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Effects of Conformation on the Stereochemistry of Solvent Attack on Benzylic *β*-Hydroxycarbocations: Mechanisms of Epoxide Hydrolysis Reactions

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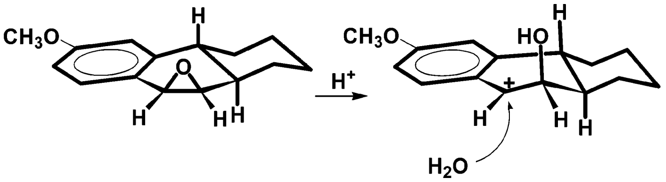
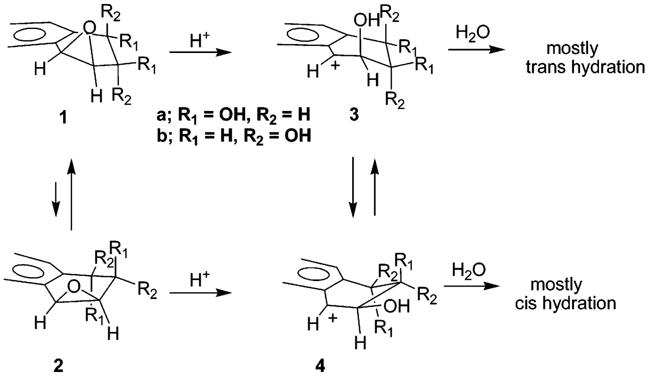


The rates and products from the acid-catalyzed and the pH-independent reactions of two diastereomeric 6-methoxy-*trans*-1,2,3,4,4a,10a-hexahydrophenanthrene 9,10-oxides (**5b** and **7b**), along with their cis and trans chlorohydrins, have been determined in dioxane/water solutions. The mechanisms of the acid-catalyzed hydrolysis of **5b** and **7b** involve rate-limiting formation of benzylic carbocations (**6b** and **8b**), which have sufficient lifetimes to be trapped by azide ion. Each carbocation is stabilized by the 6-methoxy group and held in single conformation by the adjacent trans-fused cyclohexane ring. The stereochemistry of the attack of water on each carbocation is independent of whether the precursor is an epoxide, a cis chlorohydrin, or a trans chlorohydrin, and the major diol hydrolysis product from each compound results from the axial attack of a solvent molecule on the carbocation intermediate. The hydrolysis of the trans chlorohydrin formed from the reaction of **5b** with HCl exhibits a common ion rate depression. The major product from the pH-independent reaction of **5b** is a trans diol, and the major product from the pH-independent reaction of **7b** is an isomeric ketone. The rate of the pH-independent reaction of **7b** is $>10^4$ times faster than that of **5b**.

Introduction

The acid-catalyzed hydrolyses of epoxides occur to yield diols resulting from cis and/or trans hydration, and the cis/trans hydration ratio depends on a number of factors.[1] If the solvent attack and the epoxide C−O bond breaking are concerted, a complete inversion at carbon occurs. If the epoxide ring opening occurs to yield a carbocation intermediate, then the attack of the solvent from either side of the carbocationic center may lead to both retention and inversion of configuration at this carbon. For the reactions that are stepwise, the cis/trans hydration ratio varies from almost complete trans hydration to mostly cis hydration. For example, acid-catalyzed hydrolysis of a benzo[*a*]pyrene 7,8-diol 9,10-epoxide **1a** (Scheme 1, only angular ring shown) yields 95% of trans tetrol and only 5% of cis tetrol.[2] However, a diasteromeric benzo[*a*]pyrene 7,8-diol

SCHEME 1



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[1] For reviews, see (a) Rosowsky, A. In *Heterocyclic Compounds with Three- and Four-Membered Rings*, Part 1; Weissberber, A., Ed.; Interscience: New York, 1964; pp 1−523. (b) Buchanan, J. G.; Sable, H. Z. In *Selective Organic Transformations*; Thyagarajan, B. S., Ed.; Wiley-Interscience: New York, 1972; Vol. 2, pp 1−95. (c) Whalen, D. L. *Adv. Phys. Org. Chem.* **2005**, *40*, 247−298.

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10.1021/jo061003i CCC: \$33.50

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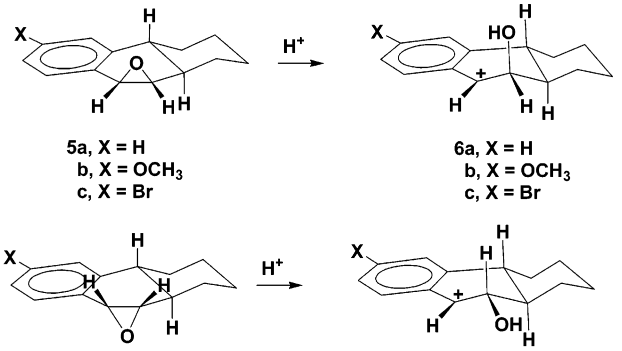


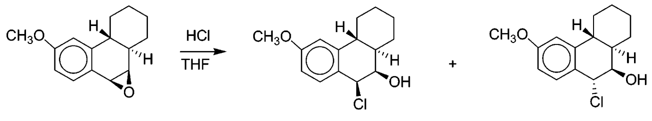
5a, X = H
b, X = OCH$_3$
c, X = Br

6a, X = H
b, X = OCH$_3$
c, X = Br

7a, X = H
b, X = OCH$_3$
c, X = Br

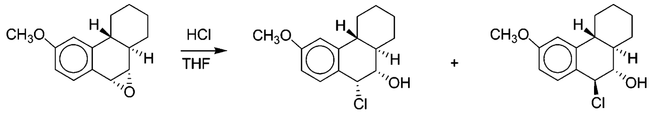
8a, X = H
b, X = OCH$_3$
c, X = Br

SCHEME 3



5b **9** **10**

SCHEME 4



7b **11** **12**

9,10-epoxide **1b** yields 90% of cis tetrol and only 10% of trans tetrol.[2] Both of these reactions proceed via carbocations that have sufficient lifetimes in water solutions to react with external nucleophiles faster than they react with water.[3,4]

The stereochemistry of the attack of the solvent on the carbocation intermediates from the reaction of **1a** and **1b** have been interpreted in terms of energetically favored axial attack of water on individual carbocation conformations.[5,6] This interpretation is complicated by the fact that there are two conformations of the intermediate carbocation. The axial attack of solvent on one conformation (**3**) leads to trans hydration, and the axial attack of solvent on the second conformation (**4**) leads to cis hydration.

A study of the acid-catalyzed hydrolysis of two diastereomeric hexahydrophenanthrene 9,10-oxides **5a** and **7a** provides evidence that axial attack of water on substituted cyclohexenyl carbocations is favored over equatorial attack of water.[6] The reaction of **5a** with H^+ yields carbocation **6a**, which is constrained to a single conformation in which the hydroxyl group is located in an axial position. The reaction of **7a** with H^+ yields carbocation **8a**, which is constrained to a single conformation in which the hydroxyl group is located in an equatorial position (Scheme 2). Conformation **6a** is structurally related to **3**, and conformation **8a** is structurally related to **4**. Acid-catalyzed hydrolysis of **5a** yields exclusively (>99%) the trans diol, the product formed from axial attack of water on **6a**. Acid-catalyzed hydrolysis of **7a** yields 75% of cis diol, the result of axial attack of water on **8a**, and 25% of trans diol, the result of equatorial attack of water on **8a**. These observations support the proposal that axial attack of water on carbocations such as **3** and **4** is favored over equatorial attack of water.

