Kinetics and Mechanism of Epoxy Ether Hydrolysis. I. Mechanism of the Hydrolysis of an Acyclic Hemiacetal Intermediate[1]

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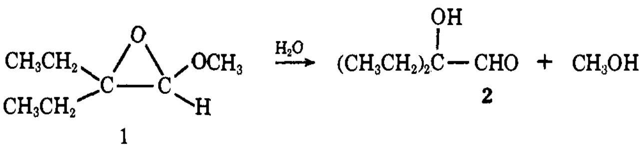
Abstract: 1-Methoxy-2-ethyl-1,2-epoxybutane (**1**) undergoes facile hydrolysis to give methanol and 2-ethyl-2-hydroxybutanal (**2**) *via* two consecutive, kinetically first-order reactions. The first step, ring cleavage of **1**, becomes rate determining at pH values greater than 8.0. The second step, which becomes the kinetically observable process at lower values of pH, has been identified as the hydrolysis of the hemiacetal intermediate, $Et_2C(OH)CH(OMe)OH$ (**3**). Detailed kinetic analysis of the **3** → **2** transformation is presented. The hydrolysis of this hemiacetal is subject to catalysis by H_3O^+, H_2O, OH^-, and Brønsted acids and bases. The Brønsted α and β values are 0.33 and 0.56, respectively. The solvent deuterium isotope effect on the hydronium ion catalyzed reaction, k_H/k_D, is 1.11 ± 0.04 and $\Delta S^\ddagger$ is -15 ± 3 cal mol^{-1} deg^{-1}. Corresponding values for the pH-independent reaction are $k_{H_2O}/k_{D_2O} = 1.67 \pm 0.14$ and $\Delta S^\ddagger = -31 \pm 2$ cal mol^{-1} deg^{-1}. The hydroxide-induced reaction has $k_{OH}/k_{OD} = \sim 0.8$. These results are interpreted in terms of a transition state for catalysis by HA which contains hemiacetal, acid, and at least one water molecule acting as a proton acceptor. On the other hand, the base-catalyzed and pH-independent reactions are thought to involve ionization of the hemiacetal prior to a rate-determining step in which the expulsion of methoxide is general acid assisted. The general kinetic behavior of 1-methoxy-1-phenyl-2-methyl-1,2-epoxybutane (**4**) has been found to be similar to that of **1**.

Acetal hydrolysis is a multistep reaction which usually involves protonated stubstrate, carboxonium ion, and hemiacetal as consecutive, discrete intermediates along the path toward formation of aldehyde product.[3] In principle, therefore, the formation of any one of at least four moieties could become rate determining. The normal mode of hydrolysis is *via* the A1 mechanism,[3] *i.e.*, rate-limiting formation of carboxonium ion. Two other mechanisms have also been discussed recently. Fife has tentatively suggested that the hydrolysis of 2-phenyl-2,4,4,5,5-pentamethyl-1,3-dioxolane[4] may proceed with rate-determining attack of the intermediate carboxonium ion by water. Slow proton transfer to substrate (most likely concerted with C–O bond breaking) has been implicated as the mechanism for the hydrolysis of weakly basic acetals[5–7] or of reactants, such as tropone diethyl ketal,[8] which form a particularly stable carboxonium ion.

In the present study we examine the fourth mechanistic possibility, hydrolysis of the intermediate hemiacetal as the rate-determining stage of acetal hydrolysis. We have also been able to study in detail the kinetics of the hydrolysis of our hemiacetal precursor, the epoxy ether **1**. This study is reported in the following paper.[9]

Results

The products of the hydrolysis of **1** were found to be methanol and 2-ethyl-2-hydroxybutanal (**2**). The rate of formation of **2** was monitored spectrophotometrically. Derived first-order rate constants for the pH-independent and H_3O^+- and OH^--catalyzed reactions are plotted as a function of pH in Figure 1. The rate profile features a maximum at pH 8.0, indicating a change in rate-determining step. At pH values in the neighborhood of the rate maximum, the reaction exhibits an induction period, as shown in Figure 2, which can be analyzed in terms of the equations for two consecutive first-order reactions.[10]



The reaction occurring on the low side of the pH-rate maximum, which is the main concern of this paper, shows catalysis by Brønsted acids and bases according to eq 1, where HA and A^- comprise an acid–conjugate base pair. The rate constants k_H and k_{H_2O} were evaluated from the slopes and intercepts of plots of k_{obsd} *vs.* $[H_3O^+]$ in 10^{-4}–4×10^{-5} *M* solutions of $HClO_4$ in 10% dioxane–water (v/v).

$$k_{obsd} = k_H[H_3O^+] + k_{H_2O} + k_{OH}[OH^-] + k_{HA}[HA] + k_A[A^-] \quad (1)$$

Plots of k_{obsd} *vs.* [HA], where HA is acetic, formic, and cacodylic acid, respectively, are shown in Figures 3–5. The marked increase of slope with increasing pH indicates strong general base catalysis. The fact

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[1] Based on the Ph.D. Theses of A. L. M., 1971, and M. A. P., 1969; presented in part at the 157th National Meeting of the American Chemical Society, Minneapolis, Minn., April 1969.

