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Kinetics of the Hydrolysis of Fluoromethyl Methyl Ether in Neutral to Alkaline Solution[1a]

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The kinetics of the hydrolysis of fluoromethyl methyl ether have been determined in aqueous solution at 25 °C in the pH range 7–13 by following the rate of release of hydrogen ions. The reaction is simple first order with k = 1.6–2.1 × 10^{-3} s^{-1} and shows no mass law effect in the presence of 0.1 M NaF. The mechanisms of hydrolysis consistent with these facts are discussed and compared to those for chloromethyl methyl ether, bis(chloromethyl) ether, and glycosyl halides.

As a part of a study of the stepwise mechanisms of carbonyl group addition–elimination reactions, we initiated a study of the kinetics of the hydrolysis of fluoromethyl methyl ether (FME). In particular, we had hoped to establish the relative reactivities of various nucleophiles toward the methoxymethyl cation as a model for nucleophilicity toward a protonated carbonyl group. In the limited study reported here this goal has not been realized, and further work has been postponed at least temporarily because of the demonstrated carcinogenic nature of the related chloromethyl methyl ether, which is used as the starting material for the preparation of the title compound, and the possible toxicity of FME itself.[2] However, since there are no reports (known to us) of quantitative studies of the hydrolysis of simple α-fluoroalkyl ethers, these results are of interest for comparison with the hydrolysis of chloromethyl methyl ether,[3] and with the chemical[4] and enzymatic[5] hydrolyses of glycosyl fluorides.

Experimental Section

Preparation and Characterization of Fluoromethyl Methyl Ether. The method of preparation is that of Via,[6] and is similar except for solvent to that described by Tullock and Coffman.[7] A total of 70 g (0.9 mol) of chloromethyl methyl ether (Eastman) was added over a period of 12 h to a refluxing suspension of 82 g (2 mol) of sodium fluoride (Baker analytical reagent, powder form) in 500 ml of purified[8] acetonitrile. A small distillation head was mounted atop the reflux condenser, and the low-boiling FME collected with a dry ice cooled Dewar condenser, with the collection flask also cooled by dry ice. About 25 ml of a water-white product was collected in this way, then transferred to and sealed in Pyrex ampules, and stored at −20 or −70 °C. The above operations were carried out with a nitrogen atmosphere.

The product thus obtained is very temperature sensitive. If the ether was allowed to stand (in a sealed vessel) at 0 °C for a short time, the color of the product changed to yellow and then deep red. Even at −20 °C the material in the ampules took on a yellow color (unless a small amount of triisopropylamine had been added). Furthermore, attempts to use a "cow" type distilling receiver resulted in decomposition of the product and deposition in the receiver of a white solid (uncharacterized, but probably paraformaldehyde).

The FME used in the analyses and in the kinetics experiments described below was redistilled in a trap-to-trap manner at atmospheric pressure under nitrogen, with the receiver cooled with liquid nitrogen and the pot in ice. In some cases a small amount of triisopropylamine was added to the pot since this seemed to aid the distillation. The redistilled ether was stored at −70 °C. For the kinetic studies described below, a solution of FME in anhydrous methanol was prepared by adding 5 ml of dry ice chilled methanol to about 1.5 ml of redistilled FME and was stored at −78 °C in a 14/20 ⅋-stoppered heavy-walled test tube.

The purity of the redistilled FME was checked by GLC and ^{1}H NMR analyses. With an Aerograph Hy-Fy gas chromatograph, which has a hydrogen-flame detector, we found that we could obtain excellent resolution of reactants and products using a 5 ft × 0.125 in. column of 15% XF-1150 on 60–80 Chromosorb W at room temperature. Samples were introduced by using a dry ice cooled 10-μl Hamilton syringe to quickly take an aliquot of ether from a dry ice–acetone cooled flask and inject it into the chromatograph. The redistilled FME yielded four well-resolved peaks that in order of increasing retention time had relative areas of 15:3:1:~0.1. The first peak is assumed to be due to FME. The second and third peaks have retention times identical with those of dimethoxymethane and acetone, respectively. The fourth peak was not assigned, but it was demonstrated that this peak was not due to chloromethyl methyl ether, acetonitrile, or methanol. GLC analysis of the chloromethyl methyl ether starting material showed that it contained a small amount of a contaminant with the same retention time as dimethoxymethane. The acetone in the product probably arose from the opening of the flask containing the fluoro ether while it was suspended in a dry ice–acetone bath, since it did not come from the cooling of the syringe.

