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Transition-State Effects in Acid-Catalyzed Aryl Epoxide Hydrolyses

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The hydronium ion-catalyzed hydrolyses of 5-methoxyindene 1,2-oxide and of 6-methoxy-1,2,3,4-tetrohydronaphthalene-1,2-epoxide were each found to yield 75−80% of cis diol and only 20−25% of trans diol as hydrolysis products. The relative stabilities of the cis and trans diols in each system were determined by treating either cis or trans diols with perchloric acid in water solutions and following the approach to an equilibrium cis/trans mixture as a function of time. These studies establish that the trans diol in each system is more stable than the corresponding cis diol. Thus, acid-catalyzed hydrolysis of each epoxide, which proceeds via a carbocation intermediate, yields the less stable cis diol as the major product. Transition-state effects, presumably of a hydrogen-bonding nature, selectively stabilize the transition state for attack of water on the intermediate 2-hydroxy-1-indanyl carbocation leading to the less stable cis diol in this system. Transition-state effects must also be responsible for formation of the less stable cis diol as the major product in the acid-catalyzed hydrolysis of 5-methoxy-1,2,3,4-tetrahydronaphthalene 1,2-epoxide. However, in this system steric effects at the transition state may be more important than hydrogen bonding in determining the cis/trans diol product ratio. The synthesis of 5-methoxyindene 1,2-oxide and a study of its rate of reaction as a function of pH in water and dioxane−water solutions are reported. Both an acid-catalyzed reaction leading to only diol products and a pH-independent reaction yielding 71% of 5-methoxy-2-indanone and 29% of diols are observed; the half-life of its pH-independent reaction in water is only 2.4 s.

Introduction

The acid-catalyzed reactions of epoxides to form diols and other compounds have been extensively studied.[1] In this reaction, the C−O bond that undergoes the greater extent of cleavage is generally the one between oxygen and the more highly substituted carbon.[2] In the hydrolysis of 1,2-disubstituted epoxides, the diol product can potentially be the result of syn or anti hydration. Acid-catalyzed hydrolyses of alkene oxides such as *cis*- and *trans*-2-butene oxides[3] and cycloalkene oxides such as cyclohexene oxide[4] yield only diols resulting from anti hydration. It is thought that these epoxide hydrolysis reactions occur by an A-2 mechanism in which epoxide C−O bond cleavage and attack of water on protonated epoxide are concerted.[5]

Acid-catalyzed hydrolyses of aryl and vinyl epoxides, in contrast, yield mixtures of cis and trans diols in varying cis/trans ratios.[6−9] For example, the cis/trans diol ratio from acid-catalyzed hydrolysis of 1,2,3,4-tetrahydronaphthalene 1,2-epoxides is highly sensitive to the electronic effects of substituents in the 6-position of the aromatic ring (Scheme 1).[6] Acid-catalyzed hydrolysis of **1a** yields 5% of cis diol **3a** and 95% of trans diol **4a**, whereas acid-catalyzed hydrolysis of **1b** gives 80% of cis diol **3b** and only 20% of trans diol **4b**. These results have been rationalized by a mechanism in which there are two conformations of the carbocation intermediate **2**, each reacting with solvent to yield diols in different cis/trans ratios.

The acid-catalyzed hydrolyses of para-substituted 1-phenylcyclohexene oxides yield mixtures of cis and trans diols, and the percent of cis diol is reported to increase systematically with the increasing electron-donating ability of the para-substituent from only 7.5% for a nitro substituent to 95.2% for a methoxyl substituent.[8] A later study of the hydrolyses of these epoxides under conditions in which the diols were stable showed that the acid-catalyzed hydrolyses of the H-, CH_3-, and CH_3O-substituted epoxides indeed yield cis diol as the major product

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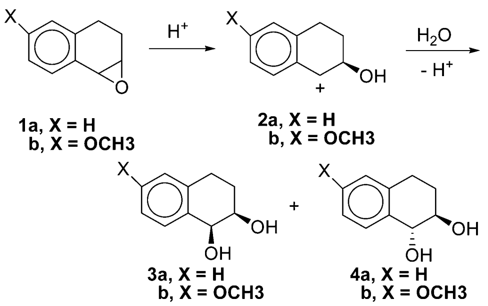

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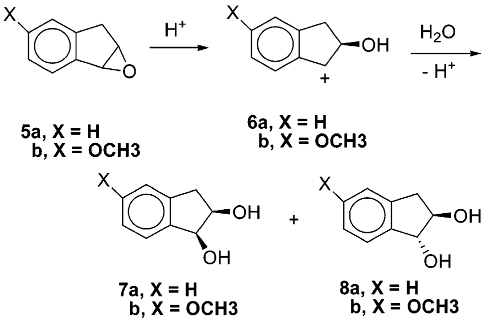

(>65%) but that the cis/trans diol product ratio does not change significantly as the para substituent is changed from hydrogen to the more electron-donating substituents methyl and methoxyl.[9] From rate−product studies of the hydrolysis of 1-(*p*-methoxyphenyl)cyclohexene oxide in solutions containing varying concentrations of sodium azide, it was concluded that an intermediate carbocation is formed in a rate-limiting step and that the diol products are formed from attack of water on a carbocation intermediate. It was also determined from equilibration studies that the cis diol in this system is more stable than the trans diol, and therefore it was suggested that factors that contribute to the greater stability of the cis diol product also contributed to the lowering of the transition state energy for attack of water on the carbocation leading the to major cis diol product.[9]

To ascertain whether product stability plays an important role in determining the cis:trans diol ratio from the acid-catalyzed hydrolysis of aryl epoxides in general, we have established the relative stabilities of *cis*- and *trans*-5-methoxy-1,2-indandiols and of *cis*- and *trans*-6-methoxy-1,2,3,4-tetrahydronaphthalene-1,2-diols and have compared the equilibrium cis/trans ratios of the stereoisomeric diols with the ratio of cis and trans diols formed from acid-catalyzed hydrolysis of the corresponding epoxides. The acid-catalyzed hydrolysis of indene oxide **5a** is reported to yield cis and trans diols **7a** and **8a** (Scheme 2) in a 75:25 ratio,[10,11] but the preparation and study of the reactions of 5-methoxyindene oxide **5b** have not been reported. We have therefore synthesized **5b** and also report a study of its hydrolysis reactions along with the equilibration study of its cis and trans diol hydrolysis products.

