Acid-Catalyzed Hydrolysis of *cis*- and *trans*-Anethole Oxides: Discrete Carbocation Intermediates and Syn/Anti Hydration Ratios

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Received November 9, 1992

Rate and product studies of the hydronium ion-catalyzed hydrolysis reactions of *trans*-anethole oxide (**12b**) and its geometric isomer, *cis*-anethole oxide (13b), were carried out. Acid-catalyzed hydrolysis of *trans*-anethole oxide is 50 times faster than that of its cis isomer and this difference in reactivity is attributed to steric interactions between the cis-β-CH_3 and the aryl group in the transition state for hydrolysis of *cis*-anethole oxide that are not present in the transition state for the acid-catalyzed hydrolysis of *trans*-anethole oxide. Carbocation intermediates in the hydrolysis of both **12b** and **13b** are trapped, subsequent to their rate-limiting formation, by azide ion. Identical diol product mixtures from the acid-catalyzed hydrolysis of both **12b** and **13b**, and identical azide product mixtures from their reactions in solutions at low pH containing sodium azide, suggest that both **12b** and **13b** react to form a common discrete carbocation intermediate and that products are derived from reaction of this intermediate with nucleophiles. Molecular modeling calculations suggest that there are three minimum energy conformations of this carbocation intermediate. Results are interpreted in terms of a mechanism in which rotation about the C_α–C_β bond of the intermediate is rapid relative to the rate at which it reacts with solvent or other nucleophiles. Mechanisms involving concerted addition of solvent are ruled out.

Introduction

The mechanism of acid-catalyzed addition of nucleophiles to epoxides has been of considerable interest because of the discovery that epoxides are intermediates in the metabolism of polycyclic aromatic hydrocarbons and other unsaturated compounds. The carcinogenicity of some of these compounds has been attributed to the reactions of their epoxide metabolites, in particular their reactions with DNA in which covalent binding to nucleophilic base sites in the DNA occur.[1]

The acid-catalyzed reactions of epoxides have received considerable attention.[2-4] On the basis of rate data for the hydrolysis of various epoxides in aqueous acid solutions, it was initially concluded that even simple epoxides hydrolyze by A-1 mechanisms, i.e., carbocation intermediates were involved.[5] In the acid-catalyzed hydrolysis of simple epoxides, water molecules generally add preferentially to the more highly substituted carbon that is better able to stabilize positive charge. It was later recognized that primary and secondary carbocations in water are very unstable and therefore the A-1 mechanism was discarded in favor of either A-2 or "borderline A-2" mechanisms[6,7] involving attack of a water molecule on a protonated epoxide intermediate. The A-2 mechanisms were also consistent with the observations that most acid-catalyzed epoxide ring openings, even at tertiary carbon centers, proceed with complete inversion at the reaction center.[7]

The conjugation of an epoxide group with vinyl or aryl groups introduces additional steric and electronic effects that can alter the mechanisms of acid-catalyzed addition of nucleophiles to these epoxides. For example, acid-catalyzed hydrolysis of the "trans" 7,8-diol 9,10-epoxide metabolite of benzo[*a*]pyrene yields mostly (95%) tetrol from anti hydration, whereas acid-catalyzed hydrolysis of the diastereomeric "cis" 7,8-diol 9,10-epoxide metabolite yields mostly tetrol resulting from syn hydration (85%).[8] For hydrolysis of bay-region cis diol epoxides and tetrahydro epoxides in the naphthalene, phenanthrene, chrysene, benz[*a*]anthracene, and benzo[*a*]pyrene ring systems, the amount of syn hydration increases with the ability of the aryl group to stabilize positive charge at the benzyl carbon.[9,10] The syn/anti hydration ratio in the acid-catalyzed hydrolysis of 1-arylcyclohexene oxides also varies with substitution in the phenyl ring.[11] The amount of syn hydration is only 7.5% when the para substituent is nitro but increases to 95% when the para substituent is methoxy. The stereochemistries of acid-catalyzed addition of water and methanol to 1-phenylcyclohexene oxides and several hexahydrophenanthrene oxides in the gas phase are

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(2) For an extensive review of epoxide chemistry prior to 1964, see: Rosowsky, A. In *Heterocyclic Compounds with Three- and Four-Membered Rings*, Part 1; Weissberger, A., Ed., 1, Interscience: New York, 1964; pp 1-523.

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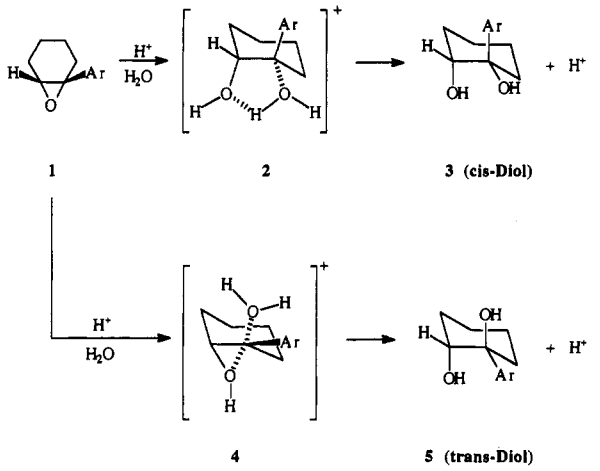
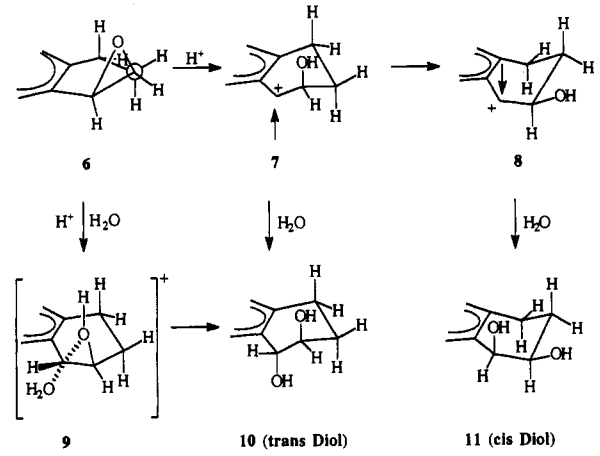
0022-3263/93/1958-2663$04.00/0

