Solvolysis of (4-Nitrophenoxy)ethylene Oxides

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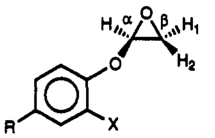
(4-Nitrophenoxy)ethylene oxide (**1a**) (2-chloro-4-nitrophenoxy)ethylene oxide (**1b**), and (4-phenylphenoxy)ethylene oxide (**1c**) were synthesized. Rates of acid-catalyzed, noncatalyzed, and hydroxide ion-catalyzed reactions for **1a** and **1b** and rates of acid-catalyzed and noncatalyzed hydrolysis of **1c** were measured in 0.1 M $NaClO_4$ solutions. Acid-catalyzed hydrolysis of **1a** is *ca.* 6200 times faster than that of 4-nitrostyrene oxide, and that of **1c** is 57 times faster than that of styrene oxide. These increased rates are attributed to stabilization of developing positive charge on the acetal carbon by the phenoxy oxygen that is present in the substituted phenoxyethylene oxides but not in the styrene oxides. The pH–rate profiles for reaction of **1a** and **1b** in 1.0 M KCl solutions over the pH range 2–14 were determined. At intermediate pH, the rates of reaction of **1a** and **1b** in 1.0 M KCl solutions are *ca.* 6–8 times faster than the corresponding rates in 0.1 M $NaClO_4$ solutions. From rate and product studies, these increased reaction rates in KCl solutions were attributed to bimolecular attack of chloride ion at the methylene carbon of the epoxide moiety. The reactivity of **1a** is greater than that of **1b** toward acid-catalyzed hydrolysis but less than that of **1b** in both noncatalyzed and hydroxide ion-catalyzed hydrolysis. Compound **1c** reacts about 73-fold faster than **1a** in acid and about 11-fold faster in the noncatalyzed reaction. From reactivity considerations, it is proposed that H_2O and HO^- also add as nucleophiles to the methylene carbon of the epoxide moieties of **1a** and **1b**, whereas H_2O adds to the acetal carbon of **1c**.

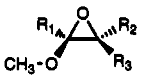
Introduction

Hydrolysis reactions of epoxides have received considerable attention, much of which is due to the observation that epoxides are intermediates in the metabolism of unsaturated and aromatic compounds[1] and may be responsible for the carcinogenic properties of many polycyclic aromatic hydrocarbons.[2]

As a part of a program in which various epoxides were examined as potential substrates and inhibitors of microsomal epoxide hydrolase,[3,4] we have synthesized the (4-nitrophenoxy)ethylene oxide compounds **1a** and **1b**. Both compounds have potential as highly chromogenic substrates for the enzyme. Although **1a** was shown to be a substrate for microsomal epoxide hydrolase,[3b] accurate determination of the enzyme-catalyzed rate required high enzyme concentrations, since the rate of spontaneous hydrolysis of **1a** was competitive with that of the enzyme-catalyzed reaction. Compound **1c** was also synthesized to assess the effect of the nitro group by comparing it with a phenyl substituent.



1a, R = NO_2; X = H
1b, R = NO_2; X = Cl
1c, R = phenyl; X = H



2a, R_1 = H; R_2 = R_3 = Et
2b, R_1 = Ph; R_2 = R_3 = Me

Compounds **1a–c** possess several structural features that make them interesting candidates for solvolytic studies. In addition to being epoxides, they are also acetals, and the oxygen of the epoxide is part of the acetal group. The hydrolysis reactions of acetals have been studied quite extensively.[5] Simple acetals generally undergo only acid-catalyzed hydrolysis, whereas certain acetals that have good leaving groups and can form stable oxonium ion intermediates also react by noncatalyzed reactions.[5c]

Acetals containing both an alkoxy and an aryloxy substituent generally undergo preferential cleavage of the aryloxy–carbon bond.[5a] Cleavage of this bond in the hydrolysis of **1**, however, is unlikely due to the instability of the three-membered oxonium ion that would result. Instead, cleavage of the epoxide oxygen bond to the aryloxy–carbon is expected to occur to produce an aryloxonium ion.

• Abstract published in *Advance ACS Abstracts*, February 1, 1994.

(1) (a) Jerina, D. M.; Daly, J. W.; Witkop, B.; Zaltzman-Nirenberg, P.; Udenfriend, S. *J. Am. Chem. Soc.* 1968, *90*, 6525. (b) Jerina, D. M.; Daly, J. W.; Witkop, B.; Zaltzman-Nirenberg, P.; Udenfriend, S. *Biochemistry* 1970, *9*, 147.

