(64) A similar effect of the octamethylene chain caused the lack of direct formation of **11b** from **1b** in the AgClO₄ catalyzed process; compare ref 53.

(65) A close similarity is assumed with the proposed mechanisms for the Ni(0) catalyzed cycloaddition of electron-deficient olefins to quadricyclane and the Ni(0) catalyzed valence isomerization of quadricyclane into norbornadiene: R. Noyori, I. Umeda, H. Kawauchi, and H. Takaya, *J. Am. Chem. Soc.*, **97**, 812 (1975).

(66) Preliminary results from the reaction of [8](2,4)-3-oxaquadricyclane (structure ii in ref 38) with Rh₂(CO)₄Cl₂ confirm the proposed mechanism; a very fast reaction occurs in which CO evolution is observed. The fast reaction of ii compared with that of **1b** is in agreement with the rhodium-catalyzed valence isomerization of quadricyclanes: H. Hogeveen and B. J. Nusse, *Tetrahedron Lett.*, 3667 (1973).

(67) For a review of the subject of oxidative addition, see J. Halpern, *Acc. Chem. Res.*, **3**, 386 (1970).

(68) The observation of about equal rates for the formation of **4a** and **4d** by the oxidative addition process may be compared with the rates of the Rh₂(norbornadiene)₂Cl₂ catalyzed reactions of homocubane and 4-methylhomocubane (the rates differ by a factor of 2.5); see ref 16b.

(69) The results from the catalyzed reactions of 2,3-dicarbomethoxy-1,4-dimethyl-7-oxanorbornadiene (NOR*) (this is the precursor of **1a**, obtained by Drs. A. Bruggink and T. B. Middelkoop in this laboratory) allow the conclusion that most probably the 7-oxanorbornadienes are not involved in the catalyzed reactions of the 3-oxaquadricyclanes. It has been found that reaction of NOR* with CF₃COOH leads to the formation of **7a**, whereas **1a** is converted into **3a** by CCl₃COOH or into **4a** by H₂SO₄; NOR* does not react with CuCl, whereas under the same conditions **1a** is converted

smoothly into **4a**; reaction of NOR* with Pd(C₆H₅CN)₂Cl₂ does not lead to **4a**, whereas the latter compound is formed from **1a** under the same conditions; finally, NOR* is converted into **4a** on treatment with Rh₂(CO)₄Cl₂, whereas under the same conditions **1a** is mainly converted into **5a**. The minor product **4a** in the latter case may formally be formed via NOR*; however, we have no indications for this and, in view of the above-mentioned results it seems unlikely.

(70) A. I. Vogel, "A Textbook of Practical Organic Chemistry", 3rd ed, Longmans, London, 1956, p 163.

(71) (a) H. Nozaki, T. Koyoma, and T. Mori, *Tetrahedron*, **25**, 5357 (1969); (b) K. Matsui, T. Mori, and H. Nozaki, *Bull. Chem. Soc. Jpn.*, **44**, 3440 (1971); (c) R. Helder, Ph.D. Thesis, University of Groningen, 1974, has described an improved synthesis of [8](2,5)furanophane.

(72) (a) The methylene carbon atoms were observed in the region of δ 28.69–22.13. No coupling constants could be obtained because of the complexity and number of signals. (b) One of the quaternary sp² carbon atoms could not be determined with certainty. (c) The chemical shifts of the octamethylene chain hydrogens could not be determined because of the low concentration of **10b** in the reaction mixture. (d) Not all the quaternary carbon atoms could be determined because of the low concentration of **10b** in the reaction mixture. (e) The exact chemical shifts of the octamethylene chain carbon atoms could not be determined because of the complexity of the signals in the area of δ 36.68–22.84; neither of the coupling constants have been estimated. (f) The chemical shifts of the octamethylene chain hydrogens have not been determined. (g) Analogous to **10b** the chemical shifts of the octamethylene chain carbon atoms could not be determined (compare 72e).

(73) H. Hogeveen and T. B. Middelkoop, *Tetrahedron Lett.*, 4325 (1973).

A Nuclear Magnetic Resonance Kinetic Study of the Acid-Catalyzed Epoxide Ring Opening of Tetramethylethylene Oxide[1]

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Abstract: The kinetics of the hydrolytic ring opening of tetramethylethylene oxide (TMEO, **1**) to form pinacol (**2**) in aqueous buffers have been investigated by nuclear magnetic resonance spectroscopy using a repetitive timed integration technique. The pseudo-first-order rate plots showed excellent linearity, >87%, and yielded observed rate coefficients which were dissected into the three components, k_0, $k_{H_3O^+}$, and k_{HA}. The velocity term, $k_{HA}[HA][1]$, arising from catalysis by molecular formic acid, leads concurrently to the formation of two products, **2** and pinacol monoformate. The overall velocity expression for the hydrolysis of **1** then is velocity = $\{k_0 + k_{H_3O^+}[H_3O^+] + k_{HA}[HA]\}[1]$. Kinetic and solvent deuterium isotope effects were examined using standard procedures and were found to be $k_{H_3O^+}/k_{D_3O^+} = 0.35$, $k_{HA}/k_{DA} = 1.6$, and $k_{H_2O}/k_{D_2O} = 1.8$. The magnitude of these isotope effects, coupled with activation parameters, product analyses under strict kinetic control, nucleophilic catalysis by a buffer component, and general acid catalysis by HA, supports the conclusion that there is participation by a nucleophile (H₂O or A⁻) in the various transition states associated with the ring-opening process. Pinacol is produced via k_0, $k_{H_3O^+}$, and the component of general acid catalysis in the k_{HA} term. Pinacol monoformate is produced via the component of nucleophilic catalysis in the k_{HA} term. Mechanisms which accommodate these data and also account for the strong orientational preference in the ring-opeing process of unsymmetrical epoxides are proposed.