Scheme I



Scheme II



reported to be substantially different than those of the corresponding reactions in solution.[12]

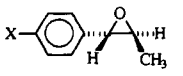
Several mechanisms have been proposed to explain changes in syn/anti hydration ratios in the acid-catalyzed hydrolysis of aryl-substituted epoxide systems in solution. An increase in the relative yield of cis diol from hydrolysis of 1-phenylcyclohexene oxides in dilute sulfuric acid solutions was attributed to stabilization of a selectively solvated carbocation **2**, leading to cis diol **3**, by electron-donating froups in the phenyl ring (Scheme I).[11] It was proposed that a competing reaction via a "borderline A-1" transition-state structure **4** yields trans diol **5**.

A different mechanism (Scheme II) was proposed to explain varying syn/anti hydration ratios in the hydrolysis of bay-region diol epoxides and tetrahydro epoxides.[9,10] It was proposed that cis diol epoxides and tetrahydro epoxides have ground-state conformations similar to that of **6**, in which hydrogens or hydroxyl groups are staggered as much as possible. Acid-catalyzed ring opening from this conformation yields a benzyl carbocation (**7**) with the newly formed hydroxyl group in an axial position. This intermediate can either react directly with solvent to give diol or rearrange to a more stable conformation (**8**), with the hydroxyl group in a pseudoequatorial position. Variation in the syn/anti hydration ratio was attributed to change in the partitioning of intermediate **7**, induced by change in the electronic effect of the para substituent.

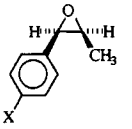
Intermediate carbocations **7** and **8** are related in structure to cyclohexenyl cations, with an aryl group replacing vinyl. From work of Goering and Josephson[13] it is known that cyclohexenyl cations undergo attack by water to generate an axial hydroxyl group. Therefore, intermediate **7** would be expected to react with solvent to yield mainly trans diol **10** and carbocation **8** would be expected to react with water to give mainly cis diol **11**. The relative amount of syn hydration from acid-catalyzed aryl epoxide hydrolysis would therefore depend upon the ratio of the rate at which intermediate carbocation **7** isomerizes to the more stable conformation **8**, compared to the rate at which **7** reacts directly with solvent to yield mostly trans diol **10**. Electron-donating groups in the aryl group would stabilize intermediate **7** toward reaction with solvent, thus allowing its isomerization to **8** (ultimately yielding cis product) to compete successfully with its reaction with solvent to yield trans diol **10**.

In the limit where **7** is too unstable to exist as an intermediate, addition of solvent will be concerted with benzyl C–O bond breaking. This concerted reaction is analogous to nucleophilic substitution at sp^3 carbon and should proceed, with inversion of configuration at the benzyl carbon, via transition state **9** to give trans diol product (A-2 mechanism). This pathway is equivalent to that in which **1** reacts to form **5** via transition state **4** (Scheme I). Since this concerted mechanism for reaction of **6** leads to the same trans diol product as that predicted from reaction of **7** with solvent, these two mechanisms cannot be distinguished by product studies. The acid-catalyzed hydrolysis of 1,2,3,4-tetrahydronaphthalene 1,2-oxide[14] serves as an example of an epoxide hydrolysis that yields mostly trans diol by reaction of solvent with an intermediate carbocation. This epoxide reacts in dilute aqueous acid solutions to yield ca. 95% trans diol, which can potentially be formed by either concerted or stepwise mechanisms. However, in this case an intermediate is trapped, subsequent to its rate-limiting formation, by chloride ion. Therefore, most of the trans diol cannot be formed by a concerted A-2 mechanism but must instead be formed by reaction of an intermediate such as **7**.

The acid-catalyzed hydrolysis of *trans*-β-methylstyrene oxide (**12a**) and its cis-β-methyl isomer (**13a**) are reported[15–17] to yield mixtures of two diastereomeric diols, resulting from syn and anti hydration of the epoxide group.



12a, X = H
b, X = OCH_3



13a, X = H
b, X = OCH_3

Hydronium ion can potentially react with both **12a** and **13a** with cleavage of the benzyl C–O bond to produce the

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same benzyl carbocation. However, the trans epoxide **12a** is reported to undergo 37–50% syn hydration and the cis epoxide **13a** is reported to give only 20% syn hydration.[15,16] Since **12a** and **13a** react to yield different product diol mixtures, their reactions forming a common carbocation intermediate cannot account for all product. At least two reaction pathways for reactions of **12a** and/or **13a** are necessary to account for the fact that they yield different product distributions. Several possible mechanisms for the acid-catalyzed reactions of **12a** and/or **13a** are their reactions by (1) competing concerted and stepwise reactions and (2) reactions forming different conformations of a discrete carbocation intermediate that undergoes bond rotation at a rate slower than the rates at which individual conformations react with solvent.

In order to determine whether acid-catalyzed hydrolysis of β-substituted styrene oxides containing an electron-donating *p*-methoxy group in the phenyl ring proceed by concerted mechanisms or instead by discrete carbocation intermediates, we have synthesized and studied the acid-catalyzed hydrolysis of *trans*-anethole oxide (**12b**) and *cis*-anethole oxide (**13b**). These diastereomeric epoxides contain a methoxy group in the para position of the phenyl ring, which would be expected to greatly stabilize benzyl carbocations and promote syn hydration if a mechanism similar to that in Scheme I applies to the reactions of β-substituted styrene oxides. The results of this study are reported in this paper.