The ^{1}H NMR spectrum of a mixture of the redistilled FME plus Me_4Si in a tightly stoppered heavy-walled NMR tube was obtained at about −50 °C using a Varian A-60 NMR spectrometer. The spectrum is consistent with the structure of FME, and indicates very small amounts of dimethoxymethane and acetone contaminants. Observed peaks were assigned as follows: A singlet at δ 2.17 was increased in size by the addition of acetone and is therefore assigned to hydrogens of

acetone. Singlets at δ 3.43 and 4.73, relative areas 3.08, were assigned to the methyl and methylene hydrogens of dimethoxymethane by comparison with the peak positions in the spectrum of an authentic sample of this compound. A singlet at δ 3.65 and a doublet (J = 60 Hz) centered at δ 5.45, relative areas 1.48, were assigned to the methyl and methylene hydrogens of FME. The observed coupling constant is consistent with a geminal ^{19}F–^{1}H coupling, e.g., in β-fluoroethanol for geminal ^{19}F–^{1}H coupling J = 46.7 Hz.[9] On the basis of these assignments, the composition of the redistilled ether is 201:13.5:1 FME:dimethoxymethane:acetone. The FME is thus about 95% pure, and contains no detected impurity that would be expected to interfere with the kinetic studies.

Other Reagents. Sodium perchlorate was Smith "anhydrous", which was ground into small lumps and dried at 130 °C for 4 h[10] before weighings. Although 0.5 M solutions of sodium fluoride and 1.0 M solutions of sodium perchlorate were slightly basic; titration with standard HCl indicated an insignificant (for our purposes) basic contaminant. A 0.481 M formaldehyde solution was prepared by dissolving (by heating to 80 °C under nitrogen) 73 g (0.083 mol) of trioxane in 100 ml of 0.001 M $HClO_4$, and diluting this solution to 500 ml. Basified aliquots of the formaldehyde were treated with iodine, and the iodine consumed in formaldehyde oxidation determined by comparison of the thiosulfate titre with that for an iodine blank.[11] Baker analytical reagent grade iodine ("100.0% I_2") was used as a primary standard to standardize sodium thiosulfate solution prepared from Fisher Certified A.C.S. grade $Na_2S_2O_3 \cdot 5H_2O$.

Procedure for Kinetic Runs. A "25-ml" three-neck flask with 14/20 ⅋ joints was used as the reaction flask. The center neck held one of the special stoppers described below, and the outer necks held glass and reference electrodes, which were positioned so that their tips were about 0.75 in. from the bottom of the flask. Even with the electrodes and a 1-in. Teflon-coated stirring bar in place, the capacity of the flask was about 35 ml. The flask was immersed to the necks in a shallow constant-temperature bath maintained at 25 ± 0.2 °C that sat atop a magnetic stirrer and was also stirred with a 1-in. magnet. With this apparatus very rapid stirring speeds were possible.

The pH of the reaction solution was monitored using a Beckman Research Model pH meter, and Beckman No. 39004 Type E-2 glass and No. 39071 fiber-junction calomel reference electrodes. Using these same electrodes but a Beckman Zeromatic pH meter, a change in pH from 13.00 to 11.7 caused by rapid addition of a small aliquot of ~10 M HCl to a rapidly stirred solution of 0.1 M NaOH is limited by the response time of the meter (~5 s). At pH's >7 we observed no interference by fluoride ion. During a kinetic run the pH of the unbuffered reaction solution was continuously monitored by using a Leeds-Northrup Speedomax H Model S strip-chart recorder with a chart speed of 0.5 in./min. The chart could be read with a precision of about 0.002 pH units, and readings obtained from the recorder agreed with those obtained directly from the meter with a maximum deviation of 0.05 pH units.