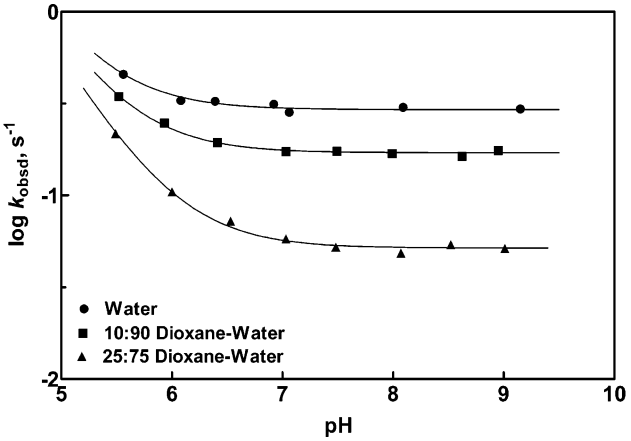

FIGURE 1. Plots of log k_{obsd} versus pH for reaction of **5b** in water, 10:90 dioxane−water and 25:75 dioxane−water (v/v), 0.1 M $NaClO_4$, 25.0 ± 0.2 °C. The solid lines are theoretical, based on eq 1 and the rate parameters listed in Table 1.

Results

5-Methoxyindene oxide (**5b**) was prepared in excellent yield by stirring a solution of *trans*-2-bromo-5-methoxyindan-1-ol in anhydrous THF with powdered potassium hydroxide. The epoxide is conveniently isolated by filtration of the reaction mixture to remove suspended KOH/KBr salts and removal of the solvent from the filtrate by rotary evaporation.

Plots of log k_{obsd} for reaction of **5b** vs pH in water, 10:90 dioxane−water, and 25:75 dioxane−water are provided in Figure 1. A pH-independent reaction of **5b** in water is the principal reaction above pH 6, with a half-life of ~2.4 s. At pH 5.5 the rate is slightly faster, suggesting the incursion of an acid-catalyzed reaction. However, at pH less than 5.5, the rate of reaction is too great to accurately measure by simple mixing technique. The rate of the pH-independent reaction is slowed significantly in dioxane−water solutions, however, whereas the bimolecular rate constant for the acid-catalyzed reaction is very similar in all three solvents. As a result, the changeover in mechanism from the pH-independent reaction to the acid-catalyzed reaction occurs at higher pH in solutions containing more dioxane, and the pH region for the acid-catalyzed reaction becomes more pronounced.

The rate data summarized in Figure 1 for the reaction of **5b** were fit to eq 1, where k_H is the second-order rate constant for the acid-catalyzed reaction and k_o is the first-order rate constant for the pH-independent reaction. A summary of the rate constants for reaction of **5b** is provided in Table 1.

$$k_{obsd} = k_H[H^+] + k_o \qquad (1)$$

Products from the acid-catalyzed hydrolysis of **5b** at pH 3.2, where >98% of the reaction is acid-catalyzed, are cis and trans diols **7b** and **8b** in a 80:20 cis/trans ratio. This ratio of diols is very similar to that from acid-catalyzed hydrolysis of indene oxide (**5a**) (cis/trans diol ratio75:25).[11]

Substitution of a methoxyl group at the 5-position results in increased rate constants for the acid-catalyzed (~10^2) and pH-independent reactions (>10^3) but does not

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TABLE 1. Summary of Rate Constants for Reaction of 5-Methoxyindene Oxide (5b) in Water, 10:90 Dioxane−Water and 25:75 Dioxane−Water Solutions, 25 °C, 0.1 M $NaClO_4$

solvent	k_H ($M^{-1}s^{-1}$)	k_o (s^{-1})
water[a]	6×10^4	$(2.93 \pm 0.04) \times 10^{-1}$
10:90 dioxane−water	$(5.92 \pm 0.20) \times 10^4$	$(1.70 \pm 0.20) \times 10^{-1}$
25:75 dioxane−water	$(5.25 \pm 0.27) \times 10^4$	$(5.17 \pm 0.11) \times 10^{-2}$

[a] Because of the high reactivity of **1b** in water, there were insufficient rate data at pH < 5.5 for calculation of an accurate value for k_H. A value of 6×10^4 $M^{-1}s^{-1}$ was assumed for this rate constant.

alter significantly the relative yields of products from each reaction.

pH-Independent Reaction of 5-Methoxyindene Oxide (5b). In water, the rate of reaction of **5b** does not change throughout the pH range 6−9. The reaction of **5b** that occurs in this pH range yields 71% of 5-methoxy-2-indanone as the major product and *cis*- and *trans*-5-methoxyindan-1,2-diols as minor products in a 75:25 ratio. Whereas the half-life for reaction of **5b** at pH > 6 in water is only 2.4 s, its half-life in 25:75 dioxane−water is 13.4 s.

The observation that the pH-independent reaction of **5b** yields ketone as a major product and both cis and trans diols as minor but significant products is intriguing. Similar products and product yields are formed from the pH-independent reactions of indene oxide **5a** and of 6-methoxy-1,2,3,4-tetrahydronaphthalene-1,2-epoxide (**1b**). Rate-limiting hydrogen migration on the ketone-forming reaction of **1b** has been proposed.[12] However, the pH-independent reaction of 1,2,3,4-tetrahydronaphthalene-1,2-oxide (**1a**) yields only trans diol.[13] The mechanism of pH-independent epoxide reactions therefore depend markedly on the structure of the epoxide. More detailed studies of the pH-independent reactions of these epoxides are in progress.

Acid-Catalyzed Equilibration of *cis*- and *trans*-5-Methoxyindan-1,2-diols and of *cis*- and *trans*-6-Methoxy-1,2,3,4-tetrahydronaphthalene-1,2-diols in Water Solutions. The approaches to an equilibrium mixture of *cis*- and *trans*-5-methoxyindan-1,2-diols from both the trans diol and a mixture of 80% cis diol/20% trans diol in 0.05 M $HClO_4$ solutions at 25 °C were monitored by HPLC as functions of time. In a similar manner, the approaches to an equilibrium cis/trans diol mixture starting from both pure *cis*- and pure *trans*-6-methoxy-1,2,3,4-tetrahydronaphthalene-1,2-diol in 0.10 M $HClO_4$ solutions were measured. Plots of % cis diol vs time for the approaches of each diol system to a cis/trans diol equilibrium mixture follow excellent pseudo-first-order kinetics and are given in Figures 2 and 3.

The isomerization of cis diol (**3b** or **7b**) and trans diol (**4b** or **8b**) is catalyzed by hydronium ion (eq 2), and the observed pseudo-first-order rate constant for approach to equilibrium from either side is equal to the sum of the forward and reverse pseudo-first-order rate constants. Therefore, $k_{obsd} = (k_1 + k_{-1})[H^+]$). Thus, the observed rate constants k_{obsd} for approach to equilibrium from either side in the acid-catalyzed equilibration of either system are the same within experimental error, cf. Figures 2−3.