Results and Discussion

trans-Anethole oxide (**12b**) and its cis isomer **13b** were synthesized by epoxidation of *trans*-anethole and *cis*-anethole, respectively, with *m*-chloroperoxybenzoic acid. It was necessary to carry out the epoxidation of *trans*-anethole in the presence of a buffer because of the instability of the epoxide product, *trans*-anethole oxide, in the presence of acidic reagents. *cis*-Anethole oxide (**13b**) was also prepared by a slight modification of a published route in which the epoxide ring was introduced by reaction of a β-hydroxy dimethylsulfonium salt with potassium *tert*-butoxide.

The rates of reaction of **12b** and **13b** in water solutions with ionic strength held constant at 0.1 M with $NaClO_4$ between pH 4 and 7 exhibited a first-order dependence on $[H^+]$.[18] Pseudo-first-order rate constants k_{obsd} for reactions of **12b** and **13b** in this pH range were fit to the equation $k_{obsd} = k_H[H^+]$, where k_H is the second-order rate constant for this acid-catalyzed reaction. Values of k_H for reactions of **12b** and **13b** were determined to be $(1.51 \pm 0.05) \times 10^4$ M^{-1} s^{-1} and $(3.17 \pm 0.21) \times 10^2$ M^{-1} s^{-1}, respectively. The reactivity of *trans*-anethole oxide (**12b**) toward acid-catalyzed hydrolysis is therefore ca. 50 times greater than that of its cis isomer **13b**.

Values of k_H for the acid-catalyzed hydrolysis of the parent *trans*-β-methylstyrene oxide (**12a**) and *cis*-β-methylstyrene oxide (**13a**) in 0.1 M $NaClO_4$ solutions (25 °C) were also determined in this study and are 12.7 ± 0.3 M^{-1} s^{-1} and 0.27 ± 0.03 M^{-1} s^{-1}, respectively. For both parent and *p*-methoxy-substituted systems, therefore, the trans-β-methyl epoxide hydrolyzes ca. 50 times faster than the corresponding cis isomer. The substituent effect of a *p*-methoxy group is thus similar in the acid-catalyzed hydrolysis of both *trans*- and *cis*-β-methylstyrene oxide systems, e.g., substitution of methoxy at the para position of **12a** or **13a** results in an increased reactivity of ca. 1.2×10^3 toward acid-catalyzed hydrolysis. This result is somewhat surprising because severe steric interactions might be expected between the *cis*-β-methyl group and the aryl group in the transition states for reactions of **13a** and **13b** that would result in twisting of the aryl group so as to substantially reduce its resonance interaction with the developing carbocation center at the benzyl carbon. It this were so, then substituent effects in the acid-catalyzed hydrolysis of the *trans*-anethole oxides **12** should be greater than those for the isomeric cis oxides **13**. This is clearly not the case. If the resonance interactions between the aryl group and epoxide functionality in the ground states of **12** and **13** are minimal, then resonance interaction between the aryl group and the developing carbocation center at the transition states for hydrolysis of **13a** and **13b** must be comparable to that achieved at the transition states for reactions of **12a** and **12b**, even at the expense of greater steric interactions.[19]

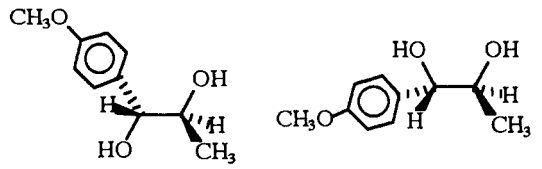
The ground states of substrates **13a** and **13b** would be expected to possess significant strain energy because of the steric interactions between the cis-β-methyl and aryl groups. It is not clear *a priori* whether the acid-catalyzed reactions of **13a** and **13b** proceed with increase or decrease in steric strain energy upon going to the transition state. The reduced reactivities of **13a** and **13b** compared to those of **12a** and **12b** can be attributed to greater steric strain at the transition states for reaction of **13a** and **13b**, *relative to the ground-state steric strain*, but cannot be attributed to destabilization of the transition state by steric inhibition of resonance.

Products from reaction of **12b** at pH 5.5 and from reaction of **13b** at pH 3.8, where both compounds react in >99% yield via the hydronium ion-catalyzed reactions, were analyzed by HPLC. Within experimental error, product mixtures from both **12b** and **13b** were identical and consisted of 20% of erythro diol **14** and 80% of threo diol **15**. Therefore, the acid-catalyzed hydrolyses of *trans*-anethole oxide (**12b**) and *cis*-anethole oxide (**13b**) proceed with 20% anti hydration:80% syn hydration and 80% anti hydration:20% syn hydration, respectively. Introduction of a methoxy group in the para position of **12a** in place of hydrogen thus results in increased syn hydration (from 40–50% to 80%) in the acid-catalyzed reaction, as observed in several other systems. However, substitution of a methoxy group in the para position of **13a** in place of hydrogen does not result in an increase in the relative yield of diol from syn hydration, which would be expected if there were a selective stabilization by the *p*-methoxy group of a transition state for syn hydration of **13b**.