[2] (a) NSF Academic Year Institute Participant, 1967–1968; NSF Trainee, 1968–1971; (b) NASA Trainee, 1968–1969.

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[8] E. Anderson and T. H. Fife, *ibid.*, **93**, 1701 (1971).

[9] A. L. Mori and L. L. Schaleger, *ibid.*, **94**, 5039 (1972).

[10] A. A. Frost and R. G. Pearson, "Kinetics and Mechanism," 2nd ed, Wiley, New York, N. Y., 1961, pp 166–169.

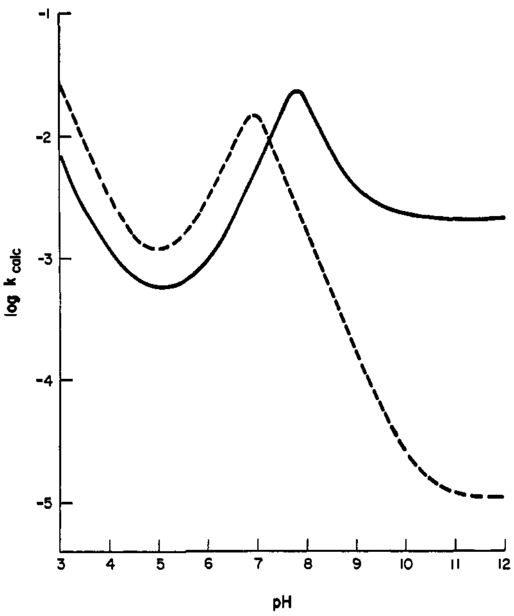

Figure 1. Rate profile for hydrolysis of **1** (solid line) and **4** (dashed line) where $k_{calcd} = k_H[H^+] + k_{H_2O} + k_{OH}[OH^-]$.

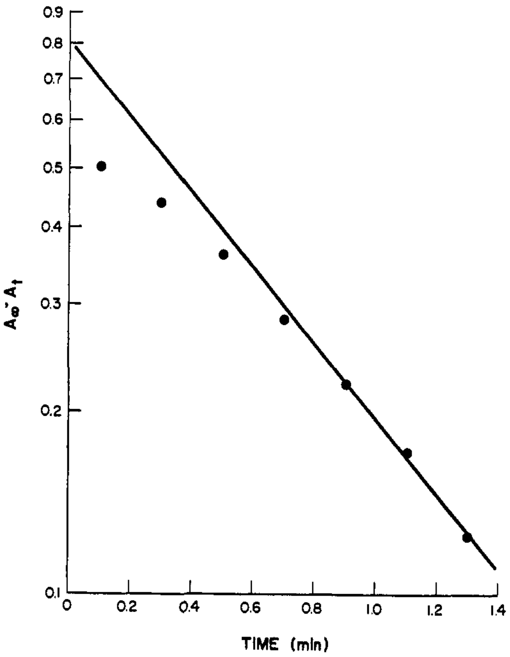

Figure 2. First-order plot for the formation of aldehyde **2** from epoxy ether **1** in triethanolamine buffer at pH 7.91 and 25° showing a marked induction period. The solid line corresponds to the limiting slope of the plot, that is, the rate constant for the second of two consecutive first-order reactions.

that the intercept passes through a minimum (Figure 3) is evidence of hydroxide ion catalysis. It is easily shown from eq 1 that this minimum should occur when $[H_3O^+] = (k_{OH}K_W/k_H)^{1/2}$, where K_W is the self-dissociation constant of water.

The 25° rate constants for these reactions including also those for catalysis by triethanolamine and triethanolammonium ion were evaluated by a least-squares treatment of the data as described in the Experimental Section and are given in Table I.

Rate coefficients for general acid catalysis at 25° are plotted against pK_a in Figure 6 to yield a slope, α, of 0.33 ± 0.02. Brønsted's β, for general base catalysis, is found to be 0.56 ± 0.06 from the plot of Figure 7. Activation parameters derived from the temperature coefficients of k_H and k_{H_2O} and solvent deuterium isotope effects upon k_H, k_{H_2O}, and k_{OH} are given in Table II. This table also includes comparative data for several apparently related reactions.