(2) For reviews, see: (a) Jerina, D. M.; Chadha, A.; Cheh, A. M.; Schurdak, M. E.; Wood, A. W.; Sayer, J. M. In *Biological Reactive Intermediates. IV. Molecular and Cellular Effects and their Impact on Human Health* (*Adv. Exp. Med. Biol.* 283); Witmer, C. M., Snyder, R., Jollow, D. J., Kalf, G. F., Kocsis, J. J., Sipes, I. G., Eds.; Plenum: New York, 1991; p 533. (b) Dipple, A.; Moschel, R. C.; Bigger, C. A. H. In *Chemical Carcinogens*, 2nd ed.; Searle, C. E., Ed.; ACS Monograph 182; American Chemical Society: Washington, DC; 1984; Vol. 1, p 41. (c) *Polycyclic Hydrocarbons and Carcinogenesis*; Harvey, R. G., Ed.; ACS Symposium Series 283, American Chemical Society: Washington, DC, 1985.

(3) (a) Oesch, F.; Jerina, D. M.; Daly, J. *Biochim. Biophys. Acta* 1971, *227*, 685. (b) Dansette P. M; DuBois, G. C.; Jerina, D. M. *Anal. Biochem.* 1979, *97*, 340.

(4) (a) Dansette, P. M.; Makedonska, V. B.; Jerina, D. M. *Arch. Biochem. Biophys.* 1978, *187*, 290. (b) Oesch, F. *Xenobiotica* 1972, *3*, 305.

(5) (a) Capon, B.; Smith, M. C.; Anderson, E.; Dahm, R. H.; Sankey, G. H.; *J. Chem Soc. B* 1969, 1038. Capon, B.; Nimmo, K. *J. Chem. Soc., Perkin Trans. 2* 1975, 1113. (b) Fife, T. H.; Natarajan, R. *J. Am. Chem. Soc.* 1986, *108*, 2425. (c) Fife, T. H. *Acc. Chem. Res.* 1972, *5*, 264. (d) Jensen, J. L.; Herold, L. R.; Lenz, P. A.; Trusty, S.; Sergi, V.; Bell, K.; Rogers, P. *J. Am. Chem. Soc.* 1979, *101*, 4672.

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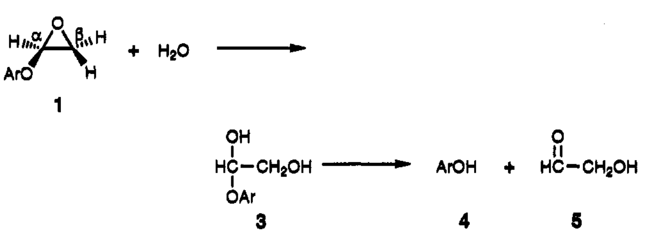
Scheme 1



The rates of reaction of **2a** and **2b** in the pH range 8–11 have previously been reported.[6] From these rate data it was determined that **2a** and **2b** react via both hydronium ion-catalyzed and noncatalyzed pathways. Acid-catalyzed methanolysis of **2a** and several other epoxy ethers with phenyl or alkyl substitution yielded acetal products that resulted from cleavage of the acetal carbon–epoxide oxygen bond.[7] Simple A-1 mechanisms for the hydronium ion-catalyzed hydrolysis reactions of **2a** and **2b** were ruled out in favor of mechanisms involving proton transfer from hydronium ion to the epoxide oxygen concerted with C–O bond cleavage. It was also concluded that the noncatalyzed reactions of **2a** and **2b** involve complex bimolecular processes.[6]

Results and Discussion

The rates of reaction of **1a** and **1b** in water solutions with ionic strength held constant at 0.1 M with sodium perchlorate or at 1.0 M with potassium chloride have been determined in the pH range 2–14. The appearance of phenol products from reaction of **1a** at pH > 6 and **1b** at pH > 4 were monitored by UV spectroscopy at 400 nm, where 4-nitrophenolate ion and 2-chloro-4-nitrophenolate ion absorb strongly. Phenol products are expected to arise from dissociation of α-hydroxy hemiacetal intermediates **3**, the "diol" hydration products of **1a** and **1b** (Scheme 1). The pK_a's of 4-nitrophenol and 2-chloro-4-nitrophenol are 7.14 and 5.45,[8] respectively. Thus, at pH values much less than their pK_a's, kinetics of phenol formation could not be followed at 400 nm since the acid forms of these phenols do not absorb appreciably at this wavelength. Therefore, reactions of 1a at pH < *ca.* 6 and of 1b at pH < *ca.* 4 were monitored at 270 and 317 nm, respectively.