Introduction

In a now classic kinetic investigation, Brønsted, Kilpatrick, and Kilpatrick[4] demonstrated that the heterolytic ring fission of simple epoxides in aqueous media was a reaction characterized by several kinetically distinguishable components. These were identified as arising from the catalytic action of hydronium ion, hydroxide ion, and the solvent. Using various buffer solutions, an attempt was made to observe general catalysis, but this discovery proved elusive.

Twenty-six years later, Long and Pritchard[5] re-examined the kinetics of epoxide hydrolysis using techniques and substrates identical with those used by Brønsted et al., but refined by ¹⁸O tracer mass spectrometry and by the study of solvent deuterium isotope effects. The latter techniques allowed Long and Pritchard to elegantly correlate each of the kinetically distinguishable catalytic components, with a characteristic reaction mechanism. In this study also the discovery of general

acid catalysis proved elusive. Since Long's original papers, several authors[6-8] have investigated certain facets of the epoxide ring-opening problem. Though this new data was not conclusive enough to provide a definitive analysis, it has made it obvious that for epoxide hydration the previously postulated A-1 mechanism exhibits a number of characteristics associated with an A-2 process.

In this paper we describe a kinetic study of the epoxide ring opening of tetramethylethylene oxide (TMEO) by nuclear magnetic resonance spectroscopy and report that this simple saturated epoxide exhibits general acid catalysis in addition to the other traditional forms of catalysis. Because of the special nature of TMEO, certain unique mechanistic problems were encountered in attempting to rationalize our experimental findings with those of other workers. These problems were resolved with the aid of recent developments in MO theory[9] allowing us to formulate a satisfactory description of the ring-opening process which is described herein.
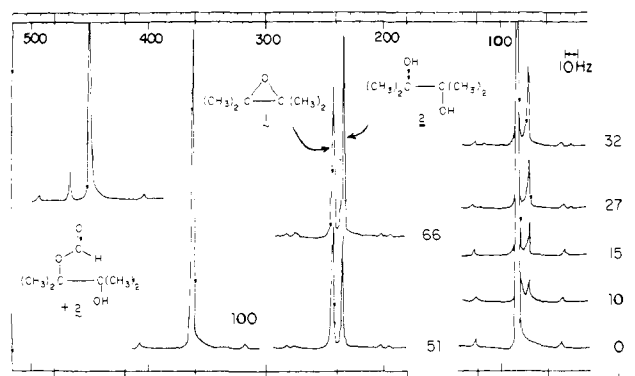
Figure 1. Nuclear magnetic resonance spectra taken during the course of hydration of tetramethylethylene oxide, TMEO, **1**, at pH 4 in aqueous $HClO_4$. The number adjacent to each curve corresponds to the percentage reaction.
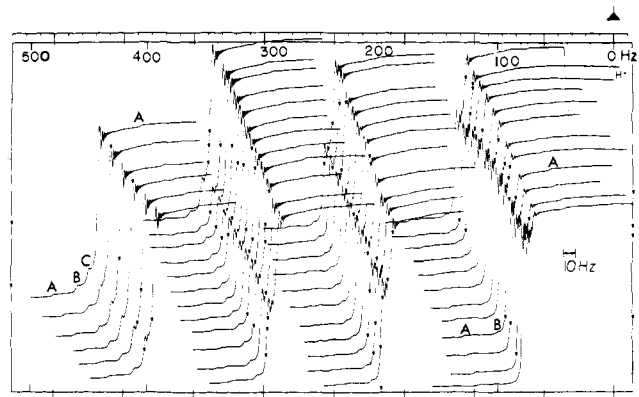

Figure 2. Integration curves as a function of time. Integrations across the chemical shift region of TMEO, **1**, and its hydration product **2**. Easily distinguishable are the spinning sidebands for the signal of **2**, labeled A, the signal for pinacol monoformate, B, and the signal for unreacted TMEO, **1**, labeled C.

The uniqueness of this study is accentuated by the recent work of several authors, who, while experimenting with a special group of unsaturated epoxides[10,11] and epoxy acetals,[12] have observed complex forms of catalysis. In an incisive study, Bruice, Jerina, and their co-workers[10] have implicated these catalytic processes a priori as a primary cause for the mutagenic and carcinogenic characteristic of many aromatic substances. While the importance of simple saturated epoxides as carcinogens should not be overlooked, very recent reports suggest that epoxy compounds are more abundant in nature than heretofore suspected[13] and that certain ones may play important roles as anticarcinogenic agents.[14] These inexplicable observations illustrate in a very striking manner the unique nature of the epoxide linkage and the singular character of its reactions.

