

Reactions of Charged Substrates. 3. The Hydrolysis of (4-Methoxybenzyl)dimethylsulfonium Chloride

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At low concentrations (ca. 10^{-4} M), the hydrolysis of (4-methoxybenzyl)dimethylsulfonium chloride (1) proceeds smoothly to completion in H_2O or D_2O at 80 °C. The rate constants measured directly by UV or NMR methods match the rate constants obtained as the ordinate intercepts of plots of k_{obsd} vs $[NaN_3]$ or $[pyridine-d_5]$. As expected, the rate constants decrease with increasing ionic strength ($NaCl$ or $NaClO_4$, $\mu = 0-2$). There is a small solvent deuterium isotope effect, $k_H/k_D = 1.1$ at $\mu = 0$ and 1.7, and the α -deuterium secondary isotope effect is $k_H/k_D = 1.26$ per deuterium. At higher concentrations (10 mM), the hydrolysis does not go to completion, with the fraction of 1 remaining reaching plateau values that are stable. Plots of the fraction of 1 remaining vs the initial concentration of 1 extrapolate to zero. Running the reaction in the presence of either Hg^{+2} or Zn^{+2} drives the reaction to completion by removing SMe_2 as the Lewis complex. While these results are consistent with common leaving group suppression of hydrolysis, they are also consistent with the establishment of an equilibrium among the starting material and the product alcohol, SMe_2 , and hydronium ion. The suppression data are fitted to the equation for the equilibrium, and running the reaction in reverse gives the amount of 1 predicted by the equation. Reinterpretation of older data in light of the equilibrium, the results reported here, and results for the nucleophilic substitution reaction suggests that the mechanism of hydrolysis is S_N1 with no ion-dipole complex intermediate.

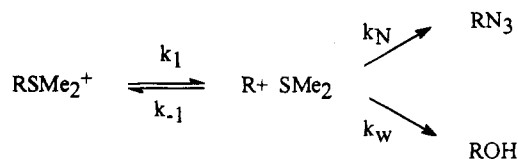
Introduction

The hydrolysis¹ and nucleophilic substitution²⁻⁵ reactions of sulfonium derivatives have been studied as prototypes of the Hughes–Ingold Type III–IV nucleophilic substitution reaction for charged substrates.³ As part of the evidence for his general ion-pair mechanism in borderline solvolysis reactions, in 1973 Sneen⁴ published kinetic and selectivity results for the hydrolysis and azide reactions of (4-methoxybenzyl)dimethylsulfonium (1) that he claimed provided evidence for an ion-dipole complex (IDC) intermediate; the alternative to the IDC mechanism is mixed S_N1/S_N2 (Scheme 1). Friedberger and Thornton⁵ studied the sulfur kinetic isotope effects (KIE) for hydrolysis of 1 and other substituted benzyl dimethylsulfonium (BDMS⁺) compounds. They suggested that hydrolysis occurs with solvent nucleophilic participation, and that an “ion-triplet sandwich” ($N_3^- \cdot R^+ \cdot SMe_2$) was an intermediate in the azide reaction.

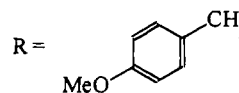
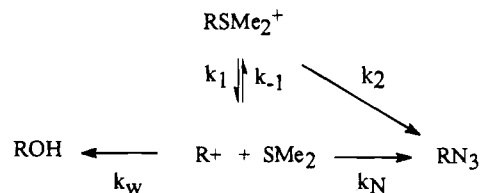
We have been studying the nucleophilic substitution reactions of 4-substituted benzylpyridiniums in water as part of a general program that has examined in some detail the mechanisms of the hydrolysis and substitution

Scheme 1

Sneen Ion-Dipole Complex Mechanism



Mixed S_N1/S_N2 Mechanism



[®] Abstract published in *Advance ACS Abstracts*, September 1, 1994.

(1) Kevill, D. N.; Anderson, S. W.; Ismail, N. H.; Fujimoto, E. K. In *Physical Organic Chemistry 1986*; Kobayashi, M., Ed.; Elsevier: Amsterdam, 1987; pp 311–320.

(2) Swain, C. G.; Kaiser, L. E. *J. Am. Chem. Soc.* **1958**, *80*, 4089–4092. Swain, C. G.; Kaiser, L. E.; Knee, T. E. *C. J. Am. Chem. Soc.* **1958**, *80*, 4092–4094. Swain, C. G.; Taylor, L. J. *J. Am. Chem. Soc.* **1962**, *84*, 2456–2457. Swain, C. G.; Rees, T.; Taylor, L. J. *J. Org. Chem.* **1963**, *28*, 2903. Swain, C. G.; Burrows, W. D.; Schowen, B. J. *J. Org. Chem.* **1968**, *33*, 2534–2536.

(3) Ingold, C. K. *Structure and Mechanism in Organic Chemistry*; Cornell University Press: Ithaca, 1953; pp 306–418.

(4) For reactions of 1: Sneen, R. A.; Felt, G. R.; Dickason, W. C. *J. Am. Chem. Soc.* **1973**, *95*, 638–639. For the ion-pair mechanism for neutral substrates: Sneen, R. A.; Larsen, J. W. *J. Am. Chem. Soc.* **1969**, *91*, 6031–6035. Sneen, R. A. *Acc. Chem. Res.* **1973**, *6*, 46–53.

(5) Friedberger, M. P.; Thornton, E. R. *J. Am. Chem. Soc.* **1976**, *98*, 2861–2865.

reactions of nicotinamide adenosine dinucleotide (NAD⁺).⁶ We found that the reaction of all 4-substituted benzyl-

(6) Johnson, R. W.; Marschner, T. M.; Oppenheimer, N. J. *J. Am. Chem. Soc.* **1988**, *110*, 2257–2263. Handlon, A. L.; Oppenheimer, N. J. *J. Org. Chem.* **1991**, *56*, 5009–5010. Schröder, S.; Buckley, N.; Oppenheimer, N. J.; Kollman, P. A. *J. Am. Chem. Soc.* **1992**, *114*, 8232–8238. Buckley, N.; Handlon, A. L.; Maltby, D.; Burlingame, A. L.; Oppenheimer, N. J., *J. Org. Chem.* **1994**, *59*, 3609–3615. Ta-Shma, R.; Oppenheimer, N. J., unpublished results. Buckley, N.; Oppenheimer, N. J., unpublished results.