In order to better characterize the mechanisms of syn and anti hydration in the acid-catalyzed hydrolysis of **12b** and **13b**, rate and product studies of their reactions in solutions containing the highly nucleophilic azide ion were carried out. The rates of reaction of **12b** and **13b** increased linearly with azide concentrations at pH 10.5–10.6. Analysis by HPLC of the solutions from reaction of **12b** at pH 10.6 in 1 M sodium azide solution and from reaction of **13b** at pH 10.6 in 4 M sodium azide solution, where the bimolecular reactions of these epoxides with azide pre-

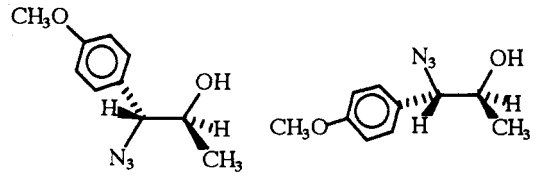
(18) The rates of reaction of **12b** at pH > ca. 8 and of **13b** at pH > ca. 7 become independent of pH, and thus changeovers in mechanisms from acid-catalyzed to noncatalyzed occur in these pH regions.

(19) Several reviewer comments on the observed substituent effects are appreciated.



erythro *threo*

14 **15**



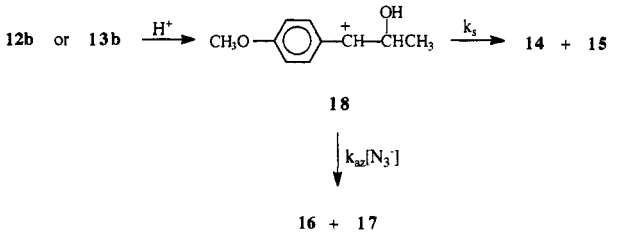
erythro *threo*

16 **17**

dominate, indicated that a single product was formed from reaction of each epoxide. The products from **12b** and **13b** have IR and ^{1}H NMR spectra consistent with structures for azide adducts in which the azido group is located exclusively at the benzyl carbons. Erythro structure **16** and threo structure **17** were assigned to the azide adducts from the bimolecular reactions of **12b** and **13b**, respectively, on the basis that inversion at the reaction center is to be expected in the bimolecular addition of azide ion to the benzyl carbons of **12b** and **13b**.

The rates and products from reaction of **12b** and **13b** in solutions at pH 5.0–5.7 containing varying concentrations of sodium azide were also determined. In this pH range, acid-catalyzed hydrolysis predominates in the absence of azide. No significant increase in rate (<5%) could be detected for reactions of **12b** and **13b** in solutions containing up to 12.5 mM sodium azide, where spectrophotometric rate constants could be accurately determined. However, a 27% yield of a mixture of azide adducts was formed from reaction of **12b** in 12.5 mM azide solution at pH 5.7 and an 18% yield of a mixture of azide adducts was formed from reaction of **13b** in 12.5 mM azide solution at pH 5.04. The compositions of the azide product mixtures from reaction of both **12b** and **13b** in solutions containing sodium azide were determined by HPLC to be identical, within experimental error, and contained 55% threo and 45% erythro adducts. The ratio of erythro: threo azide adducts remains constant as the concentration of azide is increased from 1 to 50 mM and the total yields of adducts from **12b** and **13b** increased to ca. 65% and 40%, respectively. Small kinetic terms for bimolecular addition of azide ion to either neutral epoxide or protonated epoxide might be difficult to detect over the limited concentration range for which rate constants were measured and there is the possibility that these reactions of **12b** and **13b** in solutions containing the higher concentrations of azide would become more important. However, reactions of **12b** and **13b** by these mechanisms would be expected to yield only single azide adducts resulting from inversion at the benzyl carbon and increased yields of these adducts would be expected if these reactions were significant. This is clearly not the case. The observations that identical mixtures of azide adduts are formed from

Scheme III



reactions of both epoxides are best rationalized by mechanisms involving capture of a common carbocation intermediate by azide ion, which would be expected to give both retained and inverted products. The combination of kinetic and product data demonstrate that azide ion must be capturing an intermediate, subsequent to its rate-limiting formation, in the acid-catalyzed reactions of **12b** and **13b**.

Outlined in Scheme III is a mechanism for the reactions of **12b** and **13b** in acid solutions that is consistent with all the kinetic and product data. Rate-limiting reaction of either **12b** or **13b** with hydronium ion yields benzyl carbocation **18**, which reacts with water to give 20% erythro diol **14** and 80% threo diol **15**. This intermediate must have a very significant lifetime, however, because it can be trapped with azide ion to give erythro and threo azide adducts **16** and **17** in a 45:55 ratio. From Scheme III, the mole fraction of azide products (f_{az}) is given by the equation $f_{az} = k_{az}[N_3^-]/(k_{az}[N_3^-] + k_s)$. The p$K_a$ for HN_3 is reported[20] to be 4.69 and therefore not all of the azide is in its ionized form at pH 5.0–5.5. With this value for the pK_a of HN_3 and the relative yields of diol and azide products formed from the reaction of **12b** and **13b** in solutions containing azide, the ratio k_{az}/k_s can be estimated to be ca. 21 and 33 M^{-1}, respectively. No significance is placed on the small difference between these two calculated values of k_{az}/k_s and we assume that they are estimates of the partitioning ratio of a common intermediate. If it is assumed, on the basis of arguments presented by Jencks et al.,[21] that **18** reacts with azide ion at the diffusional rate constant of ca. 5×10^9 M^{-1} s^{-1}, then k_s is calculated to be ca. 2×10^8 s^{-1}. The lifetime ($1/k_s$) of this intermediate is thus estimated to be ca. 5×10^{-9} s, which is significantly longer than the time required for bond vibration. We conclude that the intermediate from the reactions of both **12b** and **13b** is best represented as freely solvated carbocation **18**.

