

Effects of Para-Substituents on the Mechanisms of Solvolysis of Styrene Oxides

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Rate and product studies of the hydronium ion-catalyzed, hydroxide ion-catalyzed, and spontaneous reactions of styrene oxide and its *p*-CH₃O-, *p*-CH₃-, *p*-Cl-, and *p*-O₂N-derivatives in water solutions have been carried out. A Hammett correlation of log *k* for the acid-catalyzed reactions vs σ^+ gives a slope ρ^+ of -4.2 and only diol products are formed. An intermediate in the hydronium ion-catalyzed hydrolysis of *p*-methoxystyrene oxide is trapped, subsequent to its rate-limiting formation, by azide ion. The spontaneous reactions of *p*-methylstyrene oxide and styrene oxide yield only diol products, and their reactions in ¹⁸O-water indicate that $\geq 98\%$ and ca. 95%, respectively, of ¹⁸O is incorporated into the benzyl positions. Nucleophilic addition of water to the benzyl carbon of neutral epoxide is proposed as the mechanism of the primary component of the spontaneous reaction for the *p*-CH₃-, *p*-H- and *p*-Cl-substrates on the basis of a Hammett ρ of -2.0. The spontaneous rate constant for reaction of *p*-methoxystyrene oxide is much greater than that expected from a Hammett correlation for the *p*-CH₃-, *p*-H-, and *p*-Cl-styrene oxides. This increased rate is attributed to the incursion of a reaction that yields mainly (>80%) *p*-methoxyphenylacetaldehyde. The regiochemistries of addition of hydroxide ion in ¹⁸O-water to *p*-CH₃-, *p*-H-, and *p*-Cl-substituted styrene oxides and addition of methoxide ion in methanol to *p*-CH₃H, *p*-H-, *p*-Cl-, and *p*-O₂N-substituted styrene oxides were also determined and found to vary as functions of the para substituent. Addition of hydroxide and methoxide ions to the α -carbon is favored by electron-donating groups in the phenyl ring, and addition of these nucleophiles to the β -carbon is favored by electron-withdrawing groups in the phenyl ring.

Introduction

The addition reactions of aryl-substituted oxiranes in aqueous solutions under both acidic and basic conditions have received considerable attention.¹⁻⁶ Interest in these reactions has been stimulated by the fact that epoxide metabolites of polycyclic aromatic hydrocarbons, especially diol epoxides, have been implicated as the reagents responsible for the carcinogenic properties of certain hydrocarbons.⁷ The additions of cellular macromolecules and other nucleophiles to these reactive intermediates are important metabolic pathways.

It has been recognized for many years that three kinetically-distinguishable mechanisms for the hydrolysis of certain epoxides over a sufficiently wide pH range exist.^{8,9} The rate expression for their hydrolysis is given by eq 1, where k_H is the specific second-order rate constant

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

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

The acid-catalyzed hydrolysis of several phenyl-substituted styrene oxides to their corresponding styrene glycols have been reported. Hydronium ion-catalyzed hydrolyses of styrene oxide and its *cis* and *trans* β -methyl derivatives in H₂¹⁸O are reported to yield glycol products in which all of the ¹⁸O is incorporated into the benzyl hydroxyl group.¹⁰ In similar experiments, indene oxide and 1,2,3,4-tetrahydronaphthalene-1,2-oxide are reported to yield diol in which >90% of the ¹⁸O is located in the benzyl position.¹⁰ Also, attack of solvent in the acid-catalyzed methanolysis of *p*-nitrostyrene oxide occurs preferentially at the benzyl carbon.⁶ Thus, the aryl group stabilizes the transition state with positive charge developed at the benzyl position, leading to the cleavage of the benzyl C-O bond.

Although the rates of acid-catalyzed methanolysis of various phenyl-substituted styrene oxides^{3a} and acid-catalyzed hydrolysis of phenyl-substituted 1-arylcyclo-

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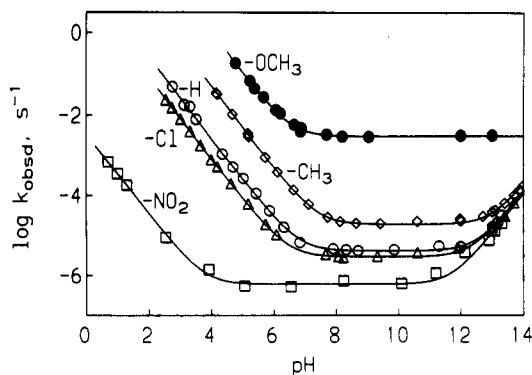


Figure 1. Plots of $\log k_{\text{obsd}}$ for hydronium ion-catalyzed hydrolysis of para-substituted styrene oxides vs pH. The lines are theoretical, based on eq 1, and the rate constants provided in Table I.

hexene oxides⁵ have been reported, no systematic study of the rates and products of hydrolysis of phenyl-substituted styrene oxides over a wide pH range has been reported. Hydrolysis of styrene oxide at pH 8–12 is reported to proceed mainly via the spontaneous pathway,^{4a} but the mechanism of this reaction was not elucidated. The spontaneous reaction of *p*-methoxystyrene oxide yields mostly aldehyde product, and an intermediate has been proposed for this reaction.^{11,12}

Rate data for the reactions of styrene oxides in aqueous hydroxide solutions have not been reported. However, reaction of unlabeled styrene oxide with hydroxide ion in H₂¹⁸O is reported to yield diol in which all of the ¹⁸O is located in the primary hydroxyl group.¹³ Thus, it would appear that hydroxide ion adds exclusively to the less hindered methylene carbon in preference to the benzyl position.

In this paper we report detailed kinetic and product studies for the reactions of a series of *p*-OCH₃-, *p*-CH₃-, *p*-H-, *p*-Cl-, and *p*-NO₂-styrene oxides in water solutions over extended pH ranges. In addition we have determined the regiochemistry of addition of methoxide ion in methanol and hydroxide ion in water to this series of substituted styrene oxides. The mechanisms of the hydronium ion-catalyzed, hydroxide ion-catalyzed, and spontaneous reactions of styrene oxides are summarized.

Results and Discussion

The pseudo-first-order rate constants (k_{obsd}) for reaction of styrene oxide and its *p*-nitro-, *p*-chloro-, *p*-methyl-, and *p*-methoxy-derivatives in water solutions as a function of pH have been determined, and plots of $\log k_{\text{obsd}}$ vs pH are provided in Figure 1. These rate data were fit to eq 1, and values of k_{H} , k_{O} , and k_{OH} are provided in Table I. For each compound studied the hydronium ion-catalyzed reaction predominates at relatively low pH and the spontaneous reaction predominates in solutions of intermediate pH values. Except for *p*-methoxystyrene oxide, each compound also exhibited a hydroxide ion-catalyzed reaction at pH > ca. 12. The rate constant for reaction of *p*-methoxystyrene oxide was independent of pH above ca.

8 and did not increase detectably in solutions containing NaOH concentrations up to 0.5 M. Even in solutions containing such high concentrations of hydroxide ion, therefore, the bimolecular addition of hydroxide ion to *p*-methoxystyrene oxide does not compete sufficiently with its spontaneous reaction to be detected kinetically.