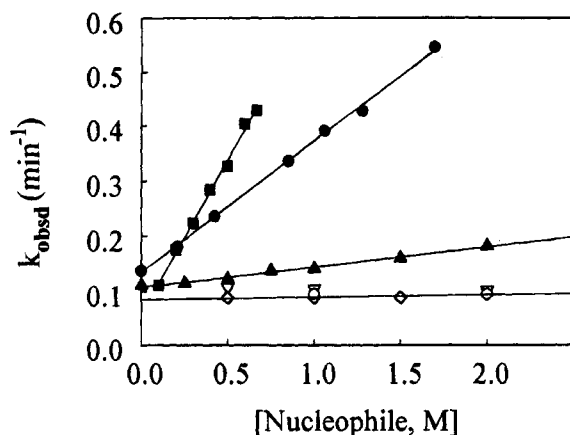


Figure 1. Plots of k_{obsd} (min^{-1}) vs [nucleophile] for the reactions of **1** with Na_2SO_3 (\blacksquare , $\mu = 2$ with Na_2SO_4), NaN_3 (\bullet , $\mu = 1.7$ with NaCl or NaClO_4), pyridine- d_5 (\blacktriangle , $\mu = 2$ with NaCl), ND_3 (\circ , no salt), NaCN (∇ , no salt), and NaOD (\diamond , $\mu = 2$ with NaCl) measured by NMR at 80°C in D_2O .⁹ The reaction with NaSCN and the kinetic technique have been reported.⁸

pyridiniums with azide is an $\text{S}_{\text{N}}2$ process, in contrast to the well-documented results of Katritzky⁷ that reaction of (4-methoxybenzyl)pyridiniums with neutral amines in chlorobenzene solvent is a borderline system; Katritzky has suggested that an IDC is an intermediate. Because of this disparity, we examined the reactions of **1** with various nucleophiles in solvent water.

We found that **1** reacted bimolecularly only with nucleophiles of intermediate hardness (N_3^- , SO_3^{2-} , SCN^- , pyridine- d_5) and not with either hard (OH^- , Cl^- , OCN^- , ND_3) or soft (CN^- , I^-) nucleophiles.^{8,9} While the full details of this study will be published elsewhere,⁹ we include here plots of k_{obsd} vs [nucleophile] for several of these reactions (Figure 1). The ordinate intercepts (k_1) were the same for reaction with N_3^- , SCN^- , and pyridine- d_5 either with ($k_1 = 0.110 \text{ min}^{-1}$, $\mu = 2$) or without ($k_1 = 0.150 \text{ min}^{-1}$) added salt to control ionic strength. (The reaction with SO_3^{2-} exhibits severe salt effects and the value of k_1 cannot be obtained easily from ordinate intercepts.) The selectivity data for reaction with azide, which will be published with the kinetic results,⁹ rule out an IDC mechanism and are discussed below. In contrast, on the basis of relative abundances in liquid secondary ion mass spectra (LSIMS) and on the results of semiempirical calculations, we found¹⁰ that the gas-phase dissociation of 4-Y-BDMS⁺ (Y = MeO, Me, H, Cl, and NO_2) is a clear-cut example of a classical Hammond and Hammett system that dissociates through an IDC.

Because of these disparate results, we felt it was imperative to establish the mechanism of hydrolysis for **1**. This task proved to be difficult, however, because of an equilibrium that is set up among starting material and products, which affects the kinetics and attempts to show common leaving group suppression (CLGS) of solvolysis. Despite the experimental difficulties encountered, the results obtained in this study and the results for the nucleophilic substitution reactions^{8,9} show that

the hydrolysis of **1** is an $\text{S}_{\text{N}}1$ reaction with no IDC intermediate. Kevill and co-workers¹¹ have recently reached the same conclusion independently.

Experimental Section

General. All chemicals and solvents were obtained from Aldrich and were used without further purification. UV kinetics were measured on a Hewlett-Packard 8452A UV-vis spectrophotometer with a thermostated cuvette holder. NMR kinetics were measured on a General Electric QE-300 NMR spectrometer with a variable temperature probe rated at $\pm 0.1^\circ\text{C}$. Tandem LSIMS were recorded under identical conditions in the positive ion mode on a 4-sector Kratos Concept II HH mass spectrometer fitted with an optically coupled 4% diode array detector on MS II.

Synthesis. **1** was routinely synthesized by mixing 1 equiv of 4-methoxybenzyl chloride and 1.1 equiv of SMe_2 in chloroform. The mixture was allowed to stand at ambient temperature, and the reaction was followed by TLC (silica, neat chloroform) until all chloride had disappeared. The chloroform solution was extracted with water, and the water layer was repeatedly extracted with chloroform and then with ether to give a water-white solution that was rotary evaporated to a clear glass under reduced pressure; extensive flashing with ethanol removed the remaining water to give a waxy white solid with >95% purity. The compound is extremely hygroscopic and was stored in a vacuum desiccator. Even with this precaution, over time the compound would turn milky; it could be purified easily by running through the extraction procedure. ¹H NMR: D_2O ($0 \delta = \text{TSP}$) δ 7.43 (d, $J = 8.6 \text{ Hz}$, 2H, aromatic AA'), 7.11 (d, $J = 8.6 \text{ Hz}$, 2H, aromatic BB'), 4.57 (s, 2H, CH_2), 3.88 (s, 3H, OMe), 2.77 (s, 6H, SMe_2). ¹³C NMR: $\text{DMSO}-d_6$ δ 160.34, 132.42, 114.94, 66.5, 55.40, 46.33, 23.32. Nontandem positive-ion LSIMS: m/z (%) 121.1 ($\text{M}^+ - \text{SMe}_2$, 100), 183.1 (M^+ , 25); m/z calcd 183.3. (Note that in tandem LSIMS the relative abundances are reversed for collisionally activated dissociation of M^+ in MSII.¹⁰)

UV Kinetics. Rate constants were measured in H_2O and D_2O with (NaCl or NaClO_4) and without exogenous salt added to control ionic strength by following the disappearance of substrate at $\lambda_{\text{max}} = 232 \text{ nm}$. Solvent was equilibrated in 1-cm cuvettes, 5–10 μL aliquots of **1** in the appropriate solvent were added and mixed, and data collection was begun immediately. The infinity value was obtained after 1 h.

