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New Insights on the Mechanisms of the pH-Independent Reactions of Benzo[*a*]pyrene 7,8-Diol 9,10-Epoxides

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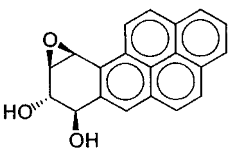
Abstract: The rates and products of the reactions of (±)-7β,8α-dihydroxy-9β,10β-epoxy-7,8,9,10-tetrahydrobenzo[*a*]pyrene (**1**) and (±)-7β,8α-dihydroxy-9α,10α-epoxy-7,8,9,10-tetrahydrobenzo[*a*]pyrene (**2**) in water and dioxane−water mixtures have been determined over a pH range wider than that of earlier studies. This study provides additional insight on the mechanisms of the pH-independent reactions of **1** and **2**. The rate profile for reaction of **1** shows acid-catalyzed hydrolysis at pH <5, a rate plateau at pH 5−9.5, a negative inflection at pH 10−11.5, and a rate increase at pH >11.5. The rate decrease between pH 10 and pH 11.5 is accompanied by a decrease in the yield of tetrols from 60% (pH 8) to 29% (pH 11.2) and is interpreted to be the result of a partial change in mechanism brought about by attack of hydroxide ion acting as a base to deprotonate a carbocation intermediate and regenerate **1** at pH >10, thus reducing the contribution of the pathway for tetrol formation in which water attacks the carbocation. The rate profile for the reaction of **2** exhibits only a single rate plateau at intermediate pH, along with increases in rate at low and high pH because of second-order reactions of **2** with H^+ and HO^-, respectively. The lack of a rate depression at pH >10 and the product studies for the reaction of **2** in dilute sodium azide solutions suggest that the tetrol-forming reactions of the pH-independent reaction of **2** are concerted or near-concerted.

Introduction

Rate profiles[1] and product studies for the acid-catalyzed[1−4] and pH-independent[1] hydrolysis reactions of 7,8-dihydroxy-9,-10-epoxide metabolites **1** and **2** of the carcinogen benzo[*a*]pyrene have been reported. Acid-catalyzed hydrolyses of **1** and **2** proceed by rate-limiting formation of benzylic carbocations, which undergo attack by water from both faces of the electron-deficient benzylic carbon to yield mixtures of cis and trans tetrols, e.g., see Scheme 1 for the reaction of **1**. Whereas acid-catalyzed hydrolysis of **1** yields 92% of cis tetrol and only 8% of trans tetrol, acid-catalyzed hydrolysis of **2** yields 95% of trans tetrol and only 5% of cis tetrol. The very different ratios of cis and trans tetrols formed from the hydrolyses of **1** and **2** have been rationalized by mechanisms involving favorable axial attack of water on the more stable conformation of the carbocation.[5,6]



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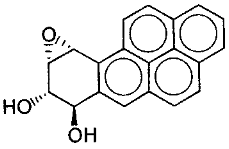
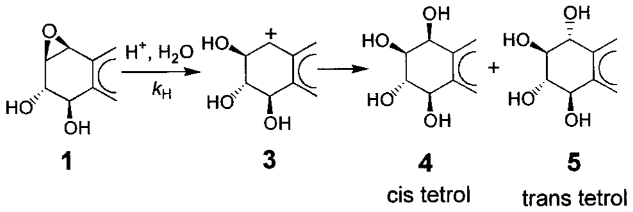
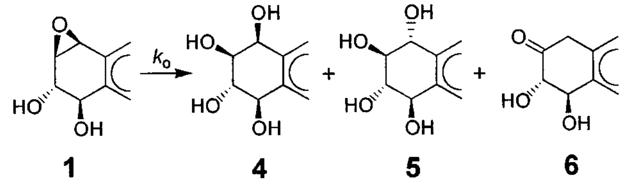


2

Scheme 1



Scheme 2



The pH-independent reaction of **1** at pH 8 yields cis and trans tetrols **4** and **5**, formed in the same ratio as that formed from the acid-catalyzed hydrolysis of **1** and a third product, ketone **6** (Scheme 2).[1] An intermediate in the tetrol-forming reaction has been detected by nucleophile trapping with azide anion and *N*-acetylcysteine.[7] This intermediate is assumed to be identical to the benzylic carbocation formed in the acid-catalyzed reaction

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because the cis to trans tetrol ratio in both acid-catalyzed and pH-independent reactions is the same.

To ascertain the mechanisms of the pH-independent reactions of **1** and **2**, often referred to as "spontaneous" reactions, we have carried out rate and product studies of their reactions over a pH range greater than that for which studies were previously reported. These new studies show that, in addition to undergoing a change in mechanism from an acid-catalyzed process to a pH-independent reaction at pH 5−6, the pH-independent reaction of **1** undergoes a further change of mechanism at pH 9.5−10.5. The pH-independent reaction of **2** does not show a similar change in mechanism. At pH >12, the rates of reaction of both **1** and **2** increase due to second-order reactions with hydroxide ion. In this paper, experiments that provide more insight on the mechanisms of the pH-independent reactions of **1** and **2** are reported and discussed.

Experimental Procedures

Materials. Diol epoxides (±)-**1** and (±)-**2** were prepared by published procedures.[8,9] (Caution: These compounds are carcinogenic and should be handled with caution.) Dioxane was distilled from sodium prior to use. All other reagents were purchased from commercial sources.

Analytical Procedures. All HPLC analyses were carried out with a Waters Nova-Pak C_{18} reverse-phase column (8 × 100 mm).