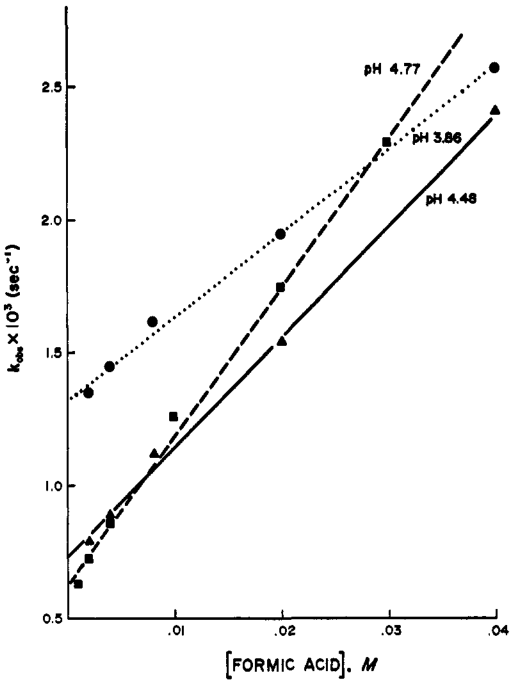

Figure 3. Observed first-order rate constants for hydrolysis of **3** in formate buffers as a function of [HCOOH] and of pH.

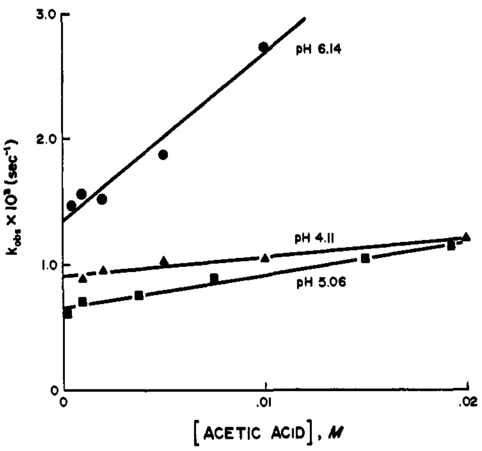

Figure 4. Observed first-order rate constants for hydrolysis of **3** in acetate buffers as a function of $[CH_3COOH]$ and of pH.

The rate profile of Figure 1 arises because the acid-catalyzed ring cleavage of **1** is rate determining at pH values greater than 8 but becomes so rapid at higher acidities that an intermediate accumulates whose decomposition becomes the kinetically observed process. This intermediate must be formed irreversibly from **1** and must be subject to strong hydroxide ion and general base catalysis.[11]

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[11] The possibility of nucleophilic catalysis is apparently ruled out by our observation that the rate at pH 4.80 (1:1 HOAc-OAc⁻ buffer) is unaffected when 0.05 *M* $NaClO_4$ is replaced by 0.05 *M* NaBr or NaI.

Table I. Rate Constants for Hydrolysis of Hemiacetal **3** at 25° in 10% Aqueous Dioxane (v/v) (μ = 0.11 Maintained with $NaClO_4$)

Catalyst: Acid	Catalyst: Base	k_A, M^{-1} sec^{-1}	k_B, M^{-1} sec^{-1}
H_3O^+	H_2O[a]	7.24 ± 0.14[b]	4.83 ± 0.14 × 10^{-4}
HCO_2H	HCO_2^-	2.76 ± 0.07 × 10^{-2}	3.44 ± 0.13 × 10^{-3}
HOAc	OAc^-	1.49 ± 0.10 × 10^{-2}	6.20 ± 0.11 × 10^{-3}
Me_2AsO_2H[c]	$Me_2AsO_2^-$	7.9 ± 0.5 × 10^{-3}	4.80 ± 0.02 × 10^{-2}
$TEAH^+$ [d]	TEA[e]	2.5 ± 0.3 × 10^{-3}	2.8 ± 0.3 × 10^{-2}
H_2O[a]	OH^-	4.83 ± 0.14 × 10^{-4}	4.63 ± 0.15 × 10^{4}

[a] Rate constant for this catalyst has units of sec^{-1}. [b] Probable error from least-squares analysis. [c] Cacodylic acid. [d] Triethanolammonium ion. [e] Triethanolamine.

Table II. Comparative 25° Kinetic Parameters for the Hydrolysis of **3** and Related Reactions

Parameter	**3** → **2**[c]	Mutarotation		Depolymerization of dimeric dihydroxyacetone[h]	Hydration of CH_3CHO
		Glucose	TMG[g]		
k_H (relative)	(1.00)	0.0014[d]	0.00070	0.0040	130[i]
k_{H_2O} (relative)	(1.00)	0.010[d]	0.77	0.013	19[i,j]
k_{OH} (relative)	(1.00)	0.0020[d]		11	0.58[j]
k_H/k_D	1.11 ± 0.04	1.37[e]	1.34		1.30[k]
k_{H_2O}/k_{D_2O}	1.67 ± 0.14	3.80[e]	3.58		3.60[k]
k_{OH}/k_{OD}	~0.8				~1[l]
$\Delta H^{\ddagger}$ (H_3O^+)[a]	11.6 ± 0.7	17.2[d]			12.1[j]
$\Delta H^{\ddagger}$ (H_2O)[a]	12.6 ± 0.9	17.2[d]			9.0[j]
$\Delta S^{\ddagger}$ (H_3O^+)[b]	−15 ± 3	−11[d]			−4[j]
$\Delta S^{\ddagger}$(H_2O)[b]	−31 ± 4	−25[d]			−38[j]
α	0.33 ± 0.02	0.3[f]		0.38	0.54[i]
β	0.56 ± 0.06	0.34[f]		0.76	

