Stereochemistry of the Spontaneous, Acid-Catalyzed and Base-Catalyzed Hydrolyses of Styrene Oxide

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The stereochemical courses of the spontaneous, hydronium ion-catalyzed and hydroxide ion-catalyzed hydrolyses of (*R*)-styrene oxide have been determined by ^{1}H NMR analysis of the bis-(+)-α-(methoxy-α-trifluoromethyl)phenylacetate diesters of the styrene glycol products from each reaction. The glycol product from the spontaneous reaction of chiral styrene oxide is the result of 93% inversion and 7% retention. This result, coupled with published results of ^{18}O-labeling experiments, indicates that essentially all of the styrene oxide that reacts with cleavage of the benzyl C–O bond yields glycol with inversion of stereochemistry at the benzyl carbon. A mechanism involving addition of neutral water concerted with benzyl C–O bond breaking is proposed for this reaction. The glycol product from the acid-catalyzed reaction was determined to be the result of 67% inversion and 33% retention at the benzyl carbon. This result, which agrees with one previous publication and contradicts that of another, reflects the stereochemistry of addition of solvent to the benzyl carbon. Consistent with a recent report that ^{18}O-hydroxide attacks the α- and β-carbons of styrene oxide at almost equal rates, styrene glycol from the reaction of chiral styrene oxide with sodium hydroxide was found to be, within experimental error, completely racemic.

Introduction

The hydrolysis of styrene oxide occurs by three, kinetically distinct mechanisms.[1,2] At pH < *ca.* 6 the acid-catalyzed hydrolysis pathway is the major one, and at pH > *ca.* 12.5 hydroxide-catalyzed hydrolysis occurs. In an intermediate pH range of *ca.* 7–11, a third reaction pathway that is characterized by first-order kinetics predominates. This reaction is referred to as a spontaneous, or noncatalyzed reaction, and yields the same styrene glycol product that is formed from both the acid- and base-catalyzed reactions. The mechanism of this noncatalyzed reaction has not been previously established. Because of our interest in better understanding the mechanisms of the spontaneous reactions that many epoxides undergo, we have determined the stereochemistry of the spontaneous hydrolysis of (*R*)-styrene oxide. In the course of this study, we have reinvestigated the stereochemistries of the acid-catalyzed and hydroxide ion-catalyzed hydrolysis of styrene oxide. To establish the stereochemical course of each mode of hydrolysis of styrene oxide, we have determined the absolute stereochemistry of the diol product from hydrolysis of (*R*)-styrene oxide by ^{1}H NMR analysis of its diester derivative of (+)-α-methoxy-α-(trifluoromethyl)phenylacetic acid.[3]

In one study, the acid-catalyzed hydrolysis of styrene oxide was reported to proceed with 67% inversion and 33% retention of configuration at the benzyl carbon.[4] In a later publication, it was reported that styrene glycol formed from the acid-catalyzed hydrolysis of (+)-styrene oxide was completely racemic.[5] These two results could suggest quite different mechanisms for the acid-catalyzed hydrolysis of styrene oxide. Completely racemic product, for example, would suggest a stepwise mechanism with an intermediate possessing a very significant lifetime relative to that for bond rotation. Significant inversion at the reaction center would suggest either a mechanism involving a very short-lived intermediate or two parallel reaction pathways. To clarify this discrepancy, we have reexamined the stereochemistry of the acid-catalyzed hydrolysis of (*R*)-styrene oxide.

Hydrolysis of (+)-styrene oxide in base solution is reported to yield (+)-styrene glycol, resulting from retention of configuration at the benzyl carbon.[5] A mechanism involving attack of hydroxide ion exclusively at the β-methylene carbon was proposed to explain the results. Recent results form our laboratory show that hydroxide ion adds to both the α- and β-carbons of styrene oxide[2] and are not consistent with earlier conclusions. We have therefore also determined the stereochemistry of the hydroxide ion-catalyzed hydrolysis of styrene oxide to clarify earlier contradictory results.