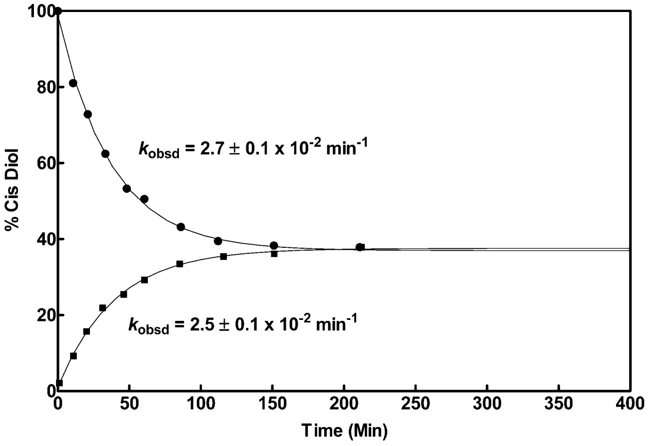

FIGURE 2. Plots of percent cis diol **7b** versus time in the equilibration reactions starting from either a mixture of 80% cis diol (**7b**)/20% trans diol (**8b**) or pure trans diol (**8b**) in 0.05 M $HClO_4^-$ water solution, 25.0 ± 0.2 °C. The lines are theoretical, based on eq 3.

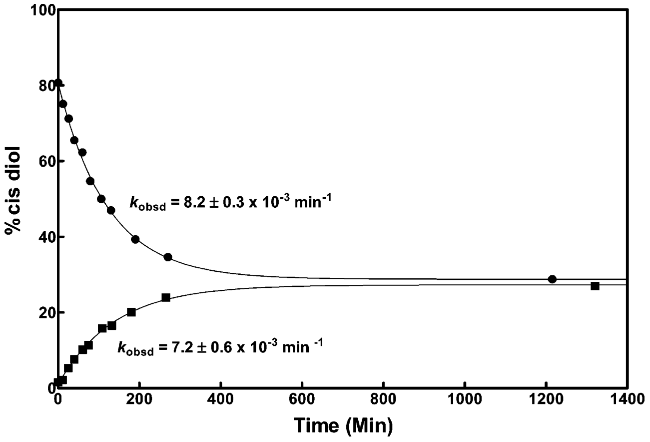

FIGURE 3. Plots of percent cis diol **3b** versus time in the equilibration reactions starting from either cis diol (**3b**) or trans diol (**4b**) in 0.10 M $HClO_4^-$ water solution, 25.0 ± 0.2 °C. The lines are theoretical, based on eq 3.

$$\text{cis diol } (\mathbf{3b} \text{ or } \mathbf{7b}) + H^+ \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \text{trans diol } (\mathbf{4b} \text{ or } \mathbf{8b}) + H^+ \quad (2)$$

Dividing k_{obsd} by [H^+] gives the average second-order rate constants of 0.15 M^{-1} min^{-1} and 0.26 M^{-1} min^{-1} for the acid-catalyzed approaches to equilibrium ($k_1 + k_{-1}$) for *cis*- and *trans*-5-methoxyindan-1,2-diols and for 6-methoxy-1,2,3,4-tetrahydronaphthalene-1,2-diols, respectively. Extrapolation of the percent composition versus time data in Figures 2 and 3 yields calculated equilibrium mixtures containing 72% trans/28% cis diols for the methoxyindan system (**7b**, **8b**) and 63% trans/37% cis diols for the methoxytetrahydronaphthalene system (**3b**, **4b**). The equilibrium constants ($K_{eq} = k_1/k_{-1}$) are calculated from the equilibrium cis:trans diol concentrations for each system, and from the equilibrium constants and values of ($k_1 + k_{-1}$), values for k_1 and k_{-1} are calculated.

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TABLE 2. Summary of Second-Order Rate Constants and Equilibrium Constants for Acid-Catalyzed Equilibration of *cis*- and *trans*-1,2,3,4-Tetrahydronaphthalene-1,2-diols (3b, 4b) and of *cis*- and *trans*-5-Methoxyindan-1,2-diols (7b, 8b) in Water Solutions, 25 °C

compd	k_1 (M^{-1} min^{-1})	k_{-1} (M^{-1} min^{-1})	K_{eq}
3b, **4b** (X = OCH_3)[a]	1.6×10^{-1}	9.6×10^{-2}	1.7
7b, **8b** (X = OCH_3)[b]	1.1×10^{-1}	4.2×10^{-2}	2.6

[a] Calculated from average values of k_{obsd} for approach to equilibrium from both **3b** and from **4b** in 0.10 M $HClO_4$ solution. [b] Calculated from average values of k_{obsd} for approach to equilibrium from both a mixture of 80% **7b**/20% **8b** and from **8b** in 0.05 M $HClO_4$ solution.

A summary of these rate and equilibrium constants is provided in Table 2.

Discussion

Diol Equilibration Studies. 5-Methoxyindan-1,2-diols and 6-methoxy-1,2,3,4-tetrahydronaphthalene-1,2-diols readily undergo acid-catalyzed isomerization in dilute perchloric acid−water solutions, and in each case the trans diol is slightly more stable than its isomeric cis diol. This result contrasts with an earlier study of the isomerization of 1-phenylcyclohexane-1,2-diols, which showed that for this system the cis diol was more stable than its isomeric trans diol. In the isomerization of 1-phenylcyclohexane-1,2-diols, change of the substituent in the para position of the phenyl ring from methoxyl to methyl did not affect the position of the equilibrium mixture of cis and trans diols. We assume, therefore, that the positions of the equilibrium mixtures of *cis*- and *trans*-indan-1,2-diols (**7a**, **8a**) and of *cis*- and *trans*-1,2,3,4-tetrahydronaphthalene-1,2-diols (**3a**, **4a**) will be very similar to those of the corresponding methoxyl-substituted systems, respectively.

Comparison of Cis/Trans Diol Product Ratios from Acid-Catalyzed Hydrolysis of Indene Oxides with Equilibrium Cis/Trans Diol Ratios. The cis/trans diol ratio from acid-catalyzed hydrolysis of 5-methoxyindene oxide (80:20) is very similar to that from acid-catalyzed hydrolysis of indene oxide (75:25). Therefore, substitution of an electron-donating methoxyl group in the aromatic ring has little effect on the cis/trans diol product ratio in this system. Although acid-catalyzed hydrolyses of indene oxide (**5a**) and 5-methoxyindene oxide (**5b**) each yield cis diol as the major product, equilibration studies of **7b** and **8b** (and presumably **7a** and **8a**) show that the trans diol is the more stable. *Thus, the acid-catalyzed hydrolysis of these epoxides each yields the less stable cis diol as the major product*. Therefore, the differences in transition state energies leading to cis and trans diols from hydrolyses of **1a**,**b** and of **5a**,**b** do not reflect the differences in energy of the products.

