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Acid-Catalyzed Phenylcyclohexene Oxide Hydrolysis: Role of Para-Phenyl Substituent on Syn:Anti Hydration Ratio

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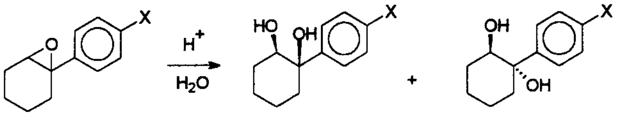
Rate and product studies of the hydronium ion-catalyzed hydrolysis of 1-phenylcyclohexene oxide and its *p*-methoxy and *p*-methyl derivatives in 1:9 dioxane−water solutions were carried out under conditions in which the diol products are stable. It is shown that the cis:trans diol ratio from hydrolysis of this series of epoxides *does not systematically increase with the electron-donating ability of the para-substituent*, contrary to conclusions in the literature. The equilibrium constants and rates for acid-catalyzed approach to equilibration of *cis*- and *trans*-1-(*p*-methoxyphenyl)cyclohexane-1,2-diol and of *cis*- and *trans*-1-(*p*-methylphenyl)cyclohexane-1,2-diol were measured, and the cis-diol was determined to be the more stable isomer in each case. An intermediate in the acid-catalyzed hydrolysis of 1-(*p*-methoxyphenyl)cyclohexene oxide is trapped, after its rate-limiting formation, by azide ion. For a series of 1-arylcyclohexene oxides, results are interpreted in terms of a mechanism in which there is a discrete carbocation intermediate, and products are determined solely by the partitioning reactions of this intermediate, with the pathway leading to the more stable product being energetically favored.

Introduction

The acid-catalyzed hydrolyses of 1-arylcyclohexene oxides **1a**−**d** yield mixtures of cis- and trans-diols **2** and **3** resulting from syn and anti hydration of the epoxide group, respectively (Scheme 1).[1] The percent of cis-diol product was reported to increase systematically with increasing electron-donating ability of the para-substituent; reported yields of cis-diol are given in parentheses. When the 4-substituent is the strongly electron-withdrawing nitro group, only very little (7.5%) of cis-diol is formed, along with the major trans-diol product. The reported yield of cis-diol product increases to 63% for X = H, 83% for X = CH$_3$ and 95.2% for X = OCH$_3$.

The mechanism proposed[1−3] to explain the substituent effect on the stereoselectivity of the acid-catalyzed hydrolysis of **1a**−**d** is outlined in Scheme 2. In this mechanism, reaction of protonated epoxide **5** leads to "intimate ion-dipole pair" **6.** Intermediate **6** can either react directly with solvent to yield anti product **8**, or isomerize to a "more cationic, solvent-separated ion−dipole pair" **7**. Ion−dipole pair **7** is proposed to collapse almost entirely to the syn product **9** under an entropically favored process. Electron-donating groups substituted in the aryl ring would stabilize the "more carbocationic" intermediate **7** more than they would the "intimate ion-dipole pair" **6**, thereby favoring the pathway leading to syn product.

Scheme 1



1a, X = OCH$_3$	**2a, X = OCH$_3$ (95.3%)**	**3a, X = OCH$_3$ (4.7%)**
b, X = CH3	**b, X = CH3 (83%)**	**b, X = CH3 (17%)**
c, X = H	**c, X = H (63%)**	**c, X = H (37%)**
d, X = NO$_2$	**d, X = NO$_2$ (7.5%)**	**d, X = NO$_2$ (92.5%)**

Substituent effects on syn/anti hydration ratios were also noted by us independently in several other systems.[4−6] Acid-catalyzed hydrolysis of 1,2,3,4-tetrahydronaphthalene-1,2-oxide (**10a**) yields 94% trans-diol and only 6% cis-diol.[4] However, acid-catalyzed hydrolysis of 6-methoxy-1,2,3,4-tetrahydronaphthalene-1,2-oxide (**10b**) yields 81% cis-diol product and 19% trans-diol product.[5] In the acid-catalyzed hydrolysis of both systems **1** and **10**, therefore, electron-donating substituents in the aromatic ring favor the reaction leading to cis-diol.

In the acid-catalyzed hydrolyses of the series of tetrahydro epoxides **11a**−**e**[5,6] and diol epoxides **12a**−**d**,[6] derived from polycyclic aromatic hydrocarbons, the relative yield of syn hydration product also increases quite dramatically with the ability of the aryl group to stabilize positive charge at the benzylic carbon of the epoxide group. The numbering after the names refers to the location of the epoxide group, and the syn:anti hydration ratios are provided in parentheses. The varying cis:trans diol product ratio from the acid-catalyzed hydrolyses of **10**−**12** were rationalized by a mechanism outlined in Scheme 3. Protonation of the epoxide group and ring opening from the more stable ground state conformation **13** yields an α-hydroxycarbocation **14**, in which the hydroxy group occupies an axial position. This carboca-

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(1) Battistini, C.; Balsamo, A.; Berti, G.; Crotti, P.; Macchia, B.; Macchia, F. *J. Chem. Soc., Chem. Commun.* **1974**, 712−713.

(2) Battistine, C.; Crotti, P.; Donatella, D.; Macchia, F. *J. Org. Chem.* **1979**, *44*, 1643−1647.

(3) Crotti, P.; Dell'Omodarme, G.; Ferretti, M.; Macchia, F. *J. Am. Chem. Soc.* **1987**, *109*, 1463−1469.

(4) Becker, A. R.; Janusy, J. M.; Bruice, T. C. *J. Am. Chem. Soc.* **1979**, *101*, 5679−5687.

(5) Gillilan, R. E.; Pohl, T. M.; Whalen, D. L. *J. Am. Chem. Soc.* **1982**, *104*, 4481−4482.

(6) Whalen, D. L.; Ross, A. M.; Yagi, H.; Karle, J. M.; Jerina, D. M. *J. Am. Chem. Soc.* **1978**, *100*, 5218−5221.

