# Vinyl Epoxide Hydrolysis Reactions

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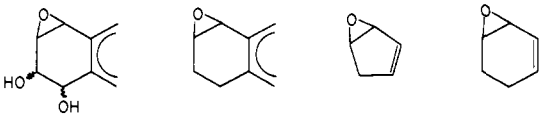
**Abstract:** The rates of hydrolysis of cyclopentadiene oxide (**3**), cyclohexadiene oxide (**4**), cycloheptadiene oxide (**5**), cyclooctadiene oxide (**6**), butadiene oxide (**7**), and styrene oxide (**8**) have been determined as a function of pH. Each epoxide exhibited acid-catalyzed hydrolysis at low pH, and **3–5** showed significant rates for "spontaneous" reaction with solvent at intermediate pH values. The hydrolyses of several of the vinyl epoxides (**4** and **5**) showed kinetic terms in $HO^-$ at pH > ca. 13. Specific chloride effects attributed to nucleophilic addition of $Cl^-$ to neutral epoxide were observed for those compounds (**3**, **4**, and **8**) hydrolyzed in KCl solutions. From kinetic and product studies, mechanisms for hydrolyses of the vinyl epoxides are postulated. Acid-catalyzed hydrolyses of **3**, **4**, **5**, and **6** were found to be A-1 in nature, proceeding via intermediate allyl cations. Product distributions depended on the structure of the cation. Mechanisms and product distributions for the spontaneous hydrolyses of vinyl epoxides were found to be variable, and dependent on the structure of the epoxide.

## Introduction

Considerable attention has been recently devoted to the solution chemistry of bay-region diol epoxides **1** derived from polycyclic aromatic hydrocarbons (PAH's) because of their roles in mutagenesis and carcinogenesis.[1] Bay-region tetrahydroepoxides **2**,

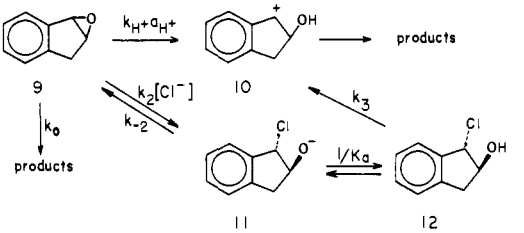


1 2 3 4

although generally not intermediates in the metabolism of PAH's, have been synthesized and can exhibit mutagenicity comparable to or greater than that of the related diol epoxides.[2]

Hydrolysis of the epoxide group in **1** and **2** at the benzyl position by both acid-catalyzed and spontaneous reactions is greatly facilitated by the carbonium ion stabilizing ability of the adjacent aryl group. For instance, the acid-catalyzed hydrolysis of the cis 7,8-diol-9,10-epoxide metabolite of benzo[*a*]pyrene (BAP),[3a] occurs ca. $10^4$ times more readily than the acid-catalyzed hydrolysis of propylene oxide.[3b] A similar difference in reactivities toward spontaneous hydrolysis also exists. Whereas the half-life for spontaneous hydrolysis of the cis BAP diol epoxide at 25 °C is ca. 30 s,[3a] the half-life for spontaneous hydrolysis of propylene oxide under similar conditions is ca. 2 weeks.[3b] Another interesting result that reveals the marked rate enhancement of acid-catalyzed hydrolysis of epoxides conjugated to aromatic rings is that 1,2,3,4-tetrahydronaphthalene 1,2-oxide (epoxide conjugated to phenyl ring) is ca. $6 \times 10^4$ times more reactive than the isomeric 1,2,3,4-tetrahydronaphthalene 2,3-oxide (epoxide not conjugated to phenyl ring).[4]

Scheme I




Conjugation of the epoxide group to a carbon–carbon double bond can also result in a high degree of reactivity toward hydrolysis. Cyclopentadiene oxide (**3**) undergoes spontaneous reaction with water above pH ca. 7 with a half-life of 2.2 min, and the bimolecular rate constant $k_{H^+}$ for acid-catalyzed hydrolysis is $3.7 \times 10^3$ $M^{-1}$ $s^{-1}$.[5] Cyclohexadiene oxide (**4**) is even more reactive toward acid-catalyzed hydrolysis, with $k_{H^+} = 1.1 \times 10^4$ $M^{-1}$ $s^{-1}$.[6] Therefore, the vinyl epoxides **3** and **4** are comparable in solvolytic reactivity to the bay-region diol epoxides and tetrahydroepoxide of benzo[*a*]pyrene.[7]

Several studies[4,7] have compared the reactions and reactivities of the parent tetrahydroepoxides **2** with their diol derivatives **1**. A preliminary report on the reactions of 1,3-cyclohexadiene oxide **4**, ("benzene tetrahydroepoxide"), the simplest tetrahydroepoxide of an aromatic system, has also appeared.[6]

In this paper, we describe the hydrolysis reactions of the vinyl epoxides **3–6**, in which the carbocyclic ring containing the epoxide group varies in size from five to eight carbons. In addition, some

5 6 7 8

reactivity data are provided for the hydrolysis of butadiene oxide (**7**) and styrene oxide (**8**), which have been shown to exhibit weak carcinogenic properties.[8]

In our preliminary publications on the solvolytic reactions of **3**,[5] **4**,[6] and **6**,[6] pH–rate profiles were generated in water solutions held at constant ionic strength with either KCl or NaCl. Chloride salts are often used as supporting electrolytes,[5,6,9,10] and we selected

(1) (a) Sims, P.; Grover, P. L.; Swaisland, A.; Pal, K.; Hewer, A. *Nature (London)* **1974**, *252*, 326. (b) Wood, A. W.; Wislocki, P. G.; Chang, R. L.; Levin, W.; Lu, A. Y. H.; Yagi, H.; Hernandez, O.; Jerina, D. M.; Conney, A. H. *Cancer Res.* **1976**, *36*, 3358. (c) Moschel, R. C.; Baird, W. M.; Dipple, A. *Biochem. Biophys. Res. Commun.* **1977**, *76*, 1092. (d) Vigny, P.; Duquesne, U.; Coulomb, H.; Tierney, B.; Grover, P. L.; Sims, P. *FEBS Lett.* **1977**, *82*, 278. (e) Wood, A. W.; Chang, R. L.; Levin, W.; Thomas, P. E.; Ryan, D.; Stoming, T. A.; Thakker, D. R.; Jerina, D. M.; Conney, A. H. *Cancer Res.* **1978**, *38*, 3398. (f) Hecht, S. S.; Bordinall, W. E.; Hoffman, D. *J. Natl. Cancer Inst.* **1974**, *53*, 1121. (g) For a review, see Jerina, D. M.; Yagi, H.; Lehr, R. E.; Thakker, D. R.; Schaeffer-Ridder, M.; Karle, J. M.; Levin, W.; Wood, A. W.; Chang, R. L.; Conney, A. H. in "Polycyclic Hydrocarbons and Cancer", Gelboin, H. V., T'so, P. O. Eds.; Academic Press: New York, 1978; Vol. 1, p 173.

(2) (a) Levin, W.; Wood, A. W.; Wislocki, P. G.; Chang, R. L.; Kapitulnik, J.; Mah, H. D.; Yagi, H.; Jerina, D. M.; Conney, A. H. In ref 1g, pp 189–202.

(3) (a) Whalen, D. L.; Montemarano, J. A.; Thakker, D. R.; Yagi, H.; Jerina, D. M. *J. Am. Chem. Soc.* **1977**, *99*, 5522. (b) Long, F. A.; Pritchard, J. G. *Ibid.* **1956**, *78*, 2663.

(4) Becker, A. R.; Janusz, J. M.; Bruice, T. C. *J. Am. Chem. Soc.* **1979**, *101*, 5679.

(5) Whalen, D. L.; Ross, A. M. *J. Am. Chem. Soc.* **1974**, *96*, 3678.

(6) Whalen, D. L. *J. Am. Chem. Soc.* **1973**, *95*, 3432.

(7) Whalen, D. L.; Ross, A. M.; Yagi, H.; Karle, J. M.; Jerina, D. M. *J. Am. Chem. Soc.* **1978**, *100*, 5218.

(8) vanDuuren, B. L.; Langseth, L.; Goldschmidt, B. M.; Orris, L. *J. Natl. Cancer Inst.* **1967**, *39*, 1217.

(9) (a) Kasperek, G. J.; Bruice, T. C. *J. Am. Chem. Soc.* **1972**, *94*, 198. (b) Kasperek, G. J.; Bruice, T. C.; Yagi, H.; Jerina, D. M. *J. Chem. Soc., Chem. Commun.* **1974**, 784. (c) Keller, J. W.; Heidelberger, C. *J. Am. Chem. Soc.* **1976**, *98*, 2328. (d) Reuben, D. M.; Bruice, T. C. *Ibid.* **1976**, *98*, 114.

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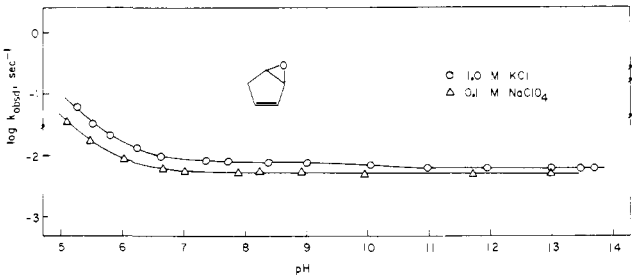



**Figure 1.** Plots of log $k_{obsd}$ vs. pH for hydrolysis of **3** in 1.0 M Kcl and 0.1 M $NaClO_4$ solutions, 25 °C. Curves are theoretical, based on eq 1 (KCl) and 2 ($NaClO_4$).