In order to allow convenient transfer by syringe of aliquots of the methanolic FME solution, we constructed gas-cooled septum stoppers. A 14/35 ⅋ inner joint, 10 cm long, was cut to the dimensions of a 14/20 joint using a glass saw, so that the bottom of the joint was left flat. A 0.125 in. thick Teflon disk with a 1.5-mm center hole was fastened with epoxy cement inside the joint and flush with the end, and then a silicone-rubber GLC septum fastened to the bottom of the joint with "Silastic Clear Sealer" (a Dow-Corning product). A small side arm through which cold nitrogen could be admitted was added about 0.5 in. above the top of the joint. One of these stoppers was used in the reaction flask, and another in the stock solution flask. Nitrogen gas cooled in a 0.25 in. i.d. × 10 ft copper coil immersed in liquid nitrogen was passed through the stoppers in order to cool a 1.0-ml or a 50-μl syringe during transfers of the stock solution. The temperature within the stopper could be brought as low as −100 °C.

To make a run, the pH meter and electrodes were first checked with a series of standard buffers. Then the reaction flask was charged with 30.0 ml of a solution of sodium hydroxide and sodium fluoride or perchlorate, and the solution stirred to allow it to come to temperature equilibrium. Cold nitrogen gas was started flowing through the stoppers in the reaction flask and fluoro ether stock solution flask. The pH recorder was started and standardized at pH = log $[OH^-]^0$ − 14.00, and after a steady baseline was reached, an aliquot of the methanolic fluoro ether was added and the nitrogen turned off. The pH was monitored until it no longer continued to change.

For the hydrolyses in 0.1 M sodium hydroxide, 0.80–85 ml of the methanolic FME solution was added to 30.0 ml of a solution 0.10 M in sodium hydroxide and 0.10 M in either sodium fluoride or sodium perchlorate. Addition of the ether solution to the sodium hydroxide caused an immediate drop in pH of 0.04–0.06 units, which is equivalent to 9–13% of the total acid released and which is probably a result of partial solvolysis of the FME in the stock solution. Useful data were obtained after allowing 1 min for the pH vs. time slope to stabilize. For the run in 10^{-3} M sodium hydroxide, the addition of 17 μl of the FME solution to the hydrolysis solution caused an immediate pH drop of ~0.4 units, which amounts to about 50% of the total acid released. Useful data were obtained after allowing 1 min for the pH vs. time slope to stabilize.

Results

Since the overall stoichiometry of the hydrolysis of FME is

$$CH_3OCH_2F + H_2O \rightarrow CH_2(OH)_2 + CH_3OH + H^+ + F^-$$

the rate of the hydrolysis can be obtained from the change in pH of the reaction solution with time. Under the basic conditions used up to 30% of the formaldehyde will be present as the hemiacetal with methanol, and therefore at basic pH's acid dissociation of formaldehyde hydrate and hemiacetal must be allowed for, and at lower pH's the protonation of fluoride ion taken into account. Depending on the pH of the hydrolysis medium two slightly different methods were used, both of which are based on the preparation of standard curves of pH vs. extent of reaction.

For hydrolyses in solutions that were initially 0.1 M in sodium hydroxide, values of the apparent pH, i.e. pH uncorrected for sodium ion response, were converted into degree of reaction by using a standard curve that was obtained by measuring the apparent pH's of a series of "synthetic reaction solutions". That is, we prepared solutions of sodium hydroxide, sodium fluoride, formaldehyde, and methanol such that