Acid-Catalyzed Hydrolyses. The reactivities of the para-substituted styrene oxides toward hydronium ion-catalyzed hydrolyses vary over ca. 7 orders of magnitude within the series as X is changed from nitro to methoxy. A plot of $\log k_{\text{H}}$ vs σ^+ for all para-substituents (Figure 2) gives a rather good Hammett correlation with a slope $\rho^+ = -4.2$. This value of ρ^+ is, as expected, very similar to the value of ρ (-4.1) reported for the acid-catalyzed methanolysis of a series of substituted styrene oxides^{3a} and indicates that significant positive charge is developed at the benzyl carbon at the transition state. This value of ρ^+ may be compared with those for the reactions of 1-phenylethyl alcohols with acid in 1:1 trifluoroethanol-water to form carbocations ($\rho^+ = -4.5$)¹⁴ and the solvolysis of 1-phenylethyl chlorides and esters in aqueous organic solvents ($\rho^+ = -5.2$ to -5.9).^{14,15}

p-Nitrostyrene oxide undergoes benzyl C–O bond cleavage in acid-catalyzed methanolysis, even though the *p*-nitro group is electron-withdrawing and should retard the rate of a reaction that results in the development of positive charge at the benzyl position. Therefore, it is reasonable to assume that other styrene oxides substituted with groups that are less electron-withdrawing than nitro should also undergo benzyl C–O bond cleavage in hydronium ion-catalyzed hydrolysis, although this has been demonstrated for only styrene oxide.¹⁰ Solvent addition to the benzyl carbon can be rationalized by either concerted attack of solvent on protonated epoxide 2 (A-2 mechanism) or by attack of solvent on a carbocation intermediate 3 (A-1 mechanism). Carbocation 3 may be generated either from 2 as outlined in Scheme I or by a reaction in which proton transfer to oxygen of neutral epoxide from hydronium ion is concerted with benzyl C–O bond cleavage. The acid-catalyzed hydrolyses of (+)-styrene oxide in water solutions are reported to yield diol products that are mostly^{16a} or completely^{16b} racemic, and these results are best interpreted by mechanisms in which the reaction proceeds primarily by an intermediate carbocation 3. Those para-substituted styrene oxides with electron-donating groups that stabilize positive charge at the benzyl position should react with hydronium ion to yield benzyl carbocations that have even longer lifetimes in water solutions than that from styrene oxide and should also hydrolyze via discrete carbocations. However, electron-withdrawing groups substituted in the phenyl ring of styrene oxide can potentially destabilize benzyl carbocations (3) such that a concerted attack of water on protonated epoxide 2 would be favored.

The stereochemistry of acid-catalyzed epoxide solvolysis may also depend on the nature of the solvent. For example, the acid-catalyzed methanolysis of (+)-styrene oxide yields product with 89% inversion of configuration at the benzyl

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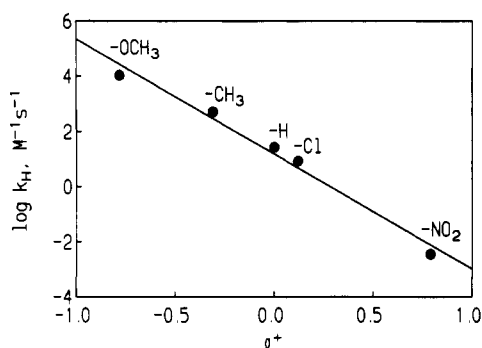
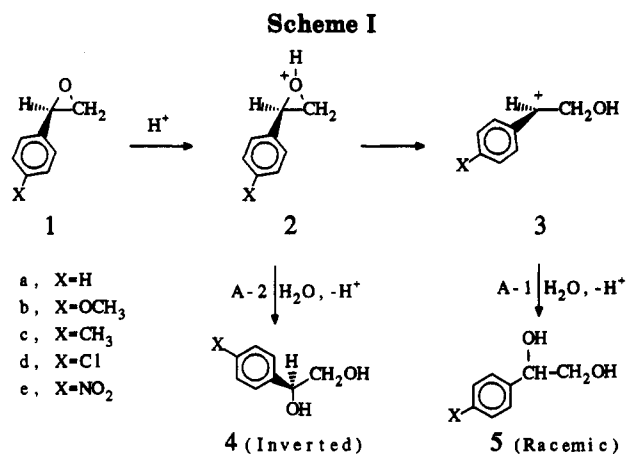
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Table I. Rate Constants for the Hydrolysis Reactions of Para-Substituted Styrene Oxides in Water Solutions at 25 °C^a

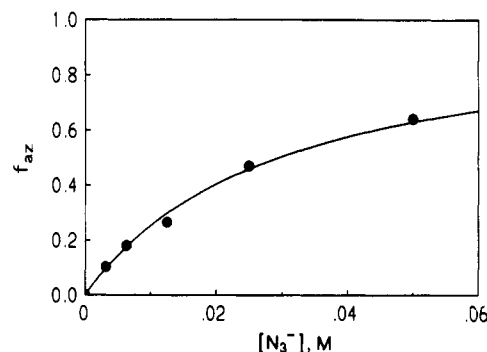
| para-substituent | $k_H, M^{-1} s^{-1}$ | k_{az}, s^{-1} | $k_{OH}, M^{-1} s^{-1}$ |
|-------------------|----------------------------------|----------------------------------|----------------------------------|
| -OCH ₃ | $(1.10 \pm 0.04) \times 10^4$ | $(3.00 \pm 0.09) \times 10^{-3}$ | - |
| -CH ₃ | $(4.89 \pm 0.09) \times 10^2$ | $(2.07 \pm 0.04) \times 10^{-5}$ | $(1.62 \pm 0.05) \times 10^{-4}$ |
| -H | 26.6 ± 0.9 | $(4.18 \pm 0.18) \times 10^{-6}$ | $(1.22 \pm 0.09) \times 10^{-4}$ |
| -Cl | 8.45 ± 0.21 | $(3.10 \pm 0.10) \times 10^{-6}$ | $(1.14 \pm 0.05) \times 10^{-4}$ |
| -NO ₂ | $(3.41 \pm 0.38) \times 10^{-3}$ | $(6.17 \pm 0.62) \times 10^{-7}$ | $(1.02 \pm 0.13) \times 10^{-4}$ |

^a For solutions containing $[HO^-] < 0.1$ M, ionic strength was held constant at 0.2 M with NaClO₄ for hydrolysis of styrene oxide (1a) and *p*-nitrostyrene oxide (1e) and at 0.1 M for hydrolyses of the remaining substituted styrene oxides in the series. For solutions with $[HO^-] > 0.2$ M for hydrolysis of 1a and 1e and 0.1 M for hydrolyses of the remaining compounds, NaClO₄ was not added to keep ionic strength constant.

**Figure 2.** Hammett plot of $\log k_H$ for hydronium ion-catalyzed hydrolysis of para-substituted styrene oxides vs σ^+ .

position,^{3d} compared to 50–66% inversion that occurs in acid-catalyzed hydrolysis.¹⁶ Several mechanisms are consistent with these results. One possibility is that the solvolyses proceed via a mechanism similar to that outlined in Scheme I in which 2 partitions to product by two pathways, one by reacting in a concerted mechanism with solvent to give product with inverted configuration and a second by ring opening to give a carbocation 3, which further reacts to give racemic product. A change in the partitioning of 2 to favor formation of the carbocation in water would account for the greater amount of racemic product formed. A second possibility is that the carbocation 3 reacts with solvent at a rate comparable to that at which it undergoes C_α-C_β bond rotation. More nucleophilic solvents would then be expected to result in greater amounts of inverted product.

