

Spontaneous Hydrolysis Reactions of *cis*- and *trans*- β -Methyl-4-methoxystyrene Oxides (Anethole Oxides): Buildup of *trans*-Anethole Oxide as an Intermediate in the Spontaneous Reaction of *cis*-Anethole Oxide

Ram S. Mohan,[†] Kostas Gavardinis,[†] Sampson Kyere,[‡] and Dale L. Whalen^{*‡}

Department of Chemistry, Illinois Wesleyan University, Bloomington, Illinois 61701, and Department of Chemistry and Biochemistry, University of Maryland, Baltimore County, Baltimore, Maryland 21250

Received September 27, 1999

Rates and products of the reactions of *trans*- and *cis*- β -methyl-4-methoxystyrene oxides (**1** and **2**) (anethole oxides) and β,β -dimethyl-4-methoxystyrene oxide (**3**) in water solutions in the pH range 4–12 have been determined. In the pH range ca. 8–12, each of these epoxides reacts by a spontaneous reaction. The spontaneous reaction of *trans*-anethole oxide (**1**) yields ca. 40% of (4-methoxyphenyl)acetone and 60% of 1-(4-methoxyphenyl)-1,2-propanediols (erythro:threo ratio ca. 3:1). The spontaneous reaction of *cis*-anethole oxide is more complicated. The yields of diol and ketone products vary with pH in the pH range 8–11, even though there is not a corresponding change in rate. These results are interpreted by a mechanism in which **2** undergoes isomerization in part to the more reactive *trans*-anethole oxide (**1**), which subsequently reacts by acid-catalyzed and/or spontaneous reactions, depending on the pH, to yield diol and ketone products. The buildup of the intermediate *trans*-anethole oxide in the spontaneous reaction of *cis*-anethole oxide was detected by ¹H NMR analysis of the reaction mixture. Other primary products of the spontaneous reaction of **2** are (4-methoxyphenyl)acetone (73%) and *threo*-1-(4-methoxyphenyl)-1,2-propanediol (ca. 3%). The rates and products of the spontaneous reaction of **2** and its β -deuterium-labeled derivative were determined, and the lack of significant kinetic and partitioning deuterium isotope effects indicates that the isomerization of **2** to ketone and to *trans*-anethole oxide must occur primarily by nonintersecting reaction pathways.

Introduction

It has been observed that epoxides generally undergo acid-catalyzed hydrolysis^{1,2} and that at intermediate pH some epoxides undergo uncatalyzed, or "spontaneous", hydrolysis.^{2,3} At higher pH, epoxide ring opening by attack of hydroxide ion may occur. The rate expression for reactions of epoxides that undergo hydrolyses by all three kinetically distinct mechanisms is therefore given by eq 1, where k_{H} is the specific second-order rate

$$k_{\text{obsd}} = k_{\text{H}}[\text{H}^+] + k_0 + k_{\text{OH}}[\text{HO}^-] \quad (1)$$

constant for the hydronium ion-catalyzed hydrolysis, k_0 is the first-order rate constant for the spontaneous hydrolysis, and k_{OH} is the second-order rate constant for the hydroxide ion-catalyzed hydrolysis.

Compounds in which the epoxide group is conjugated with an aryl or vinyl group are greatly activated toward both hydronium ion-catalyzed and spontaneous hydrolyses. The hydronium ion-catalyzed hydrolyses of aryl and vinyl epoxides generally occur via a mechanism involving an intermediate allylic or benzylic carbocation. Hydrolysis of (+)-styrene oxide, for example, yields styrene glycol that is mostly racemic,⁴ suggesting the intermediacy of a carbocation that collapses with solvent from both faces of an electron-deficient carbon center. In contrast, acid-catalyzed hydrolyses of simple, unactivated epoxides occurs with inversion at the reaction center.⁵ An A₂ mechanism with nucleophilic attack of solvent on the protonated epoxide, thus bypassing an unstable primary or secondary carbocation intermediate, has been proposed.

Products from the spontaneous reaction of epoxides are usually diols or carbonyl compounds. The mechanism of the spontaneous reaction is dependent on the structure of the epoxide. The spontaneous reaction of (+)-styrene oxide, for example, yields only styrene glycol resulting from inversion of configuration at the benzylic carbon,^{4b} suggesting that water acts as a nucleophile in attacking this position. The spontaneous reactions of 1,3-cyclohexadiene oxide^{3c} and 1,2,3,4-tetrahydronaphthalene 1,2-oxide⁶ also yield only *trans*-1,2-diol products,⁶ suggesting

[†] Illinois Wesleyan University.

[‡] University of Maryland, Baltimore County.

(1) (a) Biggs, J.; Chapman, N. B.; Finch, A. F.; Wray, V. *J. Chem. Soc. B* **1971**, 55–63. (b) Biggs, J.; Chapman, N. B.; Wray, V. *J. Chem. Soc. B* **1971**, 63–65. (c) Biggs, J.; Chapman, N. B.; Wray, V. *J. Chem. Soc. B* **1971**, 66–71. (d) Biggs, J.; Chapman, N. B.; Wray, V. *J. Chem. Soc. B* **1971**, 71–74. (e) Pritchard, J. G.; Siddiqui, I. A. *J. Chem. Soc., Perkin Trans. 2* **1973**, 452–457. (f) Parker, R. E.; Isaacs, N. S. *Chem. Rev.* **1959**, 59, 737–799.

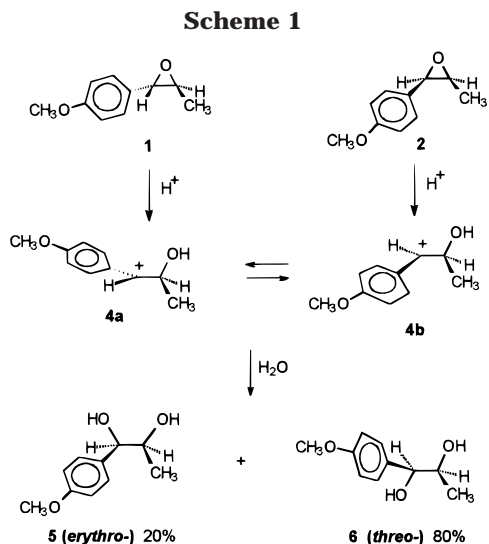
(2) (a) Bronsted, J. J.; Kilpatrick, M.; Kilpatrick, M. *J. Am. Chem. Soc.* **1929**, 51, 428–461. (b) Pritchard, J. G.; Long, F. A. *J. Am. Chem. Soc.* **1956**, 78, 2663–2667. (c) Pritchard, J. G.; Long, F. A. *J. Am. Chem. Soc.* **1956**, 78, 6008–6013.