Experimental Section

Kinetic Measurements. Kinetic measurements were made on a Varian Model T-60 nuclear magnetic resonance spectrometer, which had been tuned to give optimum resolution.[15] The spectral amplitude, integral amplitude, and filter were optimized for the particular concentrations used. The signal phase was adjusted for each sample. A run was begun by taking previously thermostated samples of TMEO (**1**) and buffer solution and at time zero mixing them thoroughly on a magnetic stir plate for 60 to 80 s. The sample was then added to a thermostated NMR tube and placed in the probe within 120 to 180 s from time zero. The signal phase and spinning rate were optimized and the integrations begun. The integrator was allowed to trace out flat baseline below and above the spinning sidebands for the main peaks. The time was noted as the integrator passed over the TMEO peak. Integrations could be performed every 20 s.

Variable-temperature kinetic studies were performed on a Varian Model HA 100 nuclear magnetic resonance spectrometer fitted with a variable-temperature probe and signal lock. Temperatures were measured by observing the chemical shift difference in hertz between the OH and CH_3 peaks of methanol.[16]

pH measurements were made on a Beckman Model 101900 research pH meter fitted with glass and SCM electrodes. The meter was temperature compensated to the kinetic temperature. Actual kinetically run samples were used for each measurement and were thermostated to the kinetic temperature prior to and during the measurement. Measurements were made in duplicate for each sample. The meter was calibrated after every fourth measurement against commercial buffer solutions at the working temperature and pH. pDs were measured in a similar manner and were computed by adding 0.4 to each pH observation made in D_2O medium.[17]

Spectrophotometric-kinetic measurements were made on a Beckman Model DU spectrophotometer fitted with a constant-temperature bath as described previously.[1] The λ_{max} of pinacolone was observed at 278 nm.

Chemicals. All salts used, $NaNO_3$, Na_2SO_4, and HCO_2Na were analytical reagent quality and were dried under vacuum for 24 h prior

to use. $NaClO_4$ was dried at 130 °C and 10^{-2} Torr until all of the water of hydration was gone. Drying was considered to be complete when no water was collected in the trap over a period of 6 h at 130 °C and 10^{-2} Torr.

Crude formic acid, 97%, was rendered anhydrous by stirring with anhydrous $CuSO_4$ for 24 h. Distillation produced a large colorless middle fraction which was fractionally frozen until the necessary quantity of mp 8.3 °C acid was acquired. This material was used for buffer preparation. The D_2O used was 99.8% deuterated as obtained from Stohler Isotope Chemicals, Inc.

Buffer solutions were made by dilution of stock concentrated buffer solution with distilled water. The predetermined amount of inert salt to make $\mu = 2.0$ was weighed into a volumetric flask, stock buffer solution measured from a buret was added, and the resultant solution was diluted to volume with distilled water. Buffer solutions made in this manner showed only a 0.10 pH change over a tenfold dilution. The ionic strength was held constant at 2.0 with $NaNO_3$ or Na_2SO_4. The latter was found to be better since the pH change was less upon dilution.

Tetramethylethylene oxide was prepared by peracid oxidation of the olefin, tetramethylethylene, according to the method of Hickinbottom and Hogg except that m-chloroperbenzoic acid was used in place of perbenzoic acid.[18] Samples used for kinetic runs were twice distilled through a 6-in. Vigreux column and were stored over anhydrous Na_2SO_4 at -5 °C until just prior to use. Analysis by a Hewlett-Packard Model 5750 research gas chromatograph indicated that 0.6% pinacolone (**3**) was present as an impurity.

Results

The acid-catalyzed hydrolysis of TMEO (**1**) to pinacol (**2**) in aqueous media can easily be observed by direct integration-repetitive scanning nuclear magnetic resonance spectroscopy. Because of anisotropy effects associated with the epoxide ring, the chemical shift of the methyl protons in **1** is
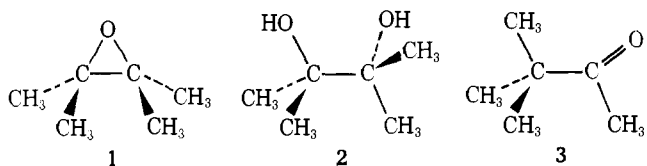
located $\sim$0.2 ppm downfield from that of the methyl protons in **2** (Figure 1). The integral for **1** (Figure 2), readily measured as a function of time, corrected for an infinity contribution, and plotted as log (area$_t$ − area$_\infty$) vs. time, is shown in Figure 3. The linearity for these pseudo-first-order rate plots was very good, extending up to 94+% of reaction. The dependence of the rate upon acidity, shown by the pH-rate profile over the pH range from 3.8 to 8.0, displays an inflection occurring between pH 7.8 and 8.2 and suggests a change in the nature of the catalytic species (Figure 4).
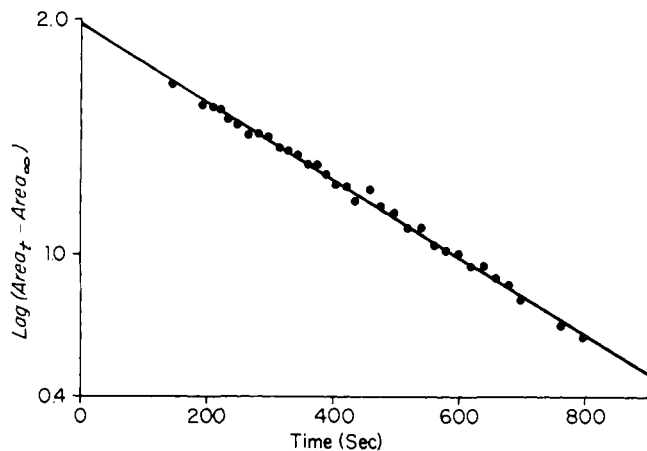
Figure 3. Plot of log (area$_t$ − area$_\infty$) vs. time for the hydration of TMEO. The linearity extends to 96% reaction at an elapsed time of 800 s. For duplicate runs at pH 4.07, 36.0 ± 0.5 °C, and ionic strength, μ = 2.0 with Na$_2$SO$_4$, k_{obsd} = 3.79 × 10^{-3} s^{-1} and 3.74 × 10^{-3} s^{-1}. The error in the reproducibility of rate coefficients was at most 3%.