Results and Discussion

The styrene glycol products from reaction of (*R*)-styrene oxide in 9:1 (v/v) water–dioxane solutions containing 0.1 M $HClO_4$ or 2.7 M KOH, and in water at pH 11.0, were isolated and converted to mixtures of diastereomeric bis-(+)-α-methoxy-α-(trifluoromethyl)phenylacetate (MTPA) diesters (**3**, Scheme 1). Under these conditions, the acid-catalyzed, base-catalyzed, and spontaneous reactions of styrene oxide, respectively, are the predominant reactions. The diester derivatives were analyzed at 300 MHz by ^{1}H NMR. In Figure 1 are the resonances at δ 6.28 and 6.17 in the NMR spectra of the diesters derived from mixtures of (*S*)- and (*R*)-styrene glycols formed in the spontaneous (a), acid-catalyzed (b) and base-catalyzed (c) reactions of (*R*)-styrene oxide. In separate experiments, commercial

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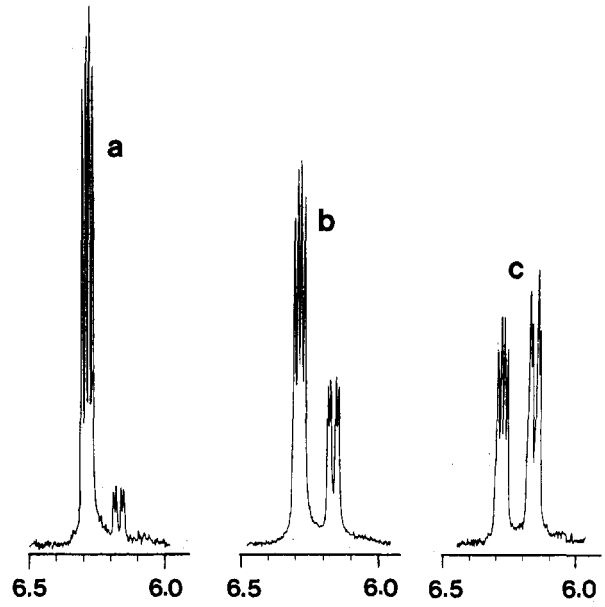
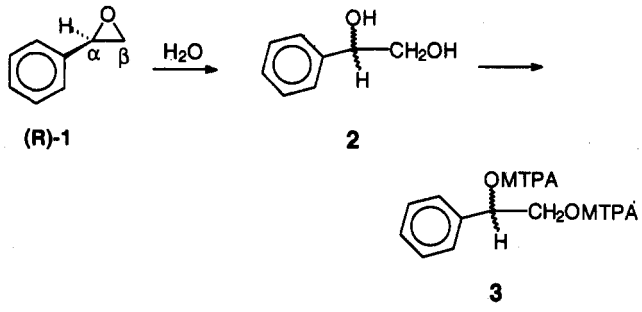


Figure 1. ^{1}H NMR resonances of the benzyl hydrogens of the (+)-α-methoxy-α-(trifluoromethyl)phenylacetate diester derivatives of styrene glycol product from hydrolysis of (*R*)-styrene oxide by the (a) spontaneous, (b) acid-catalyzed and (c) base-catalyzed pathways. The resonance centered at δ 6.17 is due to the derivative of (*R*)-styrene glycol and that centered at δ 6.28 is due to the derivative of (*S*)-styrene glycol.

Scheme 1



(*S*)-styrene glycol was conve ed to a diester derivative that possessed a benzyl res(ance only at δ 6.28, and commercial (*R*)-styrene glycol yielded a diester derivative that possessed a benzyl absorption only at δ 6.17.

Spontaneous Reaction. A knowledge of the stereochemistry associated with the spontaneous hydration of styrene oxide is essential to understanding its mechanism. Styrene glycol product resulting from complete inversion at the reaction center would suggest a mechanism in which there is *anti* addition of water, concerted with C–O bond breaking. Reaction occurring by both retention and inversion at the reaction center would require either the presence of an intermediate or two parallel reaction pathways.