In order to ascertain whether discrete carbocations with relatively long lifetimes are intermediates in the acid-catalyzed hydrolysis of any substituted styrene oxides, the hydronium ion-catalyzed reactions of *p*-methoxystyrene oxide (1b) and *p*-methylstyrene oxide (1c) have been carried out in solutions containing highly nucleophilic azide ion. The benzyl carbocations resulting from the reactions of 1b and 1c with H⁺ should have stabilities comparable

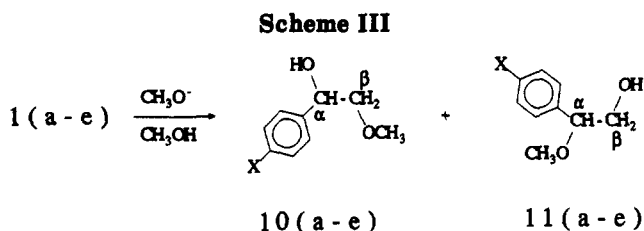
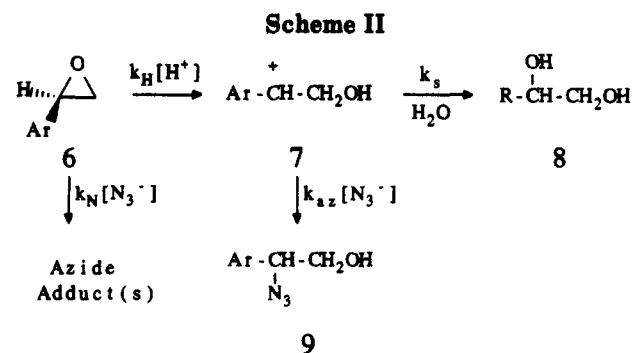
**Figure 3.** Plot of mole fraction of azide product (f_{az}) from reaction of *p*-methoxystyrene oxide (1b) at pH 5.75 (ionic strength 0.1 M with NaClO₄) vs the concentration of sodium azide ($[NaN_3]$).

to those of 1-(4-methoxyphenyl)ethyl and 1-(4-methylphenyl)ethyl carbocations, respectively, which have sufficiently long lifetimes in aqueous solutions to be trapped by azide.¹⁴ This reagent has been utilized to efficiently trap various carbocations in steps subsequent to their rate-limiting formation in the solvolysis of benzyl substrates^{14,17,18} and also traps a carbocation intermediate subsequent to its rate-limiting formation in the spontaneous reaction of a *cis*-7,8-diol 9,10-epoxide derivative of benzo[*a*]pyrene.¹⁹

The rate constants for reaction of *p*-methoxystyrene oxide at pH 5.7 in solutions containing sodium azide in concentrations up to 0.012 M were constant within ca. 2%. Reaction of 1b at pH 5.7 in 0.012 M sodium azide solution did yield, however, 26% of azide adduct. In order for a significant yield of azide adduct to be formed from the hydronium ion-catalyzed reaction of 1b at pH 5.5 without a corresponding increase in the rate constant for its reaction, azide ion must be reacting with an intermediate subsequent to its rate-limiting formation. It is presumed that this intermediate is the benzyl carbocation 3b. Product studies from reaction of 1b in solutions containing concentrations of sodium azide up to 0.05 M were carried out, and a plot of the percent yield of azide adduct as a function of the concentration of sodium azide is given in Figure 3.

Rate and product studies of the reactions of *p*-methylstyrene oxide (1c) in solutions containing sodium azide were also carried out. At pH 9.5, where the spontaneous reaction of 1c predominates over the hydronium ion-catalyzed reaction, the rate constant for reaction of 1c increases linearly with increase of sodium azide concentration. From these data a bimolecular rate constant for the addition of azide ion to neutral epoxide 1c can be

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calculated to be $8.7 \pm 0.4 \times 10^{-3} \text{ M}^{-1} \text{ s}^{-1}$. Products from the reaction of 1c at pH 5.7 in solutions containing azide ion in concentrations up to 0.05 M were also carried out. Significant yields of azide adduct were also formed from 1c at pH 5.7, e.g., 39% in 0.05 M sodium azide solution. However, the observed yields of azide adduct were always within 2–6% of the yields to be expected if all azide product resulted from nucleophilic addition of azide ion to neutral epoxide. Within our experimental error, therefore, trapping of 3c by azide ion is not detected.

A mechanism that is consistent with the above results is outlined in Scheme II. For reaction of *p*-methoxystyrene oxide $k_H[\text{H}^+] \gg k_N[\text{N}_3^-]$ and the mole ratio of azide product 9 (f_{az}) is given by the equation $f_{az} = k_{az}[\text{N}_3^-]/(k_{az}[\text{N}_3^-] + k_s)$. A nonlinear fit of f_{az} to this equation yielded a value of 34 M^{-1} for k_{az}/k_s . For reaction of the less reactive *p*-methylstyrene oxide substrate in solutions containing sodium azide $> \text{ca. } 0.01 \text{ M}$, however, $k_N[\text{N}_3^-]$ is comparable in magnitude to $k_H[\text{H}^+]$. In 0.025 M N_3^- , for example, the ratio of $k_N[\text{N}_3^-]/k_H[\text{H}^+]$ at pH 5.75 is calculated to be 0.24. Under these conditions, therefore, 19% of the product mixture from reaction of 1c is expected to be azide adduct resulting from the bimolecular reaction of azide ion with neutral epoxide (k_N pathway). If azide ion also competes successfully with water for the capture of carbocation 7 (k_{az} pathway), then additional azide adduct would be formed and the total yield of azide adducts would be greater than 19%. The actual decrease in diol yield due to azide product formation was determined experimentally from reaction of 1c in this solution to be 22%. This value is within experimental error of that expected if azide ion did not compete efficiently with water in reacting with carbocation 3c. Therefore, the k_{az}/k_s ratio for reaction of the *p*-methylbenzyl carbocation 3c, if it is indeed an intermediate in the acid-catalyzed hydrolysis of 1c, must be significantly smaller (more than an order of magnitude) than that for reaction of the *p*-methoxybenzyl carbocation 3b. This would be consistent with the results of Jencks et al., who estimate the reactivity of 1-(*p*-methylphenyl)ethyl carbocation with 1:1 trifluoroethanol–water solvent to be ca. 10^2 greater than that of the corresponding 1-(*p*-methoxyphenyl)ethyl carbocation.¹⁴

Our kinetic and product data demonstrate that 1b undergoes hydronium ion-catalyzed hydrolysis to yield a

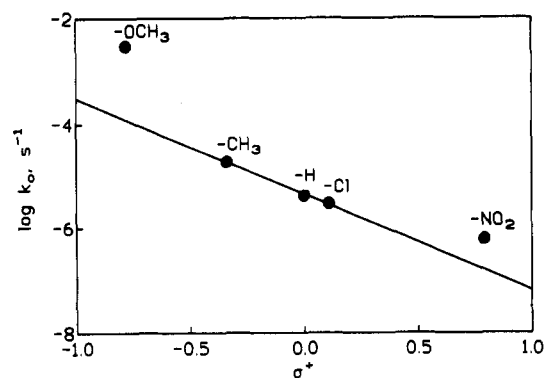


Figure 4. Hammett plot of $\log k_o$ for the spontaneous reactions of *para*-substituted styrene oxides vs σ^+ .

carbocation that has a sufficient lifetime to be trapped by the highly nucleophilic azide ion. The k_{az}/k_s ratio is much less than the value of 10^6 – 10^7 M^{-1} for reactions of very stable carbocations whose rates with solvent can be measured directly by spectrophotometric methods.²⁰ It has been argued that those carbocations with k_{az}/k_s ratios much less than 10^6 M^{-1} react with azide ion at the diffusion-limiting rate constant of ca. $5 \times 10^9 \text{ M}^{-1} \text{ s}^{-1}$.¹⁴ If this assumption is also made for reaction of 1b, then its rate constant for reaction with water (k_s) can be calculated to be $1.5 \times 10^8 \text{ s}^{-1}$ and its lifetime ($1/k_s$) calculated to be $7 \times 10^{-9} \text{ s}$. The calculated reactivity of carbocation 3b in water is very similar to those estimated for reaction of 1-(*p*-methoxyphenyl)ethyl carbocation with water ($1 \times 10^8 \text{ s}^{-1}$)¹⁴ and *p*-methoxybenzyl carbocation with 1:1 trifluoroethanol–water and 70:30 acetone–water ($2 \times 10^8 \text{ s}^{-1}$ and $7 \times 10^8 \text{ s}^{-1}$, respectively).¹⁸

It remains to be determined if those epoxides with electron-withdrawing groups in the *para* position, 1d and 1e, undergo hydronium ion-catalyzed hydrolysis in water solution via discrete carbocation intermediates 3d and 3e. The rate of reaction of the 1-(*p*-nitrophenyl)ethyl carbocation with 1:1 trifluoroethanol–water is estimated by calculation to be 10^{13} s^{-1} ,¹⁴ which would mean that its lifetime would be similar to that for a bond vibration. Carbocation 3e should have a similar reactivity with solvent and may not have a sufficient lifetime to exist as an intermediate in water.