Figure 5. Nuclear magnetic resonance spectra taken during the course of rearrangement of pinacol, **2**, in aqueous 2.0 M HClO$_4$ at 36.0 ± 0.5 °C. The chemical shift of the methyl protons in **2** is 1.2 ppm downfield from Me$_4$Si as external standard. The shifts in pinacolone are acetyl, 2.3 ppm, and *tert*-butyl, 1.1 ppm, downfield from Me$_4$Si as external standard. The number adjacent to each curve corresponds to the percentage reaction.
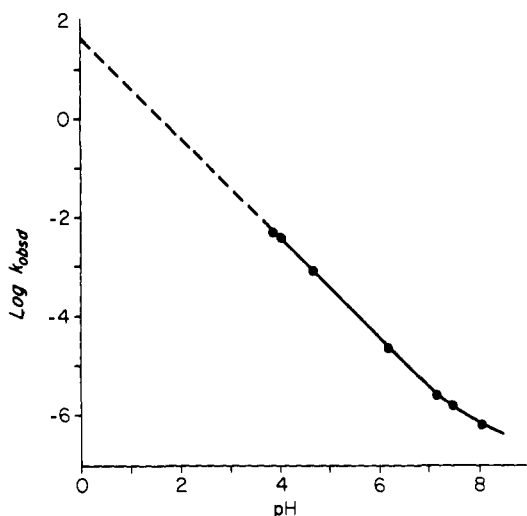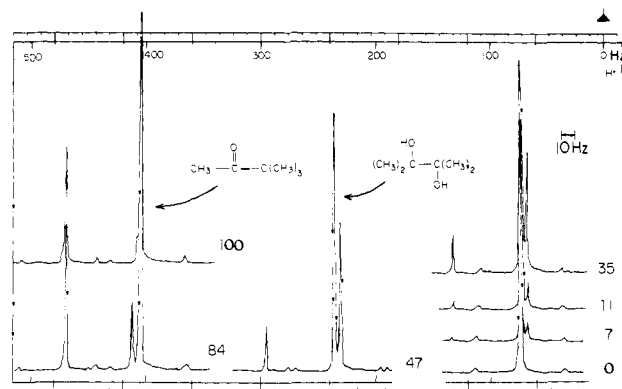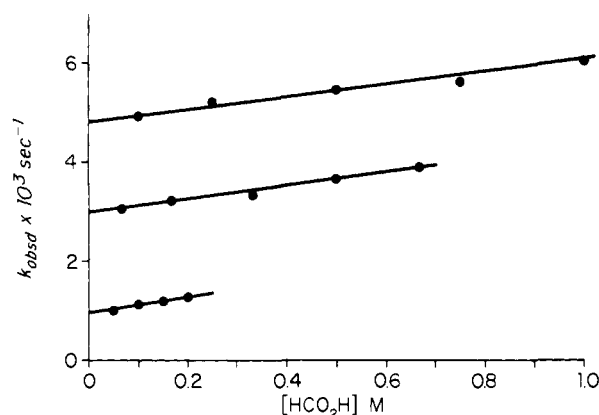

Figure 4. Plot of log k_{obsd} vs. pH for TMEO hydration at 36.0 ± 0.5 °C. A least-squares analysis of the data yielded a slope of −1.00 ± 0.02 and an intercept which corresponded to $k_{H_3O^+}$ = 38 ± 1.2 M^{-1} s^{-1}. See ref 24b.

Figure 6. Plot of k_{obsd} vs. [HCO$_2$H] for the hydration of **2** in aqueous HCO$_2^-$Na$^+$-HCO$_2$H buffer at μ = 2.0 and 36.0 ± 0.5 °C. Na$_2$SO$_4$ was used as the inert salt. When NaNO$_3$ was used to adjust the ionic strength, the same results were observed. The slope and intercept were derived from a least-squares treatment and yielded, respectively, k_{HCO_2H} = 1.39 ± 0.1 × 10^{-3} M^{-1} s^{-1} and $k_{H_3O^+}$ = 39 ± 3 M^{-1} s^{-1}. See ref 24b.

In a similar manner it was possible to measure the rate of conversion of **2** to pinacolone (**3**). In this case the ketone methyl group was located 1.1 ppm downfield from the methyl protons of **2**. The *tert*-butyl group of **3** had a chemical shift slightly upfield from **2** (Figure 5).