During initial attempts to measure CLGS in the UV, we heated saturated solutions of SMe_2 in water in the cell holder. Two cuvettes shattered violently (caution! stench!) before we abandoned this attempt.

NMR Kinetics.⁸ Rate constants were measured using the following procedure. Solvent in a standard NMR tube was heated in the probe, withdrawn, and mixed with solid substrate; the tube was returned to the probe and shimmed as rapidly as possible. For runs in D_2O , t_0 was taken as the time of addition of substrate to solvent, and rate constants were measured by following the disappearance of one of the AB doublets in the aromatic region, which gave an internal standard with product alcohol. For suppression runs and for kinetics in 0–1.0 M ZnCl_2 , disappearance of the SMe_2 singlet (at 80°C , $\delta = 2.8 \text{ ppm}$ relative to HOD at 4.3 ppm) was followed, with t_0 taken as the time constant shims were obtained (usually within 1 min).

Closed Vial Experiments. Stock solutions of **1** were made in D_2O , with or without added salt, and serially diluted into 1.5 mL Teflon-capped, thick-walled reaction vials. Vials were overfilled to give convex meniscus and then capped with the extrusion of solvent, which assured that there was no void volume. Vials were heated at 80°C in a block for 40 min and chilled in an ice bath, and the extent of reaction was measured by NMR. The fraction of **1** remaining, $f = [\text{1}]/C_0$, was taken as the ratio of the integrated value of **1** divided by the sum of the integrated values for **1** and 4-methoxybenzyl alcohol.

(7) Reviewed in Katritzky, A. R.; Brycki, B. E. *Chem. Soc. Rev.* **1990**, 19, 83–105, and elsewhere. See also Katritzky, A.; Malhotra, N.; Ford, G. P.; Anders, E.; Tropsch, J. G. *J. Org. Chem.* **1991**, 56, 5039–5044.

(8) Buckley, N.; Oppenheimer, N. *J. J. Org. Chem.* **1994**, 59, 247–249.

(9) Buckley, N.; Oppenheimer, N. J., in preparation.

(10) Buckley, N.; Maltby, D.; Burlingame, A. L.; Oppenheimer, N. J., in preparation.

(11) Kevill, D. N.; Ismail, N. H. J.; D'Souza, M. J. *J. Org. Chem.*, submitted.

Table 1. First-Order Rate Constants k_1 (min^{-1}) at 80 °C for the Hydrolysis of 1 in H_2O and D_2O at Various Ionic Strengths

	$\text{D}_2\text{O}, \mu =$				$\text{H}_2\text{O}, \mu =$	
	0	1	1.7	2	0	1.7
UV	0.150 ± 0.003		$0.123 \pm 0.003^{a,b}$		0.165 ± 0.006	0.129 ± 0.007^a
NMR	0.150^c	$0.138^{a,d}$	$0.123^{a,b,d}$	$0.110^{a,d}$		
	0.149^e	—	—	$0.106^{a,e}$		

^a NaCl. ^b NaClO₄. ^c Intercept of plot in Figure 5 for the reaction in ZnCl₂. ^d Intercept from plot of k_{obsd} vs [NaN₃]. ^e Intercept from plot of k_{obsd} vs [pyridine-*d*₅].

Studies of the Back Reaction. Stock solutions of SMe_2 were made in the following way: a known volume of D_2O was pipetted into a screw-capped vial, which was tared. An aliquot of the volatile SMe_2 was added via syringe to the vial, which was capped and shaken repeatedly to give a cloudy solution. The vial was heated gently with a heat gun until a water-white solution resulted, at which point the vial was capped. After cooling to ambient temperature, the vial was weighed and the approximate concentration of SMe_2 was calculated. Several dilutions of this stock were made to a constant volume (0.75 mL) in D_2O solutions containing a single known concentration of 4-methoxybenzyl alcohol, which served as an internal standard. NMR spectra were recorded and the exact concentration of SMe_2 was determined by comparing the integrated value of the SMe_2 singlet with the MeO singlet of the alcohol. With the exact $[\text{SMe}_2]$ determined, this stock solution and stock solutions of 4-methoxybenzyl alcohol and DCl in D_2O were serially diluted into test tubes (2 mL total volume) and placed in the capped reaction vials as described above. After heating at 80 °C in a block for 40 min, vials were cooled in an ice bath and the extent of the return reaction was measured by NMR.

Isotope Effects. Solvent isotope effects were measured by the UV method. In our NMR study^{8,9} of the nucleophilic substitution reactions of 1, we found that the sulfonium methyl and benzyl methylene protons immediately exchanged for deuterons in the presence of either NaOD or ND₃. Rate constants could be obtained by measuring the disappearance of one of the AB doublets as described above. Reactions of 1 with NaOD and ND₃ are zero order in nucleophile (Figure 1). Therefore, the values of $k_{\text{H}}/k_{\text{D}}$ for the secondary α -deuterium isotope effect could be obtained from these rate constants. This was a fortuitous result.

Results

Kinetics and Activation Values. Rate constants for the hydrolysis of 1 in H_2O and D_2O measured by UV at 80 °C were the values of slopes obtained by linear regression from plots of $\ln [A_t - A_\infty]/[A_0 - A_\infty]$ vs time (Table 1);¹² rate constants calculated with the Guggenheim method had the same values. Plots were linear over 3–4 half-lives. Values are the averages \pm SE for 4–6 determinations. Rate constants were the same in the presence of NaCl or NaClO₄, which rules out a bimolecular reaction with Cl⁻. Rate constants (k_1) used to determine the activation values from an Eyring plot¹³ (Figure 2) were taken from ordinate intercepts of plots of pseudo-first-order rate constants vs [NaN₃] in the range 60–90 °C.⁹ The values are: $\Delta H^\ddagger = 27.7 \pm 1.0$ kcal/mol; $\Delta S^\ddagger = 7.1 \pm 1.0$ gibbs/mol; $\Delta G^\ddagger_{80^\circ\text{C}} = 25.2$ kcal/mol.