PCMODEL-PI[22] molecular modeling calculations yield three minimum energy conformations for carbocation **18** (Scheme IV). These conformations are represented by the Newman projections **19**, **20**, and **22**.[23] Conformation **20** is calculated to be 0.4 kcal/mol more stable than **19** and 1.7 kcal/mol more stable than **22**. The energy barrier for conversion of **19** to **20** is calculated to be very small, 0.4 kcal/mol. The energy barrier for conversion of **22** to **20** by rotation of the methyl group past the aryl group is calculated to be 2.6 kcal/mol, and the energy barrier for conversion of **22** to **19** by rotation of the hydroxy group past the aryl group is calculated to be 1.7 kcal/mol.

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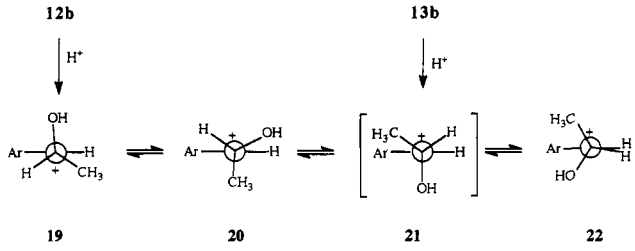
(22) PCMODEL-PI is a molecular modeling program available from Serena Software, Bloomington, IN.

(23) The H–C$^+$–C–O dihedral angles in minimized conformations **19**, **20**, and **21** are calculated to be 96°, 26° and −124°, respectively.

Scheme IV



Reaction of trans epoxide **12b** with H^+ is expected to give initially, upon epoxide ring opening, a carbocation in conformation **19**. Slight rotation about the C_α–C_β bond over a small calculated energy barrier of 0.4 kcal/mol converts **19** to **20**. Reaction of cis epoxide **13b** with H^+ is expected to give, immediately upon benzyl C–O bond cleavage, carbocationic species **21**. This structure is calculated by PCMODEL-PI to be relatively high in energy and minimizes to structure **22**. The lowest energy pathway for conversion of **22** to the more stable conformations **19** and **20** is calculated to occur by rotation of the hydroxy group past the aryl group.

The stereochemistry of addition of nucleophiles to carbocations with conformations similar to **19**, **20**, and **22** is not known. Attack of solvent or nucleophile at the less hindered bottom side of conformation **19** and at the less hindered top side of conformation **20** yield erythro and threo products, respectively, in stable, staggered conformations. Conformations **19** and **20** might be expected to interconvert rapidly relative to their rates of reaction with nucleophiles because of the very low calculated energy barrier separating them and therefore diol and azide products are most likely derived from attack of solvent on both conformations.

The observations that **13b** reacts with both H_2O and N_3^- to give the same product ratios as **12b** may be explained by several mechanisms. One possibility is that reaction of **13b** with hydronium ion yields **22**, which reacts with nucleophiles from both faces of the electron deficient benzyl carbon faster than it isomerizes to **19** and **20**, and these reactions of **21** with nucleophiles happen to give the same products in the same relative yields as the reactions of conformations **19** and **20** do. A second possibility is that interconversion of all rotational conformations is rapid relative to their rates of reaction with nucelophiles, and products from reactions of both **12b** and **13b** are derived from reactions of common conformational intermediates. Reactions of nucleophiles with **22** would be expected to lead to products possessing higher energy conformations than those from their reactions with **19** and **20**, and therefore these reactions of **22** might not be favorable relative to its conformational isomerization to **19** and **20**. Results of the azide trapping experiments suggest that the intermediate from reaction of **12b** has the same lifetime, within experimental error, as that from reaction of **13b**. Therefore, most likely all conformations of **18** interconvert rapidly relative to the rate at which they react with solvent and product is derived mainly from the reactions of the most stable carbocation conformations **19** and **20**.

Summary

The acid-catalyzed hydrolyses of **12b** and **13b** proceed by way of rate-limiting formation of a common, discrete carbocation intermediate. The ratios of syn vs anti addition of water or azide nucleophiles are determined solely by the partitioning reactions of this intermediate. Mechanisms in which there is concerted addition of solvent leading to either syn or anti hydration are thus ruled out.

Experimental Section

Instrumentation. ^1H NMR spectra were recorded at 80 MHz on an IBM NR-80 spectrometer or at 300 MHz on a Gereral Electric QE-300 spectrometer. Chemical shifts are reported relative to internal tetramethylsilane as standard. IR spectra were obtained with a Perkin-Elmer Model 1430 spectrometer. Melting points were determined with a Thomas Hoover melting point apparatus and are uncorrected. pH measurements were made with a Radiometer PHM 64 pH meter and glass combination electrode. HPLC analyses were done on a Waters Co. C18 Resolve Radial Pak column.

Kinetics Procedures. The pH–rate profiles for hydrolysis of **12b** and **13b** were generated in water solutions with ionic strength held constant at 0.1 M by addition of sodium perchlorate. For maintenance of pH for solutions with pH in the range 4–11, 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 5.5–6.3; MOPSO (3-[*N*-morpholino]-2-hydroxypropanesulfonic acid), pH 6.3–7.3; HEPES (*N*-(2-hydroxyethyl)-piperazine-*N*′-2-ethanesulfonic acid), pH 7.3–8.0; EPPS (*N*-(2-hydroxyethyl)piperazine-*N*′-3-propanesulfonic acid), pH 8.0–8.7; CHES (2-[*N*-cyclohexylamino]ethanesulfonic acid), pH 8.7–9.8; and CAPS (3-[cyclohexylamino]-1-propanesulfonic acid), pH 9.8–11.0. For most kinetic determinations, approximately 5–15 μL of a stock solution of ca. 2 mg of epoxide in 1 mL of dioxane was added to 2.0 mL of reaction solution in the thermostated cell compartment (25.0 ● 0.2 °C) of either a Gilford Response or Perkin-Elmer Lambda 4C spectrophotometer. All reactions except those for reaction of **12b** in sodium azide solutions were monitored at 231–233 nm. Reactions of **12b** in sodium azide solutions were monitored at 237 nm. Pseudo-first-order rate constants were calculated by nonlinear regression analysis of the time vs absorbance data.