In aqueous formate buffers of μ = 2.0[19] at constant pH and varying total buffer concentration, the rate of hydration showed a dependency upon the buffer concentration leading to the following form for k_{obsd}.

$$k_{obsd} = k_0 + k_{H_3O^+}[H_3O^+] + k_{HA}[HA]$$

Plots of k_{obsd} vs. [HA], where [HA] was varied by a factor of 10, at three different pHs were linear with a common slope yielding k_{HA} and intercepts which yielded a common $k_{H_3O^+}$ term (Figure 6). Extrapolation of the linear portion of the pH–rate profile to pH 0 provides a confirmatory check on the value of the $k_{H_3O^+}$ term derived above (Figure 4). Similar studies were conducted in fully deuterated (99+% D$_2$O) buffer solutions which yielded k_{DA} and $k_{D_3O^+}$ terms, respectively. The rate coefficient for the spontaneous reaction in both H$_2$O and D$_2$O was determined in the region where catalysis by specific acid was small and by general acid was negligible (Table I).

Table I. Catalytic Coefficients, Isotope Effects, and Activation Parameters for the Hydration of **1** at 36.0 ± 0.5 °C and μ = 2.0[a]

| Solvent	Sponta-neous,[b] 10^7k, s^{-1}	Specific acid,[c] k, M^{-1} s^{-1}	General acid,[d] 10^3k, M^{-1} s^{-1}	Activation[e] parameters, kcal mol^{-1}
H$_2$O	2.80 ± 0.27	39[b] ± 3	1.39 ± 0.1	E_a = 15.9 ± 0.2 $\Delta H^{\ddagger}$ = 15.3 ± 0.2
D$_2$O	1.57 ± 0.1	112 ± 3	0.86 ± 0.06	$\Delta G^{\ddagger}$ 15.8 ± 0.2
k^H/k^D	1.8 ± 0.3	0.35 ± 0.03	1.6 ± 0.2	$\Delta S^{\ddagger}$ = −1.6 ± 0.7[f]

[a] See ref 24b for a discussion of the treatment of experimental data. [b] With NaClO$_4$ as inert salt at pH 8. Corrected for the specific acid contribution. [c] The pH–rate profile extrapolates to a value of $k_{H_3O^+}$ = 38 ± 1.2 M^{-1} s^{-1}. [d] Formic acid-sodium formate buffer. Rate coefficients corrected for pH drift from buffer dilution. [e] These activation parameters refer to the process associated with $k_{H_3O^+}$. [f] In eu.

The only detectable product in these hydration reactions in dilute buffer solution was **2**; no evidence could be found for the formation of pinacolone (**3**). When the hydration reaction was followed spectrophotometrically at the λ$_{max}$ of **3**, there was no

significant change in absorbance, i.e., <0.01 absorbance units. Had even 1.0% been converted to **3** the absorbance change would have been 0.06 absorbance units. The hydration reaction must go to completion, forming **2** to the extent of 99.9+% under these conditions.[20,22] In concentrated formate buffer solutions a small amount of monoformate ester, **4**, was detected

4
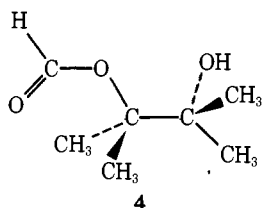
by the appearance of a singlet downfield from that of **1** and **2**. This peak persisted for a long time (over 50 half-lives of hydration) before it eventually disappeared.[23] Studies of **1** in pure formic acid have shown that ~90% is transformed into formate ester and 10% rearranged to **3**, within 3 to 5 min after mixing.[24a] The monoformate ester, **4**, has two singlet signals in the NMR, one 0.3 ppm downfield from **2**, and the other at the same chemical shift as **2** (Figure 1). A comparison of the magnitude of the buffer rate and the quantity of **4** generated suggests that the latter accounts for ~64% of the buffer rate in H$_2$O solutions.[24b,c]

Activation parameters were measured over a temperature range of 33 °C (Table I). The Brønsted plot from the catalytic data is curved with a slope of 0.8 between pK_a = 2 and 4 and of slope 0.6 at pK_a = 7.

The conditions required to bring about the rearrangement of **2** to **3** are much harsher than those required for hydration of **1**. The rearrangement only proceeds at a reasonable rate at an acid concentration >1 M. Even at 2 M HClO$_4$ and 36 °C the half-life is 10 days. Thus, the rate of epoxide hydration is 1 × 10^8 times faster than the rate of rearrangement of **2** under the same conditions.

Discussion

The results presented here are noteworthy not only because they reveal the very subtle relationship which exists between epoxide hydration and pinacolic rearrangements, but also because they represent the first observation of general acid catalysis in the hydration reaction of a simple alkyl-substituted epoxide. In several recent studies evidence from kinetic isotope effects and rearrangement products has implicated resonance stabilized carbonium ions as intermediates produced via an A-1 mechanism.[10-12] The A-2 pathway, in contrast, presupposes nucleophilic assistance in initiating and carrying forth the ring fission, concomitant with the conspicuous absence of rearranged products. In many instances of epoxide hydration the totality of available experimental evidence does not allow a clear distinction to be drawn between these mechanisms, and modifications to the A-1 or A-2 pathways must be devised in order to accommodate the results. Unique structural characteristics associated with a protonated epoxide admits of a need for a special mechanistic formulation for the ring-opening process.