In the acid-catalyzed hydrolysis of benzaldehyde acetals at low pH, hemiacetal intermediates have sufficient stability to accumulate in appreciable concentrations.[9] At pH > *ca.* 5, reaction of the hemiacetal intermediate is rapid relative to that of the acetal. The reactions of **1a** and **1b** at pH < 5 followed excellent first-order kinetics, but the buildup of intermediate hemiacetals prior to initiation of spectrophotometric observations cannot be ruled out. With increasing pH, the formation of hemiacetal should become slower, and its base-catalyzed conversion to aldehyde by expulsion of 4-nitrophenolate ion should become faster. Thus, at some intermediate pH the rates of these processes should be comparable and an induction period for formation of 4-nitrophenolate ion should be observed, if the hemiacetal accumulates. The absence of such induction periods in the reactions of **1a** and **1b** at higher pH rules out the buildup of significant concentrations of intermediate hemiacetals under these conditions.

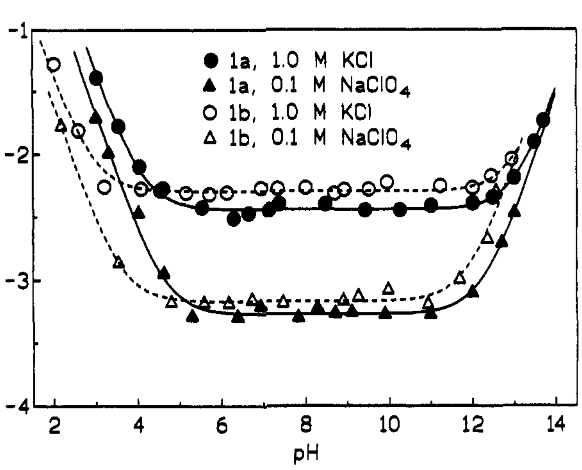


Figure 1. Plots of log k_{obsd} *vs* pH for reactions of **1a** and **1b** in water solutions of 0.1 M $NaClO_4$ and 1.0 M KCl, 25 °C.

Table 1. Rate Constants for Hydrolysis of 1a–c, Styrene Oxide, and 4-Nitrostyrene Oxide in Water at 25 °C

compd	k_H (M^{-1} s^{-1})	k_o (s^{-1})	k_{OH} (M^{-1} s^{-1})
1.0 M KCl			
1a	(43.0 ± 2.3)	$(3.6 \pm 0.1) \times 10^{-3}$	$(2.9 \pm 0.2) \times 10^{-2}$
1b	(3.8 ± 0.4)	$(5.1 \pm 0.2) \times 10^{-3}$	$(4.7 \pm 1.1) \times 10^{-2}$
0.1 M $NaClO_4$			
1a	(21.0 ± 1.5)	$(5.4 \pm 0.2) \times 10^{-4}$	$(2.9 \pm 0.3) \times 10^{-2}$
1b	(2.4 ± 0.3)	$(6.8 \pm 0.3) \times 10^{-4}$	$(7.9 \pm 1.0) \times 10^{-2}$
1c	1530	6.1×10^{-3}	*a*
styrene oxide[b]	27	4.2×10^{-6}	1.2×10^{-4}
4-nitrostyrene oxide[b]	3.4×10^{-3}	6.2×10^{-7}	1.0×10^{-4}

[a] A single measurement in 0.1 M NaOH indicated a rate constant that was identical within experimental error to k_o. Thus, we estimate $k_{OH} < 2 \times 10^{-2}$ M^{-1} s^{-1}, since this value would correspond to a 30% rate enhancement over k_o. [b] Reference 15. Ionic strength 0.2 M maintained with $NaClO_4$.

Plots of log k_{obsd}, where k_{obsd} is the observed pseudo-first-order rate constant for reaction of **1a** or **1b** *vs* pH are provided in Figure 1. The pH–rate profiles consist of three parts, each the result of a kinetically distinct reaction. At pH < *ca.* 5, rates of reaction of **1a** and **1b** increase with increasing hydronium ion concentration. Over a rather wide, intermediate pH range extending from pH *ca.* 5–12, the rates of reaction of these epoxides are independent of pH. At pH > *ca.* 12, the rates of reaction of **1a** and **1b** again increase as the concentration of hydroxide ion increases. The rate data included in Figure 1 were fit to eq 1, where k_H is the second-order rate constant for the

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

hydronium ion-catalyzed reaction, k_o is the first-order rate constant for the apparent spontaneous reaction that predominates in the intermediate pH region, and k_{OH} is the second-order rate constant for reaction of **1a** and **1b** with hydroxide ion. Values for these rate constants are summarized in Table 1.