Materials. Unless otherwise indicated, reagents were purchased from commercial suppliers and used without further purification. Sodium azide was recrystallized from aqueous ethanol solution. Sodium perchlorate was dried at 140 °C for 12 h and stored in a desiccator before use. Dioxane was distilled from sodium and tetrahydrofuran was distilled from lithium aluminum hydride. Methanol was dried by reaction with magnesium metal, followed by distillation. Water used for kinetic studies was deionized and glass-distilled.

cis-β-Methylstyrene oxide (**13a**) was prepared by *m*-chloroperoxybenzoic acid epoxidation of *cis*-β-methylstyrene in methylene chloride by a procedure similar to that previously published for its synthesis.[17b] *trans*-β-Methylstyrene oxide (**12a**)[15-17] was prepared from *trans*-β-methylstyrene by a procedure similar to that used to prepare **13a**, except that the reaction was buffered by aqueous sodium carbonate solution.

***trans*-Anethole Oxide (12b).** To a well-stirred biphasic mixture of 2.0 g of *trans*-anethole in 60 mL of methylene chloride and 60 mL of 10% sodium carbonate in water in an ice–water bath was added a solution of 5.6 g of *m*-chloroperoxybenzoic acid (85%, 0.028 mol) in 60 mL of methylene chloride over a period of 2.5 h by means of a syringe pump assembly. The methylene chloride layer was separated, washed with 10% sodium carbonate solution (3 × 25 mL) and saturated sodium chloride solution (25 mL), and dried over anhydrous sodium sulfate. Removal of the solvent on a rotary evaporator yielded 1.94 g of oil that was distilled in a short path distillation apparatus (45 °C oil bath, 0.1 mmHg) to yield 0.84 g (38%) of **12b**: ^1H NMR ($CDCl_3$) δ 1.43 (d, J = 5.2 Hz, 3 H), 3.04 (dq, J = 5.2, 2.1 Hz, 1 H), 3.52 (d, J = 2.1 Hz, 1 H), 3.79 (s, 3 H), 6.8–7.3 (m, 4 H). Anal. Calcd for $C_{10}H_{12}O_2$: C, 73.15; H, 7.37. Found: C, 73.01; H, 7.40.

***p*-Methoxypropiophenone Morpholine Enamine.** A solution of 10.0 g (0.061 mol) of *p*-methoxypropiophenone, 11.7 g (0.134 mol) of morpholine, 25 mg of *p*-toluenesulfonic acid, and 25 mL of benzene in a round-bottomed flask fitted with a reflux

condenser and Dean–Stark apparatus was heated at reflux temperature for 10 days. The solvent was removed on a rotary evaporator and the residue was distilled at reduced pressure to give 10.0 g of distillate, bp 60 °C (0.1 mmHg). ^{1}H NMR analysis of the distillate showed that it contained 20% of starting ketone and 80% of enamine: ($CDCl_3$ δ 1.58 (d, J = 6.9 Hz, 3 H, CH_3), 2.68 (m, 4 H), 3.67 (m, 4 H), 3.81 (s, 3 H, OCH_3), 4.6 (q, J = 6.9 Hz, 1 H, $CHCH_3$), 7.0 (m, 4 H). The enamine was not further purified but rather this mixture was used directly in the following reaction that converts the enamine to *cis*-anethole.

***cis*-Anethole.** A procedure of Brown et al.[24] was modified for the synthesis of **13b**. A mixture containing 80% of *p*-methoxypropiophenone morpholine enamine from the previous reaction (7.49 g), 5 mL of dry tetrahydrofuran, and 3.92 g (0.032 mol) of 9-borabicyclco[3.3.1]nonane (9-BBN) was placed in a 25-mL round-bottomed flask equipped with a reflux condenser and nitrogen inlet. The resulting turbid solution was stirred at rt under nitrogen for 3 h. The solvent was removed on a rotary evaporator and 2.0 mL of dry methanol (0.064 mol) was added. At this point the reaction mixture solidified. A distillation head was attached and 3.5 g of yellow liquid was distilled from the flask, bp 80 °C (0.5 mmHg). ^{1}H NMR analysis of this mixture indicated that it was >95% *cis*-anethole. Purification of the olefin was affected by filtration through a silica gel column with pentane as eluting solvent: ^{1}H NMR ($CDCl_3$) δ 1.88 (dd, J = 7.1, 1.6 Hz, 3 H), 3.81 (s, 3 H), 5.7 (m, 1 H), 6,35 (br d, J = 11.5 Hz, 1 H), 6.9 (m, 2 H), 7.25 (m, 2 H). Anal. Calcd for $C_{10}H_{12}O$: C, 81.04; H, 8.16. Found: C, 80.82; H, 8.22.

***cis*-Anethole oxide (13b)** was prepared by two procedures. The first method involved sodium borohydride reduction of α-methyl-α-(methylthio)-*p*-methoxyacetophenone, followed by methylation of the β-hydroxy sulfide with methyl iodide and ring closure of the dimethylsulfonium salt with potassium *tert*-butoxide in DMSO.[25] In our hands, this procedure yielded a mixture containing 90% *cis*-anethole oxide (**12b**) and 10% of *trans*-anethole oxide (**13b**). Substitution of L-Selectride in place of sodium borohydride in the above reduction reaction yielded predominantly one diastereomeric alcohol (ca. 96%), which was converted to pure cis epoxide **13b**: ^{1}H NMR ($CDCl_3$) δ 1.08 (d, J = 5.4 Hz, 3 H), 3.3 (m, 1 H), 3.80 (s, 3 H), 4.0 (d, J = 4.1 Hz, 1 H), 6.9 (m, 2 H), 7.2 (m, 2 H). ^{1}H NMR analysis of the epoxide product indicated that <2% of the trans diastereomer **12b** was present.