An argument can be made, however, that at least part of the trans diol product from acid-catalyzed hydrolysis of **5a** is formed via a mechanism in which the nucleophilic attack of solvent at the benzylic carbon and epoxide C−O bond breaking are concerted. In a similar argument, some of the trans diol from the acid-catalyzed hydrolysis of **7a** might be the result of a concerted reaction, and the cis diol could result from the reaction of **7a** with H_3O^+ at an "ion−molecule" stage[7] before transformation to a freely solvated carbocation occurs.

The acid-catalyzed hydrolyses of **5a**, **5b**, and **5c** all yield almost exclusively trans diols.[6,8] However, the cis/trans hydration ratio (75:25) for the acid-catalyzed hydrolysis of **7a** is slightly different than that from the acid-catalyzed hydrolysis of **7b** (83:17), and the cis/trans hydration ratio for hydrolysis of **7c** (31:69) is significantly different than that for **7b**.[8] The geometry of the intermediate carbocation **8** should be independent of the substituent in the phenyl ring, and, consequently, the cis/trans hydration ratio for the reaction of these carbocations with solvent also should be independent of the substituent. The different cis/trans hydration ratios for the reactions of **7a**−**c** suggest that the mechanism for hydrolysis of **7c** and perhaps that of **7a** are different than the mechanism for hydrolysis of **7b**.

A methoxyl group substituted in the para position of a phenyl ring significantly increases the lifetime of a benzylic carbocation,[9] and carbocations **6b** and **8b** are expected to have lifetimes that are much longer than the time required for solvent reorganization. Consequently, the cis/trans hydration ratios observed in the acid-catalyzed hydrolyses of methoxy-substituted epoxides **5b** and **7b** should reflect more closely the stereochemistry of solvent attack on fully formed and solvated carbocation intermediates (**6b** and **8b**).

In this study, the rates of reaction and products from the reaction of epoxides **5b** and **7b** over the pH range 5−12 in dioxane/water solutions have been determined. In the acid-catalyzed hydrolyses of **5b** and **7b**, intermediate carbocations **6b** and **8b** are trapped after their rate-limiting formations by azide ion. The diol products from the hydrolysis of chlorohydrins **9**−**12** are compared to the diol products from the hydrolysis of epoxides **5b** and **7b** (Schemes 3 and 4). A significant common ion effect on the rate of hydrolysis of chlorohydrin **10** also demonstrates that there is a carbocation intermediate, which has a sufficient lifetime to be trapped by chloride ion. Our results establish unequivocally that methoxy-substituted carbocations **6b** and **8b** have sufficient lifetimes in aqueous solutions for the solvating molecules to be relaxed before the carbocations react with solvent.

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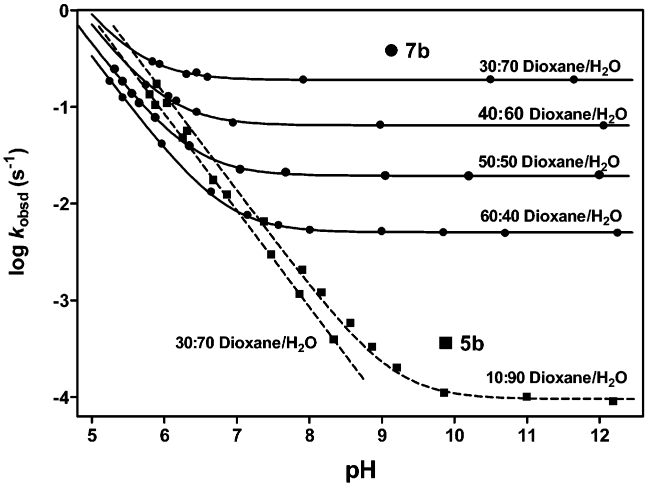
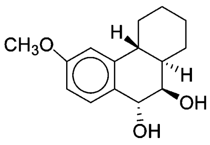


FIGURE 1. Plots of log k_{obsd} vs apparent pH for the reactions of **5b** and **7b** in dioxane/water solutions, 0.1 M $NaClO_4$, 25.0 ± 0.2 °C.

Results and Discussion

Rates and Products of the Reactions of 5b and 7b in Dioxane/Water Solutions. Hexahydrophenanthrene oxides **5b** and **7b** were synthesized by synthetic routes similar to those published,[8] and their rates of reaction in dioxane/water solutions over the pH range of ~5−12 were determined. Rate data for each epoxide fit the equation $k_{obsd} = k_H[H^+] + k_o$, and plots of log k_{obsd} vs apparent pH are given in Figure 1. A summary of k_H and k_o values is provided in Table 1.

The products from the acid-catalyzed and pH-independent reactions of **5b** and **7b** in 10:90 dioxane/water solutions were determined and are summarized in Table 2. Our product studies of the acid-catalyzed hydrolysis of **5b** and **7b** agree very well with previously published results,[8] which report that the hydrolysis of **5b** in 0.1 M H_2SO_4 in 50:50 dioxane/water yields 100% of trans diol **13** and hydrolysis of **7b** under the same conditions yields 19% of trans diol **16** and 81% of cis diol **17**.



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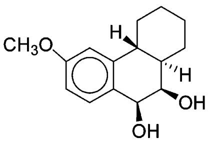

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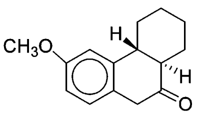

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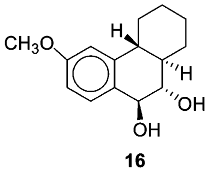

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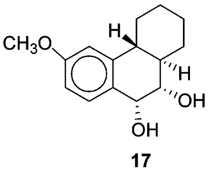

17

Trapping by Azide Ion of Intermediate Carbocations in the Acid-Catalyzed Hydrolyses of 5b and 7b. The rates and products of the reaction of **5b** in 10:90 dioxane/water at pH 6.0 and of **7b** in 60:40 dioxane/water at pH 5.6 as functions of increasing azide ion were determined. The rates of reaction of **5b** and **7b** do not change as the sodium azide concentration is increased to 0.025 M. However, the yields of diols decrease markedly as the concentration of sodium azide increases (Figure 2), indicating that an intermediate in each reaction is trapped after its rate-limiting formation by azide ion. HPLC analysis of the reaction solutions showed that two new products are formed in a 1:4 ratio from the reaction of **5b** in azide solutions, and two new products are formed in a 3:7 ratio when **7b** undergoes reaction in azide solutions. The new products were not isolated or identified but are assumed to be cis and trans azides. They undergo decomposition to other unidentified products in the reaction solutions over a period of a day.

The reactions of **5b** in sodium azide solutions are accounted for by the mechanism of Scheme 5. At pH 10.5, the rate of reaction of **5b** increases linearly with an increase in the concentration of NaN_3 indicating that azide ion acts reacts directly with **5b** in a bimolecular reaction (k_N), giving a value for k_N of 0.18 $M^{-1}\ s^{-1}$. The rate of the pH-independent reaction of **7b** does not increase with the increasing azide ion concentrations up to 4 mM, and, therefore, nucleophilic addition of azide ion to **7b** via the k_N pathway does not compete successfully with its pH-independent reaction ($k_o \gg k_N[N_3^-]$).