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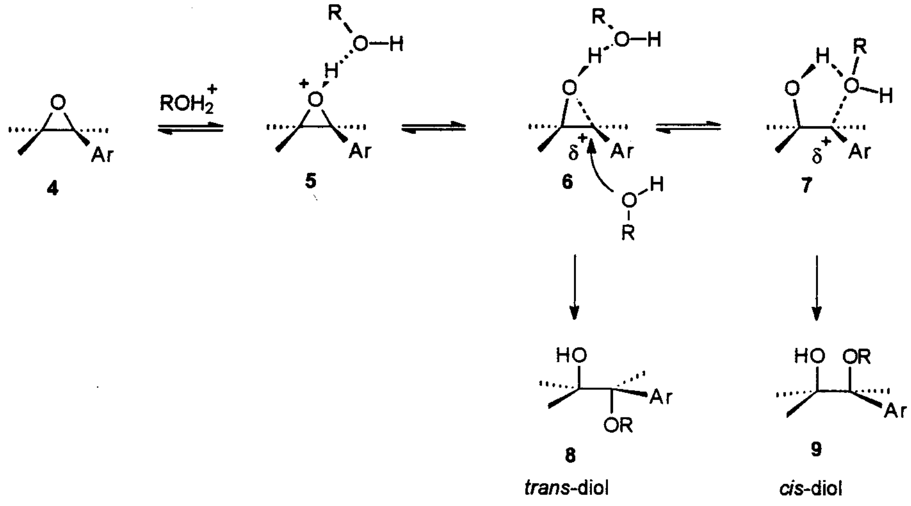
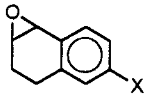
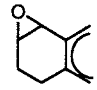
Scheme 2

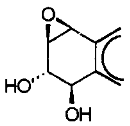




10a, X = H (6:94)
b, X = OCH$_3$ (81:19)



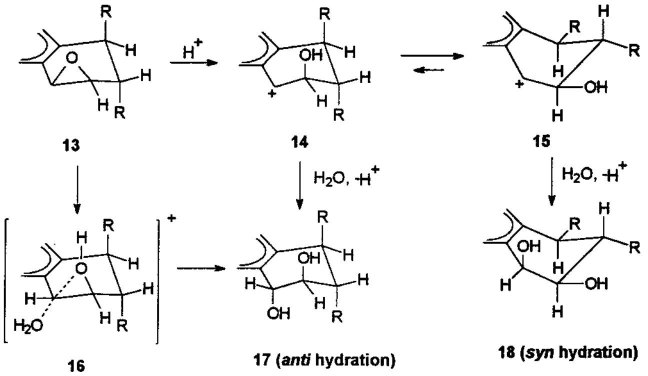
11a, naphthalene-1,2- (6:94)
b, phenanthrene-3,4- (18:82)
c, chrysene-3,4- (14:86)
d, benzo[a]anthracene-1,2- (50:50)
e, benzo[a]pyrene-9,10- (80:20)



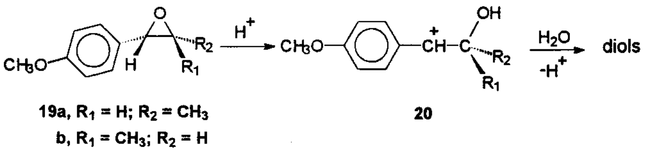
12a, phenanthrene-3,4- (50:50)
b, chrysene-3,4- (57:43)
c, benzo[a]anthracene-1,2- (75:25)
d, benzo[a]pyrene-9,10- (87:13)

tion can then partition between reaction with solvent and isomerization to a more stable conformation **15**, in which the hydroxy group occupies an equatorial position. It was rationalized that carbocations **14** and **15** are related in structure to 2-cyclohexenyl carbocations, which undergo preferential axial attack of solvent.[7] Axial attack of water on **14** and **15** would yield the trans- and cis-diols **17** and **18**, respectively. When the aryl group is not able to stabilize positive charge at the benzyl position sufficiently well, the initially formed carbocation reacts with solvent to yield trans diol faster than it isomerizes to **15**. Thus, anti hydration is favored. However, when the aryl group is better able to stabilize positive charge, e.g., when a methoxy group is substituted in the aryl group or when the aryl group itself is better able to stabilize positive charge, then conformational isomerization of **14** to the more stable isomer **15** competes with attack of water on **14**, and most of the product is derived from attack of solvent on **15**. For these systems, syn hydration is favored. For systems with electron-withdrawing groups in the aryl group, or where the carbocations **14** and **15** are too unstable to exist as intermediates in water solution, addition of solvent to protonated epoxide is expected to be concerted with benzyl C–O bond cleavage via transition state **16**. This concerted reaction is expected to occur with inversion of configuration at the benzyl carbon, and also yields trans-diol.

Scheme 3



Scheme 4



Hydrolysis reactions proceeding via a relatively unstable intermediate **14** cannot be distinguished from a concerted mechanism proceeding via transition state **16** by product studies alone. In a study of the acid-catalyzed hydrolysis of tetrahydronaphthalene oxide **10a** in potassium chloride solutions, however, it was determined that the cis/trans diol product ratio depended on the concentration of chloride ion, although the rate of reaction of **10a** was not significantly changed.[4] It was therefore concluded that chloride ion captures an intermediate, after its rate-limiting formation. Thus, a concerted mechanism for the acid-catalyzed hydrolysis of **10a** is ruled out.

The acid-catalyzed hydrolyses of *cis*- and *trans*-*β*-methyl-*p*-methoxystyrene oxides (anethole oxides) **19a** and **19b** yield the same mixture of 20% erythro- and 80% threo-diols (Scheme 4).[8] Thus, the acid-catalyzed hydrolysis of *trans*-*β*-methyl-*p*-methoxystyrene oxide proceeds with mostly syn hydration, whereas the acid-catalyzed hydrolysis of *cis*-*β*-methyl-*p*-methoxystyrene oxide pro-

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(7) Goering, H. L.; Josephson, R. R. *J. Am. Chem. Soc.* **1962**, *84*, 2779–2785.

(8) Mohan, R. S.; Whalen, D. L. *J. Org. Chem.* **1993**, *58*, 2663–2669.

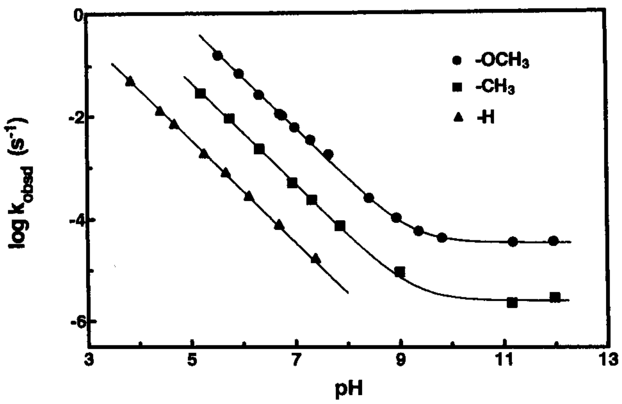

Figure 1. Plots of log k_{obsd} versus pH for reaction of 1-arylcyclohexene oxides **1a**−**c** in 1:9 dioxane−water (v/v) solutions, 25.0 ± 0.2 °C, $\mu = 0.1$ (NaClO$_4$). The solid lines are theoretical, based on eq 1 and the rate constants listed in Table 1.

ceeds with mostly anti hydration. An intermediate in these reactions, assumed to be a carbocation, is trapped by azide ion. It was proposed that the reactions of both epoxide isomers with hydronium ion yield the same discrete carbocation intermediate, and that the syn/anti product ratio is determined solely by the partitioning reactions of this intermediate with nucleophiles.