Suppression of Hydrolysis. At concentrations of ca. 10^{-4} M, the reaction goes smoothly to completion; UV samples were routinely analyzed by NMR to assure that a complete reaction had occurred. At "normal" NMR concentrations of ca. 10 mM, however, the reaction of 1 in D_2O did not go to completion and in initial experiments seemed to depend on the concentration of 1. This pattern was independent of the presence or absence of exogenous salt (NaCl or NaClO₄, Figure 3). When the

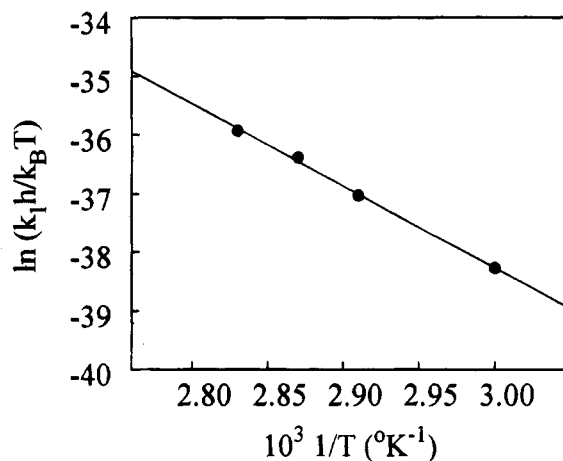


Figure 2. Eyring plot for the hydrolysis of 1. The values of k_1 were taken from the ordinate intercepts for the reaction of 1 with azide (from ref 9). The plot is linear ($r = 0.999$) and the activation values are: $\Delta H^\ddagger = 27.7 \pm 1.0$ kcal/mol; $\Delta S^\ddagger = +7.1 \pm 1.0$ gibbs/mol; $\Delta G^\ddagger_{80^\circ\text{C}} = 25.2$ kcal/mol.

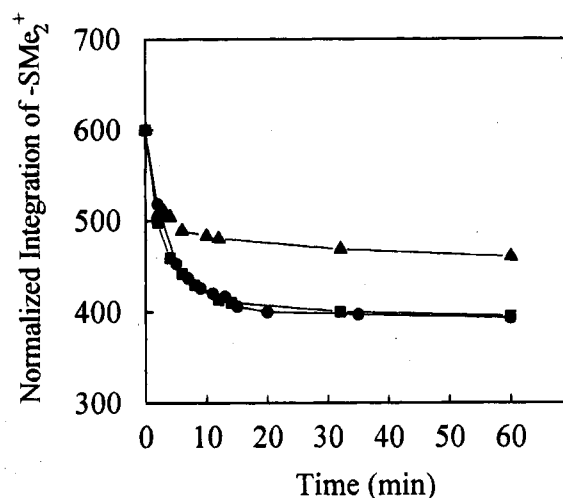


Figure 3. Plots of the normalized integrated SMe_2 signal for 1 at 80 °C in pure D_2O (●), $\mu = 1.7$ (NaCl, ■), and in pure D_2O saturated with SMe_2 and "cured" by heating at 80 °C (▲). Heating for several more hours causes no change in the 1 h value.

hydrolysis was run in solvent saturated with SMe_2 —"cured" to relieve pressure by heating at 80 °C for 20 min before adding 1 and heating in the probe of the NMR—the extent of reaction was less than without excess SMe_2 (Figure 3). The reaction did not merely slow down, however: it stopped completely.

Closed-Vial And Zn⁺² Experiments. Because of different void volumes and leaky caps, it was not possible to measure accurately the extent of reaction for equal concentrations of 1 in NMR tubes. When the reaction was run in sealed vials, however, results were reproducible. Data are the averages of duplicate determinations ($\pm 5\%$ SE) made on serial dilutions of two stock solutions with different initial concentrations; as a check, each stock solution was diluted to the same final

(12) Our value for 60 °C matches the value reported by Snee,⁴ and our 70 °C value matches closely Friedberger and Thornton's value⁵ for 69 °C. Kevill (Kevill, D. N., personal communication) found a value of $k_{\text{obsd}} = 0.148 \text{ min}^{-1}$ for the 80 °C point.

(13) Maskill, H. *The Physical Basis of Organic Chemistry*; Oxford University Press: New York, 1985; pp 247–249.

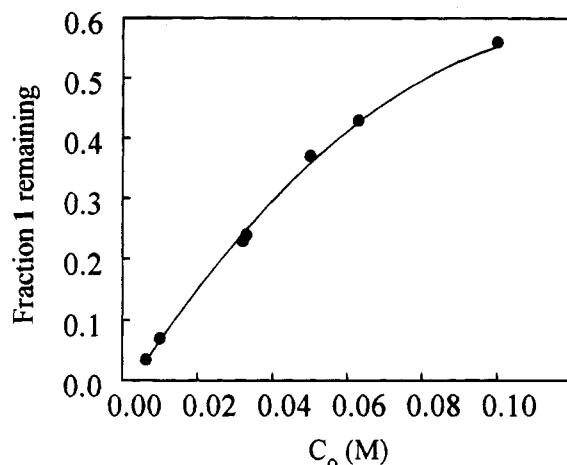


Figure 4. Plot of the fraction of **1** remaining vs the initial concentration of **1** (C_0) after heating various concentrations in sealed vials at 80 °C for 40 min. The points are averages of duplicate determinations for serial dilution of two initial concentrations, each of which was diluted to the same concentration (0.033 M) as an internal check on the method.

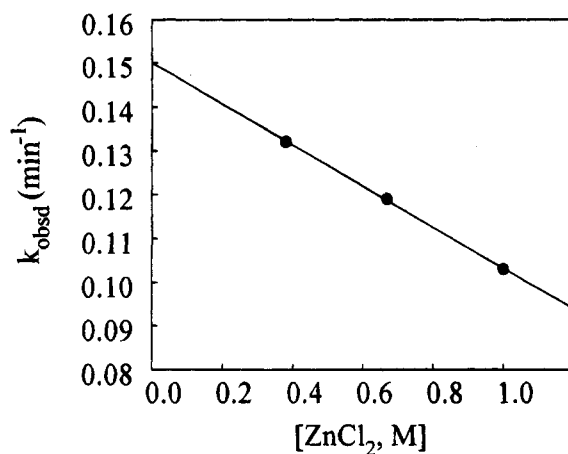


Figure 5. Plot of k_{obsd} vs $[\text{ZnCl}_2]$ for the hydrolysis of **1** at 80 °C. Points are the averages of three determinations (error bars within symbols). Plots of $\ln(A_t/A_0)$ vs t used to obtain k_{obsd} were linear over 3–4 half-lives. The plot is linear ($r = 0.9999$) and extrapolates to the value of k_{obsd} (0.150 min⁻¹) found for the hydrolysis of **1** in pure D₂O.

concentration (ca. 0.033 M). The extent of reaction depended on the initial concentration of **1** (Figure 4).¹⁴

Hydrolysis in the presence of either HgCl₂ or ZnCl₂ went smoothly to completion. For Zn⁺² reactions measured in the NMR, plots of $\ln(A_t/A_0)$ vs time were linear over 4 half-lives and gave the same rate constant at several initial concentrations of **1**. Rate constants were determined at three concentrations of ZnCl₂ (2–3 determinations, SE <±5%) and are plotted vs $[\text{ZnCl}_2]$ in Figure 5.