$$[OH^-]_{stoich} = 0.1 - \alpha$$

$$[F^-] = 0.1 + \alpha$$

$$[CH_2(OH)_2]_{stoich} = \alpha$$

$$[CH_3OH]_{stoich} = 0.5 + \alpha$$

where the subscript "stoich" indicates that the concentrations are stoichiometric or concentrations by mixing, and α is a parameter that represents the amount of FME hydrolysis, and equals $[CH_3OCH_2F]^0 - [CH_3OCH_2F]^t$. The apparent pH of each of these synthetic reaction solutions was measured, and plotted vs. log $[OH^-]_{stoich}$. The curvature of the plot at the higher pH's is that expected as a result of sodium ion response of the glass electrode and dissociation of formaldehyde hydrate and methoxymethylcarbinol. Using an expanded-scale version of this plot for the hydrolysis of FME in 0.1 M sodium hydroxide, the apparent pH at a given time was converted into a value of $[OH^-]_{stoich}$, and the plots of ln ($[OH^-]_{stoich} - [OH^-]^{\infty}_{stoich}$) vs. time prepared. Such plots for three experiments are shown in Figures 1 and 2. The first-order rate constants for FME hydrolysis obtained from the slopes of these plots are shown in Table I.

A similar method was used for the single run where the initial $[OH^-] = 10^{-3}$ M. A 30-ml aliquot of the sodium hydroxide–sodium fluoride solution was titrated potentiometrically with 0.0160 M hydrochloric acid using a buret graduated to 0.02 ml, and an expanded scale titration curve plotted. The experimental apparent pH values at various times obtained in the kinetic experiment were converted into ml_t values, and ln ($ml_\infty - ml_t$) plotted vs. time.

Measurements of the rate of FME hydrolysis in more acidic solutions does not seem possible using the above method with the glass electrode since in these solutions the electrode response becomes erratic, probably because of the presence of HF_2^- ion, which attacks the electrode.

We have so far discussed only the overall stoichiometry of FME hydrolysis. Actually this hydrolysis is a multistep process that can be written

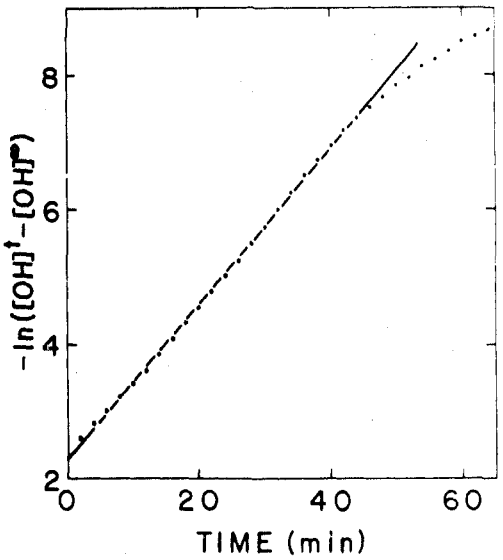

Figure 1. Plot of ln ($[OH^-]^t_{stoich} - [OH^-]^\infty_{stoich}$) vs. time for kinetic run where $[OH^-]^0_{stoich} = 0.1$ M and $[F^-]^0 = 0.1$ M.

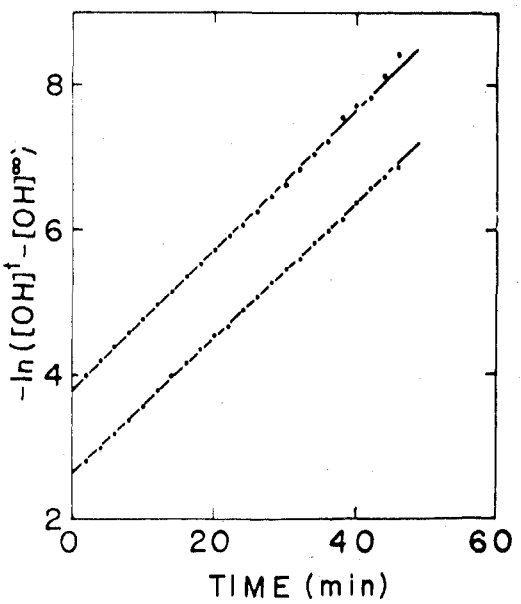

Figure 2. Plot of ln ($[OH^-]^t_{stoich} - [OH^-]^\infty_{stoich}$) vs. time for two kinetic runs where $[OH^-]^0_{stoich} = 0.1$ M, $[F^-]^0 = 0$, and $[ClO_4^-] = 0.1$ M. The upper line has been displaced upward by one ln unit.