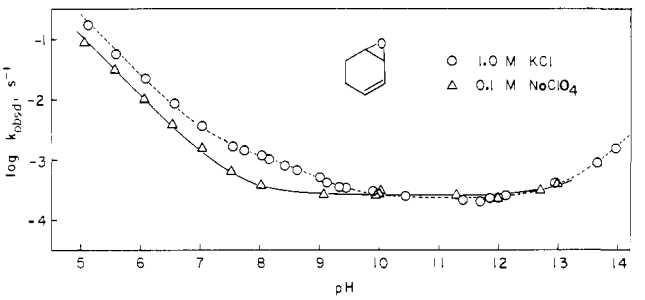



**Figure 2.** Plots of log $K_{obsd}$ vs. pH for hydrolysis of **4** in 1.0 M KCl and 0.1 M $NaClO_4$ solutions, 25 °C. Curves are theoretical, based on eq 1 (KCl) and 2 ($NaClO_4$).

these salts in order that our results might be compared with those of other laboratories. At that time we were unaware of the fact that chloride salts could complicate epoxide hydrolyses because of their nucleophilic nature.

In subsequent work,[11] we discovered that the pH–rate profile for the hydrolysis of indene oxide in 1 M KCl solutions was more complicated than the profile generated in solutions in which the added electrolyte was $NaClO_4$. The specific chloride effect was attributed to the nucleophilic addition of chloride ion to neutral epoxide **9** to yield intermediate **11**, which is in equilibrium with the protonated form **12** (a chlorohydrin). Within the pH range studied, products could therefore result (Scheme I) from three kinetically distinct mechanisms. At low pH products arise from acid-catalyzed opening of **9** ($k_{H^+}a_{H^+}$). At intermediate pH values (7.0–8.5), nucleophilic addition of chloride ion to **9** to yield **11** becomes important. In this pH range, however, **11** is protonated to yield chlorohydrin **12**, which solvolyzes rapidly via a first-order process ($k_3$) to yield products. At pH >ca. 9.5, the acid-dependent equilibrium between epoxide **9** and chlorohydrin **12**[12] shifts sufficiently in favor of epoxide such that spontaneous reaction of **9** with solvent ($k_0$) exceeds the rate of reaction of **12** ($k_3$[**12**]). Steady-state approximations for intermediates **11** and **12** provided the rate expression given in eq 1. Values of $k_{H^+}$, $k_2$, $k_{-2}K_a/k_3$,

$$k_{obsd} = k_{H^+}a_{H^+} + \frac{k_2[Cl^-]}{1 + (k_{-2}K_a/k_3a_{H^+})} + k_0 \qquad (1)$$

and $k_0$ were determined that resulted in a good fit of the experimental kinetic data to the theoretical profile. Later studies showed that the hydrolysis of other epoxides such as phenanthrene 9,10-epoxide[13] and the tetrahydroepoxides of phenanthrene[14] and naphthalene[4] in KCl solutions also exhibited substantial chloride effects.

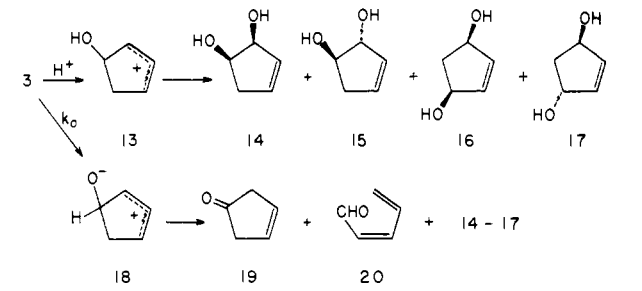
The HCl-catalyzed reaction of benzo[*a*]pyrene 4,5-oxide in 50:1 dioxan–water also yielded chlorohydrins, although the mechanism of their formation presumably involved collapse of an intermediate cation with chloride ion.[15] Addition of HCl to epoxides in nonpolar solvents such as dioxan is a general method of preparing chlorohydrins.[16] It should be pointed out that the mechanism proposed (Scheme I) for the kinetic term in chloride ion (eq 1) involves initial nucleophilic addition of chloride ion to *neutral* epoxide, followed by protonation.[17] Chlorohydrins were both kinetically detected and isolated from the hydrolysis of indene oxide (**9**) at pH <4 in KCl solutions, but in this pH range, the chlorohydrins were formed by initial protonation followed by reaction of an intermediate cation **10** with chloride ion. At higher pH (>6 for **9**), the rate of reaction of the epoxide with acid decreases until nucleophilic addition of chloride ion becomes kinetically competitive. In this higher pH range, the chlorohydrin resulting from nucleophilic addition of chloride ion to **9** is more reactive than **9**, and thus exists only in steady-state concentrations.

Table I. Rate Constants for Hydrolysis of 3–8 in $NaClO_4$ Solutions at 25 °C[a]

| compd | $k_{H^+}$, $M^{-1}$ $s^{-1}$ | $k_o$, $s^{-1}$ | $k_{HO^-}$, $M^{-1}$ $s^{-1}$ |
|---|---|---|---|
| 3 | $3.7 \pm 0.1 \times 10^3$ | $5.2 \pm 0.2 \times 10^{-3}$ | |
| 4 | $1.1 \pm 0.1 \times 10^4$ | $2.6 \pm 0.1 \times 10^{-4}$ | $1.1 \pm 0.5 \times 10^{-3}$ |
| 5 | $3.7 \pm 0.1 \times 10^3$ | $2.7 \pm 0.2 \times 10^{-5}$ | $3.0 \pm 0.4 \times 10^{-4}$ |
| 6 | $3.6 \pm 0.2$ | | |
| 7 | $1.7 \pm 0.1$ | $1.4 \pm 0.4 \times 10^{-5}$ | |
| 8 | $26.7 \pm 0.9$ | $4.1 \pm 0.2 \times 10^{-6}$ | $1.2 \pm 0.3 \times 10^{-4}$ |

[a] The concentration of $NaClO_4$ was 0.1 M for hydrolysis of **3**–**7**, and 0.2 M for hydrolysis of **8**.

Scheme II




## Results

In view of our finding of specific chloride effects in the hydrolysis of indene oxide and phenanthrene 9,10-oxide, along with subsequent reports from other laboratories, we have reexamined the hydrolysis of both **3** and **4** in solutions containing KCl and the relatively nonnucleophilic electrolyte $NaClO_4$. The pH–rate profiles for the hydrolysis of **3** and **4** in 1 M KCl and 0.1 M $NaClO_4$ solutions are provided in Figures 1 and 2. Our reason for selecting 0.1 M for the concentration of $NaClO_4$ is that standard pH electrodes provide rather stable and accurate readings in dilute $NaClO_4$ solutions, but not in more concentrated solutions (i.e., 1 M). For stable pH readings of concentrated (i.e., >0.3 M) $NaClO_4$ solutions, double junction electrodes must be used.[18]

**Cyclopentadiene Oxide (3).** The kinetic data from the hydrolysis of **3** in 0.1 M $NaClO_4$ solutions accurately fit eq 2, where $k_{H^+}$

$$k_{obsd} = k_{H^+}a_{H^+} + k_0 \qquad (2)$$

(10) Chloride salts are also commonly used for maintaining constant ionic strength in vinyl ether hydrolysis: Kresge, A. J.; Chen, H. J.; Chiang, Y. *J. Am. Chem. Soc.* **1977**, *99*, 802, 805. Kresge, A. J.; Sagatys, D. S.; Chen, H. L. *Ibid.* **1977**, *99*, 7228.

(11) Whalen, D. L.; Ross, A. M. *J. Am. Chem. Soc.* **1976**, *98*, 7859.

(12) For a review on the reversible reactions between epoxides and chlorhydrins, see: Lemieux, R. U. In "Molecular Rearrangements"; deMayo, P., Ed.; Wiley: New York, 1963; Chapter 12.

(13) Whalen, D. L.; Ross, A. M.; Dansette, P. M.; Jerina, D. M. *J. Am. Chem. Soc.* **1977**, *99*, 5672.

(14) Rogers, D. Z.; Bruice, T. C. *J. Am. Chem. Soc.* **1979**, *101*, 4713.

(15) Hylarides, M. D.; Lyle, T. A.; Daub, G. H.; Vander Jagt, D. L. *J. Org. Chem.* **1979**, *44*, 4652.

(16) For the preparation of the chlorohydrins of indene oxide by reaction of the epoxide with HCl in dioxan, see: Bodot, H.; Jullien, J.; Leblanc, E. *Bull. Soc. Chim. Fr.* **1962**, 41.

(17) This mechanism has been observed in the conversion of ethylene oxide to ethylene chlorohydrin in the pH range ca. 4–8: Bronsted, J. N.; Kilpatrick, M.; Kilpatrick, M. *J. Am. Chem. Soc.* **1929**, *51*, 428.

(18) Dennison, D. B.; Getty, G. H.; Kubler, D. G.; Shepard, D. *J. Org. Chem.* **1976**, *41*, 2344.