For a better understanding of the structure of transition states and intermediates, a knowledge of the geometric relationship between reagent and product structure is indispensable.[25] In the acid-catalyzed hydration of TMEO (**1**) in aqueous media the kinetic isotope effect, $k_{H_3O^+}/k_{D_3O^+}$ = 0.35, is fully compatible with the data observed for other epoxides, and from its magnitude implies prior equilibrium protonation.[5,10-12] The immediate chemical consequence of protonation is ring opening, and following the A-1 mechanism would lead to the formation of ion **5b** (Scheme I). This ion, however, is the known intermediate in the acid-catalyzed rearrangement

Scheme I
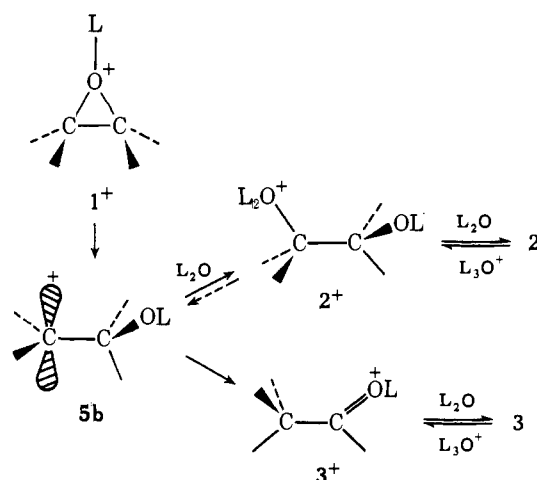
of pinacol, where isotopic tracer studies, capture experiments, and medium effects have established that partitioning occurs.[26] Thus, for every three ions of **5b** one leads to **3** and two produce **2**. However, during epoxide hydration in dilute acid under kinetic control, no **3** is formed and it seems unlikely that **5b** in that form lies on the pathway leading from **1$^+$** to **2**. It is conceivable that **1$^+$** could ring open to an ion **5a** which is similar to **5b**, but with a conformation where the improper location of the migration origin vis-a-vis the migration terminus contravenes rearrangement. Such again seems unlikely in the view of recent results from MO calculations on the conformational energies of carbonium ions.[27] Thus, the complete absence of rearrangement products, the observation of general acid catalysis and its accompanying deuterium solvent isotope effects, vide infra, in the hydration of TMEO seem to controvert the classical A-1 mechanism.

The spontaneous hydration reaction at values around neutral pH appears to have a similar mechanistic restriction since rearranged products are not observed here either. This taken together with the value for the solvent deuterium isotope effect, k_{H_2O}/k_{D_2O} = 1.8 suggests concurrent proton transfer and nucleophilic participation by water.[28] In buffer solution a small fraction of **1** (15% at most) is observed to form an adduct, **4**, which appears distinctly in the NMR spectrum.[29] A correlation of the buffer contribution to the total rate and the amount of **4** reveals that only 64 ± 6% of this rate is accounted for by this adduct. Thus, two thirds of the buffer rate represents nucleophilic catalysis. The remaining one third must be due to general acid catalysis, apparently of the form specific acid-general base.

All of this evidence seems to favor the A-2 pathway for TMEO hydration. Whalley[6] has concluded that the entropies of activation and volumes of activation for ethylene, propylene, and isobutylene oxide hydrolyses in acidic media indicate that an A-2 process is operative. It was argued, further, that the geometry of the epoxide linkage, which contains certain large bond angles, facilitates the close approach of nucleophiles and therefore predispose nucleophilic ring-opening processes.[6,8] This attractive proposal suffers, however, from the fact that unsymmetrical epoxides display a very strong orientational preference in ring opening.[8,30]

An alternative suggestion is that there exists a completely different orientation for ring opening through a bimolecular pathway for protonated and unprotonated epoxides. The protonated epoxide would have the orientation of ring opening controlled by charge density and by the magnitude of the LUMO coefficients at the oxirane carbon atoms, whereas the unprotonated form would have the orientation controlled by a different set of LUMO coefficients which now parallel steric factors. Recent MO calculations on the bridged fluoroethyl

cation[9] (which in many ways resembles protonated ethylene oxide) show that the carbons and hydrogens support large charge densities, relative to the heteroatom, **6**. Dannenberg in


X = F or possibly OH
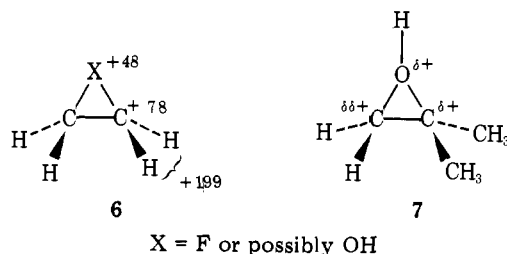
a theoretical study of the symmetrical exchange reaction of protonated alcohols with water has found that large charge densities reside upon the carbon atom at the reaction center and upon the adjacent carbon atoms and that the bond to the alcohol oxygen is stretched only very slightly in the transition state.[31a] If these results have a bearing upon the epoxide ring-opening reaction, they suggest that in protonated epoxides the oxirane carbon atoms possess considerable affinity towards nucleophiles[31b] and that the close approach of a nucleophile, e.g., H_2O, may promote bond rupture in the ring. Thus there may be a very large contribution by nucleophilic assistance to the ring opening. Certainly this would be consistent with the known stereochemical evidence for ring opening, where inversion of configuration is almost exclusively found, and it would account for the lack of rearrangement that seems to be normal in epoxide hydration in aqueous media.