In the acid-catalyzed hydrolysis of **1** and **5**, benzyl C−O bond cleavage occurs to yield benzylic carbocations, which undergo attack of water on both faces of the carbocation to yield cis and trans diols. The fact that acid-catalyzed hydrolysis of both indene oxide (**5a**) and its 5-methoxyl derivative (**5b**) yield only cis and trans diols in very similar cis/trans diol ratios suggest that the product forming steps are reaction of the solvent with carbocation intermediates. *p*-Methoxybenzyl carbocations have sufficient lifetimes in water solution to be trapped by external nucleophiles faster than they react with water.[7,9,14−16] Unsubstituted benzyl carbocations are much less stabilized, but there is evidence that they, too, exist as intermediates in water solutions.[13,14,17,18]

Evidence that both cis and trans diol products from the acid-catalyzed hydrolysis of 5-methoxyindene oxide (**5b**) are formed from attack of water on an intermediate carbocation comes from an analysis of the product mixtures from hydrolysis of **5b** in the absence and presence of azide ion at pH 5.0 and 8.0 in water solutions. The rates of reaction of **5b** in water solutions are too fast to be determined accurately, but product studies provide important information. At pH 5.0, 65−70% of **5b** reacts by the acid-catalyzed route and 30−35% reacts by the pH-independent route. At pH 8.0, >99% of **5b** reacts by the pH-independent route. At pH 5, in water solution containing 0.025 M total azide concentration, the yield of diol products from reaction of **5b** is reduced by 55%, but the ratio of cis and trans diols is not changed. At pH 8.0 in water solution containing 0.025 M total azide concentration, the yield of diols from reaction of **5b** is reduced by only 13%, and there is a corresponding reduction in yield of ketone product. These results suggest that azide ion acts as a nucleophile in its reaction with **5b** at pH 8. At pH 5.0, where the reaction of **5b** is calculated to be increased due to the acid-catalyzed pathway, the reduction in the yield of diol products due to nucleophilic attack of azide ion on **5b** should be significantly <13%. The observation that the yield of diols is instead reduced by a much greater amount (55%) suggests that in the acid-catalyzed hydrolysis of **5b**, azide ion must be reacting with a carbocation intermediate, since attack of azide ion on a protonated benzylic epoxide (or its kinetic equivalence) has not been observed in other systems.[7,9,19,20] The fact that the cis/trans diol ratio does not change rules out a concerted mechanism in which the water molecule formed from reaction of hydronium ion with **5b** collapses without dissociation to form cis diol. Were this to happen, the cis/trans diol product ratio from reaction of **5b** in azide solution would be different than that formed from the acid-catalyzed reaction of **5b** in the absence of azide ion.

Quantum chemical calculations at semiempirical, ab initio, and DFT levels of theory suggest that there is only one energy minimum structure for the 2-hydroxy-1-indanyl carbocation **6** (cf Figure 4 for **6b**) formed from reaction of indene oxides **5a** and **5b** and that the five-membered ring of the carbocation is very nearly planar. The fact that the less stable cis diol is the major product from reaction of solvent with the intermediate carbocation indicates that *there must be some effect that selectively stabilizes the transition state for cis attack of*

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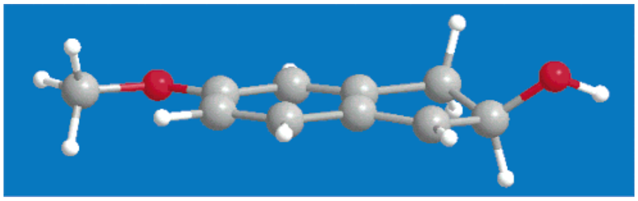

FIGURE 4. Structure of carbocation **6b**, calculated at the DFT B3LYP/6-31G* level of theory.

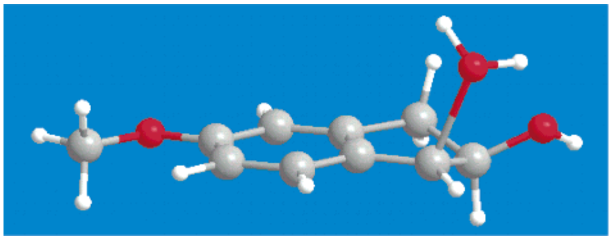

FIGURE 5. Transition structure for cis attack of water on carbocation **6b**, calculated at the MP2/6-31G* level of theory.

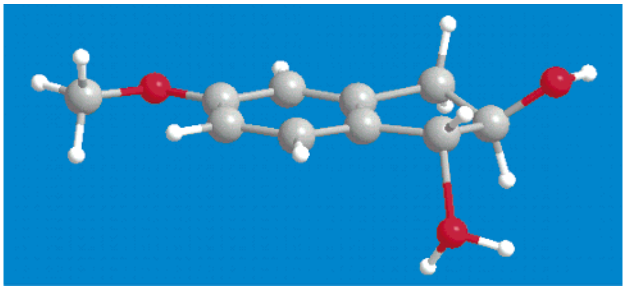

FIGURE 6. Transition structure for trans attack of water on carbocation **6b**, calculated at the MP2/6-31G* level of theory.

*water on **6** or destabilizes the transition state for trans attack of water on **6**, and this differential effect must be reduced or absent in the products.*

A possible explanation for the fact that the transition state leading to the less stable cis diol is selectively stabilized is that there is a relatively strong hydrogen bonding interaction between the attacking water molecule and the adjacent hydroxyl group at the transition state for cis attack of water on **6**, whereas hydrogen bonding between the attacking water molecule and the hydroxyl group at the transition state for trans attack of water on **6** is not possible. Transition structures calculated at the MP2/6-31G* level of theory for cis attack of water on carbocation **6** and for trans attack of water on carbocation **6** in the gas phase are given in Figures 5 and 6, respectively. The H···O hydrogen bond distance between the attacking water molecule and the C2 hydroxyl group in the transition structure for cis attack of water **7** is calculated to be 1.97 Å (O−O distance 2.60 Å). The closest hydrogen bond distance in the transition structure for trans attack of water is 3.15 Å.

Hydrogen bonding between the attacking water molecule and the water solvent is also expected to occur. For the above interpretation to be correct, the intramolecular hydrogen bond for cis attack of water (Figure 5) would have to be energetically more favorable than the hydrogen bonding between the attacking water molecule and solvent for trans attack of water (Figure 6). The hydrogen bond in the transition-state cis attack of water on **6b** is expected to be stronger than that between the two hydroxyl groups of the cis 1,2-diol product **7b** because of the partial positive charge on the water molecule at the transition state.