Reactions of 1a and 1b with Chloride Ion. Both **1a** and **1b** react six to eight times faster in 1 M KCl solution

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(9) (a) Jensen. J. L.; Lenz, P. A.; *J. Am. Chem. Soc.* 1978, *100*, 1291. (b) Capon, B. *Pure Appl. Chem.* 1977, *49*, 1001. (c) Finley, R. L.; Kubler, D. G.; McClelland, R. A. *J. Org. Chem.* 1980, *45*, 644. (d) Przystas, T. J.; Fife, T. H. *J. Am. Chem. Soc.* 1981, *103*, 4884.

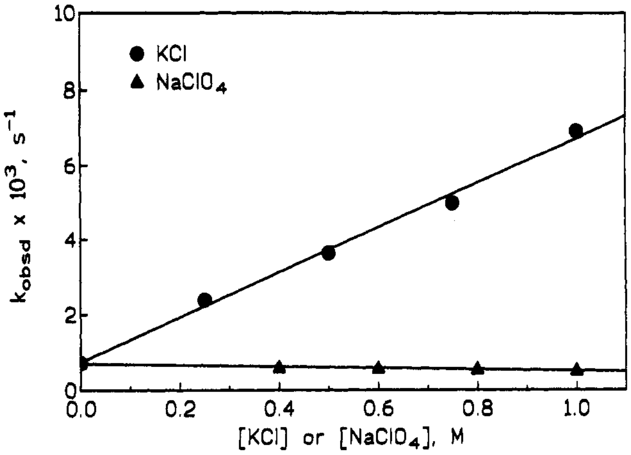

Figure 2. Plots of k_{obsd} *vs* concentration of either KCl or NaClO$_4$ for reaction of **1b** in water solutions, 25 °C. For each run in KCl solution, the pH was maintained at pH 8.40 ± 0.01 by addition of 2×10^{-3} M Tris buffer. For reactions of **1b** in NaClO$_4$ solutions, pH was maintained at 8.00 ± 0.01 by the same buffer.

at intermediate pH than in 0.1 M NaClO$_4$ solution. The acid-catalyzed hydrolyses of **1a** and **1b** are 1.5–2.0 times faster in 1.0 M KCl solutions than in 0.1 M NaClO$_4$ solutions. This increase in acid-catalyzed reaction rate is reasonably attributed to a normal salt effect.[10] The much larger effect of KCl on the spontaneous reactions of **1a** and **1b** must be due to either a very large salt effect or to a second-order nucleophilic reaction of chloride ion with substrate. In order to determine whether increased rates of reaction of (4-nitrophenoxy)ethylene oxides at intermediate pH in 1.0 M KCl solution are due to a normal salt effect of KCl, the rates of reaction of **1b** were determined in solutions at pH 8.4 containing varying concentrations of both KCl and a relatively non-nucleophilic salt, NaClO$_4$. Plots of k_{obsd} *vs* salt concentration for reactions of **1b** at pH 8.0–8.4 are shown in Figure 2. The rate of reaction of **1b** increases significantly with an increase in KCl concentration but actually decreases slightly with an increase in NaClO$_4$ concentration. We conclude from these results that there is a small negative salt effect on the spontaneous reaction of **1b** and that the kinetic term in chloride ion is due to a nucleophilic attack of chloride ion on the epoxide substrate.

Attack of chloride ion on the oxirane ring of **1a** or **1b** can potentially occur at either the acetal carbon to yield α-chloroether **7** or at the methylene carbon to yield hemiacetal **9** (Scheme 2). α-Chloro ethers are very reactive toward solvolysis,[11] and therefore **7**, if formed, might be expected to solvolyze quickly under these reaction conditions to yield phenol **4** and hydroxyacetaldehyde (**5**). The hemiacetal **9** would also be expected to dissociate very rapidly to phenol **4** and chloroacetaldehyde (**10**).