To determine if acid-catalyzed hydrolyses of arylcyclohexene oxides proceed via discrete, trappable intermediates or instead by reactions that are concerted or nearly concerted, we have examined the rates and products of the acid-catalyzed hydrolysis of arylcyclohexene oxides **1a**−**c**. Our results show that the diol products from hydrolysis of **1a** are not stable under the acidic conditions used for earlier product studies[1] and that the percent of cis-diol product actually formed in the acid-catalyzed hydrolysis of **1a** under conditions in which the diols are stable is considerably lower than that reported. Instead of a relationship in which the percent of cis-diol product from acid-catalyzed arylcyclohexene oxide hydrolysis increases systematically with increasing electron-donating ability of the para-substituent, we find that the electronic nature of the para-substituent within this series does not have a large or systematic effect on the cis/trans hydration ratio. For these epoxides, it is proposed that epoxide ring opening with hydronium ion leads to a discrete carbocation intermediate that undergoes partitioning reactions with solvent to yield cis- and trans-diol products, and that the pathway leading to the cis-diol is favored because this product is thermodynamically more stable than the trans-diol.

Results

Rate Studies. The rates of reaction of **1a**−**c** in 1:9 dioxane−water solutions over an extended pH range were determined. Plots of log k_{obsd} for reaction of these epoxides versus pH are provided in Figure 1. Rate data for reaction of **1a** and **1b** were fit to eq 1, where k_H is the second-order rate constant for the hydronium ion-catalyzed reaction and k_o is the first-order rate

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

constant for the spontaneous reaction. The spontaneous reaction of phenylcyclohexene oxide **1c** was too slow for k_o to be accurately determined. A summary of the rate constants is provided in Table 1. The increase in reactivity of ca. 1.7 × 10^2 for **1a** compared to **1c** toward acid-catalyzed hydrolysis is consistent with a mechanism in which the transition state has substantial positive charge development at the benzyl carbon. In a Hammett plot of log k_H vs σ^+ for these three epoxides, ρ^+ is calculated to be −2.8. The absolute value of ρ^+ is smaller than that observed for the acid-catalyzed hydrolysis of para-substituted styrene oxides (−4.2)[9] and reflects the lessened need for stabilization of the transition state by the para-substitutent because the benzyl carbon in **1a**−**c** is tertiary instead of secondary.

Table 1. Summary of Rate Constants for Reaction of Arylcyclohexene Oxides in 1:9 Dioxane−Water (v/v), 0.1 M NaClO$_4$, 25.0 ± 0.2 °C

compound	k_H (M^{-1} s^{-1})	k_o (s^{-1})
1a (X = OCH$_3$)	(6.00 ± 0.15) × 10^4	(3.49 ± 0.16) × 10^{-5}
1b (X = CH$_3$)	(4.91 ± 0.23) × 10^3	(2.55 ± 0.21) × 10^{-6}
1c (X = H)	(3.60 ± 0.02) × 10^2	

Spontaneous Reactions of 1a and 1b. The rates and preliminary product studies of the spontaneous reactions of **1a** and **1b** were determined, although detailed studies to determine their reaction mechanisms were not carried out. The yield of diols from the spontaneous reaction of **1a** at pH 11−12 is reduced by approximately half compared to the yield of diols from the acid-catalyzed reaction of **1a** at pH 6. Another major product with a longer HPLC retention time, presumably due to ketone product, is also formed from the spontaneous reaction. The cis:trans diol product ratio changes slightly from 74:26 in the acid-catalyzed reaction of **1a** to 61:39 in the spontaneous reaction. In contrast, the spontaneous reaction of **1b** at pH 11 yields more trans-diol than cis-diol (cis:trans = 33:67), whereas acid-catalyzed hydrolysis of **1b** at pH 5 yields mostly cis-diol (cis:trans = 83:17). The yield of diols from the spontaneous reaction of **1b** is also reduced by about half compared to that from the acid-catalyzed reaction.

Product Studies of the Acid-Catalyzed Reactions of 1a−**c.** We have observed that reaction of **1a** in 0.2 N H$_2$SO$_4$ solution at room temperature for 24 h yields 92% of cis-diol and 8% of trans-diol products, a result that is in reasonably good agreement with an earlier study in which it reported that the hydrolysis of **1a** under these conditions yields 95.3% of cis-diol and 4.7% of trans-diol.[1] We have also determined the ratios of *cis*- and trans-diol products from the hydrolysis of **1a**−**c** in 1:9 dioxane−water solutions at pH 5−6. Relative yields of cis- and trans-diol products from acid-catalyzed reactions of **1b** and **1c** 1:9 dioxane−water at pH 5.0 were found to be very similar to those reported[1] from reaction of **1b** and **1c** in 0.2 N H$_2$SO$_4$ solution for 24 h at room temperature. However, acid-catalyzed hydrolysis of **1a** at pH 6.0 yields 74% cis-diol and 26% trans-diol. This cis:trans diol ratio is significantly different than that found for hydrolysis of **1a** in 0.2 N H$_2$SO$_4$ solution. A summary of the products from acid-catalyzed hydrolysis of these epoxides is provided in Table 2. The product ratios reported[1] for reaction of **1a**−**c** in 0.2 N H$_2$SO$_4$ solution for 24 h, listed in Scheme 1, give a rather good correlation between the electron-donating ability of the para-substituent and the relative yield of cis-diol product. *However, the yields of cis-diol*

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[9] Blumenstein, J. J.; Ukachukwu, V. C.; Mohan, R. S.; Whalen, D. L. *J. Org. Chem.* **1993**, *58*, 924−932.

Table 2. Relative Yields of Diol Products from Acid-Catalyzed Hydrolysis of Arylcyclohexene Oxides 1a–c in 1:9 Dioxane–Water (v/v), 0.1 M $NaClO_4$

compound	pH[a]	cis-diol:trans-diol
1a ($X = OCH_3$)	6.0	74:26
1b ($X = CH_3$)	5.0	83:17
1c ($X = H$)	4.0	65:35

[a] pH at which epoxide was allowed to react for >10 half-lives before products were analyzed.

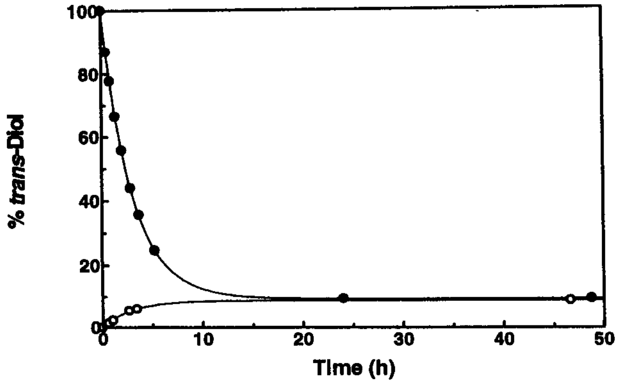


Figure 2. Plots of percent trans-diol **3a** versus time in the equilibration reactions starting from either trans-diol **3a** or cis-diol **2a** in 1:9 dioxane–water (v/v) solutions, 0.03 M $HClO_4$, 25.0 ± 0.2 °C, $\mu = 0.1$ ($NaClO_4$). The lines are theoretical, based on eq 4.