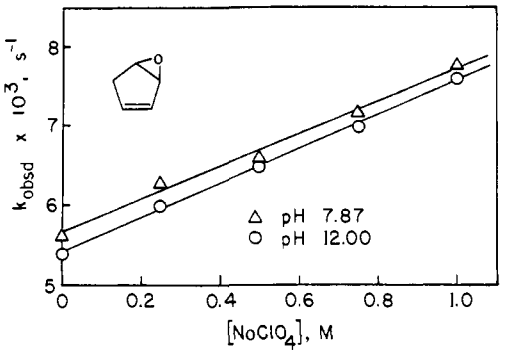



**Figure 3.** Plots of $k_{obsd}$ vs. $[NaClO_4]$ for hydrolysis of **3** at pH 7.87 and 12.00, 25 °C.

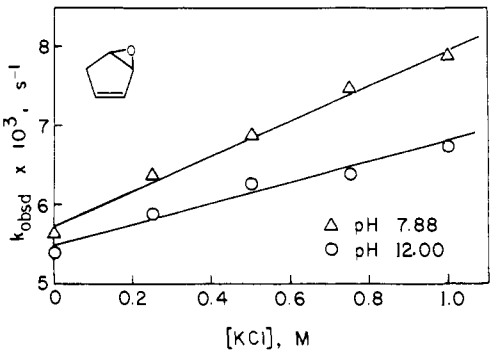



**Figure 4.** Plots of $k_{obsd}$ vs. [KCl] for hydrolysis of **3** at pH 7.88 and 12.00, 25 °C.

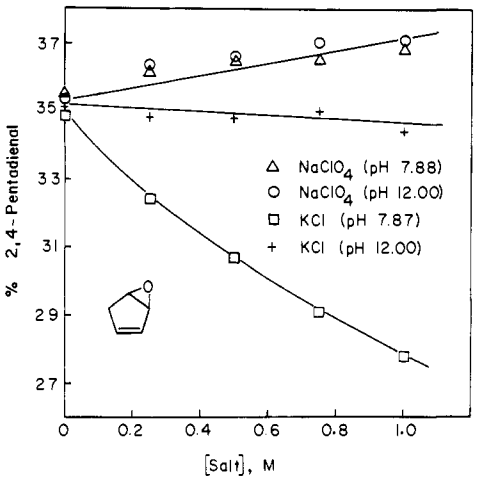



**Figure 5.** Yields of 2,4-pentadienal from hydrolysis of **3** as a function of $NaClO_4$ and KCl concentrations at pH 7.87 and 12.00. The yields of aldehyde were determined spectrophotometrically, 25 °C.

and $k_0$ are rate constants for acid-catalyzed and spontaneous reactions, respectively, and $a_{H^+}$ is the hydrogen ion activity as measured by pH electrodes. Values for the rate constants are summarized in Table I. The shape of the profile in 1 M KCl solutions (Figure 1) does not appear significantly different except that the acid-catalyzed hydrolysis is ca. 2.3 times faster in 1 M KCl, and the spontaneous reaction also appears somewhat faster. Close scrutiny of the KCl profile, however, reveals a slight inflection point at pH ~10.5. The rate of hydrolysis of **3** at pH 11 in KCl solution is only about 20% slower than that at pH 9 and, in the absence of other information, might be attributed to experimental error. We have carefully analyzed both rates and products for reaction of **3** and have concluded that this inflection point is indeed real; we have attributed it to the "chloride effect".

We have also carried out product studies on the hydrolysis of **3** in water as a function of pH. At pH 3.5, the acid-catalyzed hydrolysis of **3** yielded significant amounts of all four cis and trans 1,2- and 1,4-enediols **14–17** (Scheme II), in the ratio 25:16:16:43, respectively.[19,20] The presence of all four diols in the product mixture suggests the intermediacy of a relatively free cyclopentenyl cation **13**, and thus provides strong evidence that the reaction proceeds via an A-1 mechanism.

At pH >ca. 7, the rate for hydrolysis of **3** (Figure 1) is independent of pH, and therefore "spontaneous" reaction of **3** with the solvent occurs. The product distribution from the "spontaneous" reaction of **3** is markedly different from the product distribution from the acid-catalyzed reaction and consists of 35% 3-cyclopentenone (**19**) and 35% *cis*-2,4-pentadienal (**20**), in addition to diols **14–17**. The diol distribution is also different, with **14**, **15**, **16**, and **17** being formed in the ratio ca. 13:54:8:25, respectively.[21] Although the exact mechanism of the $k_0$ reaction for **3** is not certain, the products may be rationalized as being formed from a dipolar intermediate **18**.[22] Hydride migration in **18** provides ketone **19**, and ring opening of **18** yields dienal **20**.

Like the spontaneous reaction of indene oxide,[11] the $k_0$ reaction of **3** also favors the formation of trans 1,2-diols over cis 1,2-diols. Whereas the acid-catalyzed reaction of **3** yielded ~1.6 times more cis 1,2-diol **14** than trans 1,2-diol **15**, the $k_0$ reaction favored formation of the trans isomer (ratio ca. 4:1). However, the ratio of trans/cis 1,4 diols **17** and **16** formed from the $k_0$ reaction is rather similar to that of the acid-catalyzed reaction (trans/cis ratio ca. 3:1).

The interesting feature of the $k_0$ reaction of **3** is that significant amounts of 1,4-diols, in addition to 1,2-diols, are formed. This observation is consistent with that expected if an intermediate with substantial positive charge delocalization (perhaps **13**?) were important in product-forming steps. The different diol distributions from the $k_0$ and $k_{H^+}$ reactions, along with the formation of major amounts of **19** and **20**, indicate that protonation of the species **18**, should it exist as an intermediate, does not compete to any appreciable extent in product-forming reactions.

To verify the presence of an inflection point in the KCl profile, kinetic salt effect studies were carried out at pH values 7.88 and 12.00. Figures 3 and 4 provide the rates of hydrolysis of **3** as a function of added $NaClO_4$ or KCl. Figure 3 reveals that the kinetic $NaClO_4$ salt effect at pH 12.00 is identical within experimental error with that at pH 7.87. However, the kinetic KCl salt effect at pH 7.88 is about twice that at pH 12.00 (Figure 4). There must therefore be a partial change in mechanism in passing from pH 7.88 to 12.00 in the hydrolysis of **3** in 1 M KCl.

To further verify that hydrolysis of **3** at pH 7.88 in 1 M KCl operates in part by a mechanism different from that at pH 12.00, the yields of dienal **20** were determined accurately as a function of salt concentration (Figure 5). It can be seen from Figure 5 that the yield of this product decreases significantly with increase of KCl concentration at pH 7.87, but not at pH 12. Both at pH 7.88 and 12.00, there is a slight increase in yield of **20** with increasing $NaClO_4$ concentration. These data are all consistent with a mechanism in which part of the product in KCl solutions at pH 7.87 is formed via an intermediate chlorohydrin, but at pH

(19) (a) Hydrolysis of **3** in "distilled water" was originally reported to yield mainly the cis 1,4-diol **16** and cis 1,2-diol **14**: Korach, M.; Nielson, D. R.; Rideout, W. H. *J. Am. Chem. Soc.* **1960**, *82*, 4328. (b) Sable, H. Z.; Posternak, T. *Helv. Chim. Acta*, **1962**, *41*, 370.

(20) In a private communication, Dr. Henry Z. Sable informed us that he also obtained a mixture of all four diols **14–17** from hydrolysis of **3** in distilled water.

(21) Our original communication on the products from hydrolysis of **3** between pH 2 and 8 indicated that the ratio of 1,4-diols (**16** and **17**) to 1,2-diols (**14** and **15**) to be ca. 55:45, although much less diol and significant amounts of **19** and **20** (ca. 30–35% each) were formed at pH 8.2 (ref 5). Our original work was carried out in part in dilute KCl solutions, which we have subsequently shown can alter the product distributions. Product studies in this paper were conducted in the absence of KCl, and with the aid of GLPC (see Experimental Section).

(22) Dipolar intermediates have been postulated in the spontaneous hydrolyses of arene oxides: (a) ref 9a. (b) Kasperek, G. J.; Bruice, T. C.; Yagi, H.; Jerina, D. M. *J. Chem. Soc., Chem. Commun.* **1972**, 784.

Table II. Rate Constants for Hydrolysis of 3, 4, and 8 in 1.0 M KCl Solutions at 25 °C[a]

| compd | $k_{H^+}$, $M^{-1}$ $s^{-1}$ | $k_0$, $s^{-1}$ | $k_2$, $M^{-1}$ $s^{-1}$ | $k_{-2}K_a/k_3$, M | $k_{OH^-}$, $M^{-1}$ $s^{-1}$ |
|---|---|---|---|---|---|
| 3 | $8.7 \times 10^3$ | $6.3 \times 10^{-3}$ | $1.5 \times 10^{-3}$ | $\sim 1 \times 10^{-10}$ | |
| 4 | $2.4 \times 10^4$ | $2.2 \times 10^{-4}$ | $8.9 \times 10^{-4}$ | $2.5 \times 10^{-9}$ | $1.5 \times 10^{-3}$ |
| 8 | 35 | $4.8 \times 10^{-6}$ | $1.7 \times 10^{-5}$ | $1.3 \times 10^{-9}$ | $1.0 \times 10^{-4}$ |

[a] Determined by a weighed least-squares fit of the data to eq 4.