Kinetic Procedures. For each kinetic run, approximately 5 μL of a stock solution of **1** or **2** in dioxane (3 mM) was added to 2.0 mL of reaction solution in the thermostated cell compartment (25.0 ± 0.2 °C) of a UV−vis spectrophotometer. Reactions were monitored at 348 nm, and pseudo-first-order rate constants were calculated by nonlinear regression analysis of the absorbance vs time data. For kinetic runs at pH 5.7−9.5, approximately 10^{-3} M MES (2-[*N*-morpholino]ethanesulfonic acid), HEPES (*N*-2-(hydroxyethyl)piperazine-*N*′-2-ethanesulfonic acid), or CHES (2-[*N*-cyclohexylamino]ethanesulfonic acid) buffer was used to maintain pH. Amine buffers are both general acid catalysts and nucleophiles in the hydrolysis reactions of **2**,[10] and at the concentrations of buffer used to maintain pH, the buffer contribution to the rate is expected to be ~10% of the pH-independent rate of **2** and most likely accounts for the slightly greater rate of reaction of **2** at pH 8.5−10.0 than at pH 10−11.5, where no buffer was used for pH maintenance.

Products from Reactions of 1 in Water Solutions, 0.1 M $NaClO_4$. Aliquots (10.0 μL) of **1** in dioxane (2 mM) were added to vials containing 2.0 mL of 0.1 M $NaClO_4$ in water, 5:95 dioxane−water, or 10:90 dioxane−water (v/v) whose pH had been adjusted with either 0.1 M $HClO_4$ or 0.1 M NaOH. After being swirled, the vials were capped and allowed to stand at rt for 20−25 min. An aliquot (10.0 μL) of 1-acenaphthenol in dioxane (5 mM) was then added to each vial to serve as an HPLC standard. Buffers were not used for pH control because they efficiently catalyze the hydrolysis of **1**,[10,11] potentially resulting in changes in product ratios. The pH of each reaction solution was adjusted to ~5−8, and they were analyzed by HPLC with 60% methanol−40% water as the eluting solvent, 1.5 mL/min. Products were monitored by UV detection at 273 nm. The retention times for the trans tetrol product, cis tetrol product, and 1-acenaphthenol standard for product studies of **1** are 7.0, 10.4, and 8.6 min, respectively. The results of these analyses are summarized in Table 1. Yields of tetrol products were calculated by comparing the areas of the tetrol and standard HPLC peaks from the reaction of **1** at each pH and at pH 3.0, where only tetrol products are formed from the reaction of **1**. The HPLC retention time of ketone **6** under the conditions listed above is 16.2 min. This product is detected from the reaction of **1** at pH >7 when products are analyzed after short reaction times, e.g., <1 min for water solvent.[1,11] However, it is unstable and was not detected by HPLC analyses of the product mixtures when reaction times were 20−25 min.

Table 1. Summary of Tetrol Yields from the Reaction of **1** in Water and Dioxane−Water Solutions, 0.1 M $NaClO_4$[a]

pH[b]	solvent	*cis*-tetrol: *trans*-tetrol	yield of tetrols (%)[c]
3.00−3.15	10:90 dioxane−water	89:11	100
7.87−7.89	water	91:9	60
7.94−7.89	5:95 dioxane−water	91:9	60
8.04−8.02	10:90 dioxane−water	91:9	56
11.13−11.04	water	88:12	29
11.21−11.14	5:95 dioxane−water	88:12	29
11.25−11.22	10:90 dioxane−water	88:12	29
12.00−11.99	water	75:25	16
12.07−12.07	10:90 dioxane−water	68:32	15

[a] Reactions were allowed to proceed at rt for 20−25 min. [b] pH values are given for each solution before the addition of **1** and at the end of the reaction. [c] The percent yields of tetrols from the reaction of **1** are relative to the yield of tetrols formed from the acid-catalyzed hydrolysis of **1** at pH 3.0 in 10:90 dioxane−water.

Products from the Reaction of 2. Product studies for the reaction of **2** in water and dioxane−water solutions containing 0.1 M $NaClO_4$ and in 10:90 dioxane−water containing 0.2 M $NaClO_4$ have been published.[1,12] Acid-catalyzed hydrolysis of **2** produces 5−10% cis tetrols and 90−95% trans tetrols. The pH-independent reaction of **2**, however, forms cis and trans tetrols in a 40:60 ratio. The yield of tetrols from the pH-independent reaction of **2** is somewhat less than that from the acid-catalyzed hydrolysis, and this loss in tetrol yield is most likely due to formation of a minor amount of ketone **6**.[1,12] The pH-independent reaction of **2** has a half-life of 29 min in water at 25 °C, and ketone **6** decomposes much faster than the pH-independent rate of **2**. Therefore, it is not detected by HPLC analysis of the product mixtures.

Products from the Reaction of 2 at pH 8.3 in 10:90 Dioxane−Water Solutions Containing Sodium Azide. Aliquots (10.0 μL) of **2** in dioxane (2 mM) were added to vials containing 2.0 mL of 10:90 dioxane−water, 0.2 M $NaClO_4$, 10^{-3} M HEPES, pH 8.3, and NaN_3 in concentrations varying from 0 to 4 mM. After being swirled, the vials were capped and allowed to stand at rt for 18 h. An aliquot (10.0 μL) of 2-(1-naphthyl)ethanol in dioxane (5 mM) was then added to each vial to serve as an HPLC standard, and they were analyzed by HPLC with 60% methanol−40% water (1.2 mL/min) as the eluting solvent. Products were monitored by UV detection at 273 nm. The retention times for the trans tetrol product, cis tetrol product, and 2-(1-naphthyl)ethanol standard are 6.5, 8.3, and 10.8 min, respectively. Under these HPLC conditions, the cis and trans azidohydrin products[13] have retention times of 15.1 and 16.7 min, respectively. However, these azide products are stable for only several minutes under reaction conditions and decompose to other unidentified products other than tetrols at longer reaction times. Relative yields of tetrol products were calculated by comparing the area of the tetrol HPLC peaks with that of the standard for each sodium azide concentration, and comparing this ratio with that for reaction of **2** in the absence of azide ion. The relative yields of tetrol products from the reaction of **2** in 1, 2, 3, and 4 mM NaN_3 solutions are 56, 41, 33, and 25, respectively. The cis:trans tetrol ratio remained constant at 40:60. The reduction in yield of tetrols from the reaction of **2** in solutions containing sodium azide is assumed to be equal to the yield of azidohydrin.