*from reaction of **1a–c** in 1:9 dioxane–water solution at pH 4–6 (Table 2) do not correlate with the electron-donating ability of the para-substituent.* Under both conditions, however, cis-hydration is still the major reaction pathway.

Acid-Catalyzed Isomerization of Diols 2 and 3. To determine if diols **2a** and **3a** are stable under the reaction conditions used to study the acid-catalyzed hydrolysis of **1a**, their interconversions catalyzed by H_2SO_4 in water and $HClO_4$ in 1:9 dioxane–water were studied. A sample of pure trans-diol **3a** was subjected to the same reaction conditions used for the hydrolysis of epoxide **1a** in 0.2 N H_2SO_4. Workup of the reaction after 20 h yielded a mixture of diols **2a** and **3a** in a 92:8 ratio. This diol mixture is the same as that obtained from hydrolysis of **1a** under these conditions. Therefore, trans-diol **3a** isomerizes readily to the *cis*-isomer in 0.2 N H_2SO_4 solution, demonstrating that the trans-diol product **3a** formed from hydrolysis of **1a** *is not stable to these reaction conditions.*

To establish whether diols **2a** and **3a** are relatively stable at pH > 4 in 1:9 dioxane–water solutions, the pseudo-first-order rate constants, k_{obsd}, for conversion of **2a** or **3a** in 1:9 dioxane–water containing 0.03 M $HClO_4$ to an equilibrium mixture of **2a** and **3a** (eq 2) were determined. Figure 2 shows plots of percent composition of the reaction mixtures as functions of time, starting with either pure **2a** or pure **3a**. Values of the rate constants k_{obsd} for approach to equilibrium

$$\text{cis-diol } (\mathbf{2}) + H^+ \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \text{trans-diol } (\mathbf{3}) + H^+ \qquad (2)$$

from **2a** and **3a** were calculated to be $3.37 \pm 0.03 \times 10^{-1}$ h^{-1} and $3.49 \pm 0.01 \times 10^{-1}$ h^{-1}, respectively. These two rate constants are the same within experimental error and reflect the fact that the measured rate constant k_{obsd} for approach to an equilibrium from either direction is the sum of the forward and reverse rate constants. Thus, $k_{obsd} = (k_1 + k_{-1})[H^+]$. The half-life for approach to equilibrium of **2a** and **3a** in 0.03 M $HClO_4$ solution is ca. 2 h. Dividing k_{obsd} by $[H^+]$ gives the second-order rate constant of 11.4 $M^{-1}h^{-1}$ for acid-catalyzed approach to equilibrium ($k_1 + k_{-1}$) from **2a** or **3a**.

Table 3. Summary of Second-Order Rate Constants and Equilibrium Constants for Acid-Catalyzed Equilibration of *cis*- and *trans*-Arylcyclohexanediols 2 and 3 in 1:9 Dioxane–Water

compound	k_1 (M^{-1} h^{-1})	k_{-1} (M^{-1} h^{-1})	K_{eq}
2a, **3a** ($X = OCH_3$)[a]	1.04	10.4	0.10
2b, **3b** ($X = CH_3$)[b]	1.22×10^{-2}	0.149	0.082

[a] Calculated from values of k_{obsd} for approach to equilibrium from both **2a** and **3a** in 0.03 M $HClO_4$ solution. [b] Calculated from value of k_{obsd} for approach to equilibrium from **3b** in 0.1 M $HClO_4$ solution.

Extrapolation of the percent composition versus time data in Figure 2 for reaction of either **2a** or **3a** yields a calculated equilibrium mixture containing 91% of the cis-diol **2a** and 9% of the trans-diol **3a**. Thus, the equilibrium constant K_{eq} (k_1/k_{-1}, eq 2) is calculated to be 0.10, corresponding to a $\Delta G°$ of 1.4 kcal/mol. From the equilibrium constant and values of $(k_1 + k_{-1})$, values for k_1 and k_{-1} are calculated. A summary of these rate constants is provided in Table 3.

We have also measured the rate constant with which cis-diol **2b** ($X = CH_3$) is converted to an equilibrium mixture of *cis*- and *trans*-isomers (**2b** and **3b**). A plot of these data is provided as Supporting Information, and values of k_1, k_{-1}, and K_{eq} are provided in Table 3. The half-life for approach to equilibrium for these diols in 1:9 dioxane–water containing 0.1 M $HClO_4$ is 43 h. *p*-Methoxy-substituted diols **2a** and **3a** are approximately 70 times more reactive than *p*-methyl-substituted diols **2b** and **3b** toward acid-catalyzed equilibration. However, the *equilibrium* constant K_{eq} is very similar for the two equilibria.

Trapping of an Intermediate in the Hydrolysis of 1a by Azide Ion. To assess whether there is a discrete intermediate in the acid-catalyzed hydrolysis of **1a**, we have determined the rates and products of its reaction in 1:9 dioxane–water solutions containing sodium azide, a strong nucleophile that is very reactive with carbocations. The rate of reaction of **1a** in solutions containing sodium azide in concentrations up to 0.01 M shows no detectable change. However, the yield of diols from the reaction decreases with increasing sodium azide concentration and two new products formed in a 3:2 ratio are detected by HPLC. These products were isolated and determined to be azidohydrins, formed from capture of an intermediate carbocation **21** by azide ion (Scheme 5). The ratio of azidohydrin products is independent of the concentration of azide ion, and therefore the incursion of a second-order reaction of **1a** with azide ion to yield a single, *trans*-azidohydrin at higher concentrations of sodium azide where rate constants could not be determined spectrophotometrically does not occur. Since the yields of these azidohydrins increase with increasing azide ion concentration *without* a corresponding increase in rate constant for reaction of **1a**, the product-forming step must occur after rate-limiting formation of an intermediate.