[a] kcal mol^{-1}. [b] cal mol^{-1} deg^{-1}. [c] This work. [d] Reference 14. [e] W.H. Hamill and V. K. LaMer, *J. Phys. Chem.*, **4**, 395 (1936). [f] Reference 13. [g] Reference 15. [h] Reference 16a. [i] R. P. Bell, M. H. Rand, and K. M. A. Wynne-Jones, *Trans. Faraday Soc.*, **52**, 1093 (1956). [j] Reference 18. [k] Y. Pocker, *Proc. Chem. Soc.*, 17 (1960). [l] Y. Pocker and J. E. Meany, *J. Phys. Chem.*, **71**, 3113 (1967).

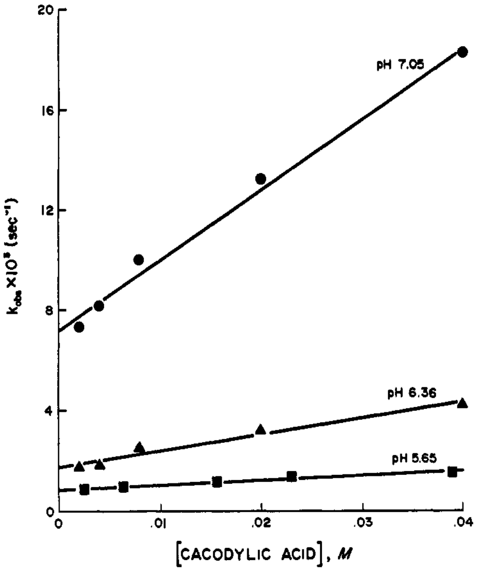

Figure 5. Observed first-order rate constants for hydrolysis of **3** as a function of [Me_2AsO_2H] and of pH.

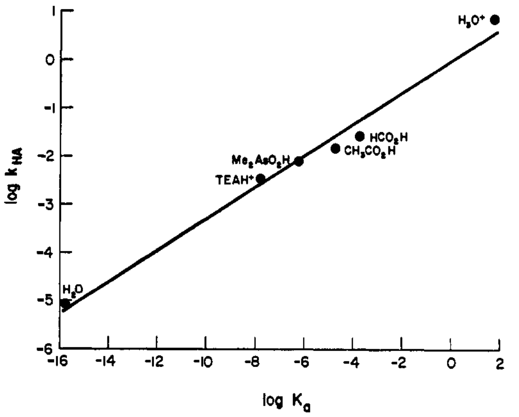

Figure 6. Brønsted plot showing general acid catalysis of the hydrolysis of **3**. $TEAH^+$ is triethanolammonium ion. All rate constants are in M^{-1} sec^{-1}.

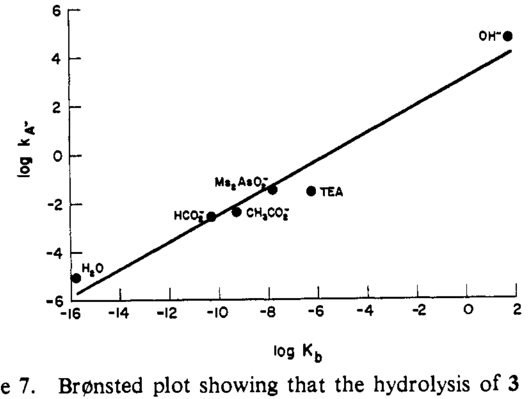

Figure 7. Brønsted plot showing that the hydrolysis of **3** is also subject to general base catalysis.

On the basis of the foregoing, we propose that the intermediate is the α-hydroxyhemiacetal **3**. This suggestion is strengthened by the similarities between the present reaction and the mutarotation of glucose (see Table II). Confirmation was obtained by semiquantitative rate measurements which showed that the rate of periodate uptake at pH 5.8 is at least 100 times greater than the rate of aldehyde formation in the absence of periodate under otherwise identical conditions. The probable course[12] of these reactions is shown in eq 2.