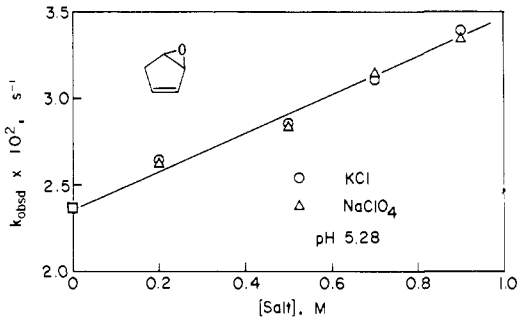



**Figure 6.** Plots of $k_{obsd}$ vs. KCl and $NaClO_4$ concentrations for hydrolysis of **3** at pH 5.28, 25 °C.

12.00 all product is formed from the $k_0$ reaction. A mechanism similar to that outlined in Scheme I provides a rationale for this observation. At pH 7.88, nucleophilic addition of $Cl^-$ to **3** provides an intermediate similar to **11**, which exists primarily in the protonated form at this pH. The intermediate chlorohydrin then hydrolyzes rapidly in a first-order reaction to yield the cyclopentenyl cation **13**, which is also formed in the acid-catalyzed process and is known not to yield 2,4-pentadienal (**20**) as a product. Evidence that a chlorohydrin is formed is also provided by the observation that when **3** is added to a 1 M KCl unbuffered solution at pH ~6–8, there is a rapid increase in pH. The pH then returns to its former value when disappearance of epoxide is complete.[23] Consumption of acid, indicated by the increase in pH, is required for chlorohydrin formation. The rapid return of the pH to its original value also indicates that the intermediate chlorohydrin is significantly more reactive than starting epoxide, thus justifying the steady-state assumption. Fitting of the rate data to eq 1 yields the rate constants outlined in Table II.

The remarkable aspect of the foregoing data and Figure 1 is that in 1.0 M KCl a kinetic term in chloride can be detected for reactions of **3**. Yet a kinetic term in hydroxide ion cannot be detected at $[HO^-] = 1$ M. For this particular substrate, therefore, it appears that $Cl^-$ is a better nucleophile than $HO^-$. For other types of substrates, such as methyl bromide in water, $HO^-$ is found to be considerably more nucleophilic than $Cl^-$.[24]

In view of the fact that $k_{H^+}$ for **3** is larger in 1 M KCl than in 0.1 M $NaClO_4$, we have also checked to see if this difference were due to a kinetic term in $Cl^-$ or to a general salt effect. The rates of reaction of **3** at pH 5.28 as a function of KCl and $NaClO_4$ concentrations were measured and are summarized in Figure 6. At this pH, $k_{H^+}a_{H^+}$ represents ca. 80% of $k_{obsd}$ (eq 1), and therefore the slopes of plots of $k_{obsd}$ vs. [salt] provide good estimates of the salt effects on $k_{H^+}$. Figure 6 shows that the salt effects of $NaClO_4$ and KCl on $k_{H^+}$ for **3** are very similar, thus suggesting that the increase brought about by KCl on $k_{H^+}$ is due primarily to a general salt effect.

**Cyclohexadiene Oxide (4).** The rate profile for hydrolysis of **4** in 1 M KCl (Figure 2) clearly indicates a more complex nature than that for 0.1 M $NaClO_4$. The data for 0.1 M $NaClO_4$ solutions were fit to eq 3, and the rate constants are provided in Table I. The data for 1 M KCl solutions provided a much better fit to eq 4 than to eq 3, and the resultant rate constants are summarized in Table II.

$$k_{obsd} = k_{H^+}a_{H^+} + \frac{k_2[Cl^-]}{1 + (k_{-2}K_a/k_3a_{H^+})} + k_0 + k_{OH^-}[OH^-] \quad (4)$$

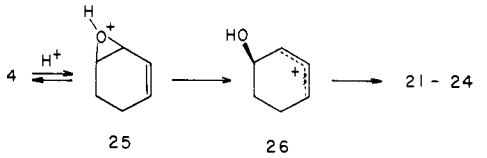
Whereas the two profiles of Figure 1 clearly do not cross, because of significant salt effects on both $k_{H^+}$ and $k_0$ for **3**, the profiles of Figure 2 appear to either coalesce or cross over in the $k_0$ region. The rates of hydrolysis of **4** as a function of $[NaClO_4]$ were therefore measured and were found to decrease slightly with increase in salt concentration. For example, the hydrolysis of **4** in 2.0 M $NaClO_4$ was found to be 22% slower than in 0.1 M $NaClO_4$. The slightly inverse kinetic salt effect on $k_0$ for **4** contrasts with the normal kinetic salt effect for **3** and suggests that the mechanism for the spontaneous hydrolysis of **4** is different from that for **3**.

Table III. Product Distributions from Hydrolysis of 4 in 0.1 M $NaClO_4$ and 1.0 M KCl Solutions at 25 °C[a]

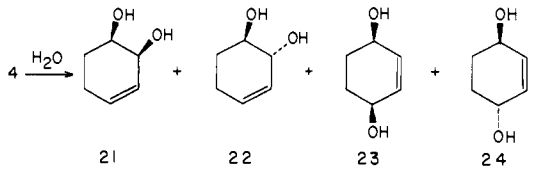
| solution | pH | 21 (%) | 22 (%) | 23 (%) | 24 (%) |
|---|---|---|---|---|---|
| 0.1 M $NaClO_4$ | 5.0 | 1 | 60 | 3 | 36 |
| | 7.0 | 2 | 65 | 4 | 27 |
| | 8.0 | 0.5 | 89 | 1 | 9 |
| | 9.0 | | 99 | | 1[b] |
| 1 M KOH | | | 99 | | 1[b] |
| 1 M KCl | 2.2 (2)[c] | 4 | 51 | 10 | 33 |
| | 3.2 (2) | 5 | 47 | 11 | 35 |
| | 8.0 (2) | 17 | 37 | 23 | 21 |
| | 9.0 (1) | 13 | 56 | 15 | 15 |
| | 10.0 (6) | 3 | 84 | 5 | 2 |
| | 11.0 (4) | | 94 | 1 | 1[b] |
| | 12.0 (1) | | 98 | | 1[b] |

[a] Products were analyzed by gas chromatography (GLPC) on a 1/8 in. × 6 ft column of 5% hyprose. [b] Number represents an upper limit. Identified by GLPC retention time only. [c] The numbers in parentheses represent yields of an unidentified product.

Scheme III. A-1 Mechanism for Hydrolysis of 4



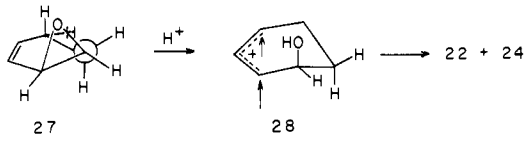

Detailed product studies for hydrolysis of **4** as a function of pH in KCl and $NaClO_4$ solutions have been completed. The products of hydrolysis are the cis and trans 1,2- and 1,4-diols **21–24**. The data listed in Table III show that in 0.1 M $NaClO_4$ solution at pH 5.0, where >99% of the reaction is calculated to be acid catalyzed (from data of Table II), the products are predominantly the trans 1,2- and 1,4-diols **22** and **24**. Only a few percent of the corresponding cis diols are formed. The fact that the acid-catalyzed reaction yielded a significant amount (ca. 40%) of 1,4-diols suggests that the mechanism for hydrolysis of **4** is also A-1 in nature (Scheme III).




The predominantly trans diol mixture from acid-catalyzed hydrolysis of **4** contrasts sharply with the diol mixture from acid-catalyzed hydrolysis of **3**, which contained nearly as much of the cis diols **14** and **15** as of the isomeric trans diols. The somewhat surprising predominance of the trans diols from **4** may be rationalized by considering the ground-state conformation of **4** and the conformation of the cyclohexenyl cation to which it is converted.

(23) This phenomenum has also been observed by Bruice et al. in the hydrolysis of naphthalene tetrahydroepoxide, ref 4.
(24) Swain, C. G.; Scott, C. B. *J. Am. Chem. Soc.* **1953**, *75*, 141.

Scheme IV. Proposed Mechanism for Acid-Catalyzed Hydrolysis of 4



Molecular models suggest that **4** has two possible conformations, a relatively "staggered" conformation A and an "eclipsed" con-

Conformotion A Conformotion B

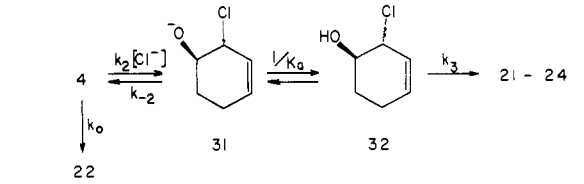
formation B. We have obtained the 250-MHz $^1H$ NMR spectrum of **4** and from decoupling experiments have determined that the epoxide hydrogen $H_2$ is coupled to the adjacent methylene hydrogens $H_{3a}$ and $H_{3b}$ by coupling constants of ca. 1.0 and 2.2 Hz.[25] These two small couplings are more consistent with conformation A, where $H_2$ is staggered between the two adjacent methylene hydrogens, than with conformation B, which should give rise to a somewhat larger coupling of $\gtrsim$5 Hz between $H_2$ and $H_{3b}$.[26] $^1H$ NMR evidence therefore suggests that the ground-state conformation of **4** is conformation A.

An attractive explanation for the predominantly trans hydration of **4** in the acid-catalyzed hydrolysis reaction is outlined in Scheme IV. If ionization of **4** were to occur from the ground-state conformation **27**, then it might be expected to lead initially to the cyclohexenyl cation **28**, in which the hydroxyl group occupies a pseudo-axial position. Goering and Josephson[27] have shown that cyclohexenyl cations undergo selective pseudo-axial attack by water, and that this attack by solvent occurs at a rate faster than conformational isomerization of the ion. Axial attack by solvent on cation **28** at a rate faster than conformation isomerization would nicely account for the trans diols **22** and **24**, the major hydrolysis products.