In the second method, **13b** was prepared by adding 0.17 g of solid *m*-chloroperoxybenzoic acid (85%, 0.84 mmol) to a stirred solution of 0.10 g (0.67 mmol) of *cis*-anethole in 5 mL of methylene chloride over a period of 10 min. After the solution was allowed to stir for an additional 10 min, an additional 15 mL of methylene chloride was added. The reaction solution was washed with 10% sodium carbonate solution (5 × 20 mL) and saturated sodium chloride solution (20 mL). It was then dried over sodium sulfate and the solvent was removed to yield 0.10 g of oil. Distillation of this material in a short path distillation apparatus (oil bath at 50 °C, 0.1 mmHg) yielded 44 mg (40%) of **13b**.

***erythro*-1-Azido-2-hydroxy-1-(4-methoxyphenyl)propane (16).** A solution of 0.2 g (1.35 mmol) of **12b** in 0.2 mL of dioxane was added to 50 mL of 2 M NaN_3 in 30:70 dioxane–H_2O at pH 10.6. The solution was allowed to stir at room temperature for 24 h. The reaction mixture was diluted with 30 mL of H_2O and extracted with ether (3 × 30 mL). The organic extracts were combined, washed with H_2O (4 × 25 mL), and dried over anhydrous sodium sulfate. The solvent was removed on a rotary evaporator to yield 0.16 g (64%) of a yellow oil. A small amount of the oil (100 mg) was purified by distillation in a short path distillation apparatus (oil bath temperature 75 °C, 0.05 mmHg): ^{1}H NMR (DMSO-d_6) δ 0.98 (d, J = 6.2 Hz, 3 H), 3.74 (s, 3 H), 3.8 (m, 1 H), 4.51 (d, J = 4.9 Hz, 1 H), 5 (d, J = 5.0 Hz, 1 H), 6.9 (br d, J = 8.7 Hz, 2 H), 7.25 (br d, J = 8.7 Hz, 2 H); IR ($CDCl_3$) 3580, 2100 cm^{-1}. Anal. Calcd for $C_{10}H_{13}N_3O_2$: C, 57.96; H, 6.34. Found: C, 57.78; H, 6.50.

In a second experiment, 18 mg of **64** in 0.2 mL of dioxane was added to 20 mL of 1.0 M NaN_3 in 5:95 dioxane–water at pH 10.6 containing 2 × 10^{-3} M CAPS buffer. The solution was placed in a water bath at 25 °C for 20 h. Under these conditions, >97% of the reaction occurs by second-order reaction of azide with **64**. The reaction solution was extracted with diethyl ether (4 × 20 mL). The ether extracts were combined, washed water (4 × 20 mL), and dried over anhydrous sodium sulfate. Removal of the solvent yielded 14 mg of oil whose ^{1}H NMR and IR spectra matched those of the erythro azido product **16**, HPLC t_R 14.7 min with 1:1 methanol–water (1.5 mL/min) as eluent.

***threo*-1-Azido-2-hydroxy-1-(4-methoxyphenyl)propane (17).** A solution of 0.18 g (1.09 mmol) of **13b** in 0.2 mL of dioxane was added to 50 mL of 4 M NaN_3 in 30:70 dioxane–H_2O at pH 10.6. The resulting solution was allowed to stir at room temperature for 60 h. The reaction mixture was diluted with 30 mL of water and extracted with ether (5 × 30 mL). The ether extracts were combined, washed with water (4 × 25 mL), and dried with anhydrous sodium sulfate. The solvent was removed on a rotary evaporator to yield 0.12 g (52 %) of a yellow oil. The oil was distilled on a short path distillation apparatus (oil bath temperature 110 °C, 0.2 mmHg), yield 30 mg: HPLC t_R 12.5 min with 1:1 methanol–water (1.5 mL/min) as eluent; ^{1}H NMR (DMSO-d_6) δ 0.85 (d, J = 6.2 Hz, 3 H), 3.7 (s, 3 H), 3.8 (m, 1 H), 4.25 (d, J = 7.6 Hz, 1 H), 5.14 (d, J = 5.1 Hz, 1 H), 7.9 (br d, J = 8.7 Hz, 2 H), 7.25 (br d, J = 8.7 Hz, 2 H); IR ($CDCl_3$) 3580, 2100 cm^{-1}. Anal. Calcd for $C_{10}H_{13}N_3O_2$: C, 57.96; H, 6.34. Found: C, 57.64; H, 6.20.

***threo*-1-(4-Methoxyphenyl)-1,2-dihydroxypropane (15).** *trans*-Anethole (0.19 g, 1.28 mmol) was dissolved in 10 mL of pyridine and 0.33 g of OsO_4 (1.29 mmol) was added. The resulting solution was stirred at room temperature for 2.5 h. A solution of 0.89 g of sodium bisulfite dissolved in a mixture of 10 mL of H_2O and 7 mL of pyridine was added and the resulting mixture allowed to stir at room temperature for 4 h. The reaction mixture was extracted with ethyl acetate (3 × 50 mL). The ethyl acetate extracts were combined, washed with water (25 mL), and dried with anhydrous sodium sulfate. The solvent was removed on a rotary evaporator to yield 0.13 g (56 %) of a light brown solid. The solid was purified by sublimation (oil bath temperature 65 °C, 0.25 mmHg) onto a cold finger: mp 63–64 °C (lit.[26] mp 62.8–63.2 °C); ^{1}H NMR δ 1.05 (d, J = 6.3 Hz, 3 H), 2.42 (br, 1 H), 3.8 (s, 3 H), 4.32 (d, J = 7.5 Hz, 1 H), 6.9 (br d, J = 8.8 Hz, 2 H), 7.2 (br d, J = 8.8 Hz, 2 H).