Results and Discussion

pH-Independent Reaction of 1. The pH−rate profiles for reaction of **1** in water, 10:90 dioxane−water, and 1:3 dioxane−water from pH 4 to pH 9.5 have been published.[1] In water at pH <~4.5, **1** hydrolyzes by an acid-catalyzed mechanism. At

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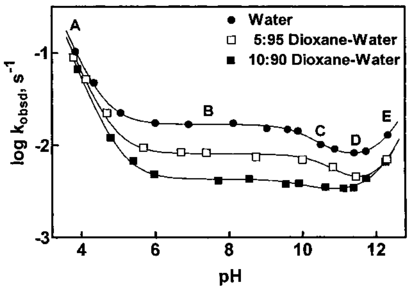


Figure 1. Plots of log k_{obsd} vs pH for the reaction of **1** in water, 5:95 dioxane−water, and 10:90 dioxane−water (v/v), 0.1 M $NaClO_4$, 25.0 ± 0.2 °C. The solid lines are theoretical, based on eq 3 and the rate parameters listed in Table 2.

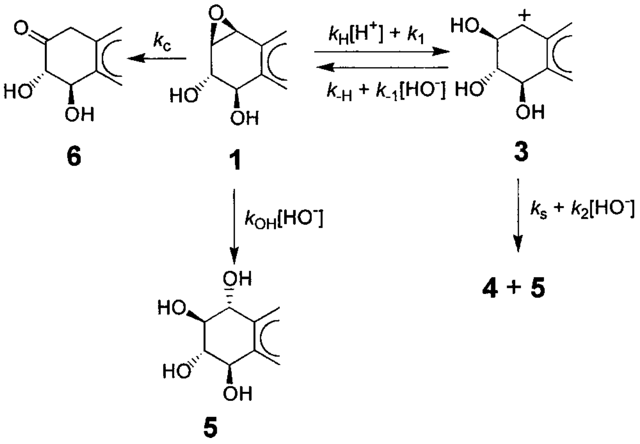
pH 4−5, there is a change in mechanism from acid-catalyzed to pH-independent hydrolysis, resulting in a rate plateau that extends from pH 5 to pH 9.5. The pH-independent reaction of **1** at pH 7−8 in 10:90 dioxane−water is reported to yield ∼7% ketone **6**, which is not stable to the reaction conditions, in addition to cis and trans tetrols.[1] Other unidentified products were also formed, presumably from the unstable ketone. Because of the instability of ketone **6**, its yield was estimated by analysis of the product mixture after one half-life for the reaction of **1**.[1] We have now determined the rates of reaction of **1** from pH 4 to pH 12.5 in water, 5:95 dioxane−water, and 10:90 dioxane−water and carried out quantitative product studies over a wider pH range than reported previously.

Plots of log k_{obsd} vs pH for the reaction of **1** in dioxane−water solutions are provided in Figure 1. These plots show, as determined earlier, a pH-dependent rate at pH <5 (region A) and a pH-independent rate at pH 5−9.5 (region B). These data are consistent with a change in mechanism for the reaction of **1** from acid-catalyzed to pH-independent at pH 4−6. However, the rate of reaction of **1** decreases again at pH 9.5−10.5 (region C), indicating another change in mechanism. Accompanying this change of rate for the reaction of **1** is a change in product distribution. The rate of reaction of **1** reaches a minimun at pH ∼11.5 (labeled D) and increases at pH >12 (region E) due to a second-order reaction of **1** with hydroxide ion.

Because of the instability of ketone **6** in water solutions, its yields from the reaction of **1** in this study were not determined directly. Instead, the relative yield of tetrols formed from the reaction of **1** at pH >5 was compared with that from its reaction at pH 3.0 in 10:90 dioxane−water, where >99% of **1** reacts by the acid-catalyzed route and only tetrols are formed. Any reduction in the relative yields of tetrols from the reaction of **1** at a higher pH is attributed to ketone formation. These data are summarized in Table 1. The cis and trans tetrol ratios given in this table are consistent with earlier studies,[1−4] which show that both the acid-catalyzed hydrolysis of **1** (pH 3) and the pH-independent reaction of **1** (pH 8) yield ∼90% cis tetrol and ∼10% trans tetrol. The total yield of tetrol products from the pH-independent reaction of **1** at pH 8, however, is reduced by 40% as compared to their yields from acid-catalyzed hydrolysis of **1**. It is assumed that the lowering of tetrol yields is due to the formation of ketone **6**, which is not stable at intermediate and higher pH and decomposes to other unidentified products.

Product studies for the reaction of **1** at pH 11.2 show that the ratio of cis and trans tetrol products is similar to that formed at lower pH. However, the yield of tetrols is reduced from 60% at pH 8 to 29% at pH 11.2. The reduction in tetrol yield from the reaction of **1** at pH >10 and the inflection point in the pH−rate profile at pH 10.5 are consistent with a change of mechanism. A mechanism for the reaction of **1** that is consistent with the pH−rate profiles and with the change in products as a function of pH is given in Scheme 3.