In an earlier work, we have shown that styrene oxide reacts by the noncatalyzed route with $H_2{}^{18}O$ to give glycol product in which *ca.* 95% of the ^{18}O is located in the benzyl hydroxyl group.[2] Thus, *ca.* 95% of the product results from addition of water to the α carbon and the remaining 5% from addition of water to the β carbon. The noncatalyzed hydrolysis of styrene oxide that occurs by cleavage of the C_β–O bond presumably involves the nucleophilic addition of a neutral water molecule to the epoxide in a concerted reaction, since a primary carbocationic species would be too unstable to be an intermediate in water solution. The bimolecular addition of nucleophiles to epoxides under alkaline conditions is generally thought to occur by an S_N2 mechanism,[6] with complete Walden inversion at the reacting carbon center. Therefore, addition of water to the β-carbon of styrene oxide is expected to occur with inversion at the β-carbon center, leading to retention at the α-carbon. The stereochemistry associated with the cleavage of the C_α–O bond, however, is uncertain. Acid-catalyzed hydrolysis of aryl-substituted epoxides often occur with both retention and inversion of the reacting carbon center.[7] 1,2,3,4-Tetrahydronaphthalene-1,2-epoxide reacts by the noncatalyzed pathway to give only diol product of *anti* hydration,[8] Other epoxides, such as 1,2-epoxy-6-methoxy-1,2,3,4-tetrahydronaphthalene[9] and 7β,8α-dihydroxy-9β,10β-epoxy-7,8,9,10-tetrahydrobenzo[*a*]pyrene,[10] however, are reported to yield more product from *syn* hydration than from *anti* hydration in the spontaneous reactions. An intermediate has been detected in the latter case.

Reaction of (*R*)-styrene oxide in water at 30 °C and pH 11.0 for 12 days (*ca.* 6 half-lives) yielded styrene glycol as the sole product. At this pH, *ca.* 97% of styrene oxide reacts by the spontaneous pathway. The glycol product was then converted to its (+)-MTPA diester derivative. From the integrations of the resonances of the benzyl hydrogens of the diester given in Figure 1a, it can be concluded that the reaction of (*R*)-styrene oxide at pH 11.0 yields 91–92% of (*S*)-styrene glycol resulting from inversion of configuration at the benzyl carbon and 8-9% of (*R*)-styrene glycol resulting from retention of configuration at the benzyl carbon. By taking into account the 3% of reaction that occurs by the base-catalyzed route leading to racemic glycol (see section on base-catalyzed hydrolysis), it can be concluded that (*R*)-styrene oxide reacts by the spontaneous pathway to yield *ca.* 93% of (*S*)-styrene glycol and *ca.* 7% of (*R*)-styrene glycol. The (*R*)-styrene glycol that is formed from the spontaneous reaction is within experimental error of that expected from the fraction of (*R*)-1 that reacts with water at the β-carbon. Therefore, the remainder of the noncatalyzed reaction of 1 (*ca.* 93%) that occurs with cleavage of the C_α–O bond must occur with complete or near complete inversion of the benzyl carbon. This observation is consistent with a mechanism in which water acts as a nucleophile and adds to the benzyl carbon of (*R*)-styrene oxide in a concerted manner (Scheme 2).

Acid-Catalyzed Hydrolysis of Styrene Oxide. The acid-catalyzed methanolysis of 1 yields only 2-methoxy-2-phenylethanol, with 89% inversion at the benzyl carbon.[11] The methanolysis of 1 therefore involves only C_α–O bond cleavage, proceeding mainly by inversion at the benzyl reaction center. Acid-catalyzed hydrolysis of 1 in water containing ^{18}O is reported to yield glycol containing ^{18}O only at the benzyl carbon, which indicates that the acid-catalyzed hydrolysis of 1 also occurs with predominant