In the two principal conformations of cis diol **7b**, the O−O distances are calculated at the density functional B3LYP/6-31G* level of theory to be 2.695 and 2.675 Å, with O−H hydrogen bond distances of 2.070 and 2.023 Å, respectively. The O−O distance in the pseudo-diequatorial conformation of trans diol **8b**, in which the two hydroxyl groups are closest, is calculated to be 3.115 Å, with an O−H hydrogen bond distance calculated to be 2.848 Å. Therefore, intramolecular hydrogen bonding in the trans diol should not be as favorable as that in the cis diol and cannot be responsible for the greater stability of the trans diol. The greater stability of the trans diol is therefore most likely due to the fact that it possesses one less gauche butane interaction than is present in the cis diol, and the strain energy introduced by the additional gauche butane interaction in the cis isomer must be greater than any stabilization resulting from intramolecular hydrogen bonding.

The Marcus intrinsic barrier for cis attack of water on carbocation **6** (Figure 5) leading to the less stable cis diol must be lower than the intrinsic barrier for trans attack of water on **6** (Figure 6) leading to the more stable trans diol.[21] The difference in the energies of the intrinsic barriers for cis and trans attacks of water on **6b** may be in part due to different degrees of imbalance between the loss of resonance stabilization and lowering of energy due to bond formation at the transition states. Differences in solvation, perhaps including favorable intramolecular hydrogen bonding in the transition state for cis attack of water, may also contribute to lowering of the intrinsic barrier for cis attack of water. Although the gas-phase transition structures (Figures 5 and 6) calculated for cis and trans attacks of water on carbocation **6b** do not take into account solvation or additional hydrogen bonding of the transition states to nearby water molecules, some insight on several factors that would affect intrinsic barriers is apparent from analysis of the structures. The calculated bond length between the benzylic carbon and the attacking water molecule at the transition state for cis attack (2.073 Å) is significantly longer than the corresponding calculated bond length for trans attack of water (1.823 Å). Also, the calculated C(7)−C(8)−C(1)−O(1) dihedral angle for trans attack of water (60.54°) is significantly reduced from the dihedral angle that the *p*-orbital of the benzylic carbon of carbocation **6b** makes with the aromatic ring (~90°), whereas the calculated C(7)−C(8)−C(1)−O(1) dihedral angle for cis attack of water (−88.39°) is not significantly changed from the dihedral angle that the benzylic *p*-orbital of **6b** makes with the aromatic ring. Thus, the benzylic carbon atom in the transition structure for trans attack of water on **6b** is calculated to have undergone a greater change in hybridization than it does for cis attack of water. The greater change in hybridization for trans attack of water would result in a greater imbalance between loss of resonance stabilization and lowering of energy due to

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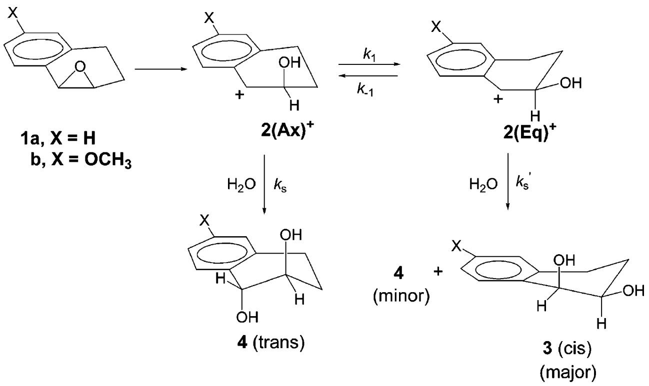
[21] Richard, J. A.; Amyes, T. L.; Toteva, M. M. *Acc. Chem. Res.* **2001**, *34*, 981−988.

SCHEME 3



bond formation at the transition state, which would contribute to an increase in the intrinsic barrier.[21] Intramolecular hydrogen bonding may therefore affect transition state structure in the gas phase and may also contribute to lowering transition state energy in solution.

Acid-Catalyzed Hydrolysis of Tetrahydronaphthalene 1,2-Epoxides. The mechanisms of acid-catalyzed hydrolysis of **1a** and **1b** are complicated by the fact that the intermediate carbocation has two conformations, one in which the hydroxyl group is in a pseudoaxial position and a second in which the hydroxyl group is in a pseudoequatorial position (Scheme 3).[6] Also, **1a** hydrolyzes to mostly (~95%) trans diol **4a**, whereas **1b** hydrolyzes to form cis diol **3b** as the major (~80%) diol product. A mechanism that has been proposed[6] to explain these observations is that epoxide **1a** reacts from its more stable conformation with H$^+$ via axial C−O bond cleavage to form carbocation **2(Ax)**$^+$ in which the hydroxyl occupies an axial position. This carbocation conformation then reacts by energetically favorable axial attack of water to yield trans diol **4** faster than it rearranges to a more stable conformation **2(Eq)**$^+$, in which the hydroxyl group occupies an equatorial position. An explanation for the observation that acid-catalyzed hydrolysis of **1b** yields mostly cis diol **3b** is that the methoxyl-stabilized carbocation has a sufficient lifetime for the more stable conformation **2(Eq)**$^+$ to be formed, and axial attack of water on **2(Eq)**$^+$ yields the major cis diol product **3b**. Whether the diol products in the acid-catalyzed hydrolysis of **1b** are formed from reaction of solvent with a single carbocation conformation or two interconverting carbocation conformations, the transition state leading to the cis diol must be stabilized by some factor that is not present in the diol products.

We have not calculated structures for “cis” and “trans” attacks of water on carbocation conformations **2(Ax)**$^+$ and **2(Eq)**$^+$. Although the transition state for attack of water on carbocation conformation **2(Ax)**$^+$ to yield cis diol (“equatorial attack”) might be energetically favored by intramolecular hydrogen bonding between the attacking water molecule and the adjacent hydroxyl group, this “cis” attack of water would generate substantial nonbonding interactions at the transition state and would force the product into an energetically unfavorable half-boat conformation.[22,23] Although “axial” attack of water on **2(Ax)**$^+$ to yield trans diol may not be stabilized by intramolecular hydrogen bonds, this transition state involves more favorable orbital overlap of the reaction center with the aromatic π-orbitals and would lead to product that would occupy an energetically favorable half-chair conformation.[22,23] Thus, conformational and resonance effects at the transition state may be more important than hydrogen bonding effects in determining the cis/trans diol ratio in the acid-catalyzed hydrolysis of tetrahydronaphthalene epoxides.

In applying the same considerations for attack of water on carbocation conformation **2(Eq)**$^+$, “axial” attack of water on **2(Eq)**$^+$ to yield cis diol would be energetically favorable because this pathway would lead to product occupying a half-chair conformation, and some further stabilization might be derived from intramolecular hydrogen bonding between the attacking water molecule and the adjacent hydroxyl group. “Equatorial” attack of water on **2(Eq)**$^+$ leading to trans diol would lead to product occupying a half-boat conformation, and intramolecular hydrogen bonding between the attacking water molecule and the adjacent hydroxyl group is not possible. The observation that the less stable cis diol **3b** is the major product from acid-catalyzed hydrolysis of **1b** may be primarily due to unfavorable nonbonding interactions at the transition state leading to trans diol, but intramolecular hydrogen bonding in the transition state leading to cis diol may contribute to making this pathway more energetically favorable.