Scheme 3



Region A. At pH <5, the rate increases with increasing $[H^+]$, and the principal reaction is acid-catalyzed hydrolysis of **1** via a carbocation intermediate to yield tetrols. The acid-catalyzed hydrolyses of a number of aryl epoxides have been shown to proceed via intermediate carbocations, formed in rate-limiting steps.[7,11,14−16] In this mechanism, therefore, it is assumed that the reaction of **1** with H^+ to form carbocation **3** is irreversible, i.e., $k_s \gg k_{-H}$.

Region B. From pH 5 to pH 9.5 (region B), **1** reacts via a pH-independent reaction to yield cis and trans tetrols (**4** and **5**) and ketone (**6**) products. It is assumed that ketone **6** is formed from a reaction pathway, most likely concerted, that is completely separate from the stepwise mechanism leading to tetrols.[17,18] The tetrol-forming pathway of the pH-independent reaction of **1** involves the rate-limiting reaction of **1** with water (k_1) to yield carbocation intermediate **3**, trappable by azide ion after its rate-limiting formation.[7] The magnitude of this rate plateau is therefore equal to the sum of k_1 and k_c.

Region C. The reduction in rate for the reaction of **1** with an increase in pH in region C is consistent with a mechanism in which hydroxide ion reacts as a base with carbocation **3** to re-form epoxide **1**, thus lowering the steady-state concentration of carbocation **3** and slowing the reaction rate for tetrol formation. In this pH region, therefore, $k_{-1}[HO^-]$ becomes comparable in magnitude to k_s. The rate-limiting step of the tetrol-forming pathway therefore changes from epoxide ring opening by water to form carbocation **3** in region B ($k_s \gg k_{-1}[HO^-]$) to trapping of carbocation **3** by water in region C ($k_{-1}[HO^-] \approx k_s$). A precedent for reversal in acid-catalyzed epoxide ring opening at pH >10 is observed in the hydrolysis of precocene I oxide,[17] and there is reversal of the general acid-catalyzed ring opening of **2** by amine bases with pK_a's >10.[10] Since the rate of ketone formation (k_c) is independent of pH and the rate of tetrol formation decreases with an increase of pH in this region, the relative yield of ketone product increases with pH.

Regions D and E. At pH 11.2 (region D), the rate of reaction of **1** is at a minimum. At this pH, several reactions contribute

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Table 2. Summary of Rate Parameters[a] for the Reaction of **1** in Water and DioxaneEnDashEnDash−Water Solutions, 0.1 M $NaClO_4$, 25 °C

rate parameter	solvent		
	water	5:95 dioxane−water	10:90 dioxane−water
k_H (M^{-1} s^{-1})	$(6.25 \pm 0.21) \times 10^2$	$(5.59 \pm 0.34) \times 10^2$	$(5.0 \pm 0.2) \times 10^2$
$(k_c + k_1)$ (s^{-1})[b]	$(1.68 \pm 0.03) \times 10^{-2}$	$(8.1 \pm 0.3) \times 10^{-3}$	$(4.3 \pm 0.1) \times 10^{-3}$
$[k_c + k_1k_2/(k_{-1} + k_2)]$ (s^{-1})[b]	$(6.9 \pm 0.3) \times 10^{-3}$	$(3.3 \pm 0.1) \times 10^{-3}$	$(3.1 \pm 0.1) \times 10^{-3}$
$(k_{-1} + k_2)/k_s$ (M^{-1})[b,d]	$(5.9 \pm 1.0) \times 10^3$	$(1.8 \pm 1.4) \times 10^3$	$(9.9 \pm 5.8) \times 10^3$
k_{OH} (M^{-1} s^{-1})[b,d]	$(2.8 \pm 0.3) \times 10^{-1}$	$(1.7 \pm 0.6) \times 10^{-1}$	$(1.9 \pm 0.2) \times 10^{-1}$
k_c (s^{-1})[c]	$(6.9 \pm 0.3) \times 10^{-3}$	$(3.3 \pm 0.1) \times 10^{-3}$	$(3.1 \pm 0.1) \times 10^{-3}$
k_1 (s^{-1})[c]	$(9.9 \pm 0.4) \times 10^{-3}$	$(4.7 \pm 1.0) \times 10^{-3}$	$(1.2 \pm 0.2) \times 10^{-3}$
k_{-1}/k_s (M^{-1})[c,d]	$(5.9 \pm 1.0) \times 10^3$	$(1.8 \pm 1.4) \times 10^3$	$(9.9 \pm 5.8) \times 10^3$

[a] Rate parameters are defined in Scheme 3. [b] Calculated from eq 3. [c] Calculated from eq 4. [d] On basis of the assignment for K_w of 10^{-14} M^2.

to the rate. The major product is ketone formed via the k_c pathway, although tetrols are also formed from both the k_1 and the k_{OH} pathways. At pH >12 (region E), the rate of the reaction of **1** increases due to a second-order reaction of **1** with hydroxide ion.

Rate Profiles. With the assumption that **3** is a steady-state intermediate and $k_s \gg k_{-H}$, the rate expression for the mechanism of Scheme 3 is given by eq 1,

$$k_{obsd} = k_c + \frac{(k_H[H^+] + k_1)(k_s + k_2[HO^-])}{k_s + (k_{-1} + k_2)[HO^-]} + k_{OH}[HO^-] \quad (1)$$

where k_{obsd} is the pseudo-first-order rate constant for the reaction of **1** at a given pH, k_c is the first-order rate constant for the rearrangement of **1** to ketone **6**, k_H is the bimolecular rate constant for the acid-catalyzed hydrolysis of **1**, k_1 is the first-order rate constant for the reaction of **1** with water to form carbocation **3** and hydroxide ion, k_s is the first-order rate constant for the reaction of **3** with water, k_{-1} is the second-order rate constant for the reaction of **3** with hydroxide ion to re-form **1**, and k_2 is the second-order rate constant for the reaction of carbocation **3** with hydroxide ion to form tetrol products. Substitution of $[HO^-] = K_w/[H^+]$ into eq 1 and rearrangement of the resulting equation yields eq 2.