Spontaneous Hydrolyses. A plot of $\log k_o$ vs σ^+ for the spontaneous reactions of styrene oxides 1a–e is given in Figure 4. In contrast to the rather good Hammett correlation that exists for the acid-catalyzed hydrolysis of 1a–e, it is clear from Figure 4 that a single correlation relating $\log k_o$ with σ^+ for all five substrates in the series does not exist. Use of σ or σ^+ constants instead of σ^+ values result in worse correlations.

The products from the spontaneous reaction of each epoxide in the series were isolated and identified. Only a single hydrolysis product, the corresponding styrene glycol resulting from hydration of the epoxide group, was detected from the spontaneous reaction of each epoxide in the series except for *p*-methoxystyrene oxide 1b. The spontaneous reaction of *p*-methoxystyrene oxide, in contrast, yields the isomeric *p*-methoxyphenylacetaldehyde as a major product (82%) and *p*-methoxystyrene glycol as a minor product (18%).^{11,12}

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To establish the regiochemistries of addition of water to styrene oxide and *p*-methylstyrene oxide by the spontaneous reaction, the reactions of 1a and 1c in $H_2^{18}O$ -enriched water solutions at intermediate pH values where the spontaneous reactions predominate were studied. The product glycols were isolated and analyzed by gas chromatography-mass spectrometry (GC-MS) with electron impact (EI) detection.²¹ From the ratio of the molecular ions in the mass spectrum of diol product resulting from addition of either ^{16}O -hydroxide or ^{18}O -hydroxide to either α - or β -carbons of the epoxide, the amount of ^{18}O incorporated into the diol was calculated and agrees well with the ratio of ^{16}O and ^{18}O in the solvent. Fragmentation of the molecular ion of the diol with C_α - C_β bond cleavage yields the benzyloxonium ion with the loss of CH_2OH . Diol product with ^{18}OH in the α -position and ^{16}OH in the β -position thus yields a $(M - CH_2^{16}OH)$ fragment ion whereas diol product with ^{16}OH in the α -position and ^{18}OH in the β -position yields a $(M - CH_2^{18}OH)$ fragment ion. Since attack of $H^{18}O$ at either the α - or β -carbons results in the incorporation of ^{18}O at that position, comparison of the ^{16}O and ^{18}O fragment ions with the ^{16}O and ^{18}O molecular ions allows the determination of the regiochemistry of attack of water. By comparing these two ratios obtained from the mass spectrum of the diol from reaction of 1c it is calculated that ca. 98% of the solvent ^{18}O that is incorporated into the diol is located at the benzyl position, thus demonstrating that the spontaneous reaction of 1c occurs completely, within our experimental error, with benzyl C-O bond cleavage. From a similar mass spectral analysis of the glycol product from the spontaneous reaction of styrene oxide, it is calculated that ca. 95% of the solvent ^{18}O that is incorporated into product is located at the benzyl position. The reactions of 1a and 1c therefore proceed either mostly or completely by benzyl C-O bond cleavage and yield only diol product.

Since σ^+ for a *p*-chloro substituent is not very large, the spontaneous reaction of *p*-chlorostyrene oxide most likely also proceeds mainly with benzyl C-O bond cleavage, by a mechanism similar to that for reaction of the *p*- CH_3 and *p*-H compounds. Therefore, a regression line is arbitrarily drawn through the data points for CH_3 -, H-, and Cl- in the Hammett plot given in Figure 4. The slope of this line yields ρ^+ of -2.0. The significantly smaller value of ρ^+ for the spontaneous reactions of 1a, 1c, and 1d, compared to that for the hydronium ion-catalyzed reaction, suggests that much less positive charge is developed at the benzyl carbon at the transition state of the spontaneous reactions for this series. Thus, water most likely acts as a nucleophile in the primary component of the spontaneous reactions of these three epoxides, adding to neutral epoxide at the benzyl carbon in a concerted manner.

The data point for the spontaneous reaction of *p*-methoxystyrene oxide 1b lies significantly above the correlation line drawn through the data points for 1a, 1c, and 1d. The major product of the spontaneous reaction of 1b is also aldehyde (82%) resulting from rearrangement of 1b.^{11,12} The incursion of this new reaction pathway, made favorable by the electron-donating methoxy group, accounts for the positive deviation of the *p*-methoxy point on the correlation line of Figure 4. Very significant positive charge must be present on the benzyl carbon at the transition state of the

aldehyde-forming reaction. Diol formation is only a minor component (18%) of the spontaneous reaction of 1b.

We have previously reported that the spontaneous reaction of *p*-methoxystyrene-*trans*- β -deuteriostyrene oxide is accompanied by scrambling of the deuterium label into the *cis*- β -position.^{11,12} An intermediate was postulated for this isomerization that might also serve as an intermediate on the pathways to aldehyde and diol products. Alternatively, aldehyde and diol products from the spontaneous reaction of 1b might be formed from parallel concerted reactions or from parallel reaction pathways without the intervention of a common intermediate. Present kinetic data do not allow distinctions between these possibilities. Identical migratory aptitudes of the *trans*- β -D and *cis*- β -D were suggested as evidence against a concerted mechanism for aldehyde formation.

The data point for *p*-nitrostyrene oxide also lies somewhat above the correlation line in Figure 4. A tentative interpretation for the deviation of this data point is that as the *para*-substituent becomes more electron-withdrawing, there is a change of mechanism from benzyl C_α -O bond cleavage to C_β -O bond cleavage, with neutral water acting as a nucleophile.

Hydroxide-Catalyzed Hydrolyses of Styrene Oxides. The rate expressions for hydrolysis of all substituted styrene oxides studied, except *p*-methoxystyrene oxide, contained a kinetic term in hydroxide ion. The bimolecular rate constants for reaction of these substituted styrene oxides are summarized in Table I. The magnitudes of the rate constants for hydroxide-catalyzed hydrolysis of the *p*- NO_2 , *p*-Cl, and *p*-H substrates are essentially the same, within experimental error, and the rate constant for hydrolysis of the *p*-methyl substrate is only slightly larger. This insensitivity of the rate of reaction of hydroxide with substituted styrene oxides has several possible explanations. One possibility is that there is a common mechanism for this reaction within the series and that there is simply little or no substituent effect on the rate of reaction. A second possibility is that hydroxide ion adds to both the α - and β -carbons and that the substituent-effect on one reaction offsets that of the other. It is known, for example, that the addition of benzylamine in ethanol to a series of substituted styrene oxides occurs at both the α - and β -positions.²² For the "normal" addition of benzylamine to the β -carbon, a Hammett ρ was determined to be +0.87. For "abnormal" addition of amine to the α -carbon (benzyl position), ρ was found to be -1.15. Although the substituent effects for addition to the α - and β -carbons do not exactly cancel, there is not a large overall effect of substituent on the rate of reaction of substituted styrene oxides with benzylamine.

The reaction of styrene oxide in sodium hydroxide- $H_2^{18}O$ solution is reported to yield styrene glycol in which all of the ^{18}O is incorporated at the β -methylene carbon.¹³ Thus, the reaction of hydroxide ion with styrene oxide would appear to be predominantly its addition to the β -methylene carbon. If ρ for addition of hydroxide ion to the β -carbon of styrene oxides is significantly positive, as observed for the addition of benzylamine in ethanol, then the reaction of hydroxide with *p*-nitrostyrene oxide should also occur at the β -position and the bimolecular rate constant should be considerably larger than that for reaction of hydroxide with styrene oxide. This is clearly

(21) Mass spectral analyses of diols from hydrolysis of epoxides in ^{18}O -water are discussed in refs 9a and 10.

(22) Parker, R. E.; Laird, R. M. *J. Am. Chem. Soc.* 1961, 83, 4277.