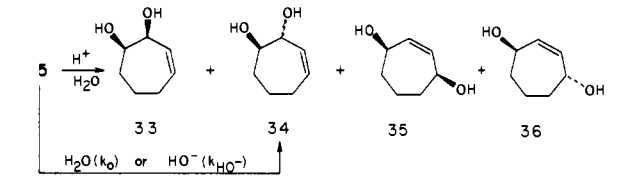
At pH 9.0 in 0.1 M $NaClO_4$, where spontaneous hydrolysis of **4** predominates, the main product ($\gtrsim$99%) is the trans 1,2-diol **22**. This same product is also formed from the reaction of KOH with **4**. The lack of rearrangement products for the spontaneous hydrolysis of **4** and similar regioselectivities and stereoselectivities for both the $k_0$ and $k_{OH^-}$ reactions suggest that water may act as a nucleophile in the reaction with neutral epoxide, via transition state **29**. Reaction of **4** with $OH^-$ presumably proceeds through transition state **30**.[28]

Acid-catalyzed hydrolysis of **4** at pH 2–3 in 1 M KCl gives a slightly different product composition compared to that from 0.1 M $NaClO_4$ (Table III), suggesting that perhaps **26** undergoes some collapse with $Cl^-$ to yield chlorohydrins, which in turn hydrolyze to diols in a slightly different ratio. At pH 8–9, the product distributions in 1 M KCl are markedly different from those in 0.1 M $NaClO_4$. At pH 8 in 1 M KCl the yield of cis diols is ca. 40%, compared to the formation of only ca. 2% cis diols in the absence of KCl. The fact that the yield of cis diols in 1 M KCl solutions is at a maximum at pH ~8, but drops off markedly at both lower and higher pH values, confirms that there is a change of mechanism in this region.

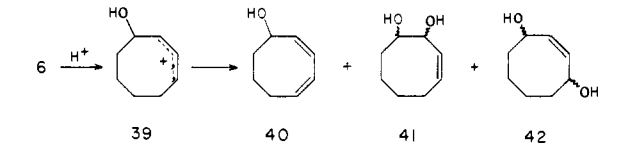
Scheme V



Scheme VI



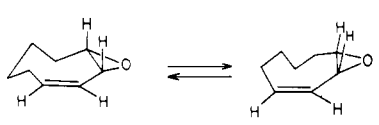
Scheme VII



The increase in yields of cis diols from **4** at pH ~8, and then decrease in yield as the pH is raised, is readily explained by the "chloride effect" outlined in Scheme V. Nucleophilic addition of $Cl^-$ to **4** leads to **31**, which upon protonation gives the chlorohydrin **32**.[29] First-order hydrolysis of **32** would provide a route to the diol mixture observed.[30] At higher pH, the equilibrium concentration of **32** decreases until $k_3[32] << k_0[4]$, and then spontaneous hydrolysis predominates.

**Cycloheptadiene Oxide (5).** Acid-catalyzed hydrolysis of **5** proceeds at a rate similar to that of **3**, and also yields significant amounts of all four possible ene-diol products **33–36** (Scheme VI). This result also suggests the intermediacy of a relatively free cycloheptenyl cation, which in turn implies an A-1 mechanism. As with cyclohexadiene oxide (**4**), the only product observed from the spontaneous and hydroxide reactions of **5** was the trans 1,2-diol **34**, most likely formed via transition states similar to **32** and **33**.

**Cyclooctadiene Oxide (6).** The medium ring epoxide **6** is very much less reactive than **3–5** toward acid-catalyzed hydrolysis and also did not exhibit a detectable spontaneous reaction in the pH range studied. It has been shown that **6** exists at room temperature as a rapidly equilibrating mixture of approximately equal amounts of two conformations, the twist-boat–chair conformation **37** and the twist-boat conformation **38**.[31] If the two conformations have



(25) The 250-MHz spectrum of 4 was determined in $CDCl_3$ solution (degassed). Absorptions were assigned as follows: $\delta$ 1.62 ($H_{3b}$), 2.01 ($H_{4b}$), 2.11 ($H_{4a}$), 2.25 ($H_{3a}$), 3.25 ($H_1$), 3.55 ($H_2$), 5.89 ($H_5$), 5.95 ($H_6$). All positions were assigned with the aid of decoupling experiments. Coupling constants (Hz) assigned were: $J_{1,2}$ = 4.1, $J_{1,6}$ = 4.1, $J_{1,5}$ = 1.5, $J_{2,3a}$ = 2.2, $J_{2,3b}$ = 1.0, $J_{2,4b}$ = 1.5, $J_{3a,3b}$ = 14.0, $J_{3a,4a}$ = 2.2, $J_{3a,4b}$ = 6.7, $J_{3b,4a}$ = 11.0, $J_{3b,4b}$ = 7.0, $J_{4a,4b}$ = 16.5, $J_{5,6}$ = 9.5.

(26) The reduced rings of the trans diol epoxides of triphenylene and benzo[*e*]pyrene possess "eclipsed" conformations similar to conformation B, and the vicinal coupling constants of the eclipsed hydrogens related to $H_2$ and $H_{3b}$ were found to be 5.0 Hz: Yagi, H.; Thakker, D. H.; Lehr, R. E.; Jerina, D. M. *J. Org. Chem.* **1979**, *44*, 3439.

(27) Goering, H. L.; Josephson, R. R. *J. Am. Chem. Soc.* **1962**, *84*, 2779.

(28) Reduction of 4 with lithium aluminum hydride occurs with addition of hydride exclusively at the allylic position: Crandall, J. K.; Banks, D. B.; Colyer, R. A.; Watkins, R. J.; Arrington, J. P. *J. Org. Chem.* **1968**, *33*, 423.

(29) Nucleophilic addition of $Cl^-$ to **4** is assumed to take place at the allylic position that $LiAlH_4$ reduction occurs at (ref 28).

(30) A mixture of chlorohydrins is obtained from reaction of **4** with HCl in dioxan. This mixture of chlorohydrins, presumably including **32**, hydrolyzed at pH 4–8 with good first-order kinetics (half-life ca. 3.4 min). At pH >9, biphasic kinetics was observed, most likely due to base-catalyzed closure of **32** to the epoxide **4** in addition to first-order hydrolysis of an isomeric chlorohydrin(s). See ref 11.

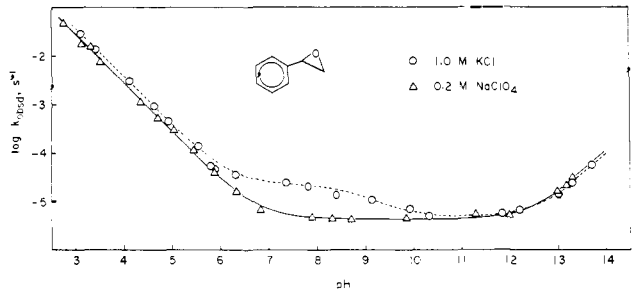
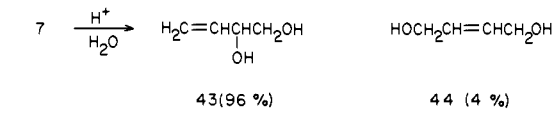



**Figure 7.** Plots of log $k_{obsd}$ vs. pH for hydrolysis of styrene oxide (**8**) in 1.0 M KCl and 0.2 M $NaClO_4$ solutions, 25 °C. Curves are theoretical, based on eq 4 (KCl) and 3 ($NaClO_4$).

Scheme VIII




comparable reactivities toward acid-catalyzed reactions, then hydrolysis of **6** would proceed via several conformationally distinct cationic intermediates of the general structure **39** (Scheme VII). The reactivity of **6** toward acid-catalyzed hydrolysis is ca. $3 \times 10^3$ times less than that of cyclohexadiene oxide (**4**), which suggests a significant increase of angle strain and/or nonbonding interactions in the medium ring at the transition state as **6** (in conformation(s) **37** and/or **38**) reacts to form the cyclooctenyl cation **39**. Evidence for the intermediacy of **39** is provided by the product distribution which consisted of both 1,2- and 1,4-diols **41** and **42**, in addition to dienol **40** resulting from deprotonation of **39**. The relative yields of **40–42** are: **40**, 35%; **41** (cis), 6%; **41** (trans), 16%; **42** (cis and trans), 43%.

**Butadiene Oxide (7).** The reactivity of **7** toward acid-catalyzed hydrolysis is also substantially less than the reactivities of **3–5**. Much of this reduced reactivity can be attributed to the fact that the allyl cation resulting from acid-catalyzed opening of **7** has one terminal primary carbon and one terminal secondary carbon, whereas intermediate allyl cations from **3–5** have two terminal secondary carbons. Therefore, the ion derived from **7** will not be stabilized by substituent groups as much as the ions from **3–5**. The products from acid-catalyzed hydrolysis of **7** are 96% 1,2-diol **43** and 4% 1,4-diol **44** (Scheme VIII). Acid-catalyzed methanolysis of **7** has been reported[32] to yield mainly 2-methoxy-3-buten-1-ol. Acid-catalyzed hydrolysis of **7** therefore most likely also proceeds via allyl C–O bond cleavage, and the very high yields of **43** from hydrolysis and 2-methoxy-3-buten-1-ol from methanolysis probably result from A-2-like transition states. Allyl cations of similar structural type generated from solvolysis of allyl bromides yield comparable amounts of products from reaction at both of the terminal carbons of the intermediate allyl cation.[33] Therefore, if **7** were to hydrolyze completely via an A-1 mechanism to yield an intermediate allyl cation, then one might expect a significant yield of the 1,4-diol **44**.