The fraction of diol products formed from the reaction of **1a** by the mechanism of Scheme 5 is equal to $k_s/(k_s +$

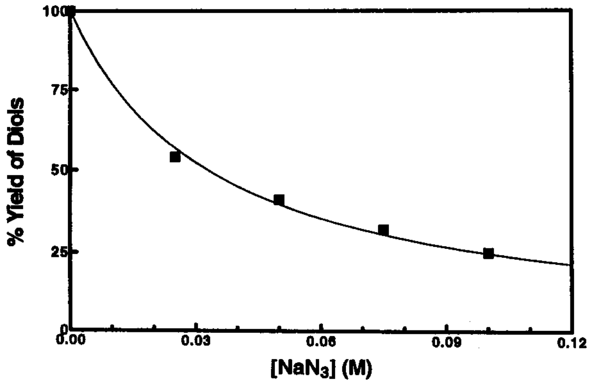
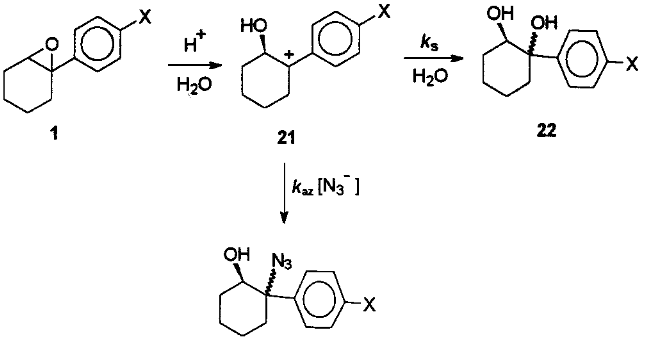


Figure 3. Plot of percent diol yield versus sodium azide concentration in the acid-catalyzed reaction of **1a** at pH 6.0 in 1:9 dioxane−water (v/v) solutions, 25.0 ± 0.2 °C, $\mu = 0.1$ ($NaClO_4$). The line is theoretical, based on eq 3 and a calculated value for k_{az}/k_s of 30 ± 1 M^{-1}.

Scheme 5



1 **21** **22** **23**

$k_{az}[N_3^-]$). The percent yield of diol products from the reaction of **1a** is therefore given by eq 3, and a plot of the percent yield of diol products versus the concentration

$$\% \text{ diol products} = \frac{100}{1 + \dfrac{k_{az}}{k_s}[N_3^-]} \tag{3}$$

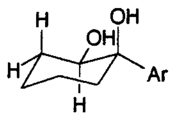
of azide ion is given in Figure 3. By fitting these data to eq 3, a value for k_{az}/k_s is calculated to be 30 M^{-1}. For carbocations that have k_{az}/k_s partitioning ratios similar to that for reaction of **1a**, it has been proposed that their reactions with azide ion occur at the diffusional limit, with a bimolecular rate constant k_{az} of ca. 5×10^9 M^{-1} s^{-1}.[10] For this value of k_{az}, a value for k_s for reaction of carbocation **21a** in 1:9 dioxane−water is calculated to be 1.7×10^8 s^{-1}. This calculated rate constant is slightly larger than k_s calculated for reaction of α-dimethyl-substituted 4-methoxybenzyl carbocation ($4\text{-}MeOC_6H_4C(CH_3)_2^+$) in 1:1 trifluoroethanol−water (1.3×10^7 s^{-1}).[11] The rate of reaction of a para-substituted benzyl carbocation with solvent generally increases as the carbocation becomes less stable.[10] However, for a series of tertiary α-substituted 4-methoxybenzyl carbocations of widely varying stabilities, the value of k_s is nearly independent of the thermodynamic stability of the carbocation.[11]

We have also carried out rate and product studies for the reaction of 1-(*p*-methylphenyl)cyclohexene oxide **1b** in solutions containing sodium azide. Hydrolysis of **1b** in 0.1 M sodium azide solution resulted in a reduction in yield of diol products by ca. 20%, and two new products assumed to be azide adducts were detected. The much lower amount of trapping of an intermediate in the reaction of **1b** by azide ion, compared to that for trapping of the intermediate in the reaction of **1a**, can be attributed to the greater reactivity toward solvent of the intermediate carbocation **21** when X = CH_3. Consequently, less of the intermediate in the reaction of **1b** will be trapped by azide ion, which most likely also reacts with **21** (X = CH_3) at or near the diffusional limit.[10] Tertiary α-substituted 4-methylbenzyl carbocations are observed to be more reactive with solvent than the corresponding α-substituted 4-methoxybenzyl carbocations.[11]

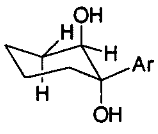
Discussion

Diol Isomerization. Values of K_{eq} listed in Table 3 for acid-catalyzed equilibration of diols with the *p*-methoxyphenyl (**2a**, **3a**) and *p*-methylphenyl groups (**2b**, **3b**) are very similar. Only 8−9% of the trans-isomer is present at equilibrium, and these results demonstrate that the cis-diol is more stable than the trans-diol for these two sets of isomers in 1:9 dioxane−water solution. The similarity of K_{eq} for interconversion of the cis- and trans-diols **2** and **3** where X = OCH_3 and CH_3 suggest that the value of K_{eq} is not greatly influenced by the para substituent. Thus, the cis-diols **2c** and **2d** should also be more stable than the corresponding trans-diols **3c** and **3d**, respectively.

From the reported heats of combustion of the cis and trans isomers of 1,2-cyclohexanediol and of 1-phenyl-1,2-cyclohexanediol,[12] the cis isomer is slightly more stable than the trans isomer in each case (ca. 0.5−1.0 kcal/mol). If the aryl group in both *cis*- and *trans*-1-arylcyclohexane-1,2-diols occupies an equatorial position, then only one hydroxy group in the cis-diol **2** would be located in an axial position (conformation **24**) whereas both hydroxy groups in the trans-diol **3** would be forced to occupy axial positions (conformation **25**). Conformation **24** (cis-diol) has two 1,3-diaxial H−OH interactions, one gauche phenyl−OH interaction, and one gauche OH−OH interaction, whereas conformation **25** (trans-diol) has four 1,3-diaxial H−OH interactions and one gauche phenyl−OH interaction.



24



25

From the rate data listed in Table 3, the half-life for approach to equilibrium of **2a** and **3a** is calculated to be 2.0 h at 25 °C in 0.03 M $HClO_4$, 1:9 dioxane−water solution. Therefore, the half-life for equilibration of these diols in 0.2 N H_2SO_4 solution is expected to be less than 1 h. In contrast, the half-life for equilibration of **2a** and **3a** at pH 6 under the condition used for our product

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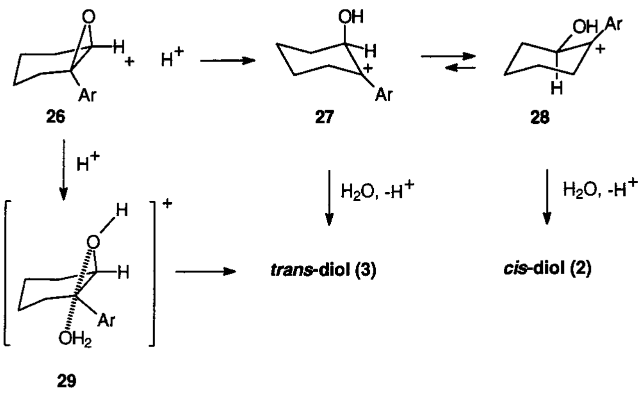
[10] Richard, J. P.; Rothenberg, M. E.; Jencks, W. P. *J. Am. Chem. Soc.* **1984**, *106*, 1361−1372.