(3) (a) Kasperek, G. J.; Bruice, T. C. *J. Am. Chem. Soc.* **1972**, 94, 198–202. (b) Blumenstein, J. J.; Ukachukwu, V. C.; Mohan, R. S.; Whalen, D. L. *J. Org. Chem.* **1993**, 58, 924–932. (c) Ross, A. M.; Pohl, T. M.; Piazza, K.; Thomas, M.; Fox, B.; Whalen, D. L. *J. Am. Chem. Soc.* **1982**, 104, 1658–1665.

(4) (a) Berti, G.; Bottari, F.; Ferrarini, P. L.; Macchia, B. *J. Org. Chem.* **1965**, 30, 4091–4096. (b) Lin, B.; Whalen, D. L. *J. Org. Chem.* **1994**, 59, 1638–1641.

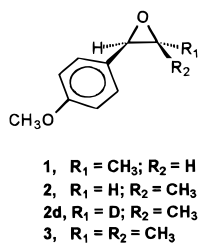
(5) Wohl, R. A. *Chimia* **1974**, 28, 1.

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



a mechanism similar to that for the spontaneous reaction of styrene oxide. 6-Methoxy-1,2,3,4-tetrahydronaphthalene 1,2-oxide, in contrast, yields 76% of ketone product, 17% of *cis*-diol and 7% of *trans*-diol product.⁷ The introduction of a group that stabilizes positive charge at the benzylic position, therefore, significantly changes the mechanism and products of the spontaneous reaction. Evidence for rate-limiting hydrogen migration on the ketone-forming component of the spontaneous reaction of 6-methoxy-1,2,3,4-tetrahydronaphthalene 1,2-oxide has been presented.⁸

trans-Anethole is metabolized to *trans*-anethole oxide in rat, and the hydrolysis of this epoxide to anethole diols is catalyzed by epoxide hydrolase.⁹ The stereoisomers of anethole diols have been characterized.¹⁰ *trans*-Anethole oxide (**1**) and its geometric isomer, *cis*-anethole oxide (**2**),



are quite reactive toward acid-catalyzed hydrolysis and yield the same mixture of erythro and threo diol products.¹¹ Identical diol product mixtures from acid-catalyzed hydrolysis of **1** and **2** suggest that there is a common benzylic carbocation intermediate and common product-forming steps (Scheme 1).

We have also measured the rates and determined the products of reaction of **1** and **2** at higher pH. At pH > ~9 for **1** and > ~7 for **2**, the rates of reaction of these epoxides become independent of pH, indicating that the spontaneous reactions predominate in these pH ranges. In contrast to the acid-catalyzed hydrolysis of **1** and **2**,

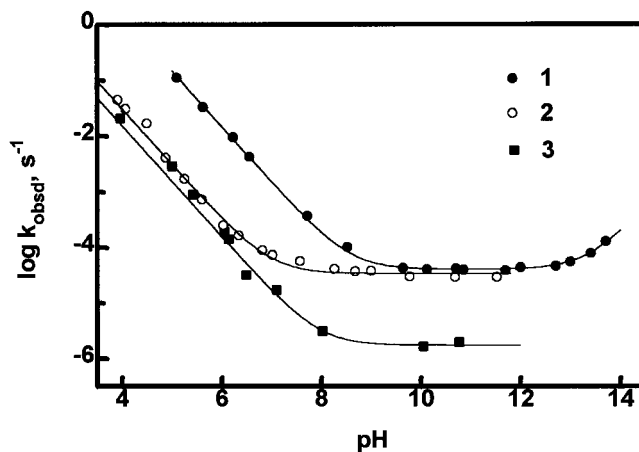


Figure 1. Plots of $\log k_{\text{obsd}}$ versus pH for reaction of **1–3** in water solutions containing 0.1 M NaClO₄, 25.0 ± 0.2 °C. The solid lines are theoretical, based on eq 1 and the rate constants listed in Table 1.

Table 1. Rate Constants for the Reactions of 1 and 2 in Water Solution (25.0 ± 0.2 °C; 0.1 M NaClO₄)

compd	k_H (M ⁻¹ s ⁻¹) ^a	k_0 (s ⁻¹)	k_{OH} (M ⁻¹ s ⁻¹)
1	$(1.51 \pm 0.05) \times 10^4$	$(4.12 \pm 0.13) \times 10^{-5}$	$(1.69 \pm 0.09) \times 10^{-4}$
2	$(3.17 \pm 0.21) \times 10^2$	$(3.42 \pm 0.24) \times 10^{-5}$	
3	$(1.58 \pm 0.23) \times 10^2$	$(1.78 \pm 0.64) \times 10^{-6}$	

^a Values of k_H for **1** and **2** are taken from ref 11.

however, the product mixture from the spontaneous reaction of **2** is significantly different from that formed in the spontaneous reaction of **1**. Also, the ratio of products from reaction of **2** in the pH region 7.5–9.5 changes, indicating a change of mechanism, *although there is not a corresponding change in rate constant*. Evidence for a buildup of *trans*-anethole oxide (**1**) as an intermediate in the spontaneous reaction of *cis*-anethole oxide (**2**) is presented, and mechanisms for the spontaneous reactions of **1** and **2** are discussed. For comparison, the rate versus pH profile for the reaction of β,β -dimethyl-4-methoxystyrene oxide (**3**) has also been determined.