Isotope Effects. The solvent isotope effects were obtained as the ratios of the UV rate constants for reaction in H₂O and D₂O from Table 1; they are $k_{\text{H}}/k_{\text{D}} = 1.1$ for water alone and $\mu = 1.7$ (NaCl) at 80 °C. The α -deuterium secondary isotope effect $k_{\text{H}}/k_{\text{D}} = 1.26$ per deuterium was obtained from the values

(14) Note that benzylpyridiniums showed the same pattern of suppression, which was most severe for the 4-MeO compound. These data also fit an equation derived assuming the equilibrium among starting material and products. Addition of exogenous pyridines suppresses the reaction further. When the hydrolysis of several 4-MeO-benzylpyridiniums was run in 2 M DCl or D₂SO₄, conditions that would either protonate most of the liberated pyridine or cause the product alcohol to form the bis-ether [Quelet, R.; Allard, J. *Bull. Chem. Soc. Fr.* **1937**, 4, 1468–1471], good linear plots were obtained over 4–5 half-lives.

for the hydrolysis in pure D₂O (Table 1) and the value for the zero-order reaction of ND₃ in D₂O, 0.095 min⁻¹ (Figure 1), with no exogenous salt added at 80 °C.

Discussion

The plots of k_{obsd} vs $[\text{nucleophile}]$ (Figure 1) for the reaction of **1** with various nucleophiles show borderline behavior for all nucleophiles: the rates do not double with a doubling of nucleophile concentration, and there are non-zero ordinate intercepts. Sneen⁴ found a similar kinetic profile for **1** at 60 °C for the reaction of 0–0.12 M azide with no control of ionic strength and interpreted his results in terms of the IDC mechanism. Kinetics alone, however, are not sufficient to differentiate one mechanism from another. In his excellent analysis of the kinetics governing the ion-pair scheme for substitution reactions, Carpenter¹⁵ has pointed out that the presence of CLGS rules out an ion-pair or IDC as an intermediate.

During attempts to measure the rate constant for hydrolysis of **1** by NMR, we found that the reaction stopped completely at the relatively high concentrations of substrate needed for these experiments and that the extent of reaction was reduced in the presence of an excess of exogenous SME₂ (Figure 3). Results of the closed-vial experiments, which were run in a manner that kept SME₂ in solution, showed that the extent of reaction was a function of the initial concentration of **1** (Figure 4), and, presumably, of the concentration of SME₂ released upon hydrolysis. Running the reaction in the presence of either 0.1 M Hg⁺² or 0–1.0 M Zn⁺² at 80 °C drives it to completion by removing SME₂ as the Lewis complex. The plot of k_{obsd} vs $[\text{ZnCl}_2]$ shown in Figure 5 is linear and extrapolates to a value of $k_{\text{obsd}} = 0.150$ min⁻¹, the value of the rate constant in the absence of exogenous salt. These results are consistent with CLGS in the hydrolysis of **1**. The dilemma remains, however, that CLGS would be expected to slow but not stop the reaction.

An alternative to CLGS that is consistent with all these results is the establishment of the equilibrium $\text{RSME}_2^+ \rightleftharpoons \text{ROH} + \text{SME}_2 + \text{H}_3\text{O}^+$ during the course of the reaction. The equation for this equilibrium is $C_0^2 = K_{\text{eq}} f/(1-f)^3$, where C_0 is the initial concentration of **1** and f is the fraction remaining at equilibrium. When the data from Figure 4 were fitted to this equation with the Marquardt–Levenberg nonlinear least-squares algorithm, the plot in Figure 6 resulted ($K_{\text{eq}} = 0.00167 \pm 0.00002$, $X^2 = 1.4 \times 10^{-8}$). Clearly an equilibrium is established. When equal concentrations (C_P) of the alcohol, SME₂, and DCl were mixed and heated in sealed vials for 40 min, the exact amount of **1** predicted by the equation was obtained. For instance, for $C_P = 0.005$ M, $f = 0.05$, and for $C_P = 0.05$ M, $f = 0.38$. Holding the concentration of alcohol and DCl constant and increasing the concentration of SME₂ incrementally pushed the reaction to the left by the amounts predicted by the equation. Because of this equilibrium, it is not possible to measure CLGS in pure water.

There are literature precedents for both the reverse and forward reactions. Badet, *et al.*,¹⁶ found that treatment of (–)-(*R*)-2-octanol with a 10–20-fold excess of SME₂ and methanesulfonic acid in methylene chloride gave the active (2-octyl)dimethylsulfonium with up to

(15) Carpenter, B. K. *Determination of Organic Reaction Mechanisms*; John Wiley & Sons: New York, 1984; pp 40–51.

(16) Badet, B.; Jacob, L.; Julia, M. *Tetrahedron* **1980**, 37, 887–890.

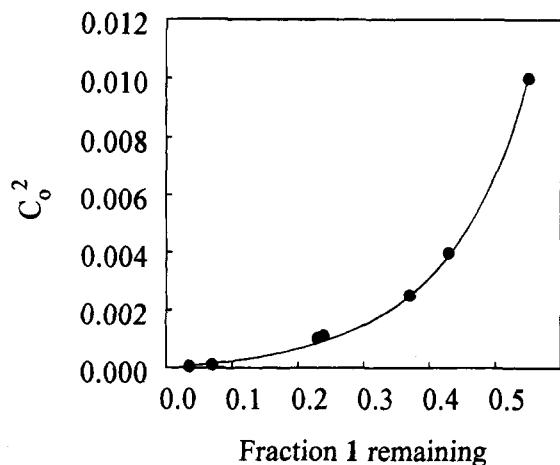


Figure 6. Plot of the square of the initial concentration of **1** (from Figure 4) vs the fraction remaining. The line is the fit of the equation $C_0^2 = K_{eq} f/(1-f)^3$, derived for the equilibrium $RSM_e_2^+ = ROH + SMe_2 + H_3O^+$, to the data by the Marquardt–Levenberg nonlinear least-squares algorithm: $K_{eq} = 0.00167 \pm 0.00002$, $X^2 = 1.4 \times 10^{-8}$.