Table II. Relative Yields^a of Diol Products from Addition of H¹⁸O⁻ to the α - and β -Carbons of Several Substituted Styrene Oxides and Corresponding Rate Constants^b k_α and k_β for These Reactions

| para-substituent | % α -addition | % β -addition | $k_\alpha \times 10^4$, M ⁻¹ s ⁻¹ | $k_\beta \times 10^4$, M ⁻¹ s ⁻¹ |
|------------------|----------------------|---------------------|---|--|
| -CH ₃ | 67 | 33 | 1.09 | 0.53 |
| -H | 51 | 49 | 0.62 | 0.60 |
| -Cl | 39 | 61 | 0.44 | 0.70 |

^a Determined by mass spectral analyses of the diols from reaction of epoxides with potassium hydroxide in O¹⁸-water. ^b Rate constants k_α and k_β were calculated by multiplying the observed rate constant k_{OH} by the fraction of α - or β -addition of hydroxide ion to the epoxide.

not the case. Instead, the bimolecular rate constant for reaction of hydroxide ion with *p*-nitrostyrene oxide is measured to be very slightly less than that for its reaction with styrene oxide. In order to resolve this apparent discrepancy and further clarify the mechanisms of reaction of hydroxide ion in water with substituted styrene oxides, we have reexamined the reaction of styrene oxide with hydroxide ion in ¹⁸O-water and have also studied the reactions of *p*-methyl- and *p*-chlorostyrene oxides with potassium hydroxide in ¹⁸O-water to determine the regiochemistries of these reactions.

The reactions of styrene oxide and its *p*-CH₃- and *p*-Cl-derivatives in 3 M KOH solution yield only diol products. It can be estimated from rate data that at this concentration of KOH approximately 89% of the reaction of *p*-methylstyrene oxide proceeds by the second-order addition of hydroxide ion and the remaining 11% occurs by the spontaneous reaction. For styrene oxide and its *p*-chloro derivative, ca. 97% of the reaction in 3 M KOH occurs by the second-order reaction with hydroxide. The diol products from reaction of each epoxide with hydroxide in both ¹⁸O-water (47% enriched) and ¹⁶O-water were analyzed by gas chromatography-mass spectrometry (GC-MS) with electron impact (EI) detection as described earlier for the analyses of diols from the spontaneous reactions of styrene oxide and its *p*-methyl derivative. The GC-MS data for the diol product from reaction of *p*-methylstyrene oxide in 3 M KOH solution must be corrected for the 11% of product that is formed from the spontaneous reaction, which results in the addition of water almost exclusively at the α -carbon.

From the GC-MS analysis of the diol product from reaction of styrene oxide in K¹⁸OH-H₂¹⁸O, we have concluded that addition of ¹⁸O-hydroxide to styrene oxide occurs equally, within experimental error, at both the α - and β -carbons (51% and 49%, respectively). The ratio of α -attack/ β -attack of hydroxide ion on styrene oxides was also found to be a function of the para-substituent. Addition of ¹⁸O-hydroxide to *p*-methylstyrene oxide occurs 63% at the α -carbon, whereas its addition to *p*-chlorostyrene occurs only 37% at the α -position. Because of the apparent instability of *p*-nitrostyrene glycol to our GC conditions, we were unable to determine the ratio of α/β attack of hydroxide ion on the corresponding epoxide.

From the ratios of α/β attack of HO⁻ and the overall rate constants for reaction of HO⁻ with styrene oxides, rate constants for reaction of HO⁻ at each carbon of the epoxide ring can be calculated and are summarized in Table II. Also summarized are the relative yields of diols resulting from attack of HO⁻ at the α - and β -carbons. Hammett plots of log k_α and log k_β for attack of hydroxide at the α - and β -carbons are plotted in Figure 5 as functions of σ for each substituent. Hammett ρ values for α - and

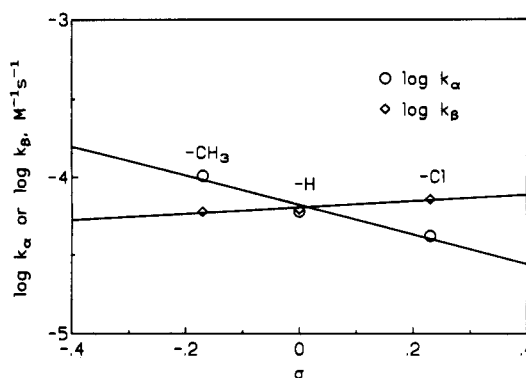


Figure 5. Hammett plots of log k_α and log k_β for addition of hydroxide ion at the α - and β -carbons of para-substituted styrene oxides vs σ .

β -addition of hydroxide ion to the substituted styrene oxides studies are calculated to be -0.9 and $+0.2$, respectively. Use of σ^n instead of σ does not result in any significant difference.

As the analyses of the diol products from reactions of substituted styrene oxides in ¹⁸O-water show, the overall rate constant for reaction of substituted styrene oxides with hydroxide ion is the sum of two rate constants for reactions that have different substituent effects. The positive ρ value for addition of hydroxide ion to the β -carbon partially offsets the negative ρ for addition of hydroxide to the α -carbon. Thus, the overall rate constant does not show a large substituent effect. It is of particular interest that the substituent effect on the addition of hydroxide to the β -methylene carbon is very small. Electron-withdrawing groups would be expected to stabilize the development of negative charge on the incipient oxygen anion on the benzyl carbon at the transition state and thus result in a positive ρ . Presumably the β -carbon, being "primary" in nature, should not bear a significant positive charge at the transition state. Any net increase in charge at this carbon at the transition state would, of course, contribute to a negative ρ . The small substituent effect may reflect a relatively "early" transition state structure in which there is only partial negative charge on the oxygen.

The Hammett ρ for addition of the negatively charged and highly basic hydroxide ion to the α -carbon of styrene oxides is significantly smaller in absolute magnitude than that for addition of neutral water. It is still negative, however, and therefore electron donating groups stabilize the transition state for this reaction. Thus, the transition state for addition of hydroxide ion may be described as one in which two negatively charged oxyanions are tightly coordinated to the benzyl carbon such that there is little positive charge on carbon. The transition state for addition of neutral water to styrene oxides is better described by a structure in which the benzyl carbon is tightly coordinated with an oxyanion and loosely coordinated with a neutral water molecule such that there is a greater degree of positive charge on the benzyl carbon than when hydroxide ion is the nucleophile.

Addition of Methoxide in Methanol to Substituted Styrene Oxides. In order to gain more insight into the mechanisms of reaction of styrene oxides with nucleophiles in hydroxylic solvents, the rates and products of reaction of substituted styrene oxides with methoxide ion in methanol were also determined. Addition of methoxide

Table III. Rate Constants^a for Reaction of Substituted Styrene Oxides with Sodium Methoxide in Methanol and %-Addition of Methoxide to the α - and β -Carbons^b

| para-substituent | $k_{\text{OMe}} \times 10^5$, $\text{M}^{-1} \text{s}^{-1}$ | α/β addition ^c | $k_{\text{OMe}}^{\alpha} \times 10^5$, $\text{M}^{-1} \text{s}^{-1}$ | $k_{\text{OMe}}^{\beta} \times 10^5$, $\text{M}^{-1} \text{s}^{-1}$ |
|-------------------------------|---|---|--|---|
| -OCH ₃ | (5.7) ^d | (70:30) ^d | | |
| -CH ₃ | 3.1 \pm 0.1 | 51:49 | 1.6 | 1.5 |
| -H | 2.1 \pm 0.1 | 38:62 | 0.8 | 1.3 |
| -Cl | 3.2 \pm 0.3 | 29:71 | 0.9 | 2.3 |
| -NO ₂ ^e | 5.7 \pm 0.2 | 15:85 | 0.8 | 4.8 |