The hydrolysis behavior of the α-phenyl epoxy ether **4** has also been studied. The pH–rate profile

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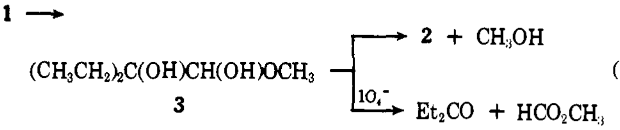
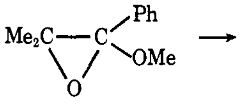
[12] The expected cleavage products methyl formate and diethyl ketone were not actually identified.



$$\mathbf{1} \longrightarrow (CH_3CH_2)_2C(OH)CH(OH)OCH_3\ (\mathbf{3}) \begin{cases} \longrightarrow \mathbf{2} + CH_3OH \\ \xrightarrow{IO_4^-} Et_2CO + HCO_2CH_3 \end{cases} \qquad (2)$$

for **4**, also shown in Figure 1, closely resembles that for **1**, the rate maximum occurring at pH 6.8. We assume therefore that the reaction being observed on the low pH side of this maximum is the hydrolysis of the hemiketal **5**. The following 25° rate constants



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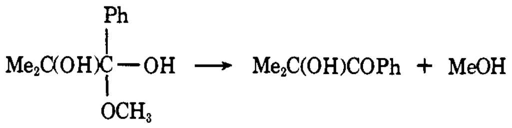

$$Me_2C(OH)C(Ph)(OCH_3)OH \longrightarrow Me_2C(OH)COPh + MeOH$$

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(10% v/v dioxane-water) were obtained: $k_H' = 27$ M^{-1} sec^{-1}, $k_{H_2O}' = 7 \times 10^{-4}$ sec^{-1}, and $k_{OH}' = 2.2 \times 10^5\ M^{-1}$ sec^{-1}.

Discussion

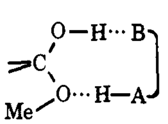
Information about the mechanism of hemiacetal hydrolysis is based largely on kinetics studies of the mutarotation of glucose[13,14] and tetra-*O*-methylglucose.[15] Bell has examined the kinetics of depolymerization of the dimers of dihydroxyacetone[16a] and glycolaldehyde.[16b] Acyclic hemiacetal hydrolysis has not previously been investigated in detail presumably because of the unavailability of appropriately reactive substrates. However, the mechanism of the hydration–dehydration of simple aldehydes and ketones and the mutarotation of glucose are known to be closely related.[15a,17]

Recent discussions of these mechanisms[15a,17–20] have been framed in terms of proton transfer occurring within cyclic association complexes such as **6**, where BAH is a bifunctional acid–base, *e.g.*, CH_3COOH, or **7a** and **7b**, where AH and B are monofunctional acids and bases, respectively. Obviously additional bridging water molecules may be inserted in **6** and **7** without altering the basic mechanistic concept.

The evidence supporting such a mechanism is largely negative—obvious alternatives to it can be ruled out. For example, the two-step mechanism given in eq 3 and 4 for general acid catalysis has been excluded[20] in the case of the dehydration of acetaldehyde hydrate in aqueous acetone[21] on the grounds that the magnitude of the overall rate constant, k_r ($= K_1k_2$), and a reasonable estimate of K_1 lead to the requirement that k_2 exceed the maximum for a diffusion-controlled process when HA is a weak acid such as water.

$$HS + HA \overset{K_1}{\rightleftharpoons} H\overset{+}{S}A + A^- \qquad (3)$$

$$H\overset{+}{S}H + A^- \xrightarrow{k_2} HA + P \qquad (4)$$



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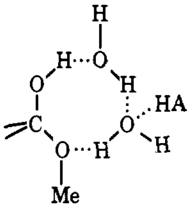

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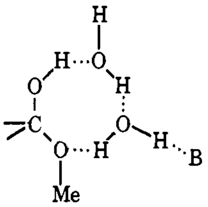

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Eigen[20] has concluded that "the only way out of these difficulties is the formulation of a concerted or cooperative mechanism where both the acidity of the catalyst HA and the basicity of its conjugate base B come into play at the same encounter."

The need for a special mechanism might be argued on other grounds as well. The kinetics of ordinary acetal hydrolysis require that the hydrolysis of the intermediate hemiacetal be much faster than that of the acetal precursor at all pH values.[3] In our system the dimethyl acetal of **2**, $Et_2C(OH)CH(OMe)_2$, may be predicted[22] to be 500 times less reactive than **3** in the H_3O^+-catalyzed reaction. However, the basicities of methoxyl oxygen in $R_2C(OH)OMe$ and $R_2C(OMe)_2$ are doubtless nearly identical. The same should be true of the stabilities of the corresponding carboxonium ions, R_2C^+OH and R_2C^+OMe. Therefore, the availability in the hemiacetal of a relatively acidic proton (p$K_a \sim 13$)[17] apparently provides the key to an understanding of the enhanced reactivity which is evinced even in acid catalysis. In other words, the transition state must contain both acid and base.