[11] Aymes, T. L.; Stevens, I. W.; Richard, J. R. *J. Org. Chem.* **1993**, *58*, 6057−6066.

[12] von Verkade, P. E.; Coops, J., Jr.; Maan, C. J.; Verkade-Sandbergen, F. A. *Ann.* **1928**, *467*, 217−239.

Scheme 6



studies (Table 2) is calculated to be 2.5 × 10^3 days. For the conditions of our product studies for acid-catalyzed hydrolysis of **1a** (Experimental Section), therefore, equilibration of the diol products **2a** and **3a** is negligible.

Diols **2b** and **3b** are much less reactive then diols **2a** and **3a** toward acid-catalyzed isomerization. Whereas the half-life for approach to equilibrium for **2a** and **3a** in 0.03 M $HClO_4$ at 25 °C in 1:9 dioxane–water solution is 2 h, the half-life for approach to equilibrium for **2b** and **3b** in 0.1 M $HClO_4$ at 25 °C in 1:9 dioxane–water solution is 43 h. Diols with hydrogen and nitro at the para-position of the phenyl ring (**2c,d** and **3c,d**) will be even more stable in acidic solution than those with methyl at the para-position (**2b**, **3b**).

The cis:trans diol mixtures formed from hydrolysis of epoxide **1a** and from reaction of trans-diol **3a** in 0.2 N H_2SO_4 at room temperature for 20 h (ca. 92:8) are very similar to the equilibrium mixture of 91% cis-diol and 9% of trans-diol in 1:9 dioxane–water. Thus, the value of K_{eq} for isomerization of these diols in 0.2 N H_2SO_4 is very close to that for their interconversion in 1:9 dioxane–water.

Mechanism of Hydrolysis of Arylcyclohexene Oxides 1a–c. From the diol product distributions summarized in Table 2 for acid-catalyzed hydrolysis of **1a–c**, it is clear that there is *not* a good correlation within this series between the relative yield of cis-diol product and the electron-donating ability of the para-substituent in the phenyl ring. Upon substitution of hydrogen at the para-position by methyl, the relative yield of cis-diol increases from 65% to 83%. However, further substitution of the methyl group by a much more electron-donating methoxy group results in a *decrease* of the relative yield of cis-diol to 74%. For the acid-catalyzed hydrolysis of epoxides **1a–c**, therefore, the relative yields of cis- and trans-diols do not change in a large or systematic way.

A mechanism that accounts for the cis:trans diol product ratio from acid-catalyzed hydrolysis of arylcyclohexene oxides **1a–c** is given in Scheme 6. In this scheme, it is assumed that axial epoxide ring opening and axial attack of solvent on the intermediate carbocation are energetically favored over equatorial ring opening and equatorial attack of solvent on the intermediate.[13] For acid-catalyzed hydrolysis of **1a–c**, axial ring opening of the epoxide (**26**) yields an intermediate carbocation, which may exist in two chair conformations, **27** and **28**. Axial attack of solvent on conformation **27** yields trans-diol product, whereas axial attack of solvent on conformation **28** yields cis-diol product. If conformations **27** and **28** are in rapid equilibrium, then the ratio of diol products will be independent of the equilibrium concentrations of carbocation conformations, but will instead depend only on the difference in energy between the transition states leading to cis- and trans-diol products (Curtin–Hammett Principle).[14] It is reasonable to assume that those factors that contribute to the greater stability of the cis-diol product will therefore contribute to the lowering of the transition state for this product-forming pathway. *In the acid-catalyzed hydrolysis of phenylcyclohexene oxides, benzo[a]pyrene diol epoxides*[15,16] *and other epoxides*[8] *that react via carbocation intermediates that are sufficiently stable to be trapped by external nucleophiles, the energy difference between the syn- and anti-hydration products may be the principal factor determining whether syn or anti hydration is favored*. For those epoxides that react with H^+ to yield carbocations that are not sufficiently stable to attain conformational equilibration, then solvent attack on the initially formed carbocation may become the major product-forming step. For other epoxides that would react with H^+ to yield extremely unstable carbocations, concerted reactions may predominate.

Mechanism of Hydrolysis of 1-(*p*-Nitrophenyl)-cyclohexene Oxide 1d and Other Phenylcyclohexene Oxides with Electron-Withdrawing Groups Substituted in the Phenyl Ring. We did not evaluate the relative stabilities of *p*-nitrophenylcyclohexane diols **2d** and **3d** in sulfuric acid solution. However, they are expected to be much more stable toward acid than other diols in the series with *p*-phenyl substituent groups that are not electron-withdrawing, and should be stable to the conditions used for hydrolysis of **1d** in 0.2 N H_2SO_4 solution.[1–3] Acid-catalyzed hydrolysis of **1d** ($X = NO_2$) and other phenylcyclohexene oxides with electron-withdrawing groups substituted in the phenyl ring results in greater yields of trans-diol,[1–3] and therefore these epoxides must react at least partially by a mechanism different than that by which **1a–c** react. The presence of the strongly withdrawing nitro group in the phenyl ring of **21d** (Scheme 5) greatly destabilizes this carbocation, and therefore a concerted pathway proceeding via transition state **29** (Scheme 6) may contribute to the much higher yield of trans-diol product. Another possibility is that reaction of **1d** with H^+ proceeds with axial opening to form the unstable carbocation conformation **27d**, which reacts with solvent by axial attack to yield trans-diol product faster than it undergoes conformational isomerization to **28d**. The exact role of solvent molecules that are closely coordinated to the transition states and/or intermediates is not clear.

Conclusions

The cis:trans diol ratio from the acid-catalyzed hydrolysis of 1-phenylcyclohexene oxide and its para-phenyl-substituted methoxy and methyl derivatives *do not depend systematically on the electron-donating ability of the para-substituent*, contrary to published conclusions. Instead, the cis:trans diol ratios from acid-catalyzed hydrolysis of these three epoxides, under conditions in

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[13] Eliel, E. L. *Stereochemistry of Carbon Compounds*; McGraw-Hill: New York, 1962; pp 230–231.