The mole fraction (f_{diol}) of diols formed from the acid-catalyzed pathway is given by the equation $f_{diol} = k_s/(k_s + k_{az}[N_3^-])$. Fitting of the product data of Figure 2 to this equation yields values for k_{az}/k_s of 115 and 45 M^{-1} for the reactions of **5b** and **7b**, respectively. It was proposed by Jencks and coworkers that low values of k_{az}/k_s (such as those noted above) are evidence that azide ion is reacting with each carbocation at the diffusional limit.[9] If it is assumed that azide ion reacts with carbocations **6b** and **8b** at the diffusional rate constant of $5 \times 10^9\ M^{-1}\ s^{-1}$, then k_s for the reactions of **6b** and **8b** with solvent are calculated to be $4.3 \times 10^7\ s^{-1}$ and $1.1 \times 10^8\ s^{-1}$, respectively. These results establish unequivocally that the diol products from the acid-catalyzed hydrolyses of both **5b** and **7b** are formed by the reaction of the solvent with intermediate carbocations that have lifetimes much longer than the time required for solvent reorganization, which is estimated to occur at a rate of $10^{11}-10^{12}\ s^{-1}$.[10]

Rates and Products for Reactions of 5b and 7b in Halide Solutions. The rates of reaction of **5b** in 10:90 dioxane/water solutions over an extended pH range were determined, and plots of log k_{obsd} vs pH for its reaction in 0.1 M $NaClO_4$, 0.5 M NaBr, and 1.0 M NaCl solutions are provided in Figure 3. The shapes of the rate profiles for the reaction of **5b** in NaBr and NaCl solutions are similar to those for the reaction of a benzo[*a*]pyrene 7,8-diol 9,10-epoxide in solutions containing halide ions[11] and are explained by the mechanism outlined in Scheme 6. Azide trapping experiments described in the previous section demonstrate that intermediate carbocations **6b** and **8b** are formed in rate-limiting steps in the acid-catalyzed reactions of **5b** and **7b**, and, therefore, $k_s \gg k_{-H}$.

The rate plateaus for the reaction of **5b** in NaBr and NaCl solutions in the pH range ~8.5−10.5 are attributed to kinetic terms for the nucleophilic addition of halide ion to **5b** to form oxyanion **18**. In this pH range, the equilibrium between oxyanion **18** and chlorohydrin **19** favors chlorohydrin, and solvolysis of **19** via carbocation **6b** to form diols is fast relative to the rate of reaction of **5b** in the absence of halide ion. Hydrolysis of **5b** at pH < 10 in either 1.0 M NaCl or 0.5 M NaBr solution yields 98% of trans diol **13** and 2% of cis diol **14**, which is the same

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TABLE 1. Summary of Rate Constants for the Reactions of 5b and 7b in Dioxane/Water (v/v) Solutions, 0.1 M NaClO$_4$, 25.0 ± 0.2 °C

compound	solvent	k_H ($M^{-1} s^{-1}$)	k_o (s^{-1})
5b	10:90 dioxane/water	$(1.36 \pm 0.06) \times 10^5$	$(9.5 \pm 0.6) \times 10^{-5}$
	30:70 dioxane/water	$(8.5 \pm 0.1) \times 10^4$	
7b	30:70 dioxane/water	$(7.2 \pm 0.5) \times 10^4$	$(1.89 \pm 0.03) \times 10^{-1}$
	40:60 dioxane/water	$(6.7 \pm 0.5) \times 10^4$	$(6.3 \pm 0.2) \times 10^{-2}$
	50:50 dioxane/water	$(4.4 \pm 0.1) \times 10^4$	$(1.94 \pm 0.03) \times 10^{-2}$
	60:40 dioxane/water	$(3.3 \pm 0.1) \times 10^4$	$(5.0 \pm 0.1) \times 10^{-3}$

TABLE 2. Product Distributions from the Acid-Catalyzed and the pH-Independent Reactions of Rigid Epoxides 5(a−c) and 7(a−c) in 10:90 Dioxane/Water, 0.1 M NaClO$_4$, 25 °C

	acid-catalyzed		pH-independent		
cmpd	% cis diol	% trans diol	% cis diol	% trans diol	% ketone
5a[a]		100		100	
5b[b]	2	98	~1	89	~10
5c[c]		100			
7a[a]	75	25	8	6	86
7b[d]	83	17	~4	~1	95
7c[b]	31	69			

[a] Reference 6. [b] pH 6.0 for the acid-catalyzed reaction and pH 10.5 for the pH-independent reaction. [c] Reference 8. [d] pH 3.0 for the acid-catalyzed reaction and pH 10.0 for the pH-independent reaction.

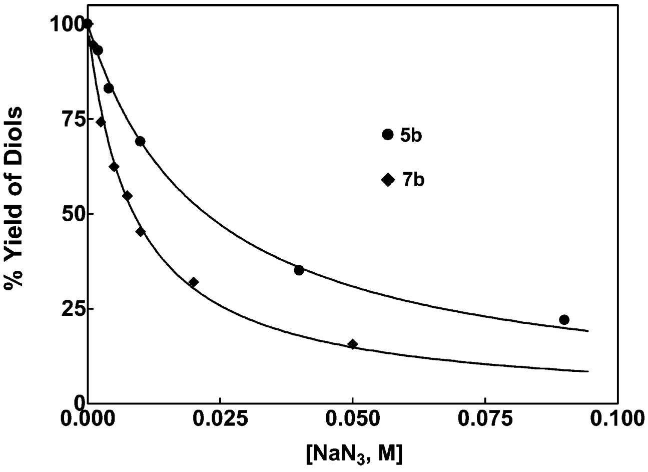
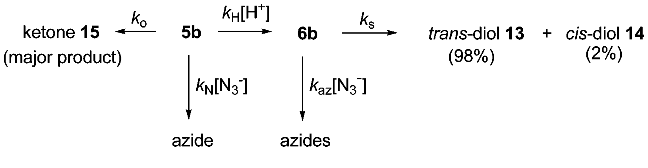


FIGURE 2. Plots of % yield of the diols from the reactions of **5b** in 10:90 dioxane/water at pH 6.0 and of **7b** in 60:40 dioxane/water at pH 5.6, $\mu = 0.1$ M (NaClO$_4$).

SCHEME 5



product mixture as that formed from the acid-catalyzed hydrolysis of **5b** in the absence of halide ion. This observation indicates that there is only one product-forming intermediate, carbocation **6b**, for the reaction of **5b** at pH < ~10 in solutions containing sufficient chloride or bromide ion concentrations.

The NaBr and NaCl rate profiles for the reaction of **5b** show a rate reduction at pH > ~10 with an inflection point at a pH of ~11. This reduction in rate is attributed to a shift in the pH-dependent equilibrium for the reaction of epoxide **5b** with H$^+$ and X$^-$ to form halohydrin **19** (eq 1). The concentration of X$^-$ is held constant, and, therefore, the concentration of **19** will depend on the pH of the solution. At pH < ~10, the pH-dependent equilibrium is shifted sufficiently far to the right, so that the halohydrin **19** that is formed by the reaction of **5b** with X$^-$ and H$^+$ hydrolyzes rapidly via the k_1 pathway. At pH > ~10, however, the equilibrium shown in eq 1 is shifted to the left resulting in a lower concentration of **19** and slowing the overall rate of reaction of **5b**. At pH > ~12, k_o[**5b**] ≫ k_1[**19**], and products are formed only via the k_o pathway.