**Styrene Oxide (8).** Many product studies on the solvolysis reactions of styrene oxide and substituted styrene oxides have been reported.[34,35] We have measured the rates of reactions of **8** as a function of pH in 0.2 M $NaClO_4$ and 1.0 M KCl solutions (Figure 7 and Tables I and II). From Figure 7 it is apparent that there is a significant chloride effect when **8** is hydrolyzed in 1 M KCl solution, and fitting the observed rates to the rate expression given by eq 4 yielded the parameters listed in Table III. In the reaction of **8** with hydroxide ion, attack of $OH^-$ occurs mainly at the primary carbon instead of at the benzyl position.[35c] The intermediate chlorohydrin from nucleophilic addition of $Cl^-$ to **8** in KCl solution might therefore be expected to be the isomer resulting from attack of $Cl^-$ at the primary position.

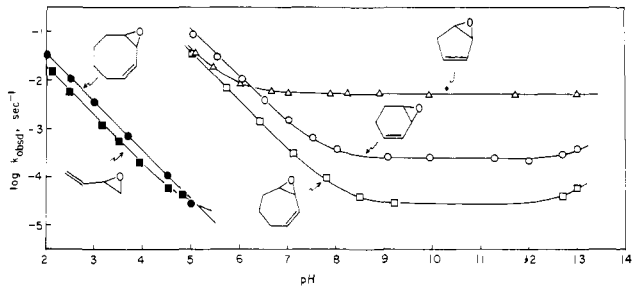



**Figure 8.** Plots of log $k_{obsd}$ vs. pH for hydrolysis of vinyl epoxides **3–7** in 0.1 M $NaClO_4$ solutions, 25 °C. Curves are theoretical, based on eq 2 or 3.

## Summary

The product distributions from the acid-catalyzed hydrolysis of **3–6** provide strong evidence that the reactions are A-1 in nature. Epoxides **3** and **5** yielded significant amounts of all four possible cis and trans 1,2 and 1,4 diols. Cyclohexadiene oxide (**4**), however, undergoes stereoselective hydration to yield mainly the trans 1,2- and trans 1,4-diols. This latter observation was explained by stereoselective attack of solvent on the intermediate cyclohexenyl cation. The reactivity of cyclooctadiene oxide (**6**) was $\lesssim 10^3$ that of the vinyl epoxides **3–5** toward acid-catalyzed hydrolysis, and this reduced reactivity was attributed to steric effects in the medium ring.

The hydrolyses of **3**, **4**, and **8** in 1 M KCl solutions were found to exhibit "chloride effects". Rate profiles for epoxides **5–7** were not generated in KCl solutions, but these compounds might also be susceptible to this effect. The profile for cyclopentadiene oxide (**3**) did not show a very noticeable chloride effect, but the profiles of cyclohexadiene oxide[4] and styrene oxide[8] exhibited more pronounced effects. The relative reactivities of **4** and **8** toward nucleophilic attack by hydroxide ion and chloride ion ($k_{OH^-}/k_2$) were found to be 1.7 and 5.9, respectively. Chloride ion is a better nucleophile than hydroxide ion toward cyclopentadiene oxide (**3**). For phenanthrene 9,10-oxide, 1,2,3,4-tetrahydrophenanthrene 3,4-oxide, and 1,2,3,4-tetrahydrophenanthrene 1,2-oxide, values of $k_{OH^-}/k_2$ were found to be 1.7, 0.9, and 1.9, respectively.[36] So the nucleophilicity of $Cl^-$ may be comparable to or greater than the nucleophilicity of $OH^-$ toward aryl and vinyl epoxides. In general, therefore, those epoxides that undergo significant nucleophilic addition of $OH^-$ at $[OH^-] = 1$ M will also exhibit an appreciable chloride effect at $[Cl^-] = 1$ M. The profiles for some epoxides such as naphthalene oxide[9a] do not exhibit a kinetic term in $OH^-$ at $[OH^-] = 1$ M, and may not show a chloride effect. In view of the fact that this effect has now been seen in the hydrolysis of a considerable number of epoxides, caution should clearly be taken when KCl is used as a supporting electrolyte in epoxide hydrolysis.

The profiles for cyclohexadiene oxide (**4**) and cycloheptadiene oxide (**5**) do not undergo crossing, and both indicate a kinetic term in $OH^-$. The mechanisms of the spontaneous hydrolyses of **4** and **5** appear to be similar, namely, nucleophilic addition of water. The profiles for cyclopentadiene oxide (**3**) and cyclohexadiene oxide (**4**) undergo crossing, however. This crossover is apparently due to the fact that the mechanism for the spontaneous reaction of **3** is different from that for **4**.

The reactivities of the vinyl epoxides **3–5** approach and in some cases surpass the reactivities of highly mutagenic and carcinogenic diol epoxides and tetrahydroepoxides of polycyclic aromatic hydrocarbons.

(31) Anet, F. A.; Yavari, I. *J. Am. Chem. Soc.* **1978**, *100*, 7814.
(32) (a) Bartlett, P. D.; Ross, S. D. *J. Am. Chem. Soc.* **1948**, *70*, 926. (b) Kadesch, R. G. *Ibid.* **1946**, *68*, 41.
(33) DeWolfe, R. H.; Young, W. G. *Chem. Rev.* **1956**, *56*, 753.
(34) Parker, R. E.; Isaacs, N. S. *Chem. Rev.* **1959**, *59*, 737.
(35) (a) Dupin, C.; Dupin, J. F. *Bull. Soc. Chim. Fr.* **1970**, 249. (b) Audier, H. E.; Dupin, J. F.; Jullien, J. *Ibid.* **1966**, 2811. (c) Audier, H. E.; Dupin, J. F.; Jullien, J. *Ibid.* **1968**, 3844. (d) Audier, H. E.; Dupin, J. F.; Jullien, J. *Ibid.* **1968**, 3850. (e) For a review, see Wohl, R. A. *Chimia*, **1974**, *28*, 1.
(36) Calculated from data of refs. 13, 14, and 37.
(37) Bruice, P. Y.; Bruice, T. C.; Dansette, P. M.; Selander, H. G.; Yagi, H.; Jerina, D. M. *J. Am. Chem. Soc.* **1976**, *98*, 2965.

## Experimental Section

Melting points were determined in capillary tubes and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer Model 257 spectrophotometer, and $^1$H NMR spectra were obtained at 60 MHz on an Hitachi Perkin-Elmer R-20A spectrometer or at 250 MHz on a Bruker spectrometer. Chemical shifts are reported relative to internal tetramethylsilane. Analyses were performed by Galbraith Laboratories, Inc., Knoxville, TN.

**Materials.** Butadiene oxide (**7**) and styrene oxide (**8**) were purchased from Aldrich Chemical Co., and were distilled under reduced pressure prior to use. Cyclopentadiene oxide (**3**) was prepared by the method of Korach and Nielson.[19a] Vinyl epoxides **4–6** were prepared by reaction of the precursor diene with 1 equiv of *m*-chloroperbenzoic acid in methylene chloride.[38]

**Kinetics.** The pH–rate profiles of **3–8** were generated in solutions that contained $\sim 10^{-3}$–$10^{-2}$ M of buffering reagent (i.e., acetic acid, cacodylic acid, Tris) for the maintenance of constant pH in the pH range 4–10. At these low concentrations, the contribution of the buffering reagent to $k_{obsd}$ was neglibible. For each kinetic run, approximately 5–15 μL of a stock solution of epoxide in dioxan was added to 2.5–3.0 mL of reaction solution in the thermostated cell compartment (25.0 ± 0.2 °C) of a Gilford 2400 spectrophotometer. The reactions of **3–8** were monitored at 269, 225, 225, 230, 215, and 225 nm, respectively.

**Acid-Catalyzed Hydrolysis of Cyclopentadiene Oxide (3).** A solution of 0.10 g of **3** in 0.10 mL of acetone was added to 10 mL of distilled water maintained at pH 4.0 with the aid of a Radiometer pH-stat assembly. The solution was stirred for 10 min at 25 °C, and the pH of the solution was then adjusted to 8.0. This reaction solution was then analyzed directly by gas chromatography (GLPC) on a 6 ft. × $^1/_4$ in. 10% hyprose column, which showed the product distribution to be 25% of the cis 1,2-diol **14** (retention time 6 min), 33% of a mixture of trans 1,2-diol **15** and cis 1,4-diol **16** (ca. 1:1 ratio, retn time 17 min), and 42% of trans 1,4-diol **17** (retn time 21 min). The reaction solution was concentrated under reduced pressure, and the products were isolated by preparative GLPC. The $^1$H NMR spectrum of **14** (250 MHz, $D_2O$) showed absorptions at δ 5.97 (1 H, m), 5.76 (1 H, m), 4.51 (1 H, m), 4.26 (1 H, m), 2.55 (1 H, m), and 2.28 (1 H, m). The $^1$H NMR spectrum of the product with retention time 17 min showed this fraction to contain approximately equal amounts of the symmetrical cis 1,4-diol **16**[39] and a second material assigned the trans 1,2 structure **15**. The major product (retn time 21 min) was identified by $^1$H NMR to be the trans diol **17**.[39]

To test the stability of the diol products toward the reaction conditions, each of the GLPC fractions isolated above was dissolved in water. The pH of each solution was then adjusted to a value near 4 and maintained for a period of time similar to that used in the reaction conditions above for hydrolysis of **14** (15 min at pH 4.2 for **14**, 11 min at pH 3.7 for the mixture of **15** and **16**, and 11 min at pH 3.5 for **17**). After adjusting the pH of the solutions back up to ca. 7–8, the solutions were analyzed by GLPC as outlined above. No isomerization to isomeric diols of different retention times was detected, thus indicating that the products were stable to the reaction conditions.