$$k_{obsd} = \frac{k_H[H^+] + (k_c + k_1 + k_Hk_2K_w/k_s)}{1 + \left(\frac{k_{-1} + k_2}{k_s}\right)\left(\frac{K_w}{[H^+]}\right)} + \frac{k_c + \left(\frac{k_1k_2}{k_{-1} + k_2}\right)}{1 + \left(\frac{k_{-1} + k_2}{k_s}\right)^{-1}\left(\frac{[H^+]}{K_w}\right)} + k_{OH}K_w/[H^+] \quad (2)$$

In eq 2, the maximum value of $k_Hk_2K_w/k_s$ in 10:90 dioxane−water can be estimated from values of k_H (5.1×10^2 M^{-1} s^{-1}),[1] k_s (1.6×10^7 s^{-1}),[7] K_w ($\sim 10^{-14}$ M^2), and a diffusion-limiting value for k_2 ($\sim 10^{10}$ M^{-1} s^{-1}) to be 3.2×10^{-9} s^{-1}. This rate term is very much smaller than the magnitude of the rate plateau $(k_c + k_1)$ for each solvent and can be neglected. Equation 2 then reduces to eq 3.

$$k_{obsd} = \frac{k_H[H^+] + (k_c + k_1)}{1 + \left(\frac{k_{-1} + k_2}{k_s}\right)\left(\frac{K_w}{[H^+]}\right)} + \frac{k_c + \left(\frac{k_1k_2}{k_{-1} + k_2}\right)}{1 + \left(\frac{k_{-1} + k_2}{k_s}\right)^{-1}\left(\frac{[H^+]}{K_w}\right)} + k_{OH}K_w/[H^+] \quad (3)$$

Rate data were fit by nonlinear regression analysis to eq 3, and with the assignment of $K_w = 10^{-14}$ M^2 for each solvent, they yielded values for k_H, $(k_c + k_1)$, $[k_c + k_1k_2/(k_{-1} + k_2)]$, and $[(k_{-1} + k_2)/k_s)]$. A summary of these kinetic parameters is provided in Table 2. Rate and product data taken together clearly show a change of mechanism for the reaction of **1** as the pH increases from 9 to 11. The rate profiles in Figure 1 show that this change of mechanism is most pronounced when the solvent is water and is not so apparent when the solvent is 10:90 dioxane−water. The pH-independent rate constant for the reaction of **1** at pH 8 $(k_c + k_1)$ is much greater than the rate constant for the acid-catalyzed hydrolysis ($k_H[H^+]$), and all of carbocation **3** formed from the k_1 pathway at this pH goes on to tetrol product via the k_s route. At this pH, the yield of ketone from the k_c route is 40%, and the yield of tetrol from the k_1 pathway is 60%. Therefore, the value of $k_c/(k_c + k_1)$, calculated from product yields, is equal to 0.40. The ratio $[k_c + k_1k_2/(k_{-1} + k_2)]/(k_c + k_1)$, calculated from parameters listed in Table 2 for the reaction of **1** in water, is equal to 0.41. This ratio is, within experimental error, the same as the ratio $k_c/(k_c + k_1)$ calculated from the product ratios, and therefore, it can be concluded that the rate term $k_1k_2/(k_{-1} + k_2)$ is small as compared to k_c. Because $k_1 \approx k_c$, then k_{-1} must be significantly larger than k_2. Thus, attack of the hydroxide on carbocation **3** to yield tetrol products, which is the reaction giving rise to the term $k_1k_2/(k_{-1} + k_2)$, is at best a minor reaction pathway. The term $(k_{-1} + k_2)/k_s$ is therefore approximately equal to k_{-1}/k_s.

By deleting $k_1k_2/(k_{-1} + k_2)$ and k_2 from eq 3, because they are small as compared to other terms in the equation, eq 3 further simplifies to eq 4.

$$k_{obsd} = \frac{k_H[H^+] + k_c + k_1}{1 + \left(\frac{k_{-1}}{k_s}\right)\frac{K_w}{[H^+]}} + \frac{k_c}{1 + \left(\frac{k_{-1}}{k_s}\right)^{-1}\left(\frac{[H^+]}{K_w}\right)} + k_{OH}K_w/[H^+] \quad (4)$$

Values of k_c, k_1, and k_{-1}/k_s calculated by fitting the data to eq 4 are given in a separate category in Table 2. From product studies,[7] it was estimated that the ratio of the bimolecular rate constant for attack of azide ion on **3** as compared to the first-order rate constant for attack of water on **3** (k_{az}/k_s) is $\sim 1.4 \times 10^3$ M^{-1}. This rate ratio is much smaller than that observed for activation-controlled reactions of carbocations with water and azide ion ($k_{az}/k_s \sim 10^7$ M^{-1})[19,20] and suggests that azide attacks **3** as a nucleophile at the diffusion-limited rate.[7,21,22] Calculated

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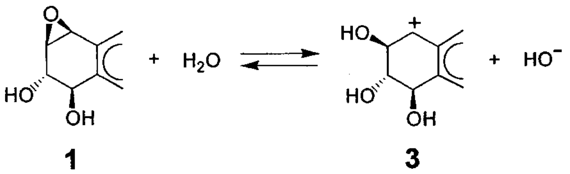
Scheme 4