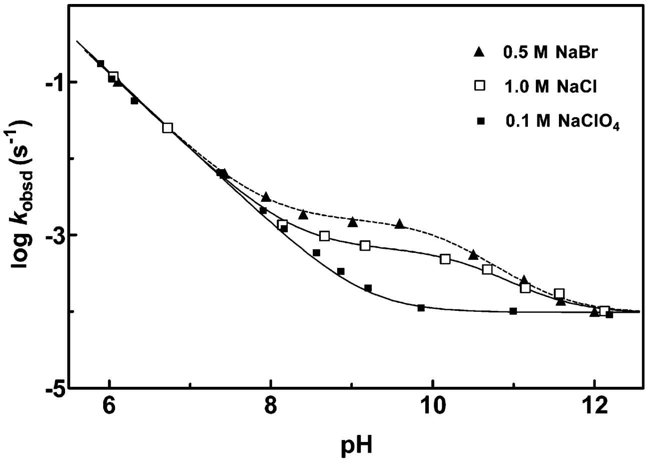
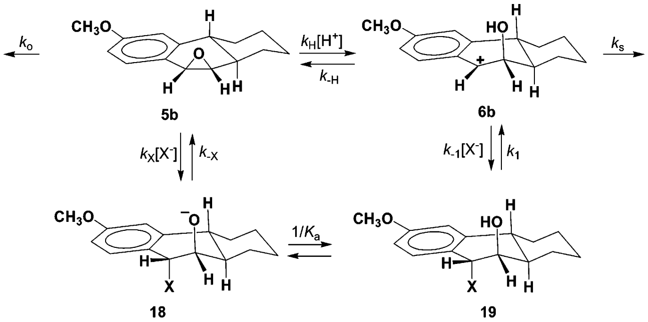


FIGURE 3. Plots of log k_{obsd} vs apparent pH for the reaction of **5b** in 10:90 dioxane/water solutions containing NaBr, NaCl, and NaClO$_4$, 25.0 ± 0.2 °C. The solid lines for the reaction of **5b** in halide solutions are theoretical, based on eq 5.

SCHEME 6



$$\mathbf{5b} + H^+ + X^- \rightleftarrows 19 \qquad (1)$$

In the pH range of ~8−11, $k_X[X^-] > k_H[H^+] + k_o$, and most of the reaction occurs via the k_X pathway. At pH < ~7, $k_H[H^+] \gg k_X[X^-]$, and nucleophilic addition of X$^-$ to **5b** is negligible. However, halohydrin **19** still may be formed from the reaction of the intermediate carbocation **6b** with X$^-$. At sufficiently low pH, the rate of the second-order reaction of **5b** with H$^+$ to form carbocation **6b** may be greater than the rate of the first-order hydrolysis of **19**, and a buildup of **19** in excess of steady-state concentration might occur. However, all kinetic runs of Figure 3 showed excellent pseudo-first-order kinetics, and no evidence for a buildup of intermediate halohydrin was observed. An induction period or biphasic kinetics would be expected if there were a significant buildup of a halohydrin intermediate. In the next section, we show that a mixture of chlorohydrins **9** and **10** is very reactive in 70:30 dioxane/water, and they are expected to be many orders of magnitude more reactive in 10:90 dioxane/water, which are the conditions for the kinetic analyses of Figure 3. For purpose of kinetic analysis, it is assumed that halohydrin **19**, its conjugate base **18**, and carbocation **6b** are all present in steady-state concentrations for the conditions of Figure 3.

The rate of reaction of **5b** is the sum of the rate of the pH-independent reaction occurring via the k_o pathway and the rate of reaction of carbocation **6b** with the solvent via the k_s pathway (eq 2) where $[\mathbf{5b}]_{tot}$ represents the concentration of added epoxide. If it is further assumed that the concentrations of halohydrin **19**, its conjugate base **18**, and carbocation **6b** are negligible, then the rate expression for k_{obsd} is given by eq 3. Application of steady-state conditions for the concentrations of **18**, **19**, and **6b** to eq 3 and the neglect of the k_{-H} term because $k_s \gg k_{-H}$ provide the rate expression given by eq 4. A value for $k_H k_{-X} K_a/k_1$ is estimated from a common chloride ion rate depression study (next section) to be small compared to $k_X[X^-]$, and elimination of this term from eq 4 gives eq 5. Fitting the data of Figure 3 to eq 5 yields values for k_X equal to $(5.8 \pm 0.5) \times 10^{-4}$ and $(3.0 \pm 0.1) \times 10^{-3}$ M^{-1} s^{-1} for nucleophilic addition of chloride ion and bromide ion, respectively, to **5b**. Values for $(k_{-X}K_a/k_1)(1 + k_{-1}[X^-]/k_s)$ were calculated to be $(3.1 \pm 0.6) \times 10^{-11}$ M and $(6.7 \pm 0.2) \times 10^{-11}$ M, respectively, for reactions of **5b** in 1.0 M NaCl and 0.5 M NaBr solutions.

$$\text{Rate} = k_{obsd}[\mathbf{5b}]_{tot} = k_o[\mathbf{5b}] + k_s[\mathbf{6b}] \qquad (2)$$

$$k_{obsd} \sim k_s[\mathbf{6b}]/[\mathbf{5b}] + k_o \qquad (3)$$

$$k_{obsd} = \frac{k_H[H^+] + k_X[X^-] + k_H k_{-X} K_a/k_1}{1 + (k_{-X}K_a/k_1[H^+])(1 + k_{-X}[X^-]/k_s)} + k_o \qquad (4)$$

$$k_{obsd} = \frac{k_H[H^+] + k_x[X^-]}{1 + (k_{-X}K_a/k_1[H^+])(1 + k_{-1}[X^-]/k_s)} + k_o \qquad (5)$$

In contrast to the pH−rate profiles for the reaction of **5b** in solutions containing halide ions, the rate profile for the reaction of **7b** in 1.0 M NaBr solution is very similar to that for the reaction of **7b** in 0.1 M NaClO$_4$ solution; that is, there is only one rate plateau corresponding to that for the pH-independent reaction (Figure 4). The nucleophilic addition of bromide ion to **7b,** therefore, does not compete successfully with the pH-independent reaction of **7b**.

Preparation and Hydrolysis Reactions of Chlorohydrins Derived from 5b. The relative yields of cis and trans chlorohydrins **9** and **10** from the reaction of **5b** with HCl vary widely with reaction conditions. When HCl in dioxane is added to a solution of **5b** in anhydrous THF, and the solvent is removed under a stream of nitrogen after several minutes, ^{1}H NMR analysis of the product mixture in dioxane-d_8 indicated a 9:1 ratio of two chlorohydrins, **A** and **B**. The spectrum of the major chlorohydrin (**A)** showed a benzylic NMR absorption at δ 5.05, and the spectrum of the minor chlorohydrin (**B**) showed a benzylic NMR absorption at δ 4.60. When a solution of **5b** in THF was added dropwise to a solution of HCl in THF and the solvent was removed after ~10 min, the ratio of chlorohydrins **A** and **B** was 1:9. Under slightly different conditions of reagent concentrations and methods of combining the reactants, the ratio of chlorohydin products **A** and **B** was intermediate in value. A 9:1 mixture of chlorohydrins **A** and **B** changed to a 1:9 mixture of **A** and **B** after standing at rt for a week. The stereochemistry of the benzylic chloro group relative to the adjacent hydroxyl group of the more stable chlorohydrin was assumed to be trans because of fewer steric interactions of the chloro group with the peri hydrogen of the aromatic ring when it is in a trans axial position. No attempt was made to separate the chlorohydrin isomers.

