonate and its α-*d*, cis-β-*d*, trans-β-*d*, and β-d_4 analogues in eight different ethanol–water, trifluoroethanol–water, and hexafluoroisopropyl alcohol–water solvents have been quantitatively fitted to a reaction mechanistic scheme involving two ion-pair intermediates. The number of adjustable mechanistic parameters is reduced by the assumption that the isotope effects on the various single steps of the mechanism are solvent independent and by the assumption that isotope effects on certain of the steps are identical. The simplex method was used to select the best values for the ion-pair partitioning ratios in each solvent and the best values for the isotope effects on the various steps of the mechanism. In general, the calculated results fit the experimental observations well within the expected experimental error. The single step isotope effects seem well-determined ("rugged") and are close to the values previously determined from observations on other secondary sulfonates. The secondary β-*d* effects on proton elimination from the tight ion pair suggest a twisted-envelope transition state structure. The mechanism will not fit satisfactorily unless significant fractions of ion-pair return are allowed in most of the solvents. The mechanism fits the results without the necessity of postulating nucleophilic solvation of the ion-pair intermediate. We believe that the approach used to fit the experimental observations to the reaction mechanistic scheme is novel and of general utility.

In earlier papers, α- and β-deuterium rate effects, product distributions, and the stereochemistry of elimination and substitution in the solvolysis of cyclopentyl *p*-bromobenzenesulfonate (I) in a series of solvents of varying nucleophilicity and polarity have been reported.[1] These results have been interpreted *qualitatively* and *semiquantitatively* in terms of a common mechanism involving two ion-pair intermediates. The influences of solvent changes on the isotope effects and product yields were rationalized on the basis of reasonable shifts in the relative rates of the various steps in the common mechanism, it being assumed that the isotope effects on the individual mechanistic steps were approximately solvent independent. In this paper, we apply a newly developed, versatile technique, which we believe is of general utility, to the *quantitative* fitting of all of these data to the proposed mechanism.

The general problem in the quantitative fitting of a reaction to a branched mechanistic scheme, such as that given below, is that in any solvent there are more unknowns than there are observable results which can be used to define them. With a given set of results, one then seeks to alter the system in some way which provides more information, for example, by a change in the solvent or by modification of the reactant with a substituent. However, since substituent and solvent changes perturb the free energies of reactants, intermediates, and transition states in a variety of ways that are difficult to account for, the relative rates of all of the single step processes of the reaction scheme change; in principle, the problem is not simplified, although linear free energy relationships can be used to give, for example, rate–product correlations.[2] However, isotopes constitute a class of substituents with properties uniquely favorable for the study of reaction mechanisms both from a theoretical and an operational standpoint.[3a]

Experience indicates that α- and β-deuterium rate effects in solvolytic reactions do not strongly depend on solvent change except when the change causes a shift in mechanism