***erythro*-1-(4-Methoxyphenyl)-1,2-dihydroxypropane (14)** was prepared by the reaction of *cis*-anethole and osmium tetroxide as outlined above for the synthesis of the erythro diol and recrystallized from a diethyl ether–ethyl acetate solution. The yield of recrystallized product was 73%: mp 111–112 °C (lit.[27] mp 116 °C); ^{1}H NMR δ 1.1 (d, J = 6.3 Hz, 3 H), 1.6 (br, 1 H), 3.8 (s, 3 H), 4.0 (m, 1 H), 4.6 (d, J = 7.5 Hz, 2 H), 6.9 (br d, J = 8.7 Hz, 2 H), 7.3 (br d, J = 8.7 Hz, 2 H).

Acid-Catalyzed Hydrolysis of *trans*-Anethole Oxide (12b). A solution of 30 mg of **12b** in 0.1 mL dioxane was added to 10 mL of a 5:95 dioxane–water solution, pH 4.3, containing 0.1 M $NaClO_4$. The resulting solution was allowed to stand at rt for 10 min and was then saturated with sodium chloride and extracted with ethyl acetate (2 × 25 mL). The ethyl acetate extracts were combined, washed with saturated sodium chloride solution (4 × 20 mL), and dried with anhydrous sodium sulfate. The solvent was removed on a rotary evaporator to yield 25 mg of an oil which was analyzed by ^{1}H NMR and HPLC on a Waters Co. Radial Pak C18 Resolve column with 50:50 methanol–water as eluent at a flow rate of 1.5 mL/min. By comparison of the NMR spectra and HPLC tracings from analyses of this oil with NMR spectra and HPLC tracing of authentic samples of **15** and **14**, it was concluded that the product mixture contained 78–79% erythro diol **14** (HPLC t_R 4.8 min) and 22–21% of threo diol **15** (HPLC t_R 3.7 min). Water solutions containing 0.1 M $NaClO_4$ in which the rates of reaction of **12b** at pH 5.5 and 6.2 were monitored for approximately 10 half-lives also analyzed directly by HPLC and

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the relative yields of products 15 and 16 were determined to 19% and 81%, respectively.

Acid-Catalyzed Hydrolysis of *cis*-Anethole Oxide (13b). A solution of 15 mg of **13b** in 0.2 mL of dioxane was added to 20 mL of 5:95 dioxane–H_2O at pH 3.0. The resulting solution was allowed to stand at room temperature for 15 min, saturated with sodium chloride, and extracted with ethyl acetate (2 × 25 mL). The organic extracts were combined, washed with water (4 × 20 mL), and dried over anhydrous sodium sulfate. The solvent was removed on a rotary evaporator to yield 11 mg of an oil. HPLC and ^1H NMR analysis of this oil as described in the previous experiment were identical within experimental error with those from the products of the acid-catalyzed hydrolysis of *trans*-anethole oxide (**12b**). It was calculated that the product mixture contained 80% of erythro diol **14** and 20% of threo diol **15**. After the rates of reaction of **13b** at pH 3.8–5.2 in 0.1 M $NaClO_4$–water solutions for ca. 10 half-lives were monitored, the solutions were also analyzed by HPLC. Integration of the HPLC tracings showed the product yields to be 80–81% **14** and 19–20% **15**.

Acid-Catalyzed Reactions of 12b and 13b in Solutions Containing Sodium Azide. Relative product yields from the reactions of **12b** and **13b** in water solutions (μ = 0.1 M $NaClO_4$) at 25 °C at pH 5.70 and 5.04, respectively, and containing sodium azide in concentrations varying from 0 to 50 mM were determined by HPLC. An aliquot (ca. 10 μL) of a solution of either **12b** or **13b** in dioxane (ca. 2 mg/mL) was added to 2.0 mL of reaction solution and the reaction was allowed to proceed for ca. 10 half-lives. An aliquot (20.0 μL) of a solution of 5 mg of 2-(4-methoxyphenyl)-1-ethanol in 25 mL of methanol was then added to serve as a standard. The solution was analyzed by reverse-phase HPLC with 1:1 methanol–water as eluent (1.5 mL/min) and UV detection at 232 nm. Retention times for diol and azide products are as follows: erythro diol **14**, 3.7 min; threo diol **15**, 4.8 min; erythro azide **16**, 14.7 min; threo azide **17** 12.5 min; standard, 6.8 min. The yields of diol products from reactions of **12b** and **13b** in the presence of sodium azide were calculated by comparing the intensities of their HPLC peaks with that of the standard, with the assumption that the yield of diol products from acid-catalyzed hydrolysis of **12b** and **13b** in the absence of sodium azide was 100%. The ratio of erythro/threo diol products from the acid-catalyzed reactions of both **12b** and **13b** in the absence of sodium azide was found to be 20:80 and this diol product ratio did not vary, within experimental error, for reactions of **12b** and **13b** in solutions containing sodium azide. The ratio of erythro/threo azide products from reactions of both **12b** and **13b** in sodium azide solutions remained constant at 54:55, within experimental error, over the entire range of sodium azide concentrations. The total yields of azide products from reactions of **12b** and **13b** at pH 5.04 and 5.70, respectively, in 50 mM sodium azide solutions were measured to be 64% and 39%, respectively.

Acknowledgment. This work was funded in part by NIH Grant CA-17278 from the National Cancer Institute and in part by a Special Research Initiative Support Award from the UMBC Designated Research Initiative Fund.