^a Obtained from slopes of least-squares plots of k_{obsd} for reaction of substrate vs concentration of sodium methoxide. Ionic strength was not held constant. Rate constants k_{OMe}^{α} and k_{OMe}^{β} for reactions of methoxide ion at the α - and β -carbons, respectively, were calculated by multiplying the total rate constant k_{obsd} by the fraction of each product formed. ^b Product yields from reaction of all epoxides except *p*-methoxystyrene oxide were determined by ¹H NMR analysis of the monomethyl ethers formed by the reaction of the epoxide in 0.55 M NaOCH₃-methanol solution. ^c Ratio of monomethyl ether products from adding of methoxide ion to the α - and β -carbons, respectively, of the styrene oxide starting material. ^d The reaction of *p*-methoxystyrene oxide in methanol solutions containing <2 M sodium methoxide exhibited biphasic kinetics. Most likely some aldehyde is formed from the spontaneous reaction of 1b in methanol and is not stable to reaction conditions. In 3.1 M NaOCH₃-methanol solution, however, the reaction of 1b adhered to rather good pseudo-first-order kinetics. The bimolecular rate constant listed was calculated from the pseudo-first-order rate constant for reaction of 1b in 3.1 M NaOCH₃ solution with the assumption that the reaction is completely second order under these conditions. The product ratio listed is also that from reaction of 1b in this solution. ^e Our kinetic and product data for *p*-nitrostyrene oxide agree very well with those previously reported, ref 6.

in methanol to *p*-nitrostyrene oxide is reported to occur 85% at the β -carbon and only 15% at the α -carbon.⁶ In this study we have also examined the addition of methoxide ion to styrene oxide and its *p*-Cl-, *p*-CH₃-, and *p*-CH₃O-derivatives. Our results show that the ratio of attack of methoxide at the α - and β -carbons is also a function of the electronic nature of the substituent, similar to that found for the addition of hydroxide ion in water.

Pseudo-first-order rate constants for reaction of styrene oxides in methanol with CH₃-, H-, Cl-, and O₂N-substituents at the para-position increased linearly with the concentration of sodium methoxide. Slopes of these plots yield bimolecular rate constants for reaction of the epoxides with methoxide and are summarized in Table III. For solutions containing sodium methoxide concentrations at much less than 3 M, plots of absorbance vs time for reaction of the *p*-methoxy derivative did not follow good first-order kinetics. Presumably some aldehyde from the first-order spontaneous rearrangement of the epoxide forms and is not stable to the highly basic solution. A second-order rate constant for reaction of the *p*-methoxy substrate in 3 M sodium methoxide-methanol is given in Table III, but may have a minor component due to the spontaneous reaction of the epoxide with neutral methanol solvent. Relative yields of monomethyl ethers resulting from attack of methoxide at the α - and β -carbons of each epoxide were determined by ¹H NMR analysis of the product mixture and are also listed in Table III.

The bimolecular rate constants for addition of methoxide ion to the series of substituted styrene oxides listed in Table III also do not vary substantially as a function of the *p*-substituent; e.g., the total range of reactivity is less than a factor of ca. 3. The reactivity of styrene oxide is measured to be slightly less than those of para-substituted derivatives with either electron-donating or electron-withdrawing groups. Multiplying the total rate constant

k_{OMe} by the fraction of product formed by attack of methoxide at the α - and β -carbons yield values for the rate constants of each reaction, and these are also summarized in Table III. From inspection of these partial rate constants it is clear that the substituent effect on the rate of addition of methoxide ion to the α -carbon of styrene oxides is very small. The substituent effect for addition of methoxide to the β -carbon of styrene oxides is somewhat larger. A Hammett plot of $\log k_{\text{OMe}}^{\beta}$ vs σ (not shown) yielded a ρ of +0.6.

Except for minor qualitative differences, the substituent effects on the rates of reaction of methoxide ion in methanol to para-substituted styrene oxides at the α - and β -carbons are quite similar to those for addition of hydroxide ion in water. Addition of the nucleophile at the α -carbon is favored by electron-donating groups, and addition of the nucleophile at the β -carbon is favored by electron-withdrawing groups. Thus, the ratio of products from α -addition vs β -addition of nucleophile is a function of the substituent. For example, reaction of *p*-methoxystyrene oxide with methoxide ion in methanol proceeds mainly via α -addition, whereas reaction of *p*-nitrostyrene oxide with methoxide ion in methanol proceeds mainly via β -addition. The substituent effects, although quite small, are sufficient to cause the product ratios to change significantly with substituent.

Experimental Section

Instrumentation. ¹H NMR spectra were recorded at 80 MHz on an IBM NR-80 spectrometer or at 300 MHz on a General Electric QE-300 spectrometer. Chemical shifts are reported relative to internal tetramethylsilane as standard. Mass spectra were obtained with a Hewlett-Packard Model 5988A GC/MS/DS.

Kinetics Procedures. The pH-rate profiles for hydrolysis of 1a-1e were generated in water solutions with ionic strength held constant at 0.1 or 0.2 by addition of sodium perchlorate as necessary. For maintenance of pH for solutions with pH in the range 4-10, ca. 10⁻³ M buffer reagent was added. Buffers used were acetic acid (pH 4.1-5.5), cacodylic acid (pH 5.6-7.1), Tris (pH 7.5-9.0), CHES (2-(*N*-cyclohexylamino)ethanesulfonic acid) (pH 8.7-9.8) and CAPS (3-(cyclohexylamine)-1-propanesulfonic acid) (pH 9.8-11.0). At the low concentrations of buffer, the contribution of the buffer to k_{obsd} was negligible. For each kinetic run, approximately 5-15 μ L of a stock solution of ca. 10-20 mg of epoxide in 1 mL of dioxane was added to 2.0 mL of reaction solution in the thermostated cell compartment (25.0 \pm 0.2 $^{\circ}$ C) of either a Gilford Response or Perkin-Elmer Lambda 4C spectrophotometer. Reactions were monitored at 232 nm for 1b-d, 225 nm for 1a, and 288 nm for 1e. Pseudo-first-order rate constants were calculated by nonlinear regression analysis of the time vs absorbance data.

The rate of hydrolysis of *p*-nitrostyrene oxide in the pH region of its spontaneous reaction (pH 4-11) was too slow ($t_{1/2}$ = 13 days at 25 $^{\circ}$ C) to be determined by the spectrophotometric method given above. Its spontaneous rate of hydrolysis was determined by HPLC analysis of the reaction solution as a function of time on a Waters Co. C18 Resolve Radial Pak column with 40:60 methanol-water as elution solvent at a flow rate of 1.5 mL/min. A chromatogram of pure epoxide had a single peak retention time 13.1 min and thus indicated that it was stable to HPLC conditions. The diol product had a retention time of 3.4 min under these analysis conditions, and an internal standard, 2-(4-methoxyphenyl)-1-ethanol, had a retention time of 5.3 min.

The rates of reaction of each styrene oxide, except *p*-methoxystyrene oxide, in methanol solutions containing 0.4-1.2 M NaOCH₃ were determined spectrophotometrically. The reactions of 1a, 1c, and 1d were monitored at 232 nm, and that of 1e was monitored at 295 nm. The bimolecular rate constant k_{OMe} for each substrate was determined from the slope of a least-

squares plot of k_{obsd} vs $[\text{NaOCH}_3]$. The absorbance at 238 nm vs time data for reaction of *p*-methoxystyrene oxide (1b) in 3 M NaOCH_3 -methanol solution exhibited reasonably good to first-order behavior, but data collected from reaction of 1b in solutions of <2 M NaOCH_3 exhibited biphasic character.