The orientation of ring opening in protonated epoxides would be controlled by the magnitude of charge and by the LUMO coefficient at the oxirane carbon atoms.[31b] Under these conditions the observed regiochemistry for nucleophile assisted ring opening would differ from that expected in classical S_N2 reactions. The normal steric control of orientation operative in classical S_N2 reactions would be contravened by frontier orbital factors. This would lead to products characteristic of a carbonium ion precursor, though such an intermediate need not necessarily occur, Scheme IIa. The orientation of the S_N2 reaction on the unprotonated epoxide would

Scheme II

(a) Charge and LUMO control of conjugate acid
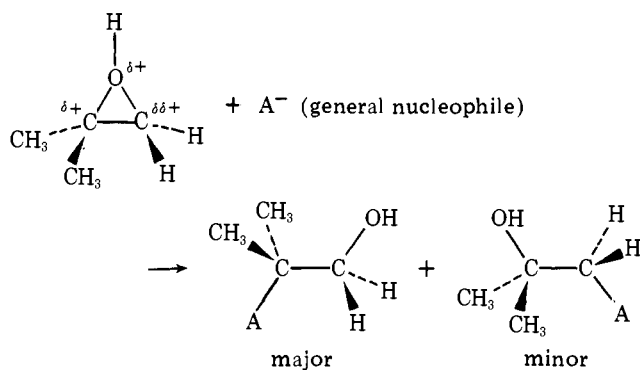
(b) Steric and LUMO control of neutral base
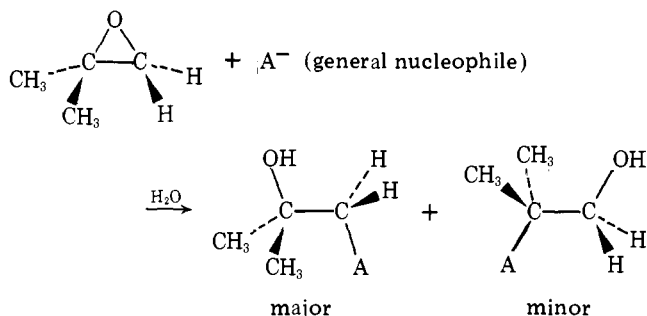
be controlled by the different frontier orbital factors and would follow normal steric effects operative in alkyl systems (Scheme IIb).

This hypothesis neither requires the formation of carbonium ions nor precludes them from occurring under conditions where nucleophiles either are in very low concentration or are absent.[8] Normally most epoxides ring open in aqueous media without the occurrence of rearrangement; yet rearrangement can be made to dominate in situations such as treatment with boron trifluoride etherate or other powerful acids in weakly nucleophilic media.[20] Thus, ion **1**$^+$ could under the proper conditions ring open to form the carbonium ion like **5b** which would partition between rearrangement and capture by available nucleophiles. It is interesting to note that the conditions required to bring about rearrangement of aliphatic epoxides in aqueous media ($[H_3O^+] \geqslant 2$ M) are a thousandfold more concentrated in acid than the conditions required to cause instantaneous ring opening $[H_3O^+] \simeq 10^{-3}$ M or pH $\simeq 3$).

The mechanism suggested for the acid-catalyzed ring opening of **1** (Scheme III) involves equilibrium protonation

Scheme III

$$1 \; + \; HA \; + \; H_2O \; \rightleftharpoons$$
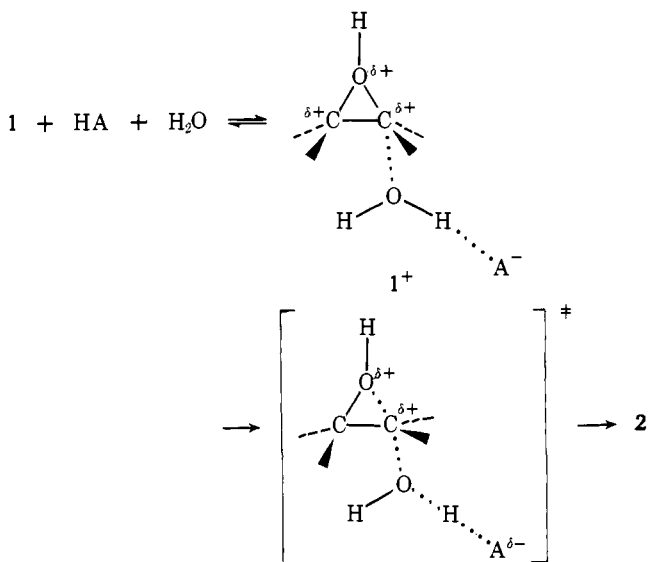
to give **1**$^+$, in which the tertiary carbons have considerable affinity for nucleophiles. A weakening and lengthening of the C–O bonds has occurred, but it is not envisioned that they have been severed.[31a] The charge density helps to "freeze" entropically a water molecule at the rear.[32,33] The conjugate base A$^-$ from the acid HA assists in proton removal in the transition state as the ring opening and attachment of nucleophile progress towards completion. Although this mechanistic thesis is consistent with all the facts, the occurrence of intermediates prior to the transition state cannot be precluded. Such intermediates could conceivably possess features which impede skeletal rearrangements. In proceeding to the transition state, their collapse to covalent material would necessarily require the aforementioned catalytic assistance. Studies now in progress are directed toward arriving at a more definitive answer concerning the question of the existence of such intermediates.