88% inversion of configuration, presumably by direct displacement on the protonated alcohol (or a concerted general acid-catalyzed reaction). Because of the vast difference in solvation between methylene chloride and water, the mechanism of our conversion may be different.

The equilibrium had been observed but not fully characterized for other sulfonium salts. Scartazzini and Mislow¹⁷ found that the reaction of *tert*-butylethylmethylsulfonium perchlorate in acetic acid stopped after ca. 25% reaction; in the presence of excess sodium acetate, the reaction appeared to behave normally, although it was not followed to completion. Kevill and Anderson¹⁸ found that the acetolysis of 1-adamantylmethylsulfonium stopped after ca. 70% reaction; addition of sodium acetate allowed the reaction to go to completion. Friedberger and Thornton⁵ found that the hydrolysis of **1** stopped after ca. 60% reaction at the relatively high concentrations (0.1 M) used to measure sulfur KIEs. They ascribed this effect to some nonspecific interaction of 4-methoxybenzyl alcohol with **1** that removed the latter from solution. In their recent study of the solvolysis of **1** in various solvent systems, Kevill and co-workers¹¹ found that an equilibrium was established in acetic and formic acids and in various aqueous mixtures of trifluoroethanol and hexafluoro-2-propanol. In the binary solvent systems, the extent of reaction increases with an increase in the water content. The equilibrium in the aqueous binary systems was suppressed by addition of pyridine. We found that pyridine-*d*₅ reacts with **1** with clean second-order kinetics and that the reaction goes to completion under *pseudo*-first order conditions (see Figure 1). In fact, with the exception of the reaction of **1** with thiocyanate that is complicated by extensive equilibria among the products,⁸ **1** reacts cleanly with basic nucleophiles without establishment of the equilibrium under *pseudo*-first order conditions and goes to completion smoothly in the presence of NaOD and ND₃ (zero order in nucleophile; Figure 1). Presumably Sneed's⁴ results were unhampered by the equilibrium because the concentration of **1** he used was low (10⁻⁴ M; see Figures

4 and 6). Thus removal of hydronium ion or SMe₂ (Figure 6) allows the reaction to go to completion.

The equilibrium may explain apparent anomalies in other studies. Darwish, *et al.*,¹⁹ found that racemization of substituted benzylethylmethylsulfonium salts bearing substituents with σ^+ values > -0.31 occurred though pyramidal inversion of the sulfonium. For (4-methoxybenzyl)ethylmethylsulfonium, however, the kinetics of methanolysis and racemization and the lack of suppression by 0.05 M SMeEt suggested that racemization occurred through an IDC mechanism. Our results suggest, however, that racemization may have occurred because of the equilibrium among starting material and products. The relatively low concentration of SMeEt used by Darwish probably had only a slight effect on the rate (see below).

Friedberger and Thornton's sulfur KIE data⁵ for the hydrolysis of **1** formed the basis for a conundrum that they went to great pains to resolve. The issue is plain enough: The Hammett plot (against σ^+ , Figure 7A) for the hydrolysis rate constants of 3- and 4-Y-BDMS⁺ show a distinct break between **1** and the 4-Me compound, which indicates a change in mechanism, but a plot of $\log k_{32}/k_{34}$ vs σ^+ is linear (Figure 7B), which indicates a common mechanism. Earlier, Hill and Fry²⁰ had found similar anomalous results for the chlorine KIEs for benzyl chlorides. Either there is a single mechanism and the break in the Hammett plot for hydrolysis rate constants reflects other factors; there are two mechanisms with a fortuitously linear sulfur KIE; sulfur KIEs are an insensitive measure of the difference between S_N1 and S_N2 mechanisms, as suggested by Harris, *et al.*,²¹ or the value for **1** is in error. The presence of the equilibrium suggests that the last possibility may be the source of the anomaly.

The ratios $k_{32}/k_{34} = (^{34}\text{S}/^{32}\text{S})_{100\%}/(^{34}\text{S}/^{32}\text{S})_{2\%}$ were obtained by mass spectrometry of SMe₂ liberated after 99.99% reaction with hydroxide (conditions that would prevent establishment of the equilibrium) and 2% reaction in water, respectively. Ratios at 2% reaction were used for all substrates except **1**, where 25% reaction was used. For data obtained at 25% reaction, where the equilibrium is well-established, the pool of liberated SMe₂ may have mixed back into substrate, and the value of $(^{34}\text{S}/^{32}\text{S})_{100\%}/(^{34}\text{S}/^{32}\text{S})_{25\%}$ may be an inaccurate measure of the KIE. (This assumes that the KIE for capture of R⁺ or displacement on ROH₂⁺ is much less than that for bond-breaking in **1**; because the barriers are low for reactions in the reverse direction compared with the barrier for bond breaking, this seems to be a reasonable assumption.) For the 2% points, however, very low concentrations of SMe₂ are in solution (Figures 4 and 6) and it is reasonable to expect that little, if any, back mixing would occur. Thus the KIE for **1** is suspect, and the value may be higher as Kevill has suggested.¹¹

The k_{32}/k_{34} values for hydrolysis of 4-Me, 4-H, and 3-Cl BDMS⁺ are almost exactly the same values obtained by Swain and Thornton²² for the reaction of hydroxide with these substrates. These values are substantially lower than the sulfur KIE for hydrolysis of *tert*-butyldimeth-

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(17) Scartazzini, R.; Mislow, K. *Tetrahedron Lett.* **1967**, 2719–2722.