[14] (a) Curtin, D. Y.; *Rec. Chem. Prog.* **1954**, *15*, 111. (b) Eliel, E. L. *Stereochemistry of Carbon Compounds*; McGraw-Hill: New York, 1962; pp 151–152.

which the diol products are stable, are very similar. Acid-catalyzed equilibration of the *cis*- and *trans*-*p*-methoxyphenylcyclohexene diols **2a** and **3a** occurs readily at pH < 2 and accounts for the higher published yield of cis-diol from the acid-catalyzed hydrolysis of **1a** in 0.2 N H_2SO_4 solution. For 1-phenylcyclohexanediols possessing *p*-methoxy and *p*-methyl substituents in the phenyl ring and presumably for other 1-arylcyclohexanediols, the cis-isomer is more stable than the trans-isomer. This observation may account for the greater yields of cis-diol from acid-catalyzed hydrolysis of 1-(*p*-methoxyphenyl), 1-(*p*-methylphenyl), and 1-phenylcyclohexene oxides. An intermediate in the acid-catalyzed hydrolysis of 1-(*p*-methoxyphenyl)cyclohexene oxide is trapped, after its rate-limiting formation, by azide ion. The acid-catalyzed hydrolysis of this series of epoxides is accommodated by a mechanism involving *rate-limiting formation of a carbocation intermediate followed by partitioning of this intermediate to diol products, with the pathway leading to the more stable cis-diol being energetically favored*.

Experimental Section

Materials. 1-(*p*-Methoxyphenyl)cyclohexene, 1-(*p*-methylphenyl)cyclohexene, and 1-phenylcyclohexene were prepared by addition of cyclohexanone to the appropriate Grignard reagent, followed by *p*-toluenesulfonic acid-catalyzed dehydration of the alcohol from the Grignard reaction.[17] Dioxane was distilled from sodium prior to use. All other reagents were purchased from commercial sources and used without further purification.

Published preparations of **1a**−**c** involved conversion of the precursor olefin to a bromohydrin followed by potassium *tert*-butoxide ring closure of the bromohydrin to form the epoxide[18] or direct epoxidation of the olefin by peroxybenzoic acid.[19] We synthesized **1a**−**c** by direct epoxidation of the olefin under biphasic, buffered conditions.

1-(*p*-Methoxyphenyl)cyclohexene Oxide (1a). A solution of 0.155 g (0.9 mmol) of *m*-chloroperoxybenzoic acid (85%) in 5 mL of methylene chloride was added dropwise over 5 min to a well-stirred biphasic mixture of 0.105 g (0.56 mmol) of 1-(*p*-methoxyphenyl)cyclohexene in 5 mL of methylene chloride and 5 mL of 10% (w/w) sodium carbonate in an ice−water bath. The reaction mixture was allowed to stir for an additional 5 min. The aqueous phase was separated from the organic phase and washed with several milliliters of methylene chloride. The methylene chloride solutions were combined, washed with 1.0 M NaOH, and dried over sodium sulfate. Removal of solvent yielded 0.11 g of crude product, which was recrystallized from pentane−diethyl ether solution to yield 82 mg (45%) of **1a**, mp 46.9−47.4 °C, lit.[18] mp 44−45 °C.

1-(*p*-Methylphenyl)cyclohexene oxide (1b) and 1-(*p*-methoxyphenyl)cyclohexene oxide (1c) were prepared by procedures similar to that for preparation of **1a**, except that the reaction time for epoxidation was increased to 30 min.

Kinetics Procedures. For each kinetic run, approximately 5 μL of a stock solution of **1** in dioxane (ca. 3 mg/mL) was added to 2.0 mL of 1:9 dioxane−water solution in the thermostated cell compartment (25.0 ± 0.2 °C) of a UV−vis spectrophotometer. The ionic strength of each solution was made to be 0.10 M with added $NaClO_4$. For maintenance of pH for solutions with pH in the range 4−10, ca.. 10^{-3} M of a buffer reagent was added. Buffers used were acetic acid (pH 4.1−5.5); MES (2-[*N*-morpholino]ethanesulfonic acid), pH 5.0−6.5; HEPES (*N*-2-hydroxyethylpiperazine-*N*′-2-ethanesulfonic acid), pH 7.0−8.0; EPPS (*N*-2-hydroxyethyl)piperazine-*N*′-3-propanesulfonic acid), pH 8.0−8.7; and CHES (2-[*N*-cyclohexylamino]ethanesulfonic acid), pH 8.5−10.0. For determining pH-rate profiles, the reactions of **1a**−**c** were monitored at 235, 240, and 225 nm, respectively. The reactions of **1a** and **1b** in solutions containing sodium azide were monitored at 240−242 nm. Pseudo-first-order rate constants were calculated by nonlinear regression analysis of the time versus absorbance data.

Analysis of Products from Acid-Catalyzed Hydrolysis of 1a−c. A 10-μL solution of each epoxide in dioxane (2 mg/mL) was added by syringe to 1.0 mL of 1:9 dioxane−water solution, containing 0.1 M $NaClO_4$, that had been adjusted to pH 6.0 for reaction of **1a**, to pH 5.0 for reaction of **1b**, and to pH 4.0 for reaction of **1c**. At these pH values, $k_H[H^+] > 100k_o$; e.g., the acid-catalyzed reaction predominates. The reaction solutions of **1a** and **1b** were thoroughly mixed and allowed to stand at room temperature for ca. 2 min (ca. 10 and 8.5 half-lives, respectively); the reaction solution of **1c** was allowed to stand for 4 min (ca. 12 half-lives). The solutions were then analyzed directly by reverse phase HPLC on a C_{18} column. The products were eluted with 3:2 (v/v) methanol−water as eluent at a flow rate of 1.0−1.2 mL/min and monitored by UV detection at 273 nm. Retention times for **2a** and **3a** were 6.7 and 4.1 min; for **2b** and **3b**, 11.0 and 5.8 min; for **2c** and **3c**, 10.7 and 6.7 min, respectively. A summary of the relative yields of diol products from acid-catalyzed hydrolysis of **1a**−**c** is provided in Table 2.

From larger scale reactions, diol products from hydrolyses **1a**−**c** separated by column chromatography on alumina with pentane−ether as eluent. The identities of the diol products from hydrolyses of **1a**−**c** were established by comparison of their ^1H NMR spectra with published ^1H NMR data.[18]

Acid-Catalyzed Equilibration of Diols 2a and 3a. A solution containing 30 mg of **2a** in 0.5 mL of dioxane was prepared. A 30 μL portion of this solution was added by syringe to 3.0 mL of 0.03 M $HClO_4$ in 1:9 dioxane−water ($\mu = 0.10$, $NaClO_4$) at 25.0 °C. At different time intervals, 0.3 mL of the reaction solution was removed, quenched with 0.3 mL of 0.03 M NaOH in 1:9 dioxane−water, and analyzed by reverse phase HPLC on a C_{18} column under the same conditions used for analysis of the diol products from hydrolysis of **1a**. The results of this experiment are graphically illustrated in Figure 2.