The general acid–general base mechanism apparently implies that one ought to see a third-order kinetic term, $k_3[HA][A^-]$. The formal analysis of Swain[26] may be used to derive a value of 0.11 M^{-2} sec^{-1} for k_3. However, in $HOAc-OAc^-$ buffers where such a term should have made a 30% contribution to the observed rate constant, no effect whatsoever could be detected. This failure cannot, of course, be said to rule out the cyclic transition state. In fact, molecular models[27] show that it would be extremely difficult to fit hemiacetal, HOAc, and OAc^- in a cyclic hydrogen-bonded complex and preserve normal bond angles and lengths.

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(16) (a) R. P. Bell and E. C. Baughan, *ibid.*, 1947 (1937); (b) R. P. Bell and J. P. H. Hirst, *ibid.*, 1777 (1939).

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(21) R. P. Bell and W. C. E. Higginson, *Proc. Roy. Soc., Ser. A*, **141**, 197 (1949).

(22) This calculation is based on the equation $\log k/k_0 = \rho^*\sigma^*$, with $\rho^* = -3.65$,[23] $\sigma^* = +0.35$ (derived from $\sigma^* = 0.555$ for the $-CH_2OH$ group by the addition of known values[24]), and k_0 for the hydrolysis of $MeCH(OMe)_2$[25] as 0.274 M^{-1} sec^{-1} at 25°.

(23) M. M. Kreevoy and R. W. Taft, Jr., *J. Amer. Chem. Soc.*, **77**, 5590 (1955).

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(25) "Tables of Chemical Kinetics," *Nat. Bur. Stand. (U. S.) Circ.*, **No. 510**, 22 (1951).

(26) C. G. Swain, *J. Amer. Chem. Soc.*, **72**, 4578 (1950).

(27) Framework molecular orbital models employed 109 and/or 120° bond angles and 2.8-Å oxygen–oxygen hydrogen bond distances.

On the other hand, these models do suggest that cyclic complexes containing hemiacetal plus three water molecules or one molecule each of HOAc (or OAc^-) and H_2O are structurally reasonable.[28]

However, we do not feel that the evidence in hand really permits extended speculation about the disposition of solvent molecules in the transition state or the concertedness of the overall reaction. Instead we would like to draw attention to a basic feature of the OH^- reaction which may shed some light on the nature of the pH-independent process. The hydroxide ion catalyzed reaction has been all but ignored in previous kinetics investigations of the mutarotation of glucose.

Since the pK_a of an α-hydroxyhemiacetal may be estimated[17] to be ~13, it seems very likely that the hydroxide-catalyzed reaction proceeds *via* a discrete $RCH(OCH_3)O^-$ ion intermediate as shown in eq 5 and 6. Therefore, the rate-limiting step would be the

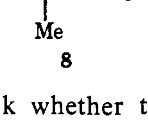
$$RCH(OCH_3)OH + OH^- \rightleftharpoons RCH(OCH_3)O^- + H_2O \quad (5)$$

$$RCH(OCH_3)O^- + H_2O \longrightarrow RCHO + CH_3OH + OH^- \quad (6)$$

general acid assisted removal of the methoxyl leaving group from $RCH(OCH_3)O^-$. The reverse of this step is of course mechanistically analogous to the base-catalyzed hydration of acetaldehyde for which a cyclic transition state has again been postulated.[18]

Methoxide ion is a very poor leaving group. The ionization of the hemiacetal should both increase the basicity of MeO and facilitate the breaking of the MeO–C ether bond. The low value of Brønsted's α for the reaction ($1 - \beta = 0.44$) suggests that the latter factor is more important. That the replacement of hydrogen by a phenyl group has relatively little effect on the rate argues that the transition state more closely resembles **6** than product, *i.e.*, that the hybridization of the central C atom is close to sp^3. However, the possibility that steric factors come into play in the case of the phenylated substrate cannot be ruled out.

The question then arises as to whether or not the pH-independent reaction involves preionization. In other words, is proton transfer from the hemiacetal complete as in the hydroxide ion catalyzed reaction or partial as in the hydronium ion catalyzed reaction?[2] The two alternative transition state preceding intermediates, shown without bridging waters, are **8** and **9**.



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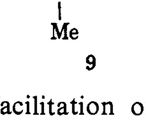

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One may ask whether the facilitation of C–O bond breaking *by* ionization would suffice to compensate for the 18 kcal mol^{-1} of energy required *for* ionization. The observed rate constant for the pH-independent reaction at 25°, 4.8×10^{-4} sec^{-1}, and the estimate[17] of 10^{-13} *M* for the acid ionization constant of **3** may be combined in the expression, $k_{H_2O} = K_ak_2$, to give a value of 5×10^9 M^{-1} sec^{-1} for k_2. This is not an impossibly large value and therefore the two-step ionization mechanism is a definite possibility for the pH-independent reaction.