$$CH_3OCH_2F + H_2O \underset{\beta_1}{\overset{k_1}{\rightleftharpoons}} CH_3OCH_2OH + H^+ + F^- \quad (1)$$

$$CH_3OCH_2OH \underset{\beta_2}{\overset{k_2}{\rightleftharpoons}} CH_2O + CH_3OH \quad (2)$$

$$CH_2O(+H_2O) \underset{\beta_3}{\overset{k_3}{\rightleftharpoons}} CH_2(OH)_2 \quad (3)$$

The use of standard curves to convert apparent pH to extent reaction involves the implicit assumption that reactions 2 and 3 are at equilibrium. We have examined this assumption in detail using computer modeling. The rate constants for reactions 2 and 3 are available in the literature. From Bell and Evans,[13] at 25 °C $\beta_3 = 1.6 \times 10^3[OH^-] + 5.1 \times 10^{-3}$, and thus since $K_{hyd} = 2 \times 10^3 = [CH_2(OH)_2]/[CH_2O]$,[14] $k_3 = 3.2 \times 10^6[OH^-] + 10$ (s^{-1}). From Le Hénaff,[15] at 20 °C $k_2 = 1.51 \times 10^3[OH^-] + 1.42 \times 10^{-3}$ and $K_{hemi} = 32 = ([CH_3OCH_2OH]\cdot[H_2O])/([CH_2(OH)_2][CH_3OH])$; thus $\beta_2 = (1.74 \times 10^6[OH^-] + 1.64)[CH_3OH]$ (s^{-1}). We will use these same values for 25 °C, and will treat $[CH_3OH]$ as a constant = 0.5 M, which is the concentration obtained by mixing 0.8 ml of methanol and 30 ml of reaction solution. Using the methods of Rodiguin and Rodiguina[16] we obtained expressions for the concentrations of CH_3OCH_2F, CH_3OCH_2OH, CH_2O, and $CH_2(OH)_2$ as a function of time, k_1 to k_3, and β_1 to β_3. Using $k_1 = 1.67 \times 10^{-3}$ s^{-1} and $\beta_1 = 0$, $[CH_3OCH_2F]^0 = 0.1$ M, and $[OH^-] = 0.1 - ([CH_3OCH_2F]^0 - [CH_3OCH_2F]^t)$ we found that even when $[CH_3OCH_2F]^t$ dropped to 10^{-7} M the ratios $[CH_2(OH)_2]/[CH_2O]$ and $[CH_2(OH)_2]/[CH_3OCH_2OH]$ were equal to the equilibrium ratios. Thus, for the hydrolysis of FME under the conditions described here step 1 is definitely rate limiting. It is interesting to note that a similar modeling of the hydrolysis of chloromethyl methyl ether using $k_1 = 1.0 \times 10^3$ (s^{-1}) and $[OH^-]$ = constant = 0.1 M shows that for this compound steps 2 and 3 would not be at equilibrium.

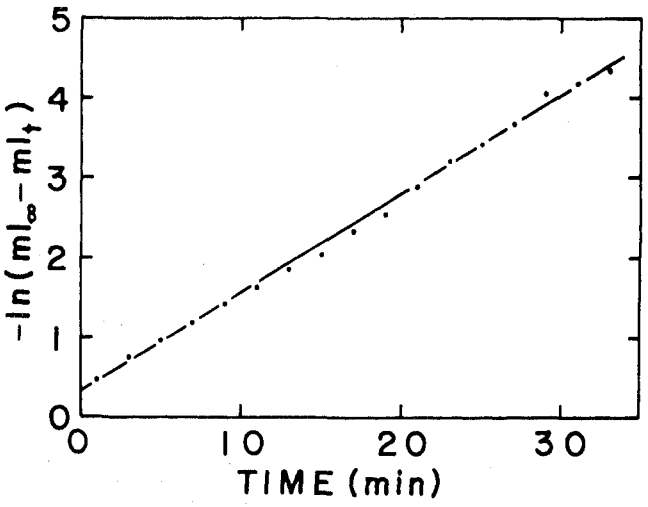

Figure 3. Plot of ln ($ml_\infty - ml_t$) vs. time for kinetic run where $[OH^-]^0_{stoich} = 10^{-3}$ M and $[F^-]^0 = 0.199$ M.