A 1-mL aliquot of the above reaction solution, prior to concentration, was diluted with 3 mL of 95% ethanol. $PtO_2$ (14 mg) was added, and the mixture was stirred under a hydrogen atmosphere for 12 h. GLPC analysis of the reaction solution as outlined above showed the products to be 25% *cis*-1,2-cyclopentanediol (retn time 4.9 min), 16% *cis*-1,3-cyclopentanediol (retn time 8.6 min), 16% *trans*-1,2-cyclopentanediol (retn time 11.2 min),[40] and 43% *trans*-1,3-cyclopentanediol (retn time 13.6 min).

**Spontaneous Hydrolysis of 3. A. Determination of Rearrangement Product Yields.** A stock solution containing 872 mg of **3** and 240 mg of methyl isobutyl ketone as a GLPC standard was prepared. Of this stock solution, 15.0 μL was added to 1.0 mL of water solution containing 0.004 M $NaH_2PO_4$ and 0.02 M $Na_2HPO_4$ (pH 7.7). The reaction solution was then stirred for 10 min (ca. 5 half-lives) at room temperature. Sodium chloride (0.4 g) was added, and the reaction solution was extracted with 1.0 mL of chloroform. GLPC analysis of this solution on a 10% diisodecyl phthalate column ($^1/_8$ in. × 12 ft, 75 °C) showed it to contain 3-cyclopentenone (**19**) (retn time 7.6 min, 35% yield based on **3**) and *cis*-2,4-pentadienal (**20**) (retn time 10.5 min, 35% yield based on **3**).

Products **19** and **20** were isolated by GLPC from hydrolysis of 1.15 g of **3** in 50 mL of water containing 0.025 M $KH_2PO_4$ and 0.025 M $K_2HPO_4$ (pH 6.6). The IR (1750 $cm^{-1}$) and $^1$H NMR [($CCl_4$, 60 MHz), δ 2.77 (s, 4 H), 6.07 (s, 2 H)] spectra of **19** were compared with the spectra of authentic **19** prepared by oxidation of 3-cyclopentenol.[41] Aldehyde **20** possessed the following spectral data: UV ($H_2O$) $\lambda_{max}$ 269 nm (ε 19 500) [lit.[42] (EtOH) $\lambda_{max}$ 260 nm (ε 19 100)]; IR ($CCl_4$) 1675 $cm^{-1}$; $^1$H NMR ($CCl_4$, 60 MHz) δ 5.4–6.0 (3 H), 6.6–7.7 (2 H), 10.12 (d, 1 H, $J$ = 8 Hz).

The 2,4-dinitrophenylhydrazone derivative of **20** possessed mp 147–148 °C (lit.[42] mp 150–151 °C). The trans isomer of **20** was prepared by oxidation of *trans*-2,4-pentadienol[43] and exhibited IR and NMR spectra different from those of **20**.

The yield of **20** was also determined spectrally by measuring the absorbance of the reaction solution at 269 nm. The yield of **20** from reaction of **3** in nonbuffered water solution maintained at pH 7.5 with the aid of a pH-stat assembly was determined to be 36% by this method.

**B. Determination of Diol Product Yields.** A sample of 0.23 g of **3** was added to 10 mL of distilled water (25 °C) maintained at pH 8.0 under argon, with the aid of a Radiometer pH-stat assembly. The reaction solution was stirred an additional 30 min at pH 8.0. A 1-mL portion of this reaction solution was diluted with 3 mL of 95% ethanol, 13 mg of $PtO_2$ was added, and the resulting mixture was stirred under a hydrogen atmosphere for 12 h. From GLPC analysis of the reaction solutions before and after hydrogenation, it was determined that the relative amounts of diols (formed in ca. 30% yield) from the spontaneous reaction of **3** are 12% cis 1,2-diol **14**, 54% trans 1,2-diol **15**, 8% cis 1,4-diol **16**, and 25% trans 1,4-diol **17**.

**Hydrolysis of Cyclohexadiene Oxide (4).** A stock solution of 0.10 g of **4** and 0.10 mL of dioxan was prepared. In a typical experiment to determine a product distribution, 5 μL of this stock solution was added to a stirred solution of either 0.1 M $NaClO_4$ or 1.0 M KCl at 25 °C, maintained at a constant pH with the aid of a Radiometer pH-stat assembly. After ≳7 half-lives for reaction, the pH of the solution was adjusted to ca. 7. An equal volume of saturated NaCl solution was added, and the resulting solution was continuously extracted with diethyl ether for 4 h. The ether solvent was removed, and the residue dissolved in ca. 0.5 mL of acetone and analyzed by GLPC on a 6 ft × $^1/_8$ in. 5% hyprose column, 135 °C. The retention times for the products are: cis 1,2-diol **21**, 8.0 min; trans 1,2-diol **22**, 13.0 min; cis 1,4-diol **23**, 22.0 min; trans 1,4-diol **24**, 25.4 min. The results are summarized in Table III. No ketone product was detected from hydrolysis of **4** at any pH value.

Diols **21–24**, after separation by preparative GLPC, were independently tested for stability in water solution at pH 3.2–3.8 for 6 min (>$10^3$ half-lives for reaction of **4**). No detectable isomerization occurred, and therefore the diol products were stable to the reaction conditions.

Identification of the diol products **21–24** was carried out by isolating each product, from a larger scale reaction, by GLPC. Each product was hydrogenated to the saturated diol, and its IR spectrum was compared with that of an authentic sample.[45]

The $^1$H NMR data for **21–24** at 250 MHz in $Me_2SO$-$d_6$ are ($J$ values in Hz): **21**[44] δ 1.50 (1 H, m), 1.65 (1 H, m), 1.90 (1 H, m), 2.05 (1 H, m), 3.55 (1 H, m, C*H*OH), 3.87 (1 H, m, C*H*OH), 4.21 (1 H, d, $J$ = 5.2, OH), 4.39 (1 H, d, $J$ = 5.7, OH), 5.57 [1 H, doublet ($J$ = 10.0) of pentets ($J$ = 1.9 H)], 5.66 [1 H, doublet ($J$ = 10.0) of triplets ($J$ = 3.2)]; **22** δ 1.43 (1 H, m), 1.72 (1 H, m), 2.00 (2 H, m), 3.37 (1 H, m), 3.74 (1 H, m), 4.63 (1 H, d, $J$ = 4.1, OH), 4.73 (1 H, d, $J$ = 5.0 OH), 5.45 [1 H, doublet ($J$ = 9.7) of quartets ($J$ = 2.2)], 5.57 (1 H, m); **23** δ 1.58 (4 H, 3 lines, separation of outermost lines = 2 Hz), 3.89 (2 H, m, C*H*OH), 4.66 (2 H, d, $J$ = 5.0, OH), 5.62 (2 H, d, $J$ = 1, CH=CH); **24** δ 1.29 (2 H, m), 1.88 (2 H, m), 4.00 (2 H, m, C*H*OH), 4.68 (2 H, d, $J$ = 5.2, OH), 5.57 (2 H, s, CH=CH).

**Hydrolysis of Cycloheptadiene Oxide (5). Acid-Catalyzed Hydrolysis.** A solution of 27 mg of **5** in 0.25 mL of dioxan was added to 10 mL of 5% (v/v) dioxan–water solution (25 °C) maintained at pH 4.0 with the aid of a Radiometer pH-stat assembly. The reaction solution was stirred for 5 min, and the pH was then adjusted to 6.9. The solvent was removed at 1 mm pressure by freeze-drying. The residue (ca. 30 mg) was dis-

(38) For published procedures for the syntheses of **3–6**, see ref 28.

(39) The $^1$H NMR spectral data for **16** and **17** have been reported: Sable, H. Z.; Ritchey, W. M.; Nordlander, J. E. *Carbohydr. Res.* **1965**, *1*, 10.

(40) The IR spectrum of this material was compared with the published IR spectrum of *trans*-1,2-cyclopentanediol; Coblentz Infrared Spectra, Sadtler Research Laboratories, Philadelphia, Pa., 1960.

(41) 3-Cyclopentenol was prepared by the procedure outlined in ref 28, and oxidized by the Jones procedure: Bowden, K.; Heilbron, I. M.; Jones, E. H. R.; Weedon, B. C. L. *J. Chem. Soc.* **1946**, 39.

(42) Boehm, E. E.; Whiting, M. C. *J. Chem. Soc.* **1963**, 2541.

(43) *trans*-2,4-Pentadien-1-ol was prepared by sulfuric acid catalyzed rearrangement of 1,4-pentadien-3-ol (Aldrich Chemical Co.). Sarrett oxidation of *trans*-2,4-pentadien-1-ol yielded *trans*-2,4-pentadienal.

(44) The $^1$H NMR spectral data for **21** in $D_2O$ are found in Sable, H. Z.; Powell, K. A.; Katchian, H.; Niewoehner, C. B.; Kadlec, S. B. *Tetrahedron* **1970**, *26*, 1509.

(45) The infrared spectra of the cis and trans isomers of 1,2-cyclohexanediol and that of *trans*-1,4-cyclohexanediol are recorded in the collection of infrared spectra by Sadtler Research Laboratories, Philadelphia, Pa., 1967. These diols and also the isomeric *cis*-1,4-cyclohexanediol may be purchased (as mixtures) from Aldrich Chemical Co., Milwaukee, Wis.

solved in a small volume of acetone and analyzed by GLPC on a 5% hyprose column (6 ft × $^1/_4$ in., 145 °C). Three GLPC peaks were observed: retn times 8.0 min (36%), 19.4 min (27%), and 22.5 min (36%).