Summary

5-Methoxyindene 1,2-oxide (**5b**), 5-methoxyindan-*cis*-1,2-diol and 5-methoxyindan-*trans*-1,2-diol were synthesized. The cis stereochemistry is assigned to the diol resulting from the reaction of 5-methoxyindene with osmium tetroxide, followed by a reductive workup. This procedure is known to yield only cis diols.[24] Rate and product studies of the hydrolysis of **5b** over the pH range 5.5−9 are summarized. The hydronium ion-catalyzed hydrolyses of 5-methoxyindene 1,2-oxide (**5b**) and of 6-methoxy-1,2,3,4-tetrohydronaphthalene 1,2-epoxide (**1b**) yield 75−80% of cis diol and only 20−25% of trans diol as hydrolysis products, although the trans diol in each system is the more stable. Transition- state effects that selectively stabilize the transition state leading to cis diol and/or destabilize the transition state leading to the trans diol must therefore be important. Energetically favorable intramolecular hydrogen bonding of the attacking water molecule with the adjacent hydroxyl group in the transition state for cis attack of water on the 2-hydroxyindan-1-yl carbocation provides a rationale for the observation that the less stable cis diol is the major product from acid-catalyzed hydrolysis of 5-methoxyindene oxide. If so, this transition-state stabilization for cis attack of water on a carbocation may play a role in all epoxide hydrolysis reactions where such hydrogen bonding is possible. Transition-state effects that favor cis diol formation in the acid-catalyzed hydrolysis of 6-methoxy-1,2,3,4-tetrohydronaphthalene 1,2-epoxide, however, may be due mainly to unfavorable steric interactions at the transition

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[22] Goering, H. L.; Josephson, R. R. *J. Am. Chem. Soc.* **1962**, *84*, 2779−2785.

[23] Goering, H. L.; Vlazny, J. C. *J. Am. Chem. Soc.* **1979**, *101*, 1801−1805.

[24] Fieser, M.; Fieser, L. F. *Reagents for Organic Synthesis*; John Wiley and Sons: New York, 1967; pp 759−764.

state for trans attack of water on the intermediate carbocation. Intramolecular hydrogen bonding at the transition state for cis diol formation in the acid-catalyzed hydrolysis of this epoxide may still play a role in determining the cis:trans diol ratio, but steric effects at the transition states may play a greater role.

Experimental Section

Materials and Methods. Dioxane and THF were distilled from sodium prior to use. All other reagents were purchased from commercial sources. Quantum-chemical calculations were performed with the molecular modeling programs Titan and Spartan04 (Wavefunction, Inc.). The pH values given throughout are those measured by the glass electrode, and for 10:90 and 25:75 dioxane−water solutions correspond to apparent pH values. The activity of hydrogen ion measured by the glass electrode was assumed to be equal to the concentration of hydrogen ion.

Procedure for Monitoring Rates of Reaction of 5-Methoxyindene Oxide (5b). For each kinetic run, approximately 10−15 μL of a stock solution of **5b** in dioxane (1 mg/mL) was added to 2.0 mL of water or dioxane−water solution in the thermostated cell compartment (25.0 ± 0.2 °C) of a UV−vis spectrophotometer. Reactions were monitored at 230 nm, and pseudo-first-order rate constants were calculated by nonlinear regression analysis of the absorbance vs time data.

5-Methoxyindene. The acid-catalyzed dehydration of 5-methoxy-1-indanol was accomplished by a slight modification of the procedure of Winter, Godse, and Gessner,[25] and this procedure is supplied as Supporting Information. The resulting 5-methoxyindene was converted to the known trans bromohydrin[26] by reaction with *N*-bromoacetamide in 3:1 THF−water, and this procedure is also supplied as Supporting Information.

5-Methoxyindene Oxide (5b). A mixture 3.65 g of freshly ground potassium hydroxide pellets (85%, ground under a nitrogen atmosphere) and 1.01 g of *trans*-5-methoxy-*trans*-2-bromo-1-indanol in 50 mL of THF was vigorously stirred at rt for 1 h. The solid salts were filtered and washed with diethyl ether. The solvent was removed from the filtrate under reduced pressure to yield 0.66 g of clear oil, which was distilled in a short-path distillation apparatus at an oil bath temperature of 110 °C (0.5 mm) to yield 0.61 g (90%) of 5-methoxyindene oxide: ^{1}H NMR (CDCl$_3$, 200 MHz) δ 7.40 (d, $J = 8.1$ Hz, 1 H), 6.79 (1 H), 6.71 (dd, $J = 8.1$, 2.4 Hz, 1 H), 4.22 (d, $J = 2.9$ Hz, 1 H), 4.12 (t, $J = 2.9$ Hz, 1 H), 3.78 (s, 3 H), 3.18 (d, $J = 18.3$ Hz, 1 H), 2.96 (dd, $J = 18.3$, 2.9 Hz, 1 H). Anal. Calcd for $C_{10}H_{10}O_2$: C, 74.05; H, 6.22. Found: C, 73.83; H, 6.24

Acid-Catalyzed Hydrolysis of 5-Methoxyindene Oxide. Analytical. A solution (25 μL) of 2.3 mg of 5-methoxyindene oxide in 1.0 mL of dioxane was added to 1.0 mL of 0.1 M $NaClO_4$ solution in which the pH had been adjusted to 3.2. The reaction mixture was swirled and allowed to stand at room temperature for 5 min. An aliquot (15 μL) of a solution containing 2.5 mg of *trans*-acenaphene-7,8-diol in 1.0 mL of methanol was added to serve as a standard, and the pH of the reaction solution was then adjusted to 5−7. The resulting solution was analyzed by reversed-phase HPLC on a C_{18} column with 35:65 methanol−water as eluting solvent. Products were monitored by UV detection at 265 nm. The cis diol **7b** (retention time 6.8 min) and trans diol **8b** (retention time 5.2 min) were the major products, formed in a 79:21 ratio. The retention time of the acenaphthene diol standard was 12.5 min. A very minor peak (∼2%) having a retention time of 20.1 min was also present in the HPLC tracing of the reaction mixture. No peak (<1%) with the retention time of 5-methoxy-2-indanone (21.1 min) could be detected.