Table I. First-Order Rate Constants (s^{-1}) for Hydrolysis of Fluoromethyl Methyl Ether at 25 °C

$[F^-]^0$, M	$[OH^-]^0_{stoich}$, M	$[OH^-]^\infty_{stoich}$, M	k, s^{-1}
0.100	0.100	7.08×10^{-3}	1.92×10^{-3}
0[a]	0.100	1.57×10^{-2}	1.56×10^{-3}
0[a]	0.100	1.70×10^{-2}	1.61×10^{-3}
0.199	0.001	1.8×10^{-7}	2.06×10^{-3}

[a] $[NaClO_4] = 0.100$ M.

Discussion

We have found that in 0.1—2×10^{-7} M sodium hydroxide, the hydrolysis of FME is kinetically first order in fluoro ether only. These results can be accommodated by an SN1 mechanism of hydrolysis, eq 4

$$CH_3OCH_2F \xrightarrow{\text{r.d.}} CH_3OCH_2^+ + F^-$$
$$CH_3OCH_2^+ + (H_2O \text{ or } OH^-) \rightarrow (CH_3OCH_2OH \rightleftharpoons CH_2(OH)_2 + CH_3OH) + H^+ + F^- \quad (4)$$

where an intermediate resonance-stabilized methoxymethyl cation is formed and then captured by water or hydroxide ion, but not by fluoride ion. Such a mechanism would be analogous to that for the acid-catalyzed hydrolysis of formals and acetals.[17] Our results are also consistent with an SN2 mechanism, eq 5

$$CH_3OCH_2F + H_2O \xrightarrow{\text{r.d.}} (CH_3OCH_2OH \rightleftharpoons CH_2(OH)_2 + CH_3OH) + H^+ + F^- \quad (5)$$

in which water but not hydroxide ion directly displaces fluoride ion from the fluoro ether.

As noted in the introduction, if the mechanism were SN1 we had hoped to see a fluoride ion mass-law effect[18] that would allow relative nucleophilicities toward the methoxymethyl cation to be determined. This hope was based on the fact that the methoxymethyl cation is relatively stable and therefore might be selective in reacting with nucleophiles, and on the special stability of a geminal oxygen–fluorine grouping[19] that would result from fluoride ion return to re-form FME. However, attack on the cation by water or hydroxide ion has a similar driving force, and dominance by the latter nucleophiles may also be aided by the strong solvation expected for a small ion like fluoride. In acetone–water solvents, fluoride also fails to compete with water for triphenylcarbonium ion.[20] However, better nucleophiles like hydroxylamine and semicarbazide have been used to capture the dimethoxybenzyl cation [$PhC^+(OCH_3)_2$] formed by acid-catalyzed hydrolysis of trimethyl orthobenzoate.[21] The lower rate of hydrolysis of FME in the presence of sodium perchlorate is probably a specific salt effect since it seems unlikely that perchlorate ion could compete with water for the capture of methoxymethyl cation.[22]