Hydrolysis of chlorohydrin mixtures containing either 9:1 or 1:9 cis/trans ratios in 10:90 dioxane/water solution, which did not contain added chloride ion, yielded the same diol product mixture (98% of trans diol **13** and 2% of cis diol **14**) that is formed from the acid-catalyzed hydrolysis of **5b**. These results are consistent with mechanisms in which cis chlorohydrin **9**, trans chlorohydrin **10**, and epoxide **5b** all react to form the same carbocation **6b**, and diol products are formed exclusively from the attack of the solvent on this intermediate.

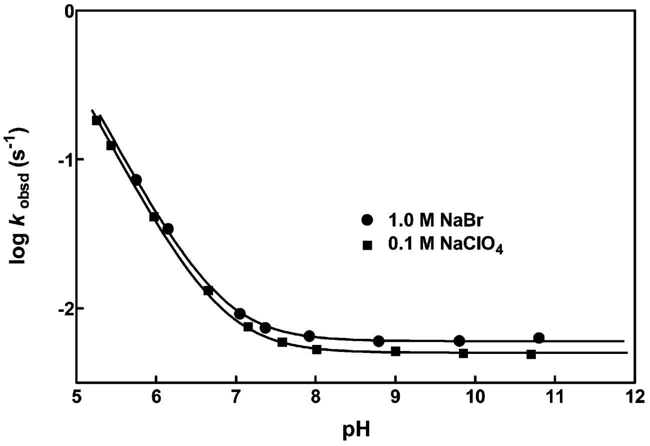


FIGURE 4. Plots of log k_{obsd} vs apparent pH for the reaction of **7b** in 60:40 dioxane/water solutions containing NaBr and NaClO$_4$, 25.0 ± 0.2 °C.

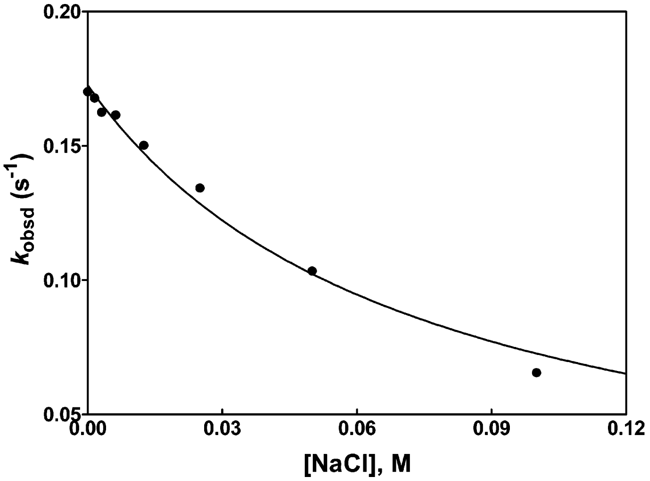
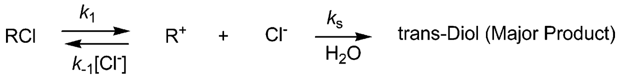


FIGURE 5. Plot of k_{obsd} for the reaction of a 10:90 mixture of chlorohydrins **9** and **10** in 30:70 dioxane/water solutions vs concentration of NaCl, 25.0 ± 0.2 °C, μ = 0.1 M (maintained with added NaClO$_4$).

SCHEME 7



Additional evidence that chlorohydrins **9** and **10** react to form a stable carbocation intermediate is that a pronounced common ion rate depression is observed when a sample of mostly trans chlorohydrin **10** (~90%) is hydrolyzed in 70:30 dioxane/water solutions (Figure 5). In this same solvent, the rate of reaction of **10** in 0.1 M $NaClO_4$ is approximately 2-fold greater than the rate in the absence of $NaClO_4$, indicating that there is a normal salt effect on the solvolysis reaction rate. The common ion rate depression observed for the reaction of **10** in solutions containing chloride ion demonstrates that there is an intermediate carbocation that has a sufficient lifetime to be captured by chloride ion, thus reforming the reactant and lowering the rate of reaction (Scheme 7). The rates of reaction for **10** follow excellent first-order kinetics, so either cis and trans chlorohydrins **9** and **10** react at very similar rates, or the capture of the intermediate carbocation **6** with chloride ion yields mostly trans chlorohydrin **10**.

The rate data shown in Figure 5 were fit to the rate equation

$$k_{\text{obsd}} = \frac{k_1}{\left(1 + \left(\frac{k_{-1}}{k_s}\right)[\text{Cl}^-]\right)}$$

and yielded values for k_1 and k_{-1}/k_s of 0.173 ± 0.002 s^{-1} and 14 ± 1 M^{-1}, respectively. This value of k_{-1}/k_s for the reaction of **10** in 60:40 dioxane/water solutions is only ~8 times smaller than the value of k_{az}/k_s (115 M^{-1} s^{-1}) for the reaction of carbocation **6b** with azide ion in 10:90 dioxane/water, and it is concluded that azide ion reacts with **6** by approximately one order of magnitude faster than chloride ion does. If azide ion reacts with **6** at the diffusional limit, then chloride ion reacts with **6** at a rate close to that of the diffusional limit.

Substitution of 14 M^{-1} for k_{-1}/k_s in the kinetic term $(k_{-X}K_a/k_1)(1 + k_{-1}[X^-]/k_s) = 3.1 \times 10^{-11}$ M in eq 5 for the reaction of **5b** in 1.0 M NaCl solution yields a value of 2.1×10^{-12} M for $k_{-X}K_a/k_1$. This value multiplied by that of k_H (1.4×10^5 M^{-1} s^{-1}) yields a value for $k_Hk_{-X}K_a/k_1$ of $\sim 3 \times 10^{-7}$ s^{-1}, which is much less than $k_X[X^-]$ for the reaction of **5b** in 1.0 M NaCl solutions, thus justifying the elimination of this term from eq 4.

Preparation and Hydrolysis of Chlorohydrins Derived from 7b. The addition of HCl in dioxane to a solution of **7b** in dioxane, followed by removal of the solvent, yielded cis and trans chlorohydrins **11** and **12** in a 60:40 ratio. Hydrolysis of this chlorohydrin mixture in 10:90 dioxane/water yielded 82% of cis diol **17** and 18% of trans diol **16**, which is a cis/trans diol ratio that is the same within experimental error as the ratio of **16** and **17** formed in the acid-catalyzed hydrolysis of **7b**. These results are consistent with a mechanism in which **11** and **12** hydrolyze via carbocation **8b**, and the diol products are derived solely from the attack of water on this intermediate.

Relative Stabilities of cis and trans Diols. Both cis diol **13** and trans diol **14** undergo isomerization in 10:90 dioxane/water solution containing 0.3 M $HClO_4$ to give an equilibrium mixture containing 66% of trans diol and 34% of cis diol. (Figure 6). Thus, the major trans diol product from acid-catalyzed hydrolysis of **5b** is slightly more stable than the isomeric cis diol. The half-life for the approach to equilibrium is 22 h.