Preparative. A solution of 0.35 g of 5-methoxyindene oxide in 2 mL of acetone was added over several minutes to 18 mL of a stirred water solution, pH 2.9, and the resulting mixture was stirred for 5 min at rt. The reaction mixture was extracted with ethyl acetate (2 × 50 mL). The ethyl acetate extracts were combined and dried over calcium sulfate. The ethyl acetate solvent was removed at aspirator pressure to yield 0.44 g of oil that solidified upon standing. Comparison of the ^{1}H NMR spectrum of this diol product mixture with the ^{1}H NMR spectra of authentic cis- and *trans*-5-methoxyindan-1,2-diols prepared independently showed that it contained both cis and trans diols in a 4:1 ratio.

Reactions of 5-Methoxyindene Oxide in Sodium Azide Solutions. Aliquots (25 μL) of a solution of 5-methoxyindene oxide in dioxane (2.3 mg/mL) were added to water solutions containing 0.1 M $NaClO_4$ and 0.025 M NaN_3−0.075 M $NaClO_4$ in which the pH was adjusted to 5.0. At this pH, it is estimated that 65−70% of the reaction of **5b** occurs via the acid-catalyzed route and 30−35% occurs via the pH-independent route. After the reactions were allowed to stand at rt for 5 min, 15 μL of a solution containing 2.5 mg of *trans*-acenaphene-7,8-diol in 1.0 mL of methanol was added to serve as a standard, and the pH of the reaction solution was then adjusted to 5−7. These solutions were analyzed by HPLC as outlined above in the analytical procedure. By comparing the areas of the diol product peaks with the area of the standard compound for the reactions of **5b** in the absence of NaN_3 and in 0.025 M NaN_3, it was calculated that the yield of diols from reaction of **5b** in 0.025 M NaN_3 solution is reduced by 55% compared to the yield of diols from **5b** when NaN_3 is absent. The trans/cis diol ratio is 0.21 when NaN_3 is not present and 0.22 when [NaN_3] is 0.025 M.

Similar product studies were carried out for the reactions of **5b** in the presence and absence of 0.025 M NaN_3 at pH 8.0−8.1, where > 99% of the reaction if via the pH-independent reaction. After addition of aliquots of **5b** in dioxane, the reaction solutions were allowed to stand at rt for 2 min. Standard was added, and the solutions were analyzed by HPLC. The yield of diols from the reaction of **5b** in 0.025 M NaN_3 was reduced by only 13% compared to the yield of diols from **5b** in the absence of azide at the same pH. The yield of ketone product from reaction of **5b** at pH 8 in 0.025 M NaN_3 solution was reduced by 11%.

pH-Independent Reaction of 5-Methoxyindene Oxide. An aliquot of 25 μL of a solution of 2.3 mg of 5-methoxyindene oxide in 1.0 mL of dioxane was added to 1.0 mL of 0.1 M $NaClO_4$ solution in which the pH had been adjusted to 8.0. The reaction mixture was swirled and allowed to stand at rt for 5 min. An aliquot (15 μL) of a solution containing 2.5 mg of *trans*-acenaphene-7,8-diol in 1.0 mL of methanol was added to serve as a standard, and the resulting solution was analyzed by HPLC under the same conditions used for analysis of the products from acid-catalyzed hydrolysis of **5b**. The retention times of cis diol **7b**, trans diol **8b**, 5-methoxyindan-2-one, and acenaphthene diol standard were 6.8, 5.2, 21.1, and 12.5 min. The relative areas of **7b**, **8b**, and 5-methoxy-2-indanone in the HLPC tracing were 5.0:19.9:75.1. Since the relative extinction coefficients of diols and ketone at 265 nm were not determined, the relative areas of cis and trans diol HPLC peaks from reactions of **5b** at pH 8.5 and at pH 3.2 were compared with the area of the standard acenaphene diol HPLC peak. With the assumption that the yield of diols from the acid-catalyzed hydrolysis of **5b** is 100%, the yields of cis diol **7b** and trans diol **8b** from the pH-independent hydrolysis of **5b** are calculated to be 23.0% and 5.8%, respectively. The remainder of the product (71%) from reaction of **5b** at pH 8.5 is assumed to be 5-methoxy-2-indanone.

***5*-Methoxy-*cis*-1,2-indandiol (7b).** A solution of 221 mg (1.51 mmol) of 5-methoxyindene and 360 mg (1.42 mmol) of osmium tetraoxide in 3.5 mL of pyridine was stirred at rt for

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[25] Winter, J. C.; Godse, D. D.; Gessner, P. K. *J. Org. Chem.* **1965**, *30*, 3231−3233.

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2.5 h. The reaction mixture was diluted with a solution of 0.63 g of sodium bisulfite, 0.3 mL of water, and 6.4 mL of pyridine and stirred at rt for 4 h. The reaction solution was extracted three times with ethyl acetate (total 200 mL), and the combined extracts was washed with 25 mL of water and dried over calcium sulfate. The solvent was removed at reduced pressure and the residue was sublimed (0.1 mm, 110 °C oil bath temperature) to yield 100 mg (39%) of cis diol **7b**, mp 95−97 °C. Recrystallization of this material from ether−ethyl acetate solution yielded **7b**: mp 99−101 °C; ^{1}H NMR (DMSO-d_6, 200 MHz) δ 7.18 (d, J = 7.9 Hz, 1 H), 6.7 (2 H), 4.82 (d, J = 6.4 Hz, 1 H), 4.67 (apparent triplet, J_{avg} = 5.6 Hz, 1 H), 4.56 (d, J = 5.3 Hz, 1 H), 4.19 (apparent pentet, J_{avg} = 5.1 Hz), 3.70 (s, 3 H), 2.88 (dd, J = 15.8, 5.9 Hz, 1 H), 2.71 (dd, J = 15.8, 4.4 Hz, 1 H). Anal. Calcd for $C_{10}H_{12}O_3$: C, 66.69; H, 6.66. Found: C, 66.48; H, 6.87.

***5*-Methoxy-*trans*-1,2-indandiol Dibenzoate.** A solution of 2.34 g of iodine in 45 mL benzene was added dropwise to a stirred mixture of 4.20 g silver benzoate in 35 mL benzene under a nitrogen atmosphere. The mixture was stirred an additional 30 min at rt. A solution of 1.33 g of 5-methoxyindene in 10 mL benzene was then added dropwise with continued stirring of the reaction mixture. The resulting mixture was heated at reflux for 4 h. The reaction mixture was cooled and filtered. The benzene solvent was removed at aspirator pressure to yield 4.04 g of a viscous oil. ^{1}H NMR (CDCl$_3$, 200 MHz) δ 6.62 (d, J = 3.0 Hz, 1 H), 5.86 (apparent pentet, J_{avg} = 3.6 Hz, 1 H), 3.82 (s, 3 H), 3.74 (dd, partially overlapping with absorption at δ 3.82, J = 17.0, 7.4 Hz, 1 H), 3.07 (dd, J = 17.0, 4.2 Hz, 1 H). The crude dibenzoate, without purification, was hydrolyzed to the trans diol **8b**.