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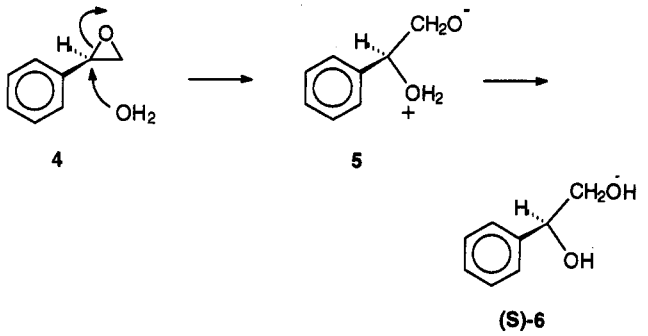
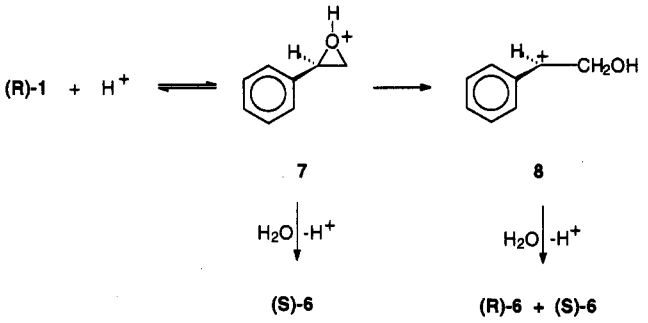
Scheme 2



4 5 (S)-6

Scheme 3



7 8 (S)-6 (R)-6 + (S)-6

C_α–O bond cleavage.[12] In a study of the acid catalyzed hydrolysis of chiral 1 it is reported that the glycol product is completely racemic,[5] suggesting that a freely solvated carbocation intermediate was involved.

Integration of the benzyl hydrogen resonances of the MTPA diester derivative of the glycol from the hydronium ion-catalyzed hydrolysis of (*R*)-1 (Figure 1b) in 0.1 M $HClO_4$ (1:9 dioxane–water) shows that this reaction proceeds with 67% inversion and 33% retention at the benzyl carbon. This result is in agreement with that reported by Berti et al.[4] and clearly shows that there is significant net inversion at the benzyl carbon. The fact that acid-catalyzed methanolysis of 1 gives more inverted product is expected on the basis that methanol is somewhat more nucleophilic than water and also less polar, thus providing less stabilization of the carbocation.

Partial racemization occurring in the acid-catalyzed hydrolysis of chiral 1 is consistent with either of several mechanisms outlined in Scheme 3. One possibility is that a protonated epoxide intermediate **7** partitions between concerted reaction with water to yield inverted glycol product and ring-opening to yield a benzyl carbocation 8. If rotation about the C_α–C_β bond in 8 is rapid relative to the rate of its reaction with solvent, then racemic glycol would be formed from this pathway. Another possibility is that the protonated epoxide intermediate **7** opens up completely to yield carbocation 8, but that the rate of C_α–C_β bond rotation in this intermediate is comparable to the rate of attack by solvent on this intermediate to yield glycol. Further work is in progress to distinguish between these two possibilities.

Hydroxide-Catalyzed Hydrolysis of Styrene Oxide. From a study of the reaction of styrene oxide in ^{18}O-water containing sodium hydroxide, it was concluded that addition of hydroxide ion occurred completely at the β-carbon.[13] It was subsequently reported that the hydrolysis of (+)-styrene oxide in base solution yielded styrene glycol with complete retention of configuration at the α-carbon,[5] which supported the original conclusion that hydroxide added only to the β-carbon. We have recently studied the reaction of styrene oxide with hydroxide ion in ^{18}O water, however, and have concluded that hydroxide adds almost equally to both the α and β carbons.[2] If these reactions proceed with complete inversion at the reaction center, as expected for the addition of a nucleophile to an epoxide, then the reaction of (*R*)-1 should actually yield racemic styrene glycol. The ^1H NMR spectrum of the benzyl resonances of the MTPA diesters of the glycol product from reaction of (*R*)-1 in 2.7 M KOH solution, where >98% of the reaction of 1 occurs by its second order reaction with hydroxide, is shown in Figure 1c. The ratio of the resonances due to *R* and *S* product was measured to be 48:52, and consequently hydroxide-catalyzed hydrolysis of (*R*)-1 yields glycol product that is racemic, within experimental error. Although this observation, taken by itself, might be somewhat surprising, it is completely consistent with a mechanism in which hydroxide adds equally to both the α and β carbons of (*R*)-1, with inversion of configuration at the carbon being attacked.