The large negative entropy of activation associated with the spontaneous reaction may be taken as evidence for the development of considerable zwitterionic character in the transition state. It is significant in this regard that the standard entropy change associated with the autoionization of water,[30] −19 cal mol^{-1} deg^{-1}, is about the same as the difference, $\Delta\Delta S^{\ddagger}$, between the H_3O^+-catalyzed and pH-independent reactions of **3**.

On the other hand, it is worth noting that k_{H_2O} fits the Brønsted α and β plots equally well, implying a continuity of mechanism as catalyst is varied from H_3O^+ to OH^-. This observation is of dubious significance, however, inasmuch as the slopes of these plots are in fact largely determined by the values of the extreme points.

Further elucidation of the mechanism of hemiacetal hydrolysis might be effected through a detailed analysis of deuterium isotope effects such as attempted by Huang, Robinson, and Long[15a] for mutarotation of tetra-*O*-methylglucose. Such studies are in progress. It suffices for the nonce to note that the isotope effects on the H_3O^+ and H_2O rates are consistent with those observed previously and that on the OH^- reaction is in accord with expectations. If K_H/K_D for eq 5 is about 4.5/7.4, based on analogy,[31] then the observed k_{OH}/k_{OD} of ~0.8 is explained by an isotope effect on eq 6 of 1.3.

Experimental Section

Materials. 1-Methoxy-2-ethyl-1,2-epoxybutane (**1**) and 1-methoxy-1-phenyl-2-methyl-1,2-epoxybutane (**4**) were prepared from the corresponding α-bromoaldehyde and α-bromo ketone, respectively, by the method of Stevens and Coffield.[32] Dioxane was purified by passing it through a column of neutral alumina.

2-Bromo-2-ethylbutanal was obtained by adding bromine with stirring to freshly distilled 2-ethylbutanal (Aldrich Chemical Co.) in cold glacial acetic acid. After warming to room temperature HBr was removed under reduced pressure and the mixture was shaken with twice the volume of water. The lower oily layer was washed with aqueous Na_2CO_3 and water, taken up in ether, and dried over $MgSO_4$. The ether was removed and the residue distilled to give a 38% yield of product, bp 43° (4 mm), $n^{25}D$ 1.4567.

1-Methoxy-2-ethyl-1,2-epoxybutane (1), prepared in 52% yield from 2-bromo-2-ethylbutanal and freshly prepared anhydrous sodium methoxide in anhydrous methanol, had: bp 46° (6 mm); $n^{25}D$ 1.4710; $\delta_{\mathrm{TMS}}^{\mathrm{CCl_4}}$ 4.2 (s, 1 H), 3.4 (s, 3 H), 1.5 (m, 4 H), 0.8 (m, 6 H); $\nu_{\max}^{\mathrm{neat}}$ 1250, 900, and 825 cm^{-1} (epoxide bands[33]) and no carbonyl absorption; mass spectrum 130 (parent) and 73 (base).

Anal. Calcd for $C_7H_{14}O_2$: C, 64.56; H, 10.86. Found: C, 64.30; H, 10.80.

1-Methoxy-1-phenyl-2-methyl-1,2-epoxypropane (4), prepared from α-bromoisobutyrophenone[34] and sodium methoxide as described above in 50% yield, had bp 54-56° (0.07 mm) [lit.[32] 68-70° (3 mm)], and $n^{25}D$ 1.4840. The structure was confirmed by ^1H nmr, mass, and infrared spectra.

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[28] The models neatly substantiate Bell's suggestion[29] that HOAc and OAc^- each replace two water molecules.

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Product Analysis. To 100 ml of 10^{-4} *M* $HClO_4$ was added 8.61 g of **1** at room temperature. After 2 hr the solution was extracted with five 50-ml portions of ether. The ether was removed, leaving 6.76 g of residual liquid. Analysis of the residue by glc showed one major component (95%), water, methanol, and a minor component (1.5%) judged to be the dimethyl acetal of **2** by comparative retention times.

The major component was identified as 2-ethyl-2-hydroxybutanal: bp 59–60° (26 mm); $\delta_{TMS}^{C_3D_6O}$ 0.8 (t, $J = 7$ Hz, 6 H), 1.8 (m, 4 H), 4.2 (br s, 1 H, O*H*), 9.51 (s, 1 H, C*H*O); ν^{neat} 3450, 2720 (sh), and 1720 cm^{-1}; mass spectrum 116 (parent), 45 (base).

Anal. Calcd for $C_6H_{12}O_2$: C, 62.02; H, 10.43. Found: C, 61.84, 61.99; H, 10.30, 10.36.