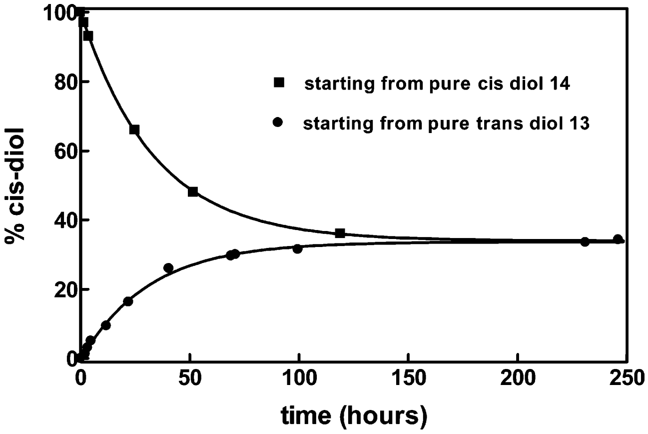
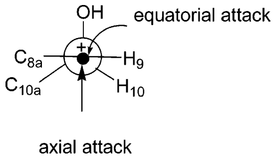


FIGURE 6. Plots of percent cis diol **14** vs time in the equilibration reactions starting from either cis diol **14** or trans diol **13** in 0.3 M $HClO_4$, 10:90 dioxane/water, 25 ± 0.2 °C.

Diols **15** and **16** also undergo acid-catalyzed interconversion, but the rates of equilibration were not determined. When a mixture of cis and trans diols **17** and **16** (82:16 ratio) in 10:90 dioxane/water solution containing 0.05 M $HClO_4$ stood at rt for 6 days, the cis/trans diol ratio changed from 82:18 to 25:75 indicating that the trans isomer is the more stable isomer. Therefore, acid-catalyzed hydrolysis of epoxide **7b** yields the less stable cis diol **17** as the major product. Transition state effects, possibly including both steric and hydrogen bonding effects, therefore must selectively stabilize the transition state leading to the less stable product.[12]

Stereochemical Factors in the Attack of Water on Carbocations 6b and 8b. The axial attack of water on carbocation **6b** to give trans diol **13** (~98%) is highly favored over the equatorial attack of water to give cis diol **14** (~2%). The axial attack of water on carbocation **8b** (~82%) to give cis diol **17** also is favored but to a somewhat lesser extent. Newman projections of the intermediate carbocations are provided in structures **20** and **21**. The energetically favored axial attacks by the solvent on both **20** and **21** appear to be due primarily to steric factors. In each case, the axial attack of the solvent is expected to proceed with a smooth change of geometry from that of the carbocation intermediate to that of a half-chair conformation of the diol product.[13] The equatorial attack of water on **20** would force eclipsing interactions between H-9 and H-10 at the transition state and also might result in a decrease of the $C_{8a}-C_9-C_{10}-C_{10a}$ dihedral angle. Destabilization of the transition state by these steric factors must be greater than any stabilization due to hydrogen bonding between the attacking water molecule and the C_{10} hydroxyl group. Those factors responsible for the greater amount of the equatorial attack



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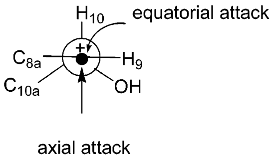

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[12] Sampson, K.; Paik, A.; Duvall, B.; Whalen, D. L. *J. Org. Chem.* **2004**, *69*, 5204−5211.

[13] The axial attack of the solvent on substituted cyclohexenyl carbocations is energetically favored over the equatorial attack. See Goering, H. L.; Josephson, R. R. *J. Am. Chem. Soc.* **1962**, *84*, 2779−2785.

of solvent on **21** as compared to the equatorial attack of solvent on **20** are not clear. One possibility is that the equatorial attack of solvent on **21** leads to the more stable trans diol, whereas the equatorial attack of solvent on **20** leads to the less stable cis diol.

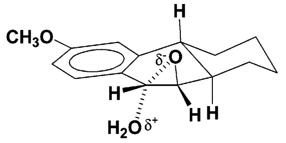
Mechanisms of Acid-Catalyzed Epoxide Hydrolysis as Functions of Carbocation Lifetimes. The mechanisms of the acid-catalyzed hydrolysis of rigid epoxides **5** and **7** containing substituent groups that destabilize carbocations sufficiently, and of other epoxides that react to form carbocations with lifetimes that are either on the order of or shorter than the time required for the solvent to reorganize, will be different from the mechanisms of the reactions of **5b** and **7b**. The sulfuric acid-catalyzed hydrolysis of **7c** in 50:50 dioxane/water is reported to yield 31% of cis diol and 69% of trans diol,[8] which are formed in a ratio substantially different from the 83:17 cis/trans diol ratio for the acid-catalyzed hydrolysis of **7b** in 10:90 dioxane/water. An electron-withdrawing group substituted in the phenyl ring will destabilize the carbocation formed in the acid-catalyzed hydrolysis of the corresponding epoxide. The rate of reaction of the 1-(*m*-bromophenyl)ethyl carbocation with 1:1 TFE/H_2O solvent is estimated to be $\sim 10^{12}$ s^{-1},[9] and carbocation **8c** should have a comparable reactivity. Solvent reorganization occurs with approximately the same rate constant, so as carbocation **8c** is formed in the acid-catalyzed hydrolysis of **7c**, it may react with solvent before complete solvent relaxation occurs, resulting in an increased yield of trans diol.

The cis/trans diol product ratio (75:25) from acid-catalyzed hydrolysis of **7a** in 10:90 dioxane/water also is somewhat different than the cis/trans diol ratio from the acid-catalyzed hydrolysis of **7b** (83:17) in the same solvent. The lifetime of the 1-phenylethyl carbocation in 50:50 TFE/H_2O is still close to the time required for solvent reorganization, although it is estimated to be slightly longer than that of the 1-(*m*-bromophenyl) carbocation.[9] Therefore, it is possible that the slightly higher yield of the trans diol product from the acid-catalyzed hydrolysis of **7a** is also because of the reaction of the intermediate carbocation with the solvent before complete relaxation of the solvent molecules solvating the carbocation.

The acid-catalyzed hydrolysis of **5a**, **5b**, and **5c** each yield >98% of trans diol product. The reaction of **5b** clearly proceeds via a fully formed carbocation **6b**, which is surrounded by a relaxed solvent shell, that undergoes energetically favorable axial attack of the solvent to yield trans diol. The carbocations formed from the reactions of **5a** and **5c** are much less stable than **6b**, however, and the nucleophilic addition by the solvent to the benzylic carbon of these epoxides in the hydrolysis reaction may be concerted or near concerted with the epoxide C−O bond breaking to yield the same trans diol product.

The pH-Independent Reactions of 5b and 7b. The relative reactivities of **5b** and **7b** toward acid-catalyzed hydrolysis are very similar. For example, the k_H for the acid-catalyzed hydrolysis of **5b** in 30:70 dioxane/water is approximately 20% larger than the k_H for the acid-catalyzed hydrolysis of **7b**. However, the rate of the pH-independent reaction of **7b** is much greater than the corresponding rate of **5b**. If it is assumed that the rate of the pH-independent reaction of **7b** is increased by 10-fold as the solvent is changed from 30:70 dioxane/water to 10:90 dioxane/water and this rate is compared to the rate of the pH-independent reaction of **5b** in the same solvent, then the pH-independent rate for **7b** is calculated to be $\sim 2 \times 10^4$ times greater than that for **5b**. For comparison, the pH-independent rate constant for the reaction of **7a** is only 40 times larger than that for **5a**. From two point Hammett σ ρ correlations for the rate enhancement due to a para-methoxy substituent, ρ^+ for the pH-independent reaction of **5** is calculated to be −1.7, which suggests some positive charge development on C-9 at the transition state. However, ρ^+ for the pH-independent reaction of **7** is calculated to be −5.2, which indicates a very large positive charge development on C-9 at the transition state. When the published rate data[6] for the reactions of **5a** and **7a** are compared with the rate data for **5b** and **7b** in this work, ρ^+ for the acid-catalyzed hydrolysis of **5** and **7** can be estimated to be −3.1 and −2.2, respectively.