Materials. Unless otherwise indicated, reagents were purchased from commercial suppliers and used without further purification. Dioxane was distilled from sodium, and tetrahydrofuran was distilled from lithium aluminum hydride. Commercial styrene oxide was distilled at reduced before use. *p*-Methylstyrene oxide (1c)²³ and *p*-chlorostyrene oxide (1d)²⁴ were prepared in 60–65% yield as vacuum-distilled product from the reaction of the appropriate substituted benzaldehyde with dimethylsulfonium methylide in the procedure described by Corey and Chaykovsky.²⁴ *p*-Methoxystyrene oxide (1b) and *p*-nitrostyrene oxide (1e) were prepared from *p*-methoxystyrene bromohydrin²⁵ and *p*-nitrostyrene bromohydrin,^{25,26} respectively. These bromohydrins have been previously converted under basic conditions in good yields to the epoxides by several procedures. A modified procedure for conversion of bromohydrins to epoxides with base was used in this work. This modified procedure is given below for synthesis of *p*-nitrostyrene oxide and is especially useful for the synthesis of some epoxides that are very reactive with water, even at higher pH. The yield of vacuum-distilled *p*-methoxystyrene oxide prepared by this procedure outlined below for the synthesis of *p*-nitrostyrene oxide was 69%.

***p*-Nitrostyrene Oxide (1e).** A solution of 0.90 g of *p*-nitrostyrene bromohydrin^{25,26} in 40 mL of THF was stirred with 2.06 g of powdered KOH at rt for 2 h. The suspended potassium hydroxide and potassium bromide salts were collected by suction filtration and washed with diethyl ether. Solvent was removed from the filtrate, and the residue was vacuum-sublimed at an oil bath temperature of 70–100 °C (0.2 mm) to yield 0.49 g of product (81%), mp 83–84 °C [lit.²⁶ mp 84–86 °C].

Products from Acid-Catalyzed Hydrolyses of 1a–e. Approximately 25 mg of each epoxide in ca. 0.1 mL of dioxane was added to 13 mL of dilute perchloric acid solution at pH 3.9 for 1a, 4.0 for 1b, 3.2 for 1c, and 2.6 for 1d. The reaction solutions were stirred for 10–12 half-lives, and the pH of each reaction solution was then adjusted to 6–8 by addition of base. A small portion of the solution was saved for HPLC analysis, and the remainder was extracted several times with ethyl acetate (total 50 mL). The solvent was removed and the residue sublimed at reduced pressure (ca. 1 mmHg). The ¹H NMR spectrum of each sample was consistent with that expected for pure diol from hydration of the epoxide, and HPLC analyses of the reaction solutions showed in each case only one major peak. The mp's of the diol sublimes from reaction of 1a–d were 65.0–65.5 °C [lit.²⁷ mp 63–64 °C], 78.5–79.5 °C [lit.²⁷ mp 79–81 °C], 76.0–76.5 °C [lit.²⁷ mp 76–77 °C], and 76.5–78.0 °C [lit.²⁸ mp 82 °C], respectively.

The ¹H NMR spectrum of the product mixture from reaction of *p*-nitrostyrene oxide in 0.5 M HClO_4 solution (1:1 dioxane-water) for 5 h at rt was consistent with that expected for a mixture containing mainly *p*-nitrostyrene glycol²⁹ (ca. 93%), along with a minor amount (ca. 7%) of *p*-nitrophenylacetaldehyde.

Products from Spontaneous Hydrolysis of *p*-Methoxystyrene Oxide (1b). To a solution of 1.0 mL of 0.1 M NaClO_4 in water, with pH adjusted to 8.5 and degassed by bubbling argon through it, was added 20 μL of a stock solution of 20 mg of freshly-prepared epoxide in 2.0 mL dioxane. The vial was quickly capped, and the solution was allowed to stand for 45 min at rt. The pH of the reaction solution changed less than 0.1 pH unit during this time period. An aliquot of 20 μL of a solution of 5.8 mg of *p*-methoxybenzyl alcohol in methanol was then added to serve as an HPLC standard, and the pH was adjusted to ca. 7. The solution was analyzed by HPLC with a Waters Radial Pak C18

Resolve column with 40% methanol–60% water as elution solvent, 1.5 mL/min. This analysis showed the presence of two products, one minor one with a retention time of 6.0 min due to *p*-methoxystyrene glycol and a second major one with a retention time of 17.3 min due to *p*-methoxyphenylacetaldehyde. The retention time for the standard was 10.7 min. A parallel reaction of *p*-methoxystyrene oxide at pH 4 was carried out on the same scale, and the same aliquot of HPLC standard was added at the end of the reaction. Since it was determined that the acid-catalyzed hydrolysis of 1a yielded only diol product, it was assumed that the yield of diol from this reaction was 100%. By comparing the integrated areas of the diol and standard peaks from the spontaneous reaction and comparing this ratio with that of the acid-catalyzed reaction, the yield of diol from the spontaneous reaction was determined to be 18%. The remaining product (82%) was assumed to be all aldehyde. Reactions were carried out in triplicate, and calculated yields of products within each set agreed to within 1%.

In a larger-scale reaction of *p*-methoxystyrene oxide at pH 9.0, the products were extracted from the reaction solution into diethyl ether. After drying the solution and removing the solvent, the aldehyde product was isolated by preparative GLPC on a 1/4-in. Hyprose column at 150 °C, retention time 16 min; 80-MHz ¹H NMR δ 3.62 (d, $J = 2.4$ Hz, 2 H), 3.82 (s, 3 H), 6.89 (d, $J = 8.8$ Hz, 2 H), 7.14 (d, $J = 8.8$ Hz, 2 H), 9.71 (t, $J = 2.4$ Hz, 1 H); mass spectrum (EI) m/z 150 (M^+), 121 ($M^+ - \text{CHO}$, 100).

Products from Reaction of *p*-Methoxystyrene Oxide (1b) at pH 5.75 in Solutions Containing Sodium Azide. In each of a series of vials, 2.0 mL of solution containing sodium azide in concentrations up to 0.05 M (ionic strength 0.1 M with NaClO_4), pH 5.75, containing 2×10^{-3} M MES (2-(*N*-morpholino)ethanesulfonic acid) was introduced, and the solution was degassed by bubbling argon through it. To each vial was added 10.0 μL of a stock solution of 20 mg of 1b in 2.0 mL of dioxane, and the vial was capped. The reaction solutions were allowed to stand at rt for >10 half-lives. To each of solution was then added 20 μL of a solution of 6 mg of *p*-methoxybenzyl alcohol in methanol to serve as an HPLC standard, and the pH was adjusted to ca. 7. Reaction solutions were analyzed by HPLC as outlined above for analysis of the products from the spontaneous reaction of 1b, with UV detection at 232 nm and eluent flow rate of 2.0 mL/min. Under these conditions, the retention times of *p*-methoxystyrene glycol product and standard (*p*-methoxybenzyl alcohol) were 3.1 and 4.9 min, respectively. Another product peak with retention time 11.2 min was formed from reaction of 1b in solutions containing sodium azide, in yields that increased with increasing azide concentration. Yields of diol product were calculated from the HPLC tracings, and the remainder was assumed to be azide product. These data are summarized in Figure 3.

Products from Reaction of *p*-Methylstyrene Oxide (1c) in Sodium Azide Solutions. The general procedure outlined above for determining the yields of products from reaction of *p*-methoxystyrene oxide was used for determining the yields of products from reaction of 1c at both pH 5.75 and pH 10.4, except that 2-(4-methoxyphenyl)-1-ethanol was used as the HPLC standard. Retention times for diol product and standard were 5.1 and 7.4 min, respectively. The rates of reaction of 1c in solutions at pH 10.4 containing sodium azide in concentrations from 0 to 5 mM were determined, and from a plot of k_{obsd} vs $[\text{N}_3^-]$ the bimolecular rate constant k_N was calculated to be $8.7 \pm 0.4 \times 10^{-3} \text{ M}^{-1} \text{ s}^{-1}$. Reaction of 1c in sodium azide solutions yielded, in addition to diol product, a second product with retention time 21 min. The yields of this second product increased with increasing sodium azide concentrations. Because of the excellent rate-product correlation, this second product was assumed to be azide adduct from nucleophilic addition of azide ion to 1c. The product(s) from reaction of 1c with azide ion were not isolated or characterized.