Results and Discussion

Rate–pH Profiles. Plots of $\log k_{\text{obsd}}$ for reaction of **1–3** in water solutions vs pH are shown in Figure 1. The rate profile for reaction of **1** shows a region at pH < ca. 9 where acid-catalyzed hydrolysis predominates, a plateau at pH ca. 9.5–12.5 where the spontaneous reaction predominates, and a region at [HO⁻] > ca. 0.1 M where the reaction becomes dependent on hydroxide ion concentration. The rate profiles for reaction of **2** and **3** also show regions for acid-catalyzed hydrolysis at pH < ca. 7 and rate plateaus at intermediate pH due to the spontaneous reaction. Rate data for the reaction of **2** at pH > 12 do not conform to good first-order kinetics, presumably due to some instability of the major ketone product from the spontaneous reaction, and therefore, the rate profile in Figure 1 for reaction of **2** does not include data above this pH.

Rate data for reaction of **1** are fit to eq 1, and rate data for reactions of **2** and **3** are fit to the equation $k_{\text{obsd}} = k_H[H^+] + k_0$. Values of the rate constants for reactions of **1–3** are summarized in Table 1. Whereas the rate constant for acid-catalyzed hydrolysis of *trans*-anethole oxide (**1**) is ca. 50 times larger than that of its *cis* isomer

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

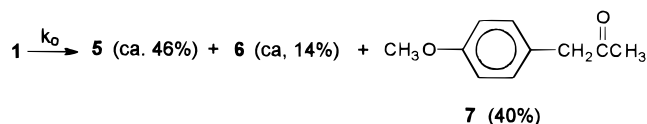
(8) Gillilan, R. E.; Pohl, T. M.; Whalen, D. L. *J. Am. Chem. Soc.* **1982**, *104*, 4482–4484.

(9) Marshall, A. D.; Caldwell, J. *Food Chem. Toxicol.* **1992**, *30*, 467.

(10) Ishida, T.; Bounds, S. V. J.; Caldwell, J.; Drake, A.; Takeshita, M. *Tetrahedron: Asymmetry* **1996**, *7*, 3113–3118.

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

Scheme 2



2, the spontaneous rate constant for reaction of **1** is only slightly greater (ca. 30–50%) than that for reaction of **2**. The lower reactivity of **2** toward acid-catalyzed hydrolysis compared to **1** has been attributed to differences in strain energy between reactants and transition states and not to a destabilization of the transition state for reaction of **2** by steric inhibition of resonance.¹¹ It is also noteworthy that the rate of the spontaneous rate for reaction of **3** is significantly slower than that for reaction of **2**, although the rates of acid-catalyzed hydrolyses of **2** and **3** are quite similar.

The reactions of both **1** and **2** at sufficiently low pH where they react > 99% by the acid-catalyzed route yield identical product mixtures within experimental error, consisting of 20% of *erythro*-1-(4-methoxyphenyl)-1,2-propanediol (**5**) and 80% of *threo*-1-(4-methoxyphenyl)-1,2-propanediol (**6**).¹¹ This observation has been interpreted in terms of a mechanism in which **1** and **2** react with H⁺ to yield the same, discrete carbocation intermediate **4**, which undergoes C_α–C_β bond rotation at a rate faster than attack by solvent at the electron-deficient benzylic carbon of the carbocation (Scheme 1).

Products of the Spontaneous Reaction of 1. At pH > ca. 9, the rate profile for reaction of **1** levels out into a plateau, indicating a change in mechanism from acid-catalyzed hydrolysis to spontaneous reaction of **1** with the solvent. The ratio of products from reaction of **1** changes gradually with increase in pH from 20% *erythro*-diol/80% *threo*-diol at pH < 5.7 to ca. 46% *erythro*-diol, 14% *threo*-diol and 40% ketone at pH 9.5–10.5 (Scheme 2). The pH at the midpoint for the changeover in mechanism is 8.5. The hydronium acid-catalyzed hydrolysis of **1** therefore results in mostly *syn* hydration, whereas, in the spontaneous hydrolysis of **1**, *anti* hydration is favored.

Products of the Spontaneous Reaction of 2. The mechanism of reaction of **2** changes from acid-catalyzed hydrolysis at low pH to spontaneous reaction at intermediate pH, with a pH of 7.0 at the midpoint for changeover in mechanism. The ratio of products from reaction of **2** changes from 20% *erythro*-diol/ 80% *threo*-diol at pH 3.8 to 7% *erythro*-diol, 23% *threo*-diol, and 70% ketone at pH 7.95, where > 90% of the reaction of **2** proceeds via the spontaneous reaction. The product mixture from the spontaneous reaction of **2** contrasts with that from the spontaneous reaction of **1** in several ways. First, considerably more ketone (ca. 80% vs 40%) is formed from the spontaneous reaction of **2**. Second, whereas the ratio of *erythro*- and *threo*-diol products from the spontaneous reaction of **1** (46% *erythro*/14% *threo*) is considerably different than that from the acid-catalyzed hydrolysis of **1** (20% *erythro*/80% *threo*), the reactions of **2** at pH < 5, where acid-catalyzed hydrolysis occurs, and at pH 8.0, where the spontaneous reaction predominates, yield diol products in approximately the same ratio (20% *erythro*/80% *threo*).

Product studies of the spontaneous reaction of **2** at pH 8.5–11.2 were also carried out. A rate plateau is present in this pH region, and if there is no change in reaction