On a larger scale reaction, 0.49 g of **5** was hydrolyzed at pH 5.0 in 30 mL of 0.1 M $NaClO_4$ solution, 25 °C, for 25 min. The reaction mixture was cloudy at first, but became clear after ca. 5 min. The reaction solution was continuously extracted with diethyl ether for 4 h to yield 0.60 g of clear oil that provided a similar GLPC analysis to the small-scale reaction. The peak at retention time 8.0 min was isolated by GLPC and shown by $^1$H NMR to be a mixture of **36** and **37** in the ratio of ca. 1:4, respectively. The products with retention times of 19.4 and 22.5 min (mp 98–100 °C) were also isolated and their $^1$H NMR spectra recorded. The data for the product with retention time 19.4 min are: ($CDCl_3$, 60 MHz) $\delta$ 1.2–1.9 (8 H), 4.35 (2 H, broad), 5.75 (2 H, m, narrow). The $^1$H NMR data for the product of retention time 22.5 min are: ($CDCl_3$, 60 Mz) $\delta$ 1.3–2.1 (8 H), 4.25 (2 H, broad), 5.73 (2 H, m, narrow). These data suggest the symmetrical 1,4-diol structures **38** and **39** for the latter two products, but further identification or differentiation was not carried out.

Control experiments showed that pure cis diol **33** and trans diol **34** (prepared by procedures following) did not isomerize to diols of different retention times when allowed to stand in water solution at pH 3.4–3.5 for 6 min.

***cis*-3-Cycloheptene-1,2-diol (33).** A solution of 0.38 g (4.04 mmol) of 1.3-cycloheptadiene and 1.04 g (4.09 mmol) of osmium tetroxide in 10.5 mL of pyridine was stirred for 2 h at room temperature. A solution of 1.90 g of sodium bisulfite, 19 mL of pyridine, and 29 mL of water was added, and stirring was continued for an additional 5 h. The reaction solution was extracted four times with methylene chloride (total 325 mL), and the combined extracts were washed with 50 mL of water. The solvent was removed and the residue sublimed at an oil bath temperature of 110 °C (0.2 mm) to yield 81 mg of **33**, mp 46–51 °C. The product was recrystallized from ether–pentane solution: mp 53–56 °C, IR ($CCl_4$) 3600–3200 cm$^{-1}$; $^1$H NMR ($CDCl_3$, 60 Mz) $\delta$ 5.3–6.1 (2 H), 4.4 (m, 1 H, C*H*OH), 3.9 (m, 1 H, C*H*OH), 3.7 (2 H, OH), 2.4–1.2 (6 H).[46]

Anal. Calcd for $C_7H_{12}O_2$: C, 65.59; H, 9.44. Found C, 65.34; H, 9.24.

***trans*-3-Cycloheptene-1,2-diol (34).** A mixture of 0.10 g of cycloheptadiene oxide (**5**), 7 mL of 2 M NaOH, and 3 mL of dioxan was stirred at room temperature under nitrogen for 3 h. (The reaction solution was cloudy at first, but became clear after ca. 1 h.) Saturated sodium chloride solution (10 mL) was added, and the aqueous solution was continuously extracted with diethyl ether for 3 h. The solvent was removed to yield 89 mg (76%) of product which crystallized upon standing. The product was recrystallized from ether–pentane solution: mp 68.5–69.5 °C; IR ($CDCl_3$) 3600–3200 cm$^{-1}$; $^1$H NMR ($CDCl_3$, 60 Mz) $\delta$ 6.1–5.4 (2 H, C=CH), 4.15 (1 H, C*H*OH), 3.4 (1 H, C*H*OH), 3.0 (2 H, OH), 2.4–1.1 (6 H).

Anal. Calcd for $C_7H_{12}O_2$: C, 65.69; H, 9.44. Found: C, 65.36; H, 9.55.

**Acid-Catalyzed Hydrolysis of Cyclooctadiene Oxide (6).** Because of the low solubility of **6** in water, product studies were carried out in aqueous acetone solutions. A solution of 0.30 g of **6** in 6 mL of acetone was added to 15 mL of 0.01 M $HClO_4$ solution, and the reaction solution was stirred for 10 min. The acetone was removed at aspirator pressure, and the aqueous solution was extracted with ethyl acetate (2 × 50 mL). The organic solution was dried over anhydrous calcium sulfate and the solvent removed to yield 0.31 g of clear oil that crystallized upon standing. The products were separated by preparative GLPC on a 5% silicone DC-550 column (5 ft × $^1/_4$ in.), 130 °C, and identified as 2,4-cyclooctadien-1-ol (**40**) (35%, retn time 1.8 m)[47] *trans*-**41** (16%, retn time 5.6 min),[48] *cis*-**41** (6%, retn time 6.2 min),[49] **42** (cis and trans) (43%, retn time 9.8 min).

The $^1$H NMR spectral data for **40** (60 MHz, $CCl_4$) are: $\delta$ 5.0–6.2 (4 H, C=CH), 4.2 (1 H, broad, C*H*OH), 1.0–2.5 (7 H). $^1$H NMR data for *trans*-**41** (250 MHz, $CDCl_3$) are: $\delta$ 5.5–5.7 (2 H, m, C=CH), 4.36 (1 H, t, J = 8, C*H*OH), 3.46 (1 H, m, C*H*OH).

The cis and trans isomers of **42** did not separate under the above GLPC conditions, but the $^1$H NMR spectrum of this fraction at 250 MHz ($Me_2SO$-$d_6$) indicated the presence of two symmetrical diols in the ratio 70:30. The major isomer possessed resonances at $\delta$ 5.41 [2 H, 4 intense lines (separation of innermost lines 2.0 Hz, separation of outermost lines 4.1 Hz), several very weak outer lines (separation 26.6 Hz)], 4.63 (2 H, d, $J$ = 4.3, OH), and 4.56 (2 H, m, C*H*OH). The minor isomer absorbed at $\delta$ 5.34 [2 H, 4 intense lines (separation of innermost lines 3.2 Hz, separation of outermost lines 5.4 Hz), several weak outer lines (separation 25.5 Hz)], 4.72 (2 H, d, $J$ = 4.0, OH), and 4.30 (2 H, doublet of triplets, separation of outermost lines 23.6 Hz).

The crude reaction mixture (0.3 g) was dissolved in warm ether–pentane solution and cooled to yield 93 mg of a mixture of the cis and trans isomers of **42** (56:44 ratio), mp 115–131 °C. Hydrogenation of this sample in 95% ethanol with added $PtO_2$ as catalyst yielded a mixture of cis and trans 1,4-cyclooctanediols. The mixture of saturated diols did not separate on GLPC, but possessed the same GLPC retention time and infrared absorption bands as authentic cis and trans 1,4-cyclooctanediols.[50]

Control experiments showed that the cis 1,2-diol **41** and a mixture of cis and trans diols **42**, when independently allowed to stand in water solution at pH 2.3 for 11 min, did not rearrange to other isomeric diols of different GLPC retention times or dihydrate to dienol **40**.

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**Registry No. 3**, 7129-41-1; **4**, 6705-51-7; **5**, 6669-45-0; **6**, 6690-12-6; **7**, 930-22-3; **8**, 96-09-3; *cis*-**14**, 694-29-1; *trans*-**15**, 29782-81-8; *cis*-**16**, 29783-26-4; *trans*-**17**, 694-47-3; **19**, 14320-37-7; *cis*-**20**, 37918-47-1; *trans*-**20**, 20432-40-0; **20** DNP, 3013-15-8; *cis*-**21**, 28981-66-0; *trans*-**22**, 20089-20-7; *cis*-**23**, 53762-85-9; *trans*-**24**, 41513-32-0; *cis*-**33**, 80559-98-4; *trans*-**34**, 80559-99-5; *trans*-**36**, 80560-00-5; **37**, 80582-67-8; **40**, 29234-93-3; *trans*-**41**, 21491-46-3; *cis*-**42**, 37996-40-0; *trans*-**42**, 37996-39-7; *cis*-1,2-cyclopentanediol, 5057-98-7; *cis*-1,3-cyclopentanediol, 16326-97-9; *trans*-1,2-cyclopentanediol, 5057-99-8; *trans*-1,3-cyclopentanediol, 16326-98-0; *trans*-2,4-pentadienol, 51042-92-3; 1,3-cycloheptadiene, 4054-38-0; 1,4-pentadien-3-ol, 922-65-6; *cis*-**41**, 37989-33-6; **43**, 497-06-3; **44**, 110-64-5.

(46) The procedure followed for this synthesis was that of Baran, J. S. *J. Org. Chem.* **1960**, *25*, 257. The low recovery of product reflects the high solubility of **33** in water. No effort was made to optimize the yield.

(47) Dienol **40** was hydrogenated to cyclooctanol.

(48) Diol **41** (trans) was hydrogenated to the known *trans*-1,2-cyclooctanediol: Cope, A.; Keough, A.; Peterson, P.; Simmons, H., Jr.; Wood, G. *J. Am. Chem. Soc.* **1957**, *79*, 3900.

(49) Identified by GLPC retention time compared to that of authentic sample (mp 121.5–123.0 °C) prepared by reaction of osmium tetroxide and 1,3-cyclooctadiene (85% yield) according to the procedure given in ref 46.

(50) Cope, A. C.; Anderson, B. C. *J. Am. Chem. Soc.* **1957**, *79*, 3892.