Yields of diol product from reaction of 1c at pH 5.75 in solutions containing sodium azide at concentrations 3.1, 6.3, 25, and 50 mM were also determined and found to be 96%, 89%, 78%, and 61%, respectively. A second product with the same retention time as that from reaction of 1c at pH 10.4 was formed in yields that increased with increasing azide concentrations. The decreased yields of diol observed with increasing azide concentrations were close (within ca. 5%) to those predicted from

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considering the rates of bimolecular reaction of **1c** with azide ion and the parallel hydrolysis reaction that occurs at pH 5.75, assuming that the decrease in diol was due entirely to the bimolecular addition of azide to neutral epoxide. If a carbocation in the acid-catalyzed hydrolysis of **1c** were efficiently trapped by azide ion, the decrease in diol yield and corresponding increase in azide yield would be much greater than that calculated if azide product resulted only from the bimolecular addition of azide to neutral epoxide.

Products from the Spontaneous Reactions of Styrene Oxide (1a), *p*-Methylstyrene Oxide (1c), and *p*-Chlorostyrene Oxide (1d). A solution of 25–30 mg of epoxide in 75 μ L of dioxane was added to 13 mL of distilled water at pH 9.5 for **1a** and **1d** and at pH 10.1 for **1c**. Solutions were stirred under argon, and pH was kept constant with a Radiometer pH-stat assembly for periods of 27 h for **1c**, 66 h for **1a**, and 75 h for **1d**. At the ends of these times, 2.0 mL of each reaction solution was quenched with 0.3 mL of 0.1 M mercaptoethanol sodium salt to react with any epoxide that had not hydrolyzed. The pH of the solutions was then adjusted to 7.0–7.5, and they were analyzed by HPLC. The remaining reaction solutions were extracted with ethyl acetate (5×10 mL), and the ethyl extracts were dried over sodium sulfate. The solvent was removed and the residue analyzed by ^1H NMR. In each case, HPLC analysis of the reaction solution showed the presence of only one product peak with the same retention time as that of the corresponding diol, and the NMR spectrum was identical to that of diol isolated from the acid-catalyzed reaction.

Hydroxide-Catalyzed Hydrolysis of 1a, 1c, and 1d in ^{18}O - and ^{16}O -Water. For each epoxide substrate, 6.0 mL of a solution of 3 mg of epoxide in 0.10 mL of dioxane was added to 0.20 mL of aqueous 3.0 M KOH solution that contained 47% ^{18}O . In a parallel set of reactions, the 3.0 M KOH solution contained only ^{16}O -water. After mixing, the reaction solutions were stirred for 4.5–5.0 h (ca. 8–12 half-lives) at rt. The reaction solution was extracted twice with ethyl acetate (1.0, 0.5 mL). The ethyl acetate extracts were combined, and the solvent was removed under a stream of nitrogen. The residue was dissolved in 0.10 mL of diethyl ether and analyzed by GC-MS with a 30-m \times 0.27-mm J & W silica BP-5 capillary column, temperature-programmed, after injection of the sample, from 120–180 $^\circ\text{C}$ at the rate of 10 $^\circ\text{C}/\text{min}$. The retention times of the diol products from **1a**, **1c**, and **1d** were 7.4, 9.2, and 11.2 min, respectively. The mass spectrometer was operated in the electron impact mode, and the intensities of up to 16 relevant individual ions from each diol were measured by single ion monitoring (SIM) over the entire GC peak. The ions selected for monitoring were those several mass units above and below the parent M^+ ion and above and below the fragment $\text{M} - \text{CH}_2\text{OH}$ ion.

From analysis of a given diol from reaction in both ^{18}O -water solutions and solutions containing only ^{16}O -water, the regiochemistry of addition of H^{18}O to the epoxide can be calculated. For example, m/z for the molecular ion of styrene glycol is 138 and m/z for the fragment derived from loss of CH_2OH is 107. Thus, the m/z for the molecular ion of styrene glycol containing ^{18}O is 140 and the m/z for loss of CH_2OH will be either 107 or 109, depending on whether there is loss of $\text{CH}_2\text{ }^{16}\text{OH}$ or $\text{CH}_2\text{ }^{18}\text{OH}$. The intensity of the 138 ion from styrene glycol was only 5–6% of that of the 107 ion but could be measured accurately by the SIM technique. In the mass spectrum of the diol formed from reaction of styrene oxide in water containing only ^{16}O , the 140/138 intensity ratio ranged from 1.1 to 1.6% for three determinations and the 109/107 intensity ratio ranged from 0.2 to 0.6% for three determinations. In the mass spectrum of the diol formed from reaction of styrene oxide in water containing

47% ^{18}O , the 140/138 intensity ratio was measured to be 85.2% and 83.6% for two determinations and the 109/107 intensity ratio was measured to be 29.2% and 29.7% for two determinations. If it is assumed that the $(\text{M} - 2)$ ion intensity for styrene glycol containing one ^{18}O is the same as the $(\text{M} - 2)$ ion intensity for styrene glycol containing only ^{16}O (ca. 2–3%), then comparing the corrected 138 and 140 intensities in the mass spectrum of the glycol product from reaction of styrene oxide in ^{18}O -enriched KOH solution gives the relative amounts of diol containing either one ^{18}O atom or only ^{16}O . From these data it is calculated that 45–46% of diol from reaction of styrene oxide in ^{18}O -enriched KOH solution contains one atom of ^{18}O . This value agrees very well with the fact that the water in the KOH solution was estimated to be 47% ^{18}O . Comparison of the 107/109 intensity ratio, after appropriate corrections, in this same mass spectrum gives the relative amounts of fragment ions containing ^{16}O and ^{18}O at the benzyl position. The amount of ^{18}O residing at the benzyl carbon of the fragment is thus calculated to be 23–24%. Comparison of the amount of ^{18}O in the benzyl position of the fragment ion (23–24%) compared to that in the diol (45–46%) provides the relative amount of ^{18}O that must be located in the benzyl position of the ^{18}O -diol (51–52%). Therefore, it can be concluded that H^{18}O^- attacks styrene oxide 51–52% at the benzyl α -carbon and 48–49% at the β -carbon.

From similar analyses of the mass spectra of diols from reactions of *p*- CH_3 and *p*- Cl oxides **1c** and **1d** in KOH/ H_2O solutions enriched with ^{18}O , the relative yields of diols from addition of hydroxide ion at the α and β carbons of the substituted styrene oxides are calculated. These results are summarized in Table II.

Products from Reaction of Styrene Oxides with Sodium Methoxide in Methanol. To 15 mL of 0.55 M NaOCH_3 in methanol was added 25–30 mg of epoxide. The reaction solution was allowed to stir under nitrogen for 5–6 half-lives (30–60 h) at rt. Methanol solvent was removed on a rotary evaporator and 7–8 mL of 1 M HClO_4 solution was added. The pH of the solution was adjusted to 7–8, a small amount was removed for HPLC analysis, and the remainder of the solution was extracted several times with ethyl acetate (total 50 mL). The solvent was removed on a rotary evaporator and the residue distilled onto a cold-finger in a sublimation apparatus at ca. 100 $^\circ\text{C}$ and 0.5 mmHg. The sublimate was dissolved in $\text{DMSO}-d_6$ and analyzed by ^1H NMR. The NMR spectrum of the monomethyl ether products from reaction of styrene oxide contained a doublet ($J = 4.5$ Hz) at δ 5.29 due to absorption of the benzyl hydroxyl proton in **10a** and a doublet of doublets ($J = 5.1, 6.5$ Hz) at δ 4.19 due to absorption of the primary hydroxyl hydrogen in **11a**. Integration of these two absorptions provides the relative yields of **10a** and **11a**. Similar analyses of the ^1H NMR spectrum of the product mixture from reaction of each of the other substituted styrene oxides provided the relative yields of monomethyl ether products, and the results are summarized in Table III. The HPLC analyses of the reaction solution from reaction of each epoxide showed only two main products, in ratios that agreed well with the ^1H NMR analyses.

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