***5*-Methoxy-*trans*-1,2-indandiol (8b).** A mixture of 1.1 g of crude 5-methoxy-*trans*-1,2-indandiol dibenzoate, 2.0 mL of 6.7 M KOH in water, and 25 mL of methanol was stirred and heated at reflux for 1 h 15 min. The reaction mixture was cooled, and most of the methanol was removed at aspirator pressure. An additional 10 mL of water was added, and the mixture was extracted twice with ethyl acetate (total 70 mL). The solvent was removed at aspirator pressure, and the diol product was sublimed (0.2 mm, oil bath temp 150−170 °C) to yield trans diol **8b** in 77% overall yield from 5-methoxyindene. The sublimed product was recrystallized from ethyl acetate to yield pure 5-methoxy-*trans*-1,2-indandiol: mp 152−153 °C; ^{1}H NMR (DMSO-d_6, 200 MHz) δ 7.18 (d, J = 9.3 Hz, 1 H), 6.7−6.8 (2 H), 5.26 (d, J = 5.9 Hz, 1 H), 5.13 (d, J = 4.9 Hz, 1 H), 4.63 (apparent triplet, J_{avg} = 5.6 Hz, 1 H), 4.06 (m, 1 H), 3.71 (s, 3 H), 3.06 (dd, J = 15.6, 6.8 Hz, 1 H), 2.56 (dd, J = 15.6, 6.4 Hz, 1 H). Anal. Calcd for $C_{10}H_{12}O_3$: C, 66.69; H, 6.66. Found: C, 66.67; H, 6.63.

5-Methoxy-2-indanone. A solution of 150 mg of 5-methoxy-1,2-indene oxide in 2.0 mL of dioxane was added to 20 mL of 0.1 M NaClO$_4$ in 1:3 dioxane−water, pH 7.23, and the resulting mixture was stirred for 5 min at rt. The solution was extracted with 75 mL of diethyl ether, and the ethereal extract was washed with water and dried over calcium sulfate. Removal of the solvent at reduced pressure yielded 100 mg of product, which was filtered through a column of 10 g of neutral alumina (III, 6% water) and sublimed (oil bath temperature 40−55 °C, 100 mmHg): mp 77−79 °C; ^{1}H NMR (CDCl$_3$, 200 MHz) δ 7.20 (d, J = 8.3 Hz), 6.8 (2 H), 3.81 (s, 3 H), 3.54 (2 H), 3.50 (2 H). Anal. Calcd for $C_{10}H_{10}O_2$: C, 74.09; H, 6.17. Found: C, 73.87; H, 6.36.

Procedure for Monitoring Rates of Equilibration of 5-Methoxy-1,2-indandiols and of 6-Methoxy-1,2,3,4-tetrahydronaphthalene-1,2-diols. The following procedure is an example of the method used to monitor the approach to equilibrium of a cis:trans diol mixture. A 120-μL portion of a solution containing 5 mg/mL of 5-methoxy-*trans*-1,2-indandiol in methanol was added to 12 mL of 0.05 M HClO$_4$ in water, maintained at 25.0 ± 0.2 °C, in a constant temperature water bath. Aliquots (1.0 mL) of the reaction solution were withdrawn at given times and quenched with 0.5 mL of 1.0 M NaOH solution. These solutions were analyzed by reversed phase HPLC on a C$_{18}$ column with 30:70 (v/v) methanol−water as eluent at a flow rate of 1.0 mL/min and monitored by UV detection at 265 nm. Under these analytical conditions, the retention time of trans diol was 8.3 min and that of cis diol 12.7 min. The results of this experiment and a similar one starting from pure 5-methoxy-*trans*-indandiol are graphically illustrated in Figure 2.

$$(\%\ \text{cis})_t = [(\%\ \text{cis})_o - (\%\ \text{cis})_{eq}]e^{-k_{obsd}t} + (\%\ \text{cis})_{eq} \qquad (3)$$

The percent of cis diol in the reaction during the equilibration experiments is given by eq 3, where (% cis)$_t$ is the percent of cis diol at a given time, (% cis)$_o$ is the initial concentration of cis diol, (% cis)$_{eq}$ is the equilibrium concentration of cis-diol, and k_{obsd} is the pseudo-first-order rate constant for the approach to equilibrium. In the equilibrium experiment starting from trans diol **8b**, fitting of (% cis)$_t$ to eq 3 yielded values of $7.2 \pm 0.6 \times 10^{-3}$ min^{-1} for k_{obsd} and 27.3 ± 0.5% for (% cis)$_{eq}$. In the equilibration experiment starting from a mixture of 80% of cis diol **7b** and 20% of trans diol **8b**, fitting of (% cis)$_t$ to eq 3 yielded values of $8.2 \pm 0.3 \times 10^{-3}$ min^{-1} for k_{obsd} and 28.8 ± 0.8% for (% cis)$_{eq}$. An average value of $k_{obsd} = 7.7 \times 10^{-3}$ min^{-1} was used to calculate the rate and equilibrium parameters given in Table 2.

In similar experimental method, the approaches to equilibrium from either pure 6-methoxy-1,2,3,4-tetrahydronaphthalene-*cis*-1,2-diol (**3b**) or its corresponding trans isomer (**4b**) in 0.10 M HClO$_4$ solution were monitored as a function of time by reverse phase HPLC with the same conditions as noted in the previous paragraph, except that 40:70 (v/v) methanol−water was used as eluent. The retention times of cis and trans diols **3b** and **4b** under these conditions were 8.9 and 7.4 min, respectively. These results are summarized graphically in Figure 3. In the approach to equilibrium from cis diol **3b**, fitting of (% cis)$_t$ to eq 3 yielded values of $(2.7 \pm 0.1) \times 10^{-2}$ min^{-1} for k_{obsd} and 37.0 ± 0.7% for (% cis)$_{eq}$. Starting from trans diol **8b,** fitting of (% cis)$_t$ to eq 3 yielded values of $(2.5 \pm 0.1) \times 10^{-2}$ min^{-1} for k_{obsd} and 37.5 ± 0.3% for (% cis)$_{eq}$. An average value of $k_{obsd} = 2.6 \times 10^{-2}$ min^{-1} was used to calculate the rate and equilibrium parameters given in Table 2.

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Supporting Information Available: Experimental procedures for the syntheses of 5-methoxyindene and *trans*-2-bromo-6-methoxyindan-1-ol; calculated structures and Cartesian coordinates for carbocation **6b** (B3LYP/6-31G*); calculated transition structures and Cartesian coordinates for cis and trans attacks of water on carbocation **6b** (MP2/6-31G*); calculated structures and Cartesian coordinates for cis and trans 5-methoxyindan-1,2-diols (B3LYP/6-31G*). This material is available free of charge via the Internet at http://pubs.acs.org.

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