(18) Kevill, D. N.; Anderson, S. W. *J. Am. Chem. Soc.* **1986**, *108*, 1579–1585.

ylsulfonium, a compound that may react by an "S_N1-like" mechanism²³ or with "some nucleophilic solvent participation";^{1,11} this issue has not been resolved fully. Because of the good match of the hydrolysis KIEs with the hydroxide KIE data, Friedberger and Thornton⁵ argued that hydrolysis of all substrates occurred with solvent nucleophilic participation. We believe that this rationale is appropriate for 4-Y-BDMS⁺ with $\sigma^+ > -0.31$: the break in the Hammett plots for the rate data indicates a change in mechanism between the 4-MeO- and the other substrates. The intermediate-hardness dependence we found⁹ for nucleophilic substitution reactions of 1 (Figure 1) also rules out direct substitution by water, which, even though it is a poor nucleophile, is a hard one. This HSAB sensitivity also tends to rule out the IDC, which should be much less selective than the bare substrate toward nucleophiles.

We note, however, that while we are suspicious of the KIE value for 1, we have no direct proof against it. It is entirely possible that the value is accurate and that the linear Hammett plot for the KIE data is fortuitous. If the Hill and Fry data²⁰ for benzyl chlorides, which show the same effect, were also judged to be in error, it would require an equilibrium involving Cl⁻. Amyes and Richard²⁴ found a common ion effect (up to 0.2 M NaCl) for the hydrolysis of 4-methoxybenzyl chloride in 50% aqueous trifluoroethanol, but they did not report any anomalous behavior over 3 half-lives. If their plot of k_{obsd} vs [Cl⁻] extrapolates to a zero rate constant at high chloride concentrations, the value of the equilibrium constant would of necessity be quite small; their plot very well may reach a plateau value. We also note, however, that the equilibrium is not unique to the sulfoniums. We have established its presence in the hydrolysis of benzylpyridiniums with four pyridine leaving groups.¹⁴ Thus the conundrum remains unanswered.

Even if the Friedberger and Thornton data were not available, we would still face the dilemma of establishing with certainty that the mechanism is S_N1. The new results obtained in the current study—the small solvent isotope effect of $k_{\text{H}}/k_{\text{D}} = 1.1$, the α -deuterium secondary isotope effect $k_{\text{H}}/k_{\text{D}} = 1.26$ per deuterium, which is near the theoretical limit for fully dissociative reactions,²⁵ and the high, positive value of $\Delta S^\ddagger = 7.1$ gibbs/mol—are consistent with either an S_N1 or IDC mechanism. Kevill^{1,11} found that the presence of exogenous SMe₂ in 95% acetone led to "modest reductions" of the specific rate constant for hydrolysis. With the well known mass-action equation $k_o/k_{\text{expt}} = (1 + \alpha [\text{SMe}_2])$, where k_o is the first order rate constant in the absence of SMe₂, k_{expt} is the rate constant in the presence of various [SMe₂], and α is the mass law constant, Kevill obtains an α value of 4.8 M⁻¹, which is similar to a value of 2.5 M⁻¹ for benzhydryldimethylsulfonium, a compound that clearly reacts by an S_N1 mechanism.¹ On the basis of this mass law effect, they argued that 1 does not react through an IDC intermediate.

Thus in order to rule out the IDC mechanism in the hydrolysis of 1, it is necessary to use other data. The kinetics and selectivities of the reaction of 1 with azide

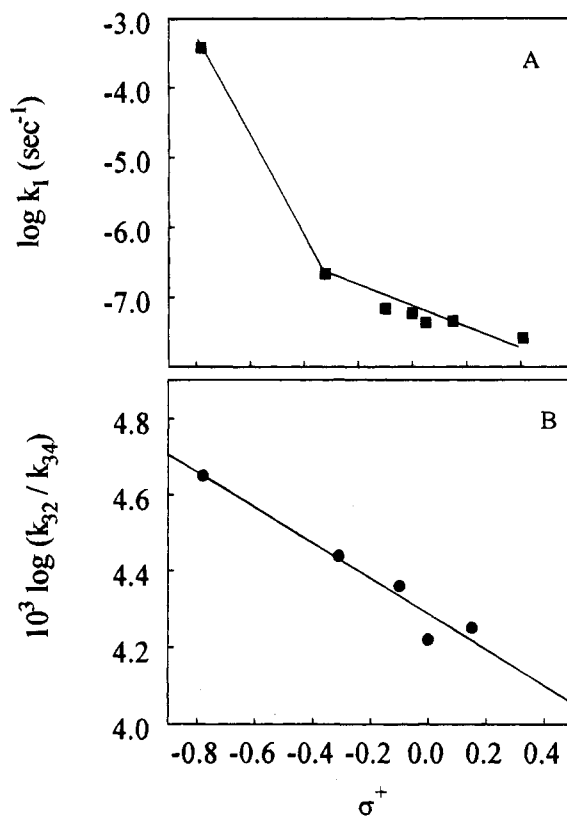


Figure 7. Hammett plots for (A) the hydrolysis (■) and (B) the sulfur KIE (●) for hydrolysis of 3- and 4-substituted BDMS⁺ at 68 °C. Data are from ref 5.

we have measured and will report in detail elsewhere⁹ are consistent with a mixed S_N1/S_N2 mechanism. Plots of k_{obsd} vs [NaN₃] at constant ionic strength are linear over most of the range of nucleophile strength and have non-zero intercepts (Figure 1). The product ratio [RN₃]/[ROH] increases smoothly with increasing azide concentration. Sneen⁴ argued that the kinetic and selectivity pattern are consistent with a mechanism in which all RN₃ arises from direct displacement on an IDC. Friedberger and Thornton⁴ pointed out that Sneen's IDC mechanism for the reaction of 1 with azide is reasonable if no azide product arises from trapping of free carbenium ion by nucleophile. If this occurs, the mechanism must be mixed S_N1/S_N2 (Scheme 1).

We found that under conditions of constant ionic strength a plot of the product ratio [RN₃]/[ROH] vs [NaN₃] (Figure 8) is fitted by

$$\frac{[\text{RN}_3]}{[\text{ROH}]} = \left(\frac{k_{\text{N}}}{k_{\text{w}}}\right)[\text{N}_3^-] \left(1 + \frac{k_2}{k_1}[\text{N}_3^-]\right) + \frac{k_2}{k_1}[\text{N}_3^-] \quad (1)$$

which was derived assuming the mixed S_N1/S_N2 mechanism,^{26,27} with k_1 (0.123 min⁻¹) and k_2 (0.238 M⁻¹ min⁻¹) the rate constants for the water-only and azide reactions at $\mu = 1.7$, respectively, and the value for carbenium ion trapping by azide, $k_{\text{N}}/k_{\text{w}} = 17$, obtained from the product ratios for 4-methoxybenzyl-4'-sulfobenzate,⁹ a water-

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(26) The value of $k_{\text{N}}/k_{\text{w}}$ depends on the presence or absence of added salt (ref 9). In the presence of azide only, the value of $k_{\text{N}}/k_{\text{w}}$ is ca. 55 over 0–0.5 M azide. The azide-only data are fit to a form of eq 1 that includes terms for a preassociated concerted bimolecular reaction with azide.