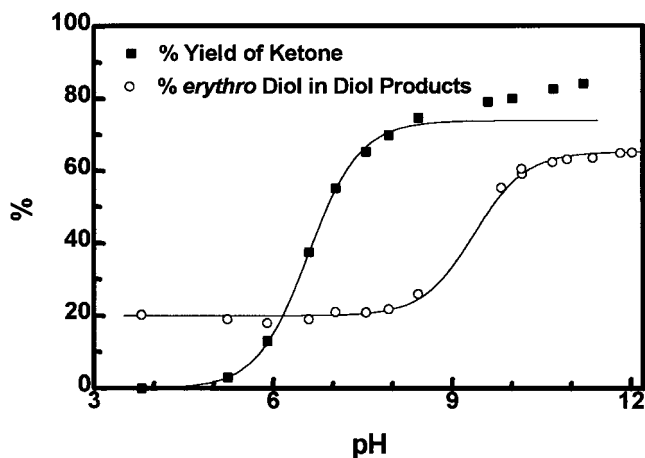


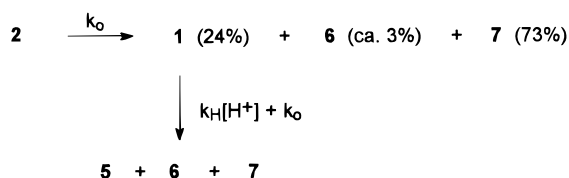
Figure 2. Plots of percent yield of (4-methoxyphenyl)acetone product formed from reaction of **2** in water solutions (0.1 M NaClO₄) versus pH and percent *erythro*-diol in the diol product mixture from reaction of **2** [(%*erythro* × 100)/(%*erythro* + %*threo*)] versus pH. The line through the data for percent yield of ketone is theoretical, based on eq 2 and the product data from reaction of **2** at pH < 8. The line through the percent *erythro*-diol product data is theoretical, based on the partitioning expected from Scheme 3 and the rate constants of Table 1.

mechanism, then the relative yields of diol and ketone products should remain constant. However, there is a gradual change in products within this pH–rate plateau until, at pH 11.0–11.5, the reaction of **2** yields 84% of ketone **7**, 10% of *erythro*-diol **5**, and 6% of *threo*-diol **6**. Thus, the yield of ketone from reaction of **2** at pH 11.2 is slightly more than expected from rate–product studies at lower pH, and the ratio of *erythro*- and *threo*-diol products changes from ca. 20:80 at pH 7.95 to ca. 65:35 at pH > 11. These results suggest that there is a further change in mechanism for product formation from **2** in the pH plateau extending from pH 8–12, even though there is no change in the rate of reaction of **2** in this pH range.

Insight into the mechanisms of reaction of **2** is obtained from plots of the percent yield of ketone product vs pH and of the ratio of *erythro*- and *threo*-diol products vs pH (Figure 2). At pH < 4, where > 99% of the reaction of **2** is acid-catalyzed, only diol products are detected from the reaction of **2**. Reaction of **2** at higher pH, however, yields ketone product. The yield of ketone product increases with increase in pH, with an inflection point at approximately pH 7. This corresponds to the pH for changeover in mechanism from acid-catalyzed to spontaneous. A reasonable rate–product correlation exists, indicating that the spontaneous reaction of **2** yields > 70% ketone. However, the yield of ketone appears to increase significantly more in the pH range 8–10, where the rate of reaction of **2** is relatively constant.

Figure 2 also shows a plot of the percent of *erythro*-diol in the diol product mixture ((%*erythro* × 100)/(%*erythro* + %*threo*)) from reaction of **2** as a function of pH. There is no detectable change in this diol product ratio from reaction of **2** between pH 3.5 and pH 8. At pH slightly less than 9, however, this ratio begins to increase with increasing pH until at pH 11.2 the yield of *erythro*-diol exceeds that of the *threo* isomer. Whereas Figure 2 shows that the change in ketone yield from reaction of **2** correlates with the change in rate constant, with a midpoint for change at approximately 7, the change in diol product ratio from reaction of **2** does not occur until

Scheme 3



the pH is > 8 . This lack of a product–rate correlation for diol formation is not consistent with a mechanism in which most of the diol products arise directly from reaction of **2**. If this were the case, then the diol ratio is expected to undergo change at pH 6–8, with a midpoint for changeover at pH 7. Instead, the diol product ratio from reaction of **2** does not undergo a change until the pH is significantly higher, above pH 8.0. The change in diol product ratio from reaction of **2** does occur in the pH range where there is a change in mechanism for reaction of *trans*-anethole oxide (**1**) from acid-catalyzed hydrolysis to spontaneous hydrolysis, where the midpoint for the change in mechanism is at pH 8.5. The observed results are readily explained by the mechanism shown in Scheme 3, in which the diol products from reaction of **2** are mostly derived from *trans*-anethole oxide (**1**), formed as a reactive intermediate in the spontaneous reaction of **2**. Thus, the spontaneous reaction of **2** proceeds in part by isomerization to its *trans* isomer **1**, which is more reactive than **2** in both acid-catalyzed and spontaneous hydrolyses. Scrambling of deuterium between the *trans* and *cis* β positions during the spontaneous reaction of *trans*- β -deutero-4-methoxystyrene oxide provides a precedent for a mechanism in which epoxide isomerization occurs during its spontaneous reaction.¹²

If the pH of the spontaneous reaction of **2** is $< \text{ca. } 8$, the *trans* isomer **1** that is formed as an intermediate reacts mostly by an acid-catalyzed reaction to yield only *erythro*- and *threo*-diols **5** and **6** in an 20:80 ratio, the same as that from the acid-catalyzed reaction of **2**. Therefore, there is no significant change in the *erythro*/*threo* diol ratio in the pH 5–8 region, even though there is a change in mechanism for reaction of **2**. However, if the pH of the spontaneous reaction of **2** is $> \text{ca. } 8$, then the *trans* isomer **1** that is formed as an intermediate reacts increasingly by the spontaneous reaction with increase in pH. Whereas the intermediate *trans*-epoxide formed in the hydrolysis of **2** at pH < 8.0 does not react to form ketone product, it does react at pH > 9.0 by the spontaneous reaction to yield 40% of ketone product. This mechanism therefore provides a rationale for both the change in *erythro*/*threo* diol ratio and the small additional increase in yield of ketone from reaction of **2** that occur at pH $> \text{ca. } 8.5$, even though there is no change in the rate of reaction of **2** above this pH.