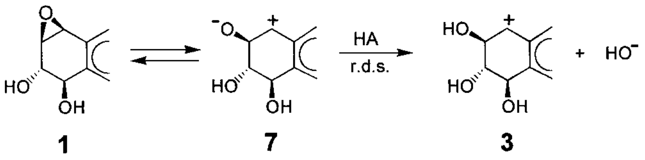
values of k_{-1}/k_s listed in Table 2 are also in the range of 10^3–10^4 M^{-1}. Since this term has a value even greater than that for k_{az}/k_s, then reaction of hydroxide ion as a base with **3** to re-form **1** must also occur at the diffusion-controlled limit. From an estimated value[7] of 1.6×10^7 s^{-1} for k_s and the value for k_{-1}/k_s listed in Table 2 for the reaction of **1** in water, k_{-1} is calculated to be 9×10^{10} M^{-1} s^{-1}. Deprotonation of **3** by hydroxide ion is estimated by pK_a considerations to be a thermodynamically favorable reaction,[7] and the resulting zwitterion is expected to close without activation to **1**. Thus, that fraction of the pH-independent reaction of **1** at pH 8 leading to carbocation **3** at pH >10 is reversed by thermodynamically favorable attack of hydroxide ion as a base on **3** to re-form **1**. Therefore, there is a partial change in the mechanism for the reaction of **1b** in the pH range 9.5–11.5. At pH 5–9.5, the general acid-catalyzed reaction of water with **1** to form carbocation **3** (k_1) is partially rate-limiting, whereas at pH >11 this step is no longer rate-limiting.

At pH >11.5, the rate of reaction of **1** increases due to the incursion of a second-order reaction with hydroxide ion. For the reaction of **1** in 10:90 dioxane–water at pH 12, the ratio of trans tetrol:cis tetrol is considerably larger than that formed from the reaction of **1** at a lower pH. This result indicates that part of the reaction of **1** at pH 12 proceeds via a bimolecular attack of hydroxide ion on **1**, leading to trans tetrol. The total yield of tetrol product does not increase substantially, however, and this result suggests that other products are also formed from this second-order reaction.

Mechanism of the Reaction of Hydroxide Ion with Carbocation 3. A structural feature of carbocation **3** that makes it different from other carbocations whose reactions with hydroxide ion have been studied previously is the presence of an α-OH group that is expected to be at least several pK_a units more acidic than other OH groups because it is located adjacent to a carbocationic center.[7] Possessing both an electrophilic carbon center and a relatively acidic OH group, **3** can react with hydroxide ion by two competing mechanisms, one in which hydroxide acts as a base (k_{-1}) and the second in which hydroxide acts as a nucleophile (k_2). The fact that k_{-1} is greater than k_2 deserves special comment. This condition must hold because if $k_2 \gg k_{-1}$ there would be no reversal of the carbocation-forming reaction and consequently there would be no negative deviation of the rate profiles for the reaction of **1** at pH >10. Hydroxide ion must therefore react with **3** more rapidly as a base to form epoxide **1** than as a nucleophile to form tetrols **4** and **5**. The cation–anion combination reaction of **3** with hydroxide ion to form tetrol product must therefore occur at a rate less than the diffusion-controlled limit, which appears somewhat surprising.

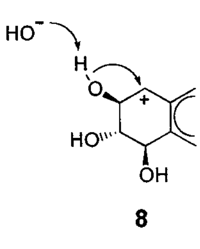
The reaction of **3** with hydroxide ion to form **1** is the microscopic reverse of the reaction of **1** with water to form **3** and hydroxide ion (Scheme 4). In considering the mechanism of the reaction of hydroxide ion with **3**, it is therefore useful to consider the mechanism of the epoxide ring opening reaction. General acid-catalyzed epoxide ring opening reactions of **1** by acids with pK_a's less than that of **3** obey Jencks' rule[23] for concerted general acid–base catalysis because the pK_a of the catalyst is intermediate between the initial and the final pK_a values of the substrate site.[7] A stepwise mechanism for the general acid-catalyzed pathway involving rate-limiting protonation of zwitterion intermediate **7** by the general acid (Scheme 5) has been ruled out.[7] Because the epoxide ring opening reaction catalyzed by general acids is a concerted process, the microscopic reverse reaction involving attack of a general base on carbocation **3** to form epoxide **1** must also be concerted. A special problem for a concerted mechanism arises however when water reacts with **1** to yield carbocation **3** and hydroxide ion. The proton donor in this case, water, has a pK_a higher than that of the product carbocation **3**, and Jencks' rule for concerted general acid–base catalysis is violated. A concerted mechanism for this reaction is "enforced,"[24] however, if the zwitterion structure **7** is too unstable to exist as an intermediate, i.e., it collapses without activation to **1**. The encounter complex formed from deprotonation of **3** by hydroxide ion will not have a significant lifetime, and the rate-limiting step for the epoxide ring opening reaction catalyzed by water must be a physical process such as diffusion of hydroxide ion away from the carbocation and/or conformational isomerization of the carbocation.[7] This physical process must also be the rate-limiting step in the reverse reaction of hydroxide ion with **3** to form **1**.

Scheme 5

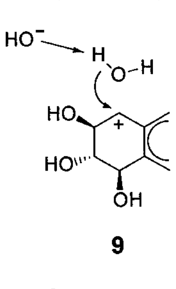


The hydroxide ion that is generated from the reaction of **1** with water must be present initially in an encounter complex, and there must be some feature that prevents this ion from simply collapsing with the electrophilic benzylic carbocation to form tetrol product faster than it diffuses away. One possibility is that the newly generated ion pair might be oriented such that only unfavorable equatorial attack of hydroxide on the electrophilic carbon is possible.