The percent of trans-diol in the reaction solution during the equilibration experiments is given by eq 4, where $(\%\ \text{trans})_t$

$$(\%\ \text{trans})_t = [(\%\ \text{trans})_0 - (\%\ \text{trans})_{eq}]\ e^{-k_{obsd}\,t} + (\%\ \text{trans})_{eq} \quad (4)$$

is the percent of trans-diol at a given time, $(\%\ \text{trans})_0$ is the initial concentration of trans-diol, $(\%\ \text{trans})_{eq}$ is the equilibrium concentration of trans-diol, and k_{obsd} is the pseudo-first-order rate constant for the approach to equilibrium. In the equilibrium experiment starting from pure trans-diol **3a**, fitting of $(\%\ \text{trans})_t$ to eq 4 yielded values of $3.37 \pm 0.03 \times 10^{-1}\ h^{-1}$ for k_{obsd} and $9.44 \pm 0.27\%$ for $(\%\ \text{trans})_{eq}$. In the equilibration experiment starting from pure cis-diol **2a**, fitting of $(\%\ \text{trans})_t$ to eq 4 yielded values of $3.49 \pm 0.01 \times 10^{-1}\ h^{-1}$ and $8.84 \pm 0.14\%$ for k_{obsd} and $(\%\ \text{trans})_{eq}$, respectively.

The procedure used to determine the rate constant for acid-catalyzed equilibration of **3a** in 0.03 M $HClO_4$ to an equilibrium mixture of **2a** and **3a** was also used to determine the rate constant for acid-catalyzed equilibration of **3b** to an equilibrium mixture of **2b** and **3b**, except that the concentration of $HClO_4$ used was 0.1 M instead of 0.03 M. Fitting of the diol composition to eq 4 yielded a value of $(1.61 \pm 0.13) \times 10^{-2}\ h^{-1}$ for k_{obsd} and $7.6 \pm 2.1\%$ for $(\%\text{trans})_{eq}$.

Product Studies of the Reaction of 1a in Sodium Azide Solutions. a. Analytical Procedure. Aliquots (30 μL) of **1a** in dioxane (4 mg/mL) were added to vials containing 1.0 mL of 1:9 dioxane−water containing concentrations of NaN_3

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[16] Lin, B.; Islam, N.; Friedman, S.; Yagi, H.; Jerina, D. M.; Whalen, D. L. *J. Am. Chem. Soc.* **1998**, *120*, 4327−4333.

[17] Davies, M. T.; Dobson, D. F.; Hayman, D. F.; Jackman, G. B.; Lester, M. G.; Petrow, V.; Stephenson, O.; Webb, A. A. *Tetrahedron* **1962**, *18*, 751−761.

[18] Balsamo, A.; Crotti, P.; Macchia, B.; Macchia, F. *Tetrahedron* **1973**, *29*, 2183−2188.

[19] Berti, G.; Bottari, F.; Macchia, B.; Macchia, F. *Tetrahedron* **1965**, *21*, 3277−3283.

varying between 0 and 0.1 M, with pH adjusted to 5.8−5.9 by addition of 0.1 M $HClO_4$ in 1:9 dioxane−water. Ionic strength was kept constant at 0.1 M by addition of $NaClO_4$. After addition of the epoxide, the reaction vials were capped, shaken, and allowed to stand at room temperature for ca. 5 min. An aliquot (25 μL) of **3b** in dioxane (6 mg/mL) was then added to each vial to serve as an HPLC standard. Solutions were then analyzed by HPLC on a reverse phase C_{18} column with 3:2 methanol−water as eluting solvent, 1.4 mL/min. The yields of diol products were calculated by comparing the areas of their HPLC peaks with that of the standard. The total yield of diols was lowered as the sodium azide concentration was increased. These results are graphically represented in Figure 3. Two new products, formed in a 3:2 ratio and assumed to be azide products formed from reaction of azide ion from both sides of the electron deficient benzyl carbon of the carbocation intermediate, were detected by HPLC (retention times 15 and 20 min). The yields of these products increase with increasing azide ion concentrations.

b. Preparative Procedure. A sample of crude **1a** (0.36 g) in 5 mL of dioxane was added to 50 mL of 0.5 M NaN_3 in 1:9 dioxane−water solution, pH 5.8, and the resulting solution was stirred at room temperature for 1.5 h. The reaction solution was then extracted with 100 mL of diethyl ether. The ether extract was washed with water and dried over calcium sulfate. Removal of solvent yielded 0.45 g of crude azide products. A portion of this product (0.1 g) was chromatographed on silica gel (240−400 mesh) with 1:1 diethyl ether−pentane as eluting solvent.

The minor azide product with HPLC retention time of 20 min (see Analytical Procedure above) eluted first as an oil. Approximately 20 mg of this azide was isolated; IR (CCl_4) 2110 cm^{-1}; ^1H NMR (200 MHZ, $CDCl_3$) δ 1.4−2.3 (9 H), 3.83 (4 H), 6.95 (d, $J = 9.1$ Hz, 2 H), 7.44 (d, $J = 9.1$ Hz, 2 H). Anal. Calcd for $C_{13}H_{17}O_2N_3$: C, 63.14; H, 6.93. Found: C, 63.28; H, 7.15.

Absorptions due to the OCH_3 hydrogens and the hydrogen α to the OH group are located at δ 3.8 and are not resolved. However, a COSY experiment revealed correlations between this signal and other absorptions at δ 1.2 and δ 1.7, consistent with that expected for coupling of the hydrogen α to the OH group to each of two vicinal methylene hydrogens. After several chromatography fractions containing both azide products, the major azide product with HPLC retention time of 15 min eluted and was recrystallized from diethyl ether−pentane solution to give 35 mg of crystalline product; mp 78.5−80.5 °C; IR (CCl_4) 2110 cm^{-1}; ^1H NMR (200 MHZ, $CDCl_3$) δ 1.2−2.1 (9 H), 3.82 (s, 3 H), 3.87 (dd, $J = 10.2$, 4.2 Hz, 1 H), 6.95 (d, $J = 9.1$ Hz, 2 H), 7.41 (d, $J = 9.1$ Hz, 2 H). Anal. Calcd for $C_{13}H_{17}O_2N_3$: C, 63.14; H, 6.93. Found: C, 63.35; H, 7.00.

The cis stereochemistry was assigned to the major azide product (*cis*-**23**) on the basis of the larger vicinal $^1H-^1H$ coupling between the methine hydrogen α to the OH group and the neighboring methylene hydrogens in its NMR spectrum, by analogy with the greater width of the absorption of the methine hydrogen in cis-diol **2a** compared to that of the trans-diol **3a**[18] and of related cis and trans hydroxy ethers.[3]

Supporting Information Available: Plot of percent trans-diol **3b** versus time for the approach to equilibrium of **2b** and **3b**, starting from pure **3b**, in 0.1 M $HClO_4$, 1:9 dioxane−water (v/v), 25.0 ± 0.2 °C. This material is available free of charge via the Internet at http://pubs.acs.org.

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