The percent of ketone product from the reaction of **2** as a function of pH is determined by the fraction of the reaction that proceeds by the spontaneous route and is given by eq 2. In this equation, % ketone is the amount

$$\frac{\% \text{ ketone}}{(\% \text{ ketone})_{\text{max}}} = \frac{k_0}{k_0 + k_{\text{H}^+[\text{H}^+]}} \quad (2)$$

of ketone formed at a given pH and $(\% \text{ ketone})_{\text{max}}$ is the

total amount of ketone formed directly from **2** in its spontaneous reaction. Ketone product is not detected from the acid-catalyzed reaction of **2**. Fitting of the product yield data from reaction of **2** vs pH for those pH values $< \text{pH } 8$ to eq 2 yields a value of 73% for $(\% \text{ ketone})_{\text{max}}$. The remaining 27% of product formed from the spontaneous reaction of **2** are *trans*-anethole oxide (**1**), formed as a reactive intermediate, and diols. Our complete product studies fit a model in which the spontaneous reaction of **2** yields 73% of ketone **7**, ca. 24% of *trans*-anethole oxide (**1**), and ca. 3% of *threo*-diol **6** as primary products. *trans*-Anethole oxide formed as an intermediate undergoes further reaction to form products from acid-catalyzed and/or spontaneous hydrolysis, depending upon the pH of the solution. If the pH of the solution is sufficiently high ($> \text{ca. } 9.5$) such that *trans*-anethole oxide reacts completely by the spontaneous reaction, then 40% of *trans*-anethole oxide formed as a reactive intermediate from reaction of **2** will react to yield ketone **7**. Thus, the total yield of ketone from reaction of **2** at pH 11 is 83% (73% formed directly from **2** and 10% formed from the secondary reaction of the intermediate *trans*-anethole oxide).

Detection of *trans*-Anethole Oxide as an Intermediate in the Spontaneous Reaction of *cis*-Anethole Oxide. In a simulation of the concentration of *trans*-anethole oxide that would build up in the spontaneous reaction of *cis*-anethole oxide by the mechanism outlined in Scheme 3, the values of k_0 given in Table 1 for **1** and **2**, and the assumption that the spontaneous reaction of **2** yields 24% of *trans*-anethole oxide, it is calculated that the concentration of **1** should build up to maximum of ca. 8% of the initial concentration of **2** at approximately 1 half-life for reaction of **2** (see Supporting Information). The spontaneous reaction of **2** at pH 10.5 in 5:95 dioxane–water was therefore monitored by ¹H NMR to detect the buildup of this intermediate. In Figure 3A are shown the ¹H NMR absorptions of the C_{β} -epoxide hydrogens of *cis*-anethole oxide (**2**) (δ 3.28) and *trans*-anethole oxide (**1**) (δ 3.02). In Figure 3B is shown the NMR spectrum of the reaction mixture from the spontaneous reaction of **2** after 8.5 h at room temperature, slightly more than 1 half-life for its reaction. The absorption at δ 3.02 of the β -epoxide hydrogen of *trans*-anethole oxide in the mixture from the spontaneous reaction of **2** builds up over time to ca. 7% of the epoxide mixture after reaction of **2** for 8–12 h. This absorption diminishes at longer reaction times and is not detected in the NMR spectrum of the product mixture taken after 31 h. These observations are consistent with the mechanism given in Scheme 3, in which the spontaneous reaction of **2** proceeds in part to form *trans*-anethole oxide **1**.

Deuterium Isotope Effects in the Spontaneous Reaction of *cis*-Anethole Oxide- β -*d* (2d**).** To gain information on the nature of the rate-limiting step in the spontaneous reaction of **2**, we prepared *cis*-anethole oxide labeled at the β -epoxide position with deuterium (**2d**) and compared the rates and products of its spontaneous reaction with those of **2**. The major products of the spontaneous reaction of **2** are ketone **7**, resulting from hydrogen migration from the β -position to the α -position, and *trans*-anethole oxide (**1**). A mechanism for formation of these products from **2** is given in Scheme 4. The reaction of **2** yielding ketone may occur in a single step involving concerted C–O bond breaking and hydrogen migration (path a) or via an intermediate species such

(12) a) Ukachukwu, V. C.; Blumenstein, J. J.; Whalen, D. L. *J. Am. Chem. Soc.* **1986**, *108*, 5039–5040. (b) Ukachukwu, V. C.; Whalen, D. L. *Tetrahedron Lett.* **1988**, *29*, 293–396.

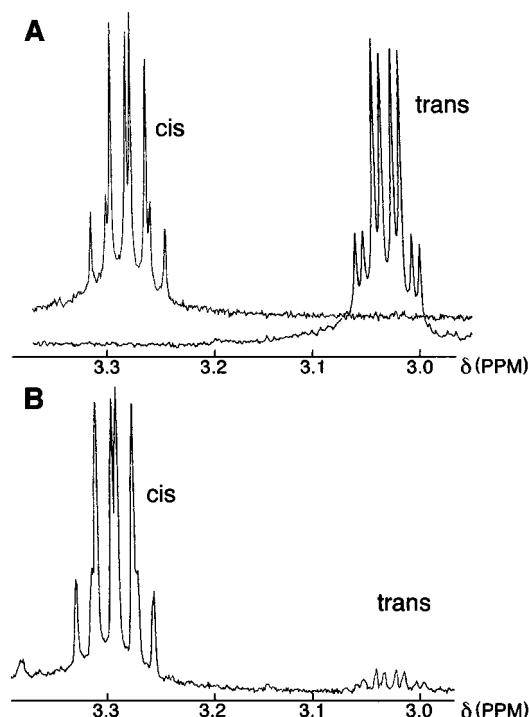
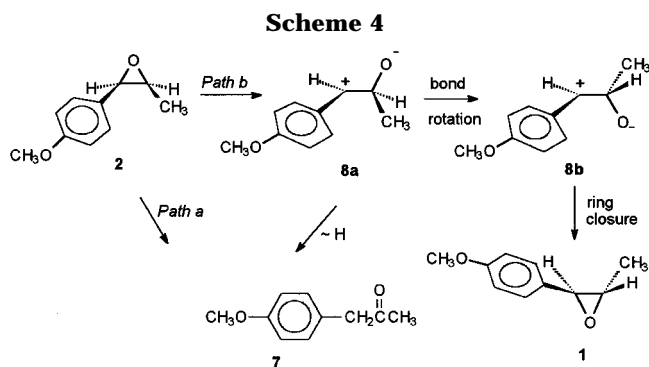