Kinetic Procedure. All kinetic measurements were carried out by monitoring the formation of aldehyde product at 290 nm (ϵ 21) or ketone product at 316 nm. The solvent used throughout was 10% dioxane–water (v/v) with μ maintained at 0.11 by $NaClO_4$ except as noted below. Buffers employed were perchloric acid (pH 3.41–4.81), formic acid (pH 3.86–4.75), acetic acid (pH 4.09–6.12), cacodylic acid (pH 5.65–7.07), and triethanolamine (pH 6.96–7.61). A 0.5 *M* stock solution of DOAc in D_2O (99.8%), prepared according to Goodall and Long,[35] was used to make up acetate buffers in 10% dioxane-D_2O (v/v). The pH meter readings were converted to pD values by adding 0.4.[36] A Radiometer Model 4 pH meter was used to determine the pH values of buffer solutions.

Reactions were started by adding 14 μl of **1** or 1.5 μl of **4** to 3 ml of a buffer solution at 25.0° in a 1-cm silica cell, shaking vigorously and replacing in the thermostated (25.0 ± 0.1°) cell compartment of a Beckman DU-2 spectrophotometer. The reactions were followed to 60–80% of completion; infinity readings were taken after 8–12 half-lives. Pseudo-first-order rate constants, k_{obsd}, were calculated by means of a computer program which utilizes a variable infinity point.[37] Swinbourne's method[38] was used as a check; satisfactory agreement between the two methods was realized in all cases.

The first-order rate constant in a solution containing an $HA-A^-$ acid–base pair was taken as

$$k_{obsd} = k_{H_2O} + k_Ha_H + k_{OH}a_{OH} + k_{HA}[HA] + k_A[A^-]$$

The rate constants k_H and k_{H_2O} were obtained from the least-squares slope and intercept, respectively, of plots of log k_{obsd} *vs.* [$HClO_4$]. Plots of k_{obsd} *vs.* [HA] at three different pH values give slopes from which may be extracted k_{HA} and k_A and intercepts which yield k_{OH}. Linear least-squares analysis was applied throughout.

Activation parameters were obtained from plots of log k_H or log k_{H_2O} *vs.* $1/T$. The temperatures, 15.0, 25.0, 30.0, and 35.0°, could be controlled to ±0.1°.

Acknowledgments. We gratefully acknowledge the support of the National Science Foundation through Grants GP-7392 and GP-14693. Computer time was donated by the University of Hawaii Computing Center. Sherwin Amimoto assisted with the computer program.

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Kinetics and Mechanism of Epoxy Ether Hydrolysis. II. Mechanism of Ring Cleavage[1]

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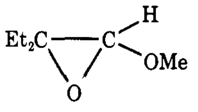
Received November 29, 1971

Abstract: The kinetics of ring cleavage of two epoxy ethers, 1-methoxy-2-ethyl-1,2-epoxybutane (**1**) and 1-methoxy-1-phenyl-2-methyl-1,2-epoxypropane (**2**), have been studied in 10% aqueous dioxane (v/v) at 25° and pH 8–13. Both substrates hydrolyze *via* pH-independent and H_3O^+-catalyzed reactions. General acid catalysis by $H_2PO_4^-$ is observed in the hydrolysis of **2**. Solvent deuterium isotope effects, k_D/k_H, for catalysis by L_3O^+ are 2.02 for **1** and 1.35 for **2**. Entropies of activation are −11 eu for **1** and −15 eu for **2**. Compound **2** reacts 10.2 times slower than **1**. These results suggest that proton transfer to ring oxygen is concerted with C–O bond breaking in relatively reactant-like transition states. The pH-independent cleavage of **1** has $k_{D_2O}/k_{H_2O} = 0.53$ and $\Delta S^{\ddagger} = -49$ eu. Catalysis by hydroxide ion is also observed although k_{OH}/k_{H_2O} is only 11 M^{-1}. The corresponding parameters for **2** are $k_{OH}/k_{H_2O} = 0.35$ and $\Delta S^{\ddagger} = -36$ eu. A bimolecular mechanism is proposed in which nucleophilic attack is concerted with proton transfer.

The hydrolysis of 1-methoxy-2-ethyl-1,2-epoxybutane (**1**) undergoes a change of mechanism in 10% aqueous dioxane (v/v) at 25° at a pH of ~8.0. The low pH reaction has been characterized[3] as the hydrolysis of the hemiacetal intermediate, $Et_2C(OH)CH(OCH_3)OH$. We turn now to the high pH reaction which involves rate-determining cleavage of the epoxide ring. The kinetics of the ring opening of 1-phenyl-2-methyl-1,2-epoxypropane (**2**) are also reported.

Epoxy ether **1** is an acetal; **2** is a ketal. Simple acetals and ketals generally hydrolyze *via* an A1 mechanism, *i.e.*, equilibrium protonation of oxygen followed by rate-determining dissociation of ROH to give a carboxonium ion.[4] However, recent work has demonstrated that the normal A1 mechanism can be modified by appropriate structural alteration.[5–9] The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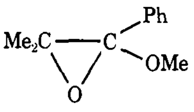
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