The reaction of hydroxide ion with **3** to form **1** (k_{-1}) can be viewed as a concerted general base-catalzyed epoxide ring closure (depicted by **8**), which is expected to occur at the diffusion-controlled limit because proton transfer from the α-OH group to the hydroxide ion is thermodynamically favorable.[7]



8



9

The reactions of stable carbocations with water are also general base-catalyzed.[25,26] It has been suggested that carbocation–hydroxide combination reactions, e.g., the reaction of hydroxide ion as a nucleophile on a carbocation, is a concerted process involving hydroxide ion-catalyzed addition of water to the electrophilic carbon (depicted by **9**).[26] In this mechanism, an unstable carbocation–hydroxide ion pair in which the hydroxide

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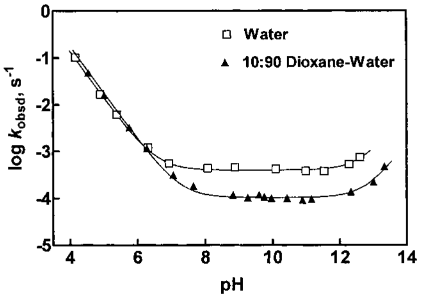
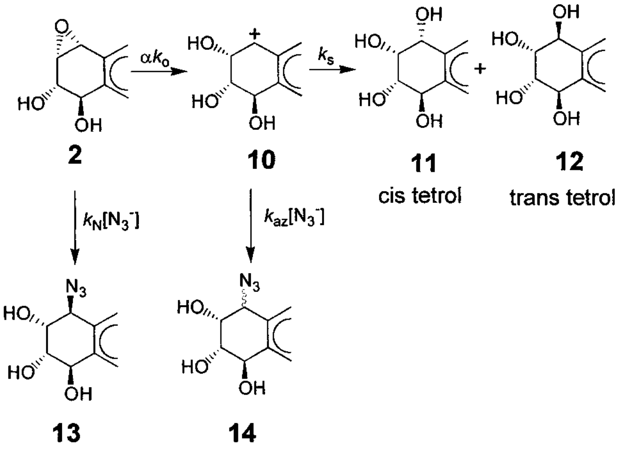


Figure 2. Plots of log k_{obsd} vs pH for the reaction of **2** in water (0.1 M $NaClO_4$) and 10:90 dioxane−water (v/v) (0.2 M $NaClO_4$), 25.0 ± 0.2 °C. The solid lines are theoretical, based on $k_{obsd} = k_H[H^+] + k_o + k_{OH}K_w/[H^+]$. For 10:90 dioxane−water solutions, published rate data were used.[11] For water solutions, fitting of the rate data yielded values of k_H, k_o, and k_{OH} equal to $(1.41 \pm 0.07) \times 10^3$ M^{-1} s^{-1}, $(4.0 \pm 0.2) \times 10^{-4}$ s^{-1}, and $(7.9 \pm 1.5) \times 10^{-3}$ M^{-1} s^{-1}, respectively.

Scheme 6



ion is not fully solvated is bypassed,[26] and thus, the concerted mechanism is enforced. Thus, although the reactions of hydroxide ion with carbocation **3** as a base and as a nucleophile appear to be rather unrelated reactions, their mechanisms may actually be very similar. The reaction of **3** with hydroxide ion (k_2) to form tetrols may occur at less than the diffusion-limited rate for the same reasons that more stable carbocations react with hydroxide ion slower than with other nucleophiles such as azide and sulfhydryl ions: deprotonation of the water molecule in **9** is not a thermodynamically favorable reaction because the water molecule is not sufficiently acidic and activation energy to generate a desolvated hydroxide ion is required.[26]

pH-Independent Reaction of 2. Rate−pH profiles for the reaction of **2** in water and in 10:90 dioxane−water are provided in Figure 2. Rate data for the reaction of **2** in 10:90 dioxane−water containing 0.2 M $NaClO_4$ are taken from ref 10, and rate data for the reaction of **2** in water containing 0.1 M $NaClO_4$ over a more extended pH range than previously reported[1] are newly acquired.

The rate profiles for the reaction of **2** shown in Figure 2 show only three distinct regions: one at pH <7 where acid-catalyzed hydrolysis predominates, a plateau at intermediate pH where pH-independent hydrolysis predominates, and a third region at pH >12 where a second-order reaction of **2** with hydroxide ion occurs. Although there appears to be a very small negative rate deviation at pH ~10 for the reaction of **2** in both solvents, this apparent change in rate is only on the order of 10% and can be attributed to the fact that 10^{-3} M buffer was used to maintain the pH of the reaction solutions at pH 5.7−9.5, but no buffer was used for the pH control of the solutions at pH >10 (see Experimental Section). The carbocation formed by the reaction of **2** with H^+ has a lifetime comparable to that formed from the reaction of **1** with H^+.[7,13] If this same carbocation were formed to any significant extent in the pH-independent reaction of **2**, then hydroxide ion should be of a sufficient concentration at pH >10 to reverse the carbocation-forming reaction, resulting in a negative rate deviation in the pH−rate profiles at pH >10. Such negative rate deviations in the rate profiles for the reaction of **2** at pH >10 are at best on the order of experimental error.

The pH-independent reaction of **2** at pH 9−11.5 in both water and 10:90 dioxane−water yields 60−62% of trans tetrol and 38−40% of cis tetrol. The carbocation formed from the reaction of **2** with H^+ reacts with solvent to form tetrols with a trans to cis ratio of 92:8 in water, and some portion of the trans tetrol formed from the pH-independent reaction of **2** could possibly be formed from the general acid-catalyzed epoxide ring opening of **2** with water to form this same carbocation. If this were the case, then hydroxide ion should react as a base with this carbocation at pH >10, reversing the carbocation-forming reaction and resulting in a slight negative rate deviation in the rate profile. The reaction pathway from the carbocation to the trans and cis tetrols in a 95:5 ratio would be suppressed, and the cis to trans tetrol ratio observed from the pH-independent reaction of **2** at pH >10 should therefore be different from the ratio of tetrols formed at pH <10. The fact that there is no change in the cis to trans tetrol ratio from the reaction of **2** from pH 8.5 to pH 11.5 is evidence against the general acid-catalyzed epoxide ring opening of **2** by water as a significant reaction pathway in the pH-independent reaction of **2**.