Figure 3. ^1H NMR absorptions of the C_β -epoxide hydrogens of *cis*- and *trans*-anethole oxides (A) and of the reaction mixture from the spontaneous reaction of *cis*-anethole oxide after reaction in 5:95 dioxane–water at pH 10.5 for 8.5 h at room temperature (B).



as zwitterion **8a/b**. If hydrogen migration occurs in the rate-limiting step, then there should be a normal kinetic deuterium isotope effect of ca. 2–3 on the ketone-forming step.¹³ Since ketone **7** is the major product (~73%) from the spontaneous reaction of **2**, then the observed isotope effect ($k_0^{\text{H}}/k_0^{\text{D}}$) of this reaction should be ~2. Isomerization of **2** to the *trans* isomer **1**, however, does not involve C–H bond breaking, and therefore, the isotope effect on the isomerization reaction should be near unity. Thus, if hydrogen migration in the ketone-forming pathway of the spontaneous reaction of **2** is rate-limiting, then the rate of the spontaneous reaction of **2d** should be approximately half that of **2**, and the relative yield of ketone product from the spontaneous reaction of **2d** should be substantially lowered. From six measurements of the rate constant ratio for reaction of **2** and **2d** in the pH range 10.3–10.9, the kinetic deuterium isotope effect $k_0^{\text{H}}/k_0^{\text{D}}$ was calculated to be 1.06 ± 0.02 . This value is much too

close to unity for the hydrogen migration step to be rate-limiting if the hydrogen atom is substantially migrated at the transition state. This small kinetic isotope effect is consistent with a mechanism in which hydrogen migration occurs after a rate-limiting step such as formation of the zwitterion **8a/b** (path b). Since hydrogen migration occurs after the rate-limiting step in this pathway, only a small secondary isotope effect due to the step forming the intermediate will be observed. However, if there is a substantial normal isotope effect on the ketone-forming step for reaction of this intermediate (**8a** → **7**), then a *partitioning* isotope effect will still be observed in which the yield of ketone from the spontaneous reaction of **2d** is reduced compared to the yield ketone from the spontaneous reaction of **2**. However, we have observed that the relative yields of ketone product from reaction of **2d** over the pH range 5–12 are identical within experimental error to the relative yields of ketone from **2**. Thus, there is neither a significant primary kinetic deuterium isotope effect nor partitioning deuterium isotope effect on product formation in the spontaneous reaction of **2d**. Therefore, ketone and *trans*-epoxide cannot both be formed from a common zwitterion intermediate but must be formed from nonintersecting reaction pathways. In the spontaneous reaction of precocene I oxide, it is proposed that ketone and diol products are formed from separate pathways that do not cross.¹⁴

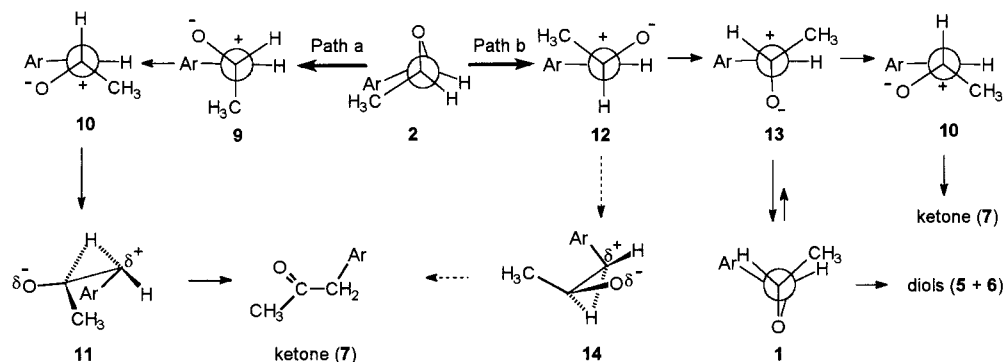
Mechanism of the Spontaneous Reaction of *cis*-Anethole Oxide (2**).** A possible mechanism for the spontaneous reaction of **2** that does not involve a common intermediate leading to formation of both ketone and *trans*-epoxide is given in Scheme 5. In this mechanism, benzylic C–O bond breaking occurs, coupled with rotation of the C_α – C_β bond either in clockwise or anticlockwise directions. The dipolar structures shown in Scheme 5 represent rotational structures along the reaction coordinates between reactants and products and are not meant to imply the existence of energy minima or the lack of hydrogen bonding to solvent. If C_α – C_β bond rotation occurs much faster than the dipolar species collapse to products, then a partitioning isotope effect should be observed. However, if bond rotation in one direction leads to one set of products and bond rotation in the other direction leads to a second set of products, then neither kinetic nor partitioning deuterium isotope effects on the reaction of **2d** will be observed.

Cleavage of the benzylic C–O bond coupled with rotation of the epoxide oxygen toward the aryl group (anticlockwise rotation) yields structures **9** and **10**. Cleavage of the benzylic C–O bond coupled with rotation of the epoxide oxygen away from the aryl group (clockwise rotation) yields structures **12** and **13**. The reaction coordinate for isomerization from *cis*-epoxide **2** to *trans*-epoxide **1** must include one structure, either **10** or **12**, with the C_β –H bond located favorably for hydrogen migration. Hydrogen migration from structure **10** leads to transition state **11**, in which the aryl and methyl groups are located in an energetically favorable *trans* relationship. However, hydrogen migration from structure **12** leads to transition state **14**, in which the aryl and methyl groups are located in a sterically unfavorable *cis* relationship. If transition state **14** is sufficiently high in energy, then **12** will undergo further bond rotation and epoxide ring closure

(13) Collins, C. J.; Rainey, W. T.; Smith, W. B.; Kaye, I. A. *J. Am. Chem. Soc.* **1959**, *81*, 460. (b) Winstein, S.; Takahashi, J. *Tetrahedron* **1958**, *2*, 316.

(14) Sayer, J. M.; Grossman, S. J.; Adusei-Poku, K. S.; Jerina, D. M. *J. Am. Chem. Soc.* **1988**, *110*, 5068–5074.