Both SN1 and SN2 mechanisms of α-halo ether solvolysis have been demonstrated. Jones and Thornton[3] have studied the solvolysis of chloromethyl methyl ether in a variety of solvents, including aqueous ethanol, acetone, and dioxane, and have concluded on the basis of the effect of solvent polarity (as measured by the Winstein–Grunwald m value) on rate, and substituent and solvent deuterium isotope effects, that a "SN1-like" mechanism of solvolysis operates. Ballinger et al.[23] had earlier arrived at a similar conclusion for solvolyses in ethanol and ethanol–ether mixtures on the basis that although added ethoxide ion caused a rate acceleration (much in excess of that caused by chloride or perchlorate ion) due to a parallel SN2 reaction, the magnitude of the acceleration was not so great as would be expected if the uncatalyzed solvolysis were SN2-like. Salomaa has compared the effect of structure on the hydrolysis of dialkoxymethanes and alkoxymethyl esters with that for the solvolyses in ethanol or ethanol–dioxane of alkoxymethyl chlorides and concluded that all three occur via alkoxymethyl cation intermediates.[24] Extrapolation of the results of Jones and Thornton[3] for solvolysis of chloromethyl methyl ether in aqueous dioxane to pure water yields $k = 6 \times 10^3\ s^{-1}$ at 25 °C, which is *at least* 3.5×10^6 times larger than the rate constant for unimolecular dissociation of FME. This leaving group effect can be compared to $k_{RCl}/k_{RF} = 1 \times 10^6$ for tritylhalide solvolysis in 85% acetone at 25 °C and $k_{RCl}/k_{RF} = 1 \times 10^5$ for *tert*-butyl halide solvolysis in 80% ethanol at 25 °C.[25]

Tou et al.[26] have studied the hydrolysis of bis(chloromethyl) ether, which because of the second chlorine hydrolyzes sufficiently slowly to be studied in pure water. The kinetics of the hydrolysis were studied in 1 and 2 M NaOH, 1 and 3 M HCl, and in pure water; in each case the hydrolysis was first order in ether only, and the rate constant for all conditions reasonably constant at about $2 \times 10^{-2}\ s^{-1}$. However, large changes in the parameters $\Delta S^{\ddagger}$ and $E^{\ddagger}$ accompanied the changes of reaction medium. Thus between 2 M NaOH and 3 M HCl, $\Delta S^{\ddagger}$ increased from −35.2 to −3.82 eu, and $E^{\ddagger}$ increased from 8.96 to 18.6 kcal/mol. Tou et al. interpreted these results to mean that the reaction mechanism changes from SN1 at high basicity to SN2 at high acidity. In the latter case they suggested that hydroxide ion displaces chloride ion from the protonated substrate. Such a mechanism seems unlikely since even if the acid dissociation constant of the protonated ether is 10^5 M, which assumes that bis(chloromethyl) ether is as basic as dimethoxymethane can be estimated to be,[27] the second-order rate constant for attack of hydroxide ion on the protonated ether must be $10^{17}\ M^{-1}\ s^{-1}$, which greatly exceeds the diffusion-controlled limit for recombination of hydroxide ions and protons, $1.4 \times 10^{11}\ M\ s^{-1}$.[28]

The results for simple α-haloalkyl ethers can be compared to those for glycosyl halides. The hydrolyses of a variety of glycopyranosyl fluorides have been found by Barnett[4] to be catalyzed by both H_3O^+ and OH^-, but no uncatalyzed reaction was reported. Hydrogen ion catalysis is attributed to assisted leaving of fluoride ion in an SN1 manner to yield a carbonium ion, which is captured by water to yield free sugar. In hydroxide ion solution, however, the reaction is SN2 like and results from attack of hydroxide ion or the C-6 hydroxyl (if there is one) at the carbon bearing fluorine. For four glycosyl fluorides that have the C-2 hydroxyls cis to the fluorine, at the minimum hydroxide ion concentration of 0.2 M and 20 °C, $k = 7.46\text{–}37.8 \times 10^{-5}\ s^{-1}$, and so for these glycosyl fluorides the uncatalyzed reaction is at least five times slower than with fluoromethyl methyl ether. (Use of the hydrogen ion catalyzed data does not lead to a different estimate.) For β-D-glucopyranosyl fluoride, in which the C-2 hydroxyl is trans to the fluorine, there is a rate acceleration relative to the α anomer of a few thousand fold, which is attributed to neighboring group participation by the hydroxyl. Various glycosyl fluorides are also hydrolyzed by enzymes whose normal function is hydrolysis[5] or phosphorolysis[29] of di- or polysaccharides. By contrast to glycosyl fluorides in methanol tetra-*O*-methyl-α-D-glucopyranosyl and mannopyranosyl chlorides solvolyze by an SN1 mechanism, and added methoxide ion leads to only a relatively small rate increase.[30]

Registry No.—FME, 460-22-0.

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