The pH-independent reactions of **5** and **7** are not all identical. The k_o reaction of **5a** yields only trans diol, and the k_o reaction of **5b** yields mostly (89%) trans diol. The lack of significant positive charge buildup on C-9 in the pH-independent reaction of **5**, which is indicated by a relatively small negative ρ^+, and the observations that epoxide **5b** reacts readily with azide ion and chloride ion nucleophiles suggest that the principal mechanism of the pH-independent reactions of **5a** and **5b** involves concerted nucleophilic addition of a water molecule to the epoxide via transition state **22**. Significant hydrogen bonding of the solvent to the developing oxyanion at the transition is expected, or perhaps proton transfer from the solvent to the developing oxyanion is coupled with the epoxide C−O bond breaking.



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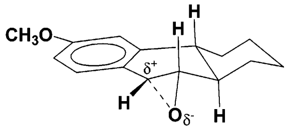

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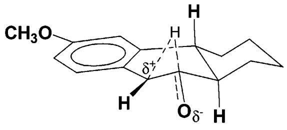

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The principal pH-independent reaction of **7a** and of **7b**, however, is rearrangement of the epoxide to a ketone. The transition state for this reaction must have a large amount of positive charge at C-9 because of the large negative ρ^+ associated with this reaction. The details of the mechanism of this particular rearrangement reaction are not known. One possibility is that the reaction is stepwise via a zwitterionic intemediate with the epoxide C−O bond breaking at an advanced stage in the transition state (**23**) of the rate-limiting step. Another possibility is that the reaction is concerted via a very unsymmetrical transition state such as **24**. A secondary kinetic deuterium isotope effect of 1.22 on the pH-independent reaction of **7a** when H-10 is substituted by deuterium suggests that there is some hydrogen migration in the rate-limiting transition state.[6] The lack of significant kinetic deuterium isotope effects in the pH-independent reactions of deuterium-labeled benzene oxide and naphthalene 1,2-oxide indicates little or no hydrogen migration in the rate-limiting steps,[14] whereas much larger kinetic deuterium isotope effects are observed in the pH-independent reactions of 6-methoxy-1,2,3,4-tetrahydronaphtha-

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(14) Kasperek, G. J.; Bruice, T. C. *J. Chem. Soc., Chem. Commun.* **1972**, 784−785.

lene oxide[15] and precocene I 1,2-epoxide.[16] This indicates substantial hydrogen migration in the rate-limiting transition states. Clearly, the nature of the pH-independent reaction involving hydrogen migration and carbonyl formation depends highly on the structure of the epoxide.

Summary

The acid-catalyzed hydrolyses of rigid epoxides **5b** and **7b** occur via intermediate carbocations **6b** and **8b**, which have lifetimes sufficiently long to undergo reactions with external nucleophiles much faster than they react with solvent. As such, they are fully developed and equilibrated with respect to solvation. These same carbocations are formed from solvolyses of cis and trans chlorohydrins derived from both **5b** and **7b**. Each carbocation reacts with solvent molecules to give cis and trans diols in ratios that are independent of whether the carbocation precursor is an epoxide, a cis chlorohydrin, or a trans chlorohydrin. Carbocations **6b** and **8b** are each constrained to a single conformation, and the axial attack of the solvent on each carbocation is energetically more favorable than the equatorial attack of the solvent. These results provide further evidence that the carbocations formed in the acid-catalyzed hydrolyses of benzo[*a*]pyrene 7,8-diol 9,10-epoxides[3,4] react with the solvent via pathways involving the stereoselective axial attack of the solvent on each carbocation conformation. It should be emphasized that electron-withdrawing substituents in the phenyl ring may destabilize the benzylic carbocation formed in the acid-catalyzed hydrolysis reaction sufficiently to change the mechanism of the diol product formation from the attack of the solvent on a fully developed and completely solvated carbocation to one involving the attack of the solvent that is concerted or nearly concerted with the benzylic C−O bond breaking. The pH-independent reaction of **5b** leads mainly to a diol product, possibly via a concerted nucleophilic addition of solvent, whereas the pH-independent reaction of **7b** leads mainly to a ketone product.

Experimental Section

Materials and Methods. Dioxane and THF were distilled from sodium prior to use. All other reagents were purchased from commercial sources and were used without further purification. Compounds **5b**, **7b**, **13**, and **14** were synthesized by published procedures.[8] The pH values given throughout this paper are those measured by the glass electrode, and for the dioxane/water solutions, they correspond to apparent pH values. All solvent ratios are v:v.

Chlorohydrins 9 and 10. The reactions of **5b** with HCl in anhydrous dioxane/THF solutions yield mixtures of **9** and **10** that depend on the reaction conditions. **Procedure (a).** A solution of 0.10 mL of 4 M HCl in dioxane was added to 10 mg of **5b** in 1.0 mL of THF. The reaction solution was stirred and allowed to stand at rt for 5 min. The solvent was removed by a stream of nitrogen gas, and the residue was analyzed by ^{1}H NMR. The NMR spectrum indicated the presence of one major chlorohydrin (∼90%) with these absorptions: (300 MHz, dioxane-d_8) δ 0.75−1.65 (8H), 2.21 (m, 2H)), 2.52 (m, 1H), 3.45 (s, 3 H), 3.64 (dd, $J = 1.2$, 2.1 Hz), 5.05 (d, $J = 1.2$ Hz), 6.46 (dd, $J = 2.4$, 8.4 Hz), 6.52 (d, $J = 2.4$ Hz), 7.18 (d, $J = 8.4$ Hz). The stereochemistry of the major product from this procedure was later assigned to be cis. **Procedure (b).** A solution of 10 mg of **5b** in 1.0 mL of THF was added in drops with stirring to 1.0 mL of 0.04 M HCl in 99:1 THF/dioxane. The reaction solution was stirred an additional 5 min, and the solvent was removed by a stream of nitrogen. The ^{1}H NMR spectrum of the product indicated the presence of a second major chlorohydrin (∼90%) with these absorptions: (300 MHz, dioxane-d_8) δ 0.95−1.65 (8H), 2.21−2.40 (m, 3H), 3.46 (s, 3H), 3.65 (dd, $J = 1.2$, 2.1 Hz), 4.69 (d, $J = 2.1$ Hz), 6.47 (dd, $J = 2.4$, 8.4 Hz), 6.55 (d, $J = 2.4$ Hz), 6.95 (d, $J = 8.4$ Hz). The stereochemistry of the major product from this procedure was later assigned to be trans. **Procedure (c).** A solution of 1.0 mL of 0.04 M HCl in 99:1 THF/dioxane was added in drops with stirring to a solution of 10 mg of **5b** in 1.0 mL of THF. The solution was stirred for an additional 5 min, and the solvent was removed with a stream of nitrogen. NMR analysis of the product mixture indicated a 35:65 ratio of cis and trans chlorohydrins **9** and **10**.