Experimental Section

Materials. (*R*)-(+)-Styrene oxide, (*R*)- and (*S*)-styrene glycols, and (+)-α-methoxy-α-(trifluoromethyl)phenylacetic acid (MTPA) were purchased from commercial suppliers. The acid chloride of MTPA was prepared as described by Dale and Mosher.[3]

Spontaneous Hydrolysis of (*R*)-Styrene Oxide. To a stirred solution of 25 mL of water containing 10^{-3} M potassium hydroxide (pH 11.00) that was degassed by bubbling nitrogen through it, a sample of commercial (*R*)-styrene oxide (10.2 mg) was added. The solution was sealed under nitrogen and allowed to stir at 30 °C for 12 days, *ca.* 6 half-lives. Under these conditions, *ca.* 97% of styrene oxide reacts by the spontaneous route and the remaining 3% reacts by hydroxide catalysis.[1] The reaction solution was extracted two times with 50 mL of ethyl acetate. The extracts were combined and dried over $CaSO_4$, and the solvent was removed to yield 15 mg of crude glycol product as a white solid. This material was converted to its (+)-α-methoxy-α-(trifluoromethyl)phenylacetate diester, without further purification, by the general procedure given below.

Acid-Catalyzed Hydrolysis of (*R*)-Styrene Oxide. A solution of 65 mg of (*R*)-styrene oxide in 5 mL of 0.1 M $HClO_4$ in 1:9 (v/v) dioxane–water was stirred for 5 min at rt. An additional 2 mL of water was added and the solution was extracted twice with ethyl acetate (10 mL, 5 mL). The ethyl acetate extracts were combined, washed with 2 mL of water, and dried over $CaSO_4$. The solvent was removed to yield 68 mg (91%) of styrene glycol. A 12-mg sample of this material was converted, without further purification, to its (+)-α-methoxy-α-(trifluoromethyl)phenylacetate diester for NMR analysis.

Base-Catalyzed Hydrolysis of (*R*)-Styrene Oxide. A solution of 14 mg of (*R*)-styrene oxide in 10 mL of 2.7 M potassium hydroxide in 10 mL of 1:9 dioxane–water solution was stirred for 5 h at rt (*ca.* 8 half-lives). The product was isolated by extraction into ethyl acetate as described above to yield 12 mg (75%) of styrene glycol product that was converted without further purification to its (+)-α-methoxy-α-(trifluoromethyl)phenylacetate diester.

General Procedure for Converting Styrene Glycol to Its (+)-α-Methoxy-α-(trifluoromethyl)phenylacetate Diester. Approximately 12 mg of commercial (*R*)-, commercial (*S*)-, commercial racemic, or product sample of styrene glycol was added to a solution of 70 mg of (+)-α-methoxy-α-(trifluoromethyl)-phenylacetyl chloride in 0.5 mL of pyridine. The reaction solution

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(13) Audier, H. D.; Dupin, J. F.; Jullien, J. *Bull. Soc. Chim. Fr.* **1968**, *9*, 3844.

was allowed to stand at rt for 3 days. It was diluted with 1 mL of water and extracted with 5 mL of ethyl acetate. The ethyl acetate solution was washed with 2 mL of 2 M HCl and 2 mL of 10% sodium carbonate solution. It was then dried over $CaSO_4$ and the solvent was removed to yield *ca.* 50 mg (80%) of diester derivative. Product mixtures, without further purification, were analyzed for diasteromeric composition by ^1H NMR.

A small sample of the MTPA diester of racemic styrene glycol was purified by rapid silica gel chromatography: ^1H NMR ($CDCl_3$) δ 7.3 (m, aromatic), 6.28 (dd, J = 7.5, 3.9), 6.17 (dd, J = 8.5, 2.9), (4.65, m,), 4.49 (m), 3.34, 3.36, 3.40, 3.64. Anal. Calcd for $C_{28}H_{24}O_6F_6$: C, 58.95; H, 4.24. Found: C, 58.82; H, 4.30.

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