Scheme 5



via structure **13** to *trans*-epoxide **1** faster than it will go to ketone product via the transition structure **14**. A mechanism that is consistent with our results involves epoxide ring opening and bond rotation partially in a clockwise direction about the C_{α} - C_{β} bond to form mostly isomeric epoxide **1** and partially in an anticlockwise direction about the C_{α} - C_{β} bond to form mostly ketone product via the lower energy transition state **11** for hydrogen migration. However, *epoxide ring opening in a particular direction must be committed to lead to a particular product mixture*. The hydrogen migration step will thus not be rate-limiting. These rearrangement pathways for conversion of **2** to isomeric epoxide and ketone products may be examples of "asynchronous concerted" reactions,¹⁵ in which epoxide ring opening is essentially complete before bond rotation or hydrogen migration occurs.

Mechanism of Diol Formation in the Spontaneous Reaction of *trans*-Anethole Oxide (1). Whereas the spontaneous reaction of *cis*-anethole oxide (**2**) yields very little (~3%) diol product as primary product, the spontaneous reaction of the *trans* epoxide yields substantial (~60%) diol product, in addition to ketone **7**. The ratio of erythro:threo diol products from this reaction (~3:1) is substantially different than the erythro:threo diol ratio from the acid-catalyzed hydrolysis of **1** (~20:80). One possible mechanism for diol formation in the spontaneous reaction of an epoxide involves general acid-catalyzed epoxide ring opening by water to yield a solvationally equilibrated carbocation, which reacts with water to yield the same diol mixture as that formed from reaction of the epoxide with hydronium ion.¹⁶ If all of the *threo*-diol from the spontaneous reaction of **1** were formed from reaction of water with carbocation **4**, then ~14% of *threo*-diol and ~3–4% of *erythro*-diol would arise from this pathway. This mechanism, if operative, would account for approximately 30% of the diol product from the spontaneous reaction of **1**. The remaining 70% of diol product (*erythro*-diol) would have to be formed via another reaction pathway.

The detailed mechanisms of diol formation in the spontaneous reaction of **1** remain uncertain. The percent of erythro isomer in the diol product mixture is observed to increase slightly from ~70% at pH 10.5 to ~80% at pH 11.8, although the rate of the reaction of **1** does not appear to change significantly (Figure 1). The slightly lower yield of *threo*-diol from reaction of **1** at higher pH

is consistent with a mechanism in which some of the *threo*-diol is formed from general acid-catalyzed epoxide ring opening by water to yield carbocation **4**, which at higher pH reacts with hydroxide ion to re-form **1** faster than it reacts with water to form mostly *threo*-diol. However, concerted reactions for formation of both *erythro*- and *threo*-diols cannot be ruled out. The major *erythro*-diol product is that expected from anti addition of solvent to the benzylic carbon of **1**. Most of this diol might therefore be formed by nucleophilic addition of water to **1**, concerted with epoxide ring opening.

pH-Rate Profile for Reaction of β,β -Dimethyl-4-methoxystyrene Oxide (3). Both acid-catalyzed and spontaneous reactions of **3** in 0.1 M NaClO₄ solution yield 1-(4-methoxyphenyl)-1,2-dihydroxy-2-methylpropane. The value of k_H for acid-catalyzed hydrolysis of **3** is much closer to that for acid-catalyzed hydrolysis of **2** than to that of **1**, suggesting that the steric and electronic factors of a *cis*- β -methyl group for these two reactions are very similar. *trans*- β -Methyl-4-methoxystyrene oxide ($k_H = 1.5 \times 10^4 \text{ s}^{-1}$) is only slightly more reactive than 4-methoxystyrene oxide ($k_H = 1.1 \times 10^4 \text{ s}^{-1}$),^{12a} and therefore, the introduction of a *trans*- β -methyl group has little effect on the reactivity of the epoxide group toward acid-catalyzed hydrolysis. The rate of the spontaneous reaction for **3**, however, is much less than that for reaction of **2**. The significantly lower reactivity of **3** toward spontaneous hydrolysis can be attributed in part to the fact that methyl migration to form ketone is not favorable. Greater torsional strain introduced by the two β -methyl groups upon going to the transition state will also contribute toward reduction of the reaction rate.

Summary

The spontaneous reaction of *trans*-anethole oxide yields 40% of 1-(4-methoxyphenyl)-2-propanone (**7**), in addition to 60% of a mixture of *erythro*- and *threo*-diols **5** and **6** in a 3:1 ratio. Thus, spontaneous hydrolysis of **1** gives mainly anti-hydration of the epoxide group. The two major primary products of the spontaneous reaction of *cis*-anethole oxide are ketone **7** and *trans*-anethole oxide, formed in a ratio of ca. 3:1. *trans*-Anethole oxide, however, is formed only as a reactive intermediate and reacts further to form diol and ketone products by acid-catalyzed and/or spontaneous reactions, depending on the pH of the solution. Thus, the spontaneous reaction of *cis*-anethole oxide involves partial isomerization to the *trans* isomer. Kinetic and product deuterium isotope effects in the spontaneous reaction of **2** are best explained by a

(15) Coxon, J. M.; Maclagan, R. G. A. R.; Rauk, A.; Thorpe, A.; Whalen, D. *J. Am. Chem. Soc.* **1997**, *119*, 4712–4718.

(16) Islam, N. B.; Gupta, S. C.; Yagi, H.; Jerina, D. M.; Whalen, D. L. *J. Am. Chem. Soc.* **1990**, *112*, 6363–6369.

mechanism in which ketone product **7** and *trans*-epoxide product **1** arise primarily from nonintersecting reaction pathways.

Experimental Section

General Methods. NMR spectra were recorded at 80 MHz except for the experiment in which *trans*-anethole oxide was detected by ^1H NMR as an intermediate in the spontaneous reaction of *cis*-anethole oxide. For this experiment, spectra were recorded at 270 MHz.