When a 90:10 cis/trans mixture of **9** and **10** was allowed to stand for a week, it had changed to a 10:90 cis/trans mixture. It is assumed that the cis chlorohydrin **9** is less stable than the trans chlorohydrin **10**, in which the chloro group occupies an axial position with less steric interaction with the peri hydrogen of the phenyl ring. Addition of either chlorohydrin mixture from Procedures (a) or (b) to 10:90 dioxane/water solution yielded the same diol product mixture (98% of **13** and 2% of **14**) as that formed in the acid-catalyzed hydrolysis of **5b** in the same solvent. The chlorohydrins are very reactive, and their general characterizations are based on the observation that they readily hydrolyze to form the known trans and cis diols **13** and **14**.

Chlorohydrins 11 and 12. A solution of 4 M HCl in anhydrous dioxane (0.10 mL) was added to a stirred solution of 20 mg of epoxide **7b** in 1.0 mL of dioxane, and the solvent was immediately removed by rotary evaporation. ^{1}H NMR analysis of the residue showed one absorption at δ 5.33 (d, $J = 3.6$ Hz) and a second absorption at δ 5.04 (d, $J = 8.4$ Hz) in a 6:4 ratio. The absorption at δ 5.33 was assigned to the benzylic hydrogen of cis chlorohydrin **11**, and the absorption at δ 5.04 was assigned to the benzylic hydrogen of trans chlorohydrin **12**. The ratio of chlorohydrin products varied with reaction times and conditions. When a mixture of **11** and **12** in $CDCl_3$ was allowed to stand at rt, the chlorohydrins had reacted to form ketone **15**. No attempt was made to further separate or purify **11** and **12**, and their structural assignment was based on the observation that they underwent hydrolysis in 10:90 dioxane/water to yield the cis and trans diols **17** and **16** in an 82:18 ratio, which is the same ratio as that formed from acid-catalyzed hydrolysis of **7b**.

Kinetics. For each kinetic run, ∼5 μL of a stock solution of **5b** or **7b** in dioxane (6 mg/mL) was added to 2.0 mL of a reaction solution in a thermostated cell compartment (25.0 ± 0.2 °C) of a UV−vis spectrophotometer. The pH of each solution was maintained by ∼10^{-3} M of the following buffers: pH 5.0−6.5, (2-[*N*-Morpholino]ethanesulfonic acid) (MES); pH 7.0−7.5, (*N*-2-hydroxyethyl-piperazine-*N*-2-ethenesulfonic acid) (HEPES); pH 8.0−10.0, and (2-[*N*-cyclohexylamino]ethanesulfonic acid) (CHES). For solutions with pH 11 and higher, a buffer was not used. The pH of each buffer solution was preadjusted with 0.1 M $HClO_4$ or 0.1 M NaOH. The reactions were monitored by UV detection at 235 nm. Pseudo-first-order rate constants were calculated by nonlinear regression analysis of the absorbance vs time data.

The procedures for determining the rates of reaction of **5b** and **7b** in solutions containing sodium azide and sodium chloride were similar to those of the above kinetics studies. These reactions were monitored by UV detection at 240 nm.

For reactions of a 10:90 mixture of chlorohydrins **9** and **10** in solutions containing various chloride concentrations, ionic strength was kept constant at 0.1 M by mixing 0.1 M NaCl with 0.1 M $NaClO_4$ in 70:30 dioxane/water. Reactions were monitored by UV detection at 238 nm.

Product Studies. A 25 μL sample of a stock solution (10 mg/mL) of **5b** or **7b** was added to 2.0 mL of 10:90 dioxane/water solution containing 10^{-3} M buffer. The pH of the dioxane/water

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[15] Gillilan, R. E.; Pohl, T. M.; Whalen, D. L. *J. Am. Chem. Soc.* **1982**, *104*, 4482−4484.

[16] Sayer, J. M.; Grossman, S. J.; Adusei-Poku, K. S.; Jerina, D. M. *J. Am. Chem. Soc.* **1988**, *110*, 5068−5074.

solutions were adjusted to 6.0 and 10.5 for the acid-catalyzed and the pH-independent reactions of **5b** and to 3.0 and 10.0 for the acid-catalyzed and the pH-independent reactions of **7b**. After ∼10 half-lives for each reaction, 20 mL of a solution of acenaphthenol (3 mg/mL) was added to serve as a standard. The pH of each solution was then adjusted to ca. 5−9 before HPLC analysis on a reverse phase C_{18} column with 60:40 methanol/water as an eluting solvent (1.0 mL/min). The products were detected by UV absorption at 269 nm. The yields of diols were calculated by comparing the areas of their HPLC peaks to that of the standard (retention time 9.3 min). The yields of the ketones from the pH-independent reactions of **5b** and **7b** were estimated by comparing the relative yield of the diols at pH >10 with the yields of the diols from the acid-catalyzed reactions, and assuming that the yields of the diols from the acid-catalyzed reactions were 100%. The yield of each ketone was assumed to be equal to the difference between the yield of the diols at pH > 10 and the yield of the diols from the acid-catalyzed reaction. The trans and cis diols **13** and **14** from hydrolysis of **5b** had retention times of 6.5 and 16 min, respectively, and the trans and cis diols **16** and **17** from hydrolysis of **7b** had retention times of 12.5 and 13.0 min, respectively. The azidohydrins formed from the reactions of **5b** and **7b** were not stable, but were assigned to HPLC peaks having retention times of 42 and 44 min (from **5b**), and 33 and 42 min (from **7b**). Ketone **15** underwent decomposition under the long reaction times for the pH-independent reaction of **5b**, although a peak at 48 min, which may be due to **15**, was observed.

The pH-Independent Reaction of 7b. The Isolation of Ketone 15. A solution of 6.5 mg of **7b** in 0.1 mL of dioxane was added to a stirred solution of 1.8 mL of dioxane and 6.2 mL of 0.1 M $NaClO_4$ in which the apparent pH was preadjusted to 9.6. After an additional 3 min of stirring at rt, the reaction solution was diluted with water and extracted with diethyl ether. The diethyl ether solution was washed twice with water and once with saturated NaCl solution. The ether solution was dried over calcium sulfate, and the solvent was removed to yield 4.0 mg of ketone **15**. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 3.54 (s, 2H), 3.82 (s, 3H), 6.77 (dd, $J = 8.3$, 2.3 Hz, 1H), 6.89 (d, $J = 2.3$ Hz, 1H), 7.05 (d, $J = 8.3$ Hz, 1H); HRMS−FAB ($M + H^+$) calcd for $C_{15}H_{19}O_2$, 231.1385; found, 231.1354. Ketone **15** was reported to be the main product formed from the reaction of **7b** with Cl_3CCO_2H in benzene.[8]

Acid-Catalyzed Equilibration of 13 and 14. Each diol (10 mg) was dissolved in 0.5 mL of dioxane, and the resulting solution was added to 10 mL of 0.3 M $HClO_4$ in 10:90 dioxane/water solution. This solution was placed in a water bath at 25.0 °C. A portion (0.3 mL) of the diol solution was removed at various time intervals and quenched with 0.3 mL of 0.3 M NaOH prior to HPLC analysis under the conditions noted above. Summaries of the data are provided in Figure 6.

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