Summary

The repetitive timed integration kinetic method has revealed that two concurrent mechanisms contribute to the catalytic term k_{HA} associated with the ring opening of tetramethylene oxide in aqueous buffers. One contributing mechanism is associated with nucleophilic catalysis and involves an attack by A$^-$ on the protonated epoxide; the other contributing mechanism is associated with general acid catalysis. Isotope effects and activation parameters have been interpreted in terms of

a nucleophilic attack by water upon the protonated epoxide. The proposed mechanism was discussed in the light of recent contributions from MO calculations, data from previous studies on related epoxides, and the present results. A direct consequence of mechanistic analysis is a new view of the orientation of epoxide ring opening, which may apply to other cyclic onium compounds.

References and Notes

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(15) The resolution of the T-60 was adjusted before each experiment using 1% Me₄Si in CDCl₃ solution. Typical resolution as measured from the width at half-height of the Me₄Si peak run at 100-Hz sweep width and 50-s sweep time was 0.7–1.0 Hz.

(16) We gratefully acknowledge the assistance of Mr. B. Nist in obtaining the variable-temperature NMR kinetic data. The temperature calibration was based on the standard procedure described in the V-4341/V-6057 Variable Temperature Accessory Manual, Varian Analytical Instrument Division, Publication No. 87-202-006 B168, p 22.

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(19) No evidence of nucleophilic catalysis was found for either NaNO₃ or Na₂SO₄ when used to control the ionic strength. The $k_{H_3O^+}$ and k_{HA} terms were the same within experimental error for both salts.

(20) Studies of the reaction of **1** in strong acids, 1 to 5 M HClO₄, show how the activity of water influences the nature of the products. At low acidities only hydration occurs, but at high acidities small amounts of **3** are observed even within 2 to 3 min after mixing. The slow rate of rearrangement of **2** in these media precludes the formation of **3** from **2**. Therefore there must be a path open for rearrangement of **1** to **3** independent of **2**, which operates only at high acidities or where the activity of water is low. This has been found true also in the reactions of **1** in trifluoroacetic acid and pure formic acid. Many rearrangement reactions of epoxides have been observed in nonaqueous acidic media, such as boron trifluoride etherate, MgBr₂-ether, and AlCl₃, as well as in concentrated mineral acids.[21]

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(22) By independent measurement of the rate of conversion of **2** to **3** it was unequivocally established that over the pH range 3–8 no rearrangement occurs at 36 °C.

(23) The formate ester, **4**, undergoes slow hydrolysis to **2**. Under the conditions of epoxide hydration this hydrolysis required 2 to 3 days.

(24) (a) That this amount of rearranged product could not have arisen from the rearrangement of **4** was shown by the fact that **4** had a half-life of 47 h in formic acid. (b) The data quoted in Table I and throughout this manuscript were derived from a least-squares standard-errors program treatment of experimental data, written for an HP-67 programmable pocket calculator

(c) The percentage of products **4** and **2** were derived from four separate integrations of each run at time infinity relative to the hydration reaction of **1**. Thus, the values of the percentages of products were averages of at least 8 data points (duplicate runs) for which the standard deviation, $\sigma \leq$ 1%. Using a 7% error in the value of k_{HA} (see Table I) and a 1% error in the product ratios allows the component of the rate assignable to nucleophilic catalysis to be computed along with an error. This value is 64 ± 6% and represents the average value with standard deviation, derived by incorporating product ratios from each pH and buffer dilution in H₂O media.

$$\frac{(\text{av \% formate})k_{obsd}}{k_{HA}[HA]} = \% \text{ nucleophilic catalysis}$$

The remainder, 36 ± 6%, must then be due to general catalysis.

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(27) Conformations for the carbonium ion **5a** and **5b** differ by rotation about the C_2–C_3 bond. In **5a** the vacant "p" orbital eclipses the neighboring O–L bond, whereas in **5b** this orbital is orthogonal to the O–L bond. A theoretical analysis of the energies of these conformations has been published: R. Hoffmann, L. Radom, J. A. Pople, P. v. R. Schleyer, W. J. Hehre, and L. Salem, *J. Am. Chem. Soc.*, **94**, 6221 (1972). The energy of **5a** is expected to be ~8 kcal mol⁻¹ higher than that of **5b**. If these two ions reach thermal equilibrium prior to reaction, then the equilibrium constant favors **5b** over **5a** by a factor of 4 × 10⁵. Since ion **5b** partitions, it is expected that it would do so here with a similar partition factor. The absence of **3** in the products strongly suggests that **5b** never is formed, or it requires that $k_2[H_2O][5a]$
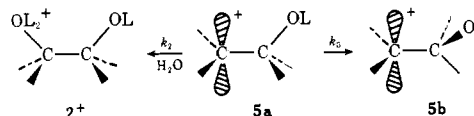
≫ $k_3[5a]$, i.e., attack of water is very much faster than C_2–C_3 bond rotation.

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