Additional evidence against general acid-catalyzed epoxide ring opening in the pH-independent reaction of **2** is obtained by observing the cis to trans tetrol product ratio and yields of azidohydrins from the reaction of **2** in 10:90 dioxane−water solutions containing sodium azide (0−4 mM) at pH 8.5. Scheme 6 outlines a possible mechanism for the reaction of **2** in solutions containing sodium azide, where some fraction α of the pH-independent rate constant k_o proceeds by the reaction of **2** with water to yield carbocation **10**, which then reacts with solvent via the k_s pathway to yield tetrol products **11** and **12**. Azide ion efficiently captures the carbocation **10** from the reaction of **2** with H^+ at pH 4.7 to yield a mixture of cis and trans azidohydrins[13] and also reacts as a nucleophile with **2** (Scheme 6) at pH 8 to produce only a trans azidohydrin.[10] The yield of azide product from the reaction of **2** in sodium azide solutions is 44% when $[N_3^-]$ is 1.0 mM and increases to 75% when $[N_3^-]$ is 4.0 mM. From the bimolecular rate constant of 9.3×10^{-2} M^{-1} s^{-1} for k_N and the pH-independent rate constant of 1.03×10^{-4} s^{-1} for k_o,[10] the yield of azide adduct expected from the bimolecular route (k_N) can be calculated. The yields of azide product calculated on this assumption are slightly higher (3−6%) than the observed yields. For example, the calculated yield of azide product from the k_N route when $[N_3^-] = 4.0$ mM is 78%. The observed yield is 75%. This rate−product correlation is quite good and shows that most of the azide product must be formed from the bimolecular (k_N) pathway. Thus, the fraction of tetrol formed from the k_s route must not be significant. For the reaction of **10** in this solvent containing azide ion, the rate ratio k_{az}/k_s was determined to be 2.6×10^2 M^{-1}.[10] Therefore, 51% of **10** would be trapped by azide ion by the k_{az} route in 4 mM azide solution to form azide products, and the remaining 49% of **10** would react with solvent by the k_s pathway to form mostly trans tetrol **12**. So, if the fraction α of the pH-independent reaction were significant, then not only would there be a greater yield of azide adduct than that actually formed but also the cis to trans tetrol ratio should increase significantly because approximately half of carbocation **10** leading to mostly trans tetrol **12** by the k_s pathway would be trapped by azide ion. We have observed that the cis to trans tetrol ratio from the reaction of **2** both in 4 mM azide solution and in the absence of azide ion is the same (37:63). It can be concluded that carbocation **10**, with a structure identical to that formed from the reaction of **2** with H^+, cannot be formed to any significant extent in the pH-independent reaction of **2**.

The exact mechanism for the formation of tetrol products from the pH-independent reaction of **2** is not clear. If water acts as a general acid in the tetrol-forming pathway, then the hydroxide ion generated in the encounter complex must collapse with the carbocationic center to form tetrol faster than it diffuses away to produce the freely solvated carbocation **10** and hydroxide ion. Significantly more cis tetrol is formed from the pH-independent reaction of **2** (38−40%) than from the acid-catalyzed hydrolysis of **2** (5−8%). This observation is in contrast to the observation that the pH-independent reactions of other diol epoxides in the "DE-2" series yield mostly trans tetrols.[27,28] A possible explanation for the greater yield of cis tetrol from the pH-independent reaction of **2** is that it reacts to form a more stable carbocation than other diol epoxides in the series, and the incipient hydroxide ion from general acid-catalyzed epoxide ring opening of **2** by water is in a position to undergo favorable axial attack on the carbocationic center. A possible mechanism for formation of trans tetrol product involves nucleophilic addition of water[29] to the benzylic carbon of **2**. Thus, cis and trans tetrols might be formed by completely different mechanisms. The mechanism(s) of tetrol formation in the pH-independent reaction of **2**, however, must involve concerted or near-concerted reactions of water with **2**.

Summary

The pH−rate profiles for the reaction of **1** exhibit a negative deviation, at pH 10−11.5, from the rate plateau for the pH-independent reaction. This rate decrease, along with a lowering in the yields of tetrol products, is attributed to a partial change in mechanism. At pH 5−10, the pH-independent reaction of **1** consists of two pathways, one pathway involving direct rearrangement of **1** to ketone **6** that does not involve a trappable intermediate and a second pathway involving rate-limiting epoxide ring opening with water to yield a carbocation **3** that reacts with solvent in a second step to yield tetrol products. At pH >10, attack of hydroxide ion on **3** to re-form **1** exceeds the rate at which water attacks **3**, thus reducing the steady-state concentration of **3** and lowering the rate of tetrol formation by attack of water on **3**. The relative yield of ketone from the pH-independent reaction of **1** therefore increases at pH >10. These results demonstrate that attack of hydroxide on carbocation **3** as a base to re-form diol epoxide **1** is much faster than its reaction as a nucleophile with carbocation **3** to form tetrol products. In contrast to the pH−rate profiles for the reaction of **1**, the profiles for the reaction of **2** do not exhibit significant negative rate deviation in the rate plateaus for the pH-independent reaction. This observation and those from rate and product studies of the reaction of **2** in solutions containing azide ion suggest that the reaction pathways for tetrol formation in the pH-independent reaction of **2** occur by concerted or near-concerted addition of water to **2**.

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