(27) This equation also gives an excellent fit to the selectivity data for the azide reaction of 4-MeO-benzyl chloride, which occurs through the mixed mechanism in aqueous acetone (ref 24).

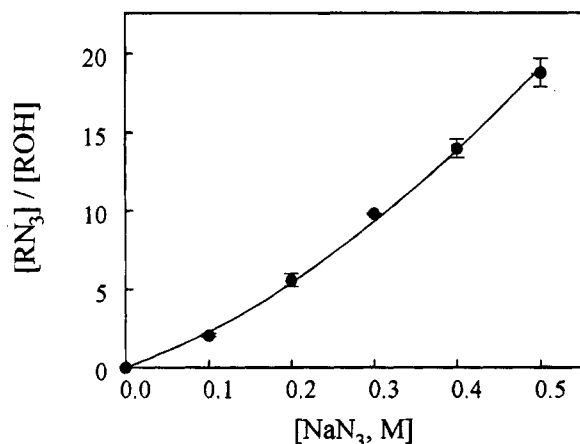


Figure 8. Plot of the product ratios vs $[\text{NaN}_3]$ for the reaction of **1** at 80°C , $\mu = 1.7$ (NaCl). The points are the experimental data obtained by integration of several peaks in CDCl_3 extracts of reaction mixtures, and the line was fit to points calculated with eq 1 using experimentally determined values for the various ratios (ref 9). Error bars are S.E.

soluble substrate that is zero order in azide at 80°C . Kevill¹¹ has reanalyzed Sneen's azide data⁴ and concluded that a k_N/k_W ratio of 21.1 M^{-1} is required to fit the 60°C data to an equation derived assuming the mixed mechanism. Our measured value for trapping of the free carbenium ion is 17 at 80°C , in excellent agreement with Kevill's estimate obtained by best fit. We believe that this fit conclusively rules out the IDC mechanism for azidolysis and hydrolysis reactions of **1**.

Ritchie²⁸ has made the bold claim that "all patterns of reactivity and selectivity arise primarily from solvent effects, and not from some inherent property of the solute reactant" and Arnett and Reich²⁹ have suggested that the failure of the Menschutkin reaction to obey the much maligned reactivity-selectivity principle is the result of solvation of the leaving group at the transition state and not the result of substituent effects. Kevill¹¹ has found only modest effects on the rate of solvolysis of **1** in a variety of solvent systems. Some of our results show dramatic effects in the activation values, however, which tend to support the contentions of Ritchie and Arnett.

For instance, we found that $\Delta\Delta S^\ddagger$ for the azide reactions of 4-methoxybenzyl-3'-cyanopyridinium and **1** is -17 gibbs/mol, which we believe reflects substantial reorganization of solvent about the hydrophilic pyridine and the lack of solvent reorganization about the hydrophobic SMe_2 at the transition state.³⁰ The hydrolysis of **1** shows the hydrophobic effect. In H_2O , Kevill¹¹ found $\Delta S^\ddagger = 13.4 \pm 1.7$ gibbs/mol, but we found that the value in D_2O is 7.1 ± 1.0 gibbs/mol; $\Delta\Delta H^\ddagger$ is much smaller (ca. 2 kcal/mol higher in H_2O). These differences are not the result of error: We measured a UV rate constant in H_2O at 80°C that falls on the line of the Eyring plot made with Kevill's data; converting our D_2O rate constants to H_2O values in the range 60 – 80°C using the k_H/k_D value of 1.1 and the conversion from constant ionic strength to pure water gives points that fall on the line as well

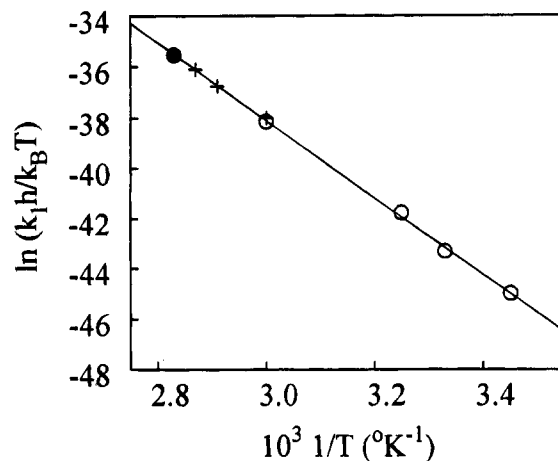


Figure 9. Eyring plot of Kevill's titrimetric rate constants¹¹ in H_2O in the range 16 – 60°C (\circ), our UV value for the rate constant at 80°C in H_2O (\bullet), and our UV rate constants in D_2O ($+$) that are converted to H_2O values using $k_H/k_D = 1.1$ and the ratio for reaction at $\mu = 0$ and 1.7. The correlation is excellent ($r = 0.9997$) and shows that there is no error between methods or laboratories.

(Figure 9). Thus this almost 2-fold difference is real and, we believe, is the result of the hydrophobic effect. Ben-Naim³¹ found that ΔS^\ddagger for the transfer of noble gases and methane and ethane from the gas phase into water was slightly more negative for D_2O than for H_2O , presumably because of the slightly stronger (5–7%) deuterium bonds, which is the trend we see in the ΔS^\ddagger values. While solvent effects are often difficult to dissect from other factors, these data may provide a fairly clear example of the importance of solvation and reactivity, at least for charged substrates that do not require extensive solvent reorganization to accommodate the creation of charge at the transition state.

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(30) The value of ΔS^\ddagger for the reaction of benzyldimethylsulfonium and trimethylsulfonium with phenoxide and hydroxide, determined by Swain and Taylor,² are in the same range (-4.4 to -7.9 gibbs/mol) as the values for the azide reaction.

(31) Summarized in Ben-Naim, A. *Solvation Thermodynamics*; Plenum Press: New York, 1987; pp 75–77.