Materials. Benzene and dioxane were distilled from sodium benzophenone ketyl. Pyridine was dried over and distilled from potassium hydroxide pellets. Sodium perchlorate was dried at 120 °C for 12 h. *trans*-Anethole oxide (**1**) and *cis*-anethole oxide (**2**) were prepared by published procedures.¹¹ β,β -Dimethyl-4-methoxystyrene oxide (**3**) was prepared by epoxidation of β,β -dimethyl-4-methoxystyrene.¹⁷

Kinetics Procedures. For each kinetic run, approximately 10 μL of a stock solution of epoxide in dioxane (ca. 1 mg/mL) was added to 2.0 mL of reaction solution in the thermostated cell compartment (25.0 \pm 0.2 °C) of a UV-vis spectrophotometer. Reactions were monitored at 231–232 nm, and pseudo-first-order rate constants were calculated by nonlinear regression analysis of the absorbance versus time data. For kinetic runs at intermediate pH, approximately 2×10^{-3} M 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, buffers were used for pH control. The contribution of buffer catalysis to k_{obsd} is generally < 3%.

Product Studies for Reaction of *trans*-Anethole Oxide (1**) and *cis*-Anethole Oxide (**2**).** Aliquots of a solution of **1** or **2** in dioxane were added to 3.0 mL of 0.1 M NaClO₄ solutions whose pH had been preadjusted by addition of 0.1 M HClO₄ or 0.1 M NaOH solutions. For reactions of **1** at pH ca. 5–10, approximately 10^{-3} M buffer was used, as outlined in the previous section for kinetic studies, to maintain pH. For reactions of **2** at pH > 9, no buffer was added for pH control. For these reaction solutions, the pH generally changed from 0.1 to 0.3 pH units during the course of the reaction. Even small rate enhancements from the buffer acid, which would catalyze the formation of diols, would affect the diol ratio significantly, since diols are minor products from the reaction of **2** above pH 9. Reaction solutions were allowed to stand at room temperature for > 8 half-lives. The pH was of the solutions was then adjusted to 5–8, and they were analyzed by reverse phase HPLC on a C₁₈ column with 1:1 methanol–water as eluent, 1.5 mL/min. Products were monitored by UV detection at 232 nm, where the extinction coefficients of diol and ketone products were determined to be very similar. Retention times of *erythro*-diol **5**, *threo*-diol **6**, and ketone **7** were 3.3, 4.1, and 7.1 min, respectively.

Spontaneous Reaction of *trans*-Anethole Oxide (1**) at pH 10.6.** A solution of **1** (28.0 mg) in 0.2 mL of dioxane was added to 20 mL of 0.1 M NaClO₄ (5:95 dioxane–H₂O, v/v) at pH 10.6 (buffered with 2×10^{-3} M CAPS) in a vial. The resulting solution was allowed to stand at room temperature

for 60 h after which time it was saturated with sodium chloride and extracted with ethyl acetate (3 \times 20 mL). The organic layer was washed with brine solution (4 \times 20 mL) and dried (Na₂SO₄), and the solvent was removed on a rotary evaporator to yield 18 mg of an oil. The ^1H NMR spectrum of this oil showed that it was a mixture of *p*-methoxyphenylacetone and the *erythro*- and *threo*-diols **5** and **6**, respectively. The ketone:diols ratio was determined by comparing the relative intensities of the integrals of the methyl absorption of the ketone with the methyl absorptions of the diols and was found to be 41:59, respectively. The *erythro*:*threo* diol ratio was calculated from the integrals of the peaks due to the hydrogens attached to the benzylic carbon atoms and was found to be 77:23, respectively. These results agreed well with product ratios determined by HPLC analysis of the reaction solutions.

Spontaneous Reaction of *cis*-Anethole Oxide at pH 10.6. A solution of **2** (16 mg) in 0.2 mL of dioxane was added to 20 mL of 5:95 dioxane–H₂O at pH 10.6 buffered with 2×10^{-3} M CAPS. The resulting solution was allowed to stir at room temperature for 60 h, after which time it was saturated with sodium chloride and extracted with ethyl acetate (5 \times 20 mL). The organic layer was washed with water (4 \times 20 mL) and dried (Na₂SO₄), and the solvent was removed on a rotary evaporator to yield 11 mg of an oil. The ^1H NMR spectrum of this oil showed that the major product of the reaction was (*p*-methoxyphenyl)acetone. The ketone:diol ratio was obtained by comparing the integrals of the absorption of the methyl group in the ^1H NMR of the ketone with the absorptions of the methyl groups of the diols and found to be 84:16. The IR spectrum of the crude oil closely resembled that of a commercial sample of (*p*-methoxyphenyl)acetone.

Detection of *trans*-Anethole Oxide as an Intermediate in the Spontaneous Reaction of *cis*-Anethole Oxide. The pH of 100 mL of 5:95 dioxane–water containing 2×10^{-3} M CAPS buffer was adjusted to 10.5, and the solution was degassed by bubbling nitrogen through it. A solution of 70 mg of *cis*-anethole oxide in 0.5 mL dioxane was added to the dioxane–water solution. A turbidity resulted, and therefore an additional 1.0 mL of dioxane was added. Nitrogen was slowly bubbled through the reaction solution. At time intervals of 6.0, 8.5, 11.5, 24.5, and 31 h, a 15 mL aliquot of the reaction solution was extracted with diethyl ether (3 \times 20 mL). The combined ethereal extracts was washed with water (3 \times 20 mL) and saturated sodium chloride solution (20 mL) and dried over anhydrous sodium sulfate. Solvent was removed to yield an oil (10–15 mg) that was dissolved in CDCl₃ and analyzed by ^1H NMR at 270 MHz.

Acknowledgment. This investigation was supported, in part, by the National Institutes of Health, National Research Service Award GM 08663 from the Minority Access to Research Careers Undergraduate Student Training in Academic Research (MARC U* STAR) Program at UMBC, and in part by Illinois Wesleyan University.

Supporting Information Available: Text and schemes describing experimental procedures for the synthesis of β -deuterio-*cis*-anethole oxide (**2d**) and β,β -dimethyl-4-methoxystyrene oxide (**3**) and the equation and graph of simulated buildup of *trans*-anethole oxide in the spontaneous reaction of *cis*-anethole oxide. This material is available free of charge via the Internet at [HTTP://pubs.acs.org](http://pubs.acs.org).

(17) Tiffeneau, M.; Lévy, J. *Bull. Soc. Chim. Fr.* **1926**, 763-782.