^{1}H NMR analysis of the products from reactions of **1a** and **1b** in 1:9 dioxane-d_8–D$_2$O solutions at pD *ca.* 8.0, containing 1.8 M KCl, indicated that the predominant product of the reaction of **1a** was chloroacetaldehyde (**10**). In addition to resonances assigned to 4-nitrophenol, the NMR spectrum of the products from **1a** contained a triplet (1 H) at δ 5.32 and a doublet (2 H) at δ 3.70. These resonances were identical to those of a sample of commercial chloroacetaldehyde in the same solvent system and were assigned to the hydrated form of the aldehyde (88% yield). In addition, minor resonances at δ 5.14 (1 H, t) and δ 3.60 (2 H, d) were assigned to the hydrate form of hydroxyacetaldehyde, formed in *ca.* 12% yield. Similar ^{1}H NMR analysis of the products from reaction of **1b** showed that approximately 90% of the product was the hydrate of chloroacetaldehyde, and the remaining 10% of product was the hydrate of hydroxyacetaldehyde. In this reaction, 1 molar equiv of 2-chloro-4-nitrophenol was also formed. Resonances that could be assigned to structure **7** from reaction of either **1a** or **1b** were absent.

In the absence of large kinetic solvent deuterium isotope effects on the spontaneous or chloride addition reactions, yields of products from reaction of **1a** and **1b** in water should be similar to those from their reactions in 1:9 dioxane–D$_2$O solutions. It can be extrapolated from the data in Table 1 that the rates of reaction of **1a** and **1b** at intermediate pH will be about 12 times faster in 1.8 M KCl solution than in 0.1 M NaClO$_4$ solution. If the increase in rate is attributed to the bimolecular attack of chloride ion at the β-carbon of the epoxy ether substrate, then approximately 90% of the nonphenolic product from reactions of **1a** and **1b** in 1.8 M KCl solutions should be be chloroacetaldehyde (**10**) (or its hydrate), as observed. The remainder of products (*ca.* 10%) consists of hydroxyacetaldehyde (**5**) (or its hydrate) and can be accounted for by spontaneous reaction of **1a** and **1b** with solvent. Thus, at most only a minor amount (< *ca.* 2%) of hydroxyacetaldehyde hydrate could possibly be formed as the result of a secondary reaction of any chloro ether **7** formed as a primary product from **1**. Within experimental error, therefore, chloride ion adds exclusively at the β-methylene carbons of **1a** and **1b** (Scheme 2).

The pH–rate profiles observed for **1a** and **1b** (Figure 1) in the presence of chloride ion are also consistent with a mechanism that involves predominant attack of chloride ion the β-methylene, rather than the acetal, carbon. Each profile exhibits a rate plateau region that extends from pH *ca.* 5 all the way to pH *ca.* 12. The rate constants associated with these plateaus are due mainly to the nucleophilic attack of chloride on epoxide substrate. The shapes of the pH–rate profiles above neutrality differ from those observed for several other epoxides in KCl solutions. In these reactions,[10,12] the rate-determining step for the process involving chloride ion can be either attack of chloride on the epoxide or solvolysis of the chlorohydrin intermediate analogous to **7** to give diol products. The nature of the rate-determining step depends on the partitioning of the chlorohydrin between reclosure of the epoxide ring and solvolysis to diol. If solvolysis of the chlorohydrin is faster than return to starting material, chloride ion attack on the epoxide is the rate-determining step, whereas if the chlorohydrin recloses to epoxide faster then it undergoes further reaction to product, then solvolysis of the chlorohydrin is rate-determining for the chloride-ion dependent reaction. As the pH is increased, regeneration of the epoxide from the anionic form of the chlorohydrin intermediate becomes rapid relative to solvolysis of the chlorohydrin, resulting in a pH-dependent change in rate-determining step for the chloride-ion

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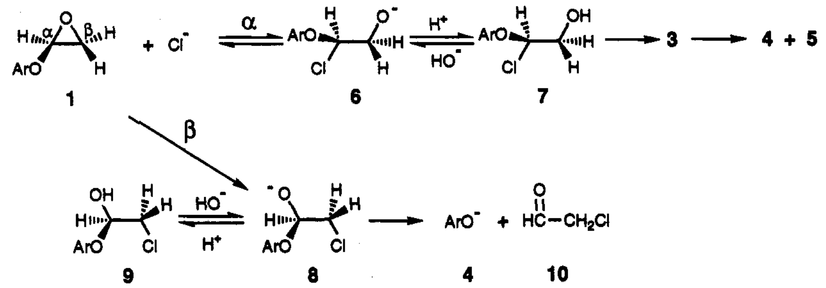
[10] Similar salt effects due to both KCl and NaClO$_4$ have been observed in the hydronium ion-catalyzed hydrolysis of vinyl epoxides: Ross, A. M.; Pohl, T. M.; Piazza, K.; Thomas, M.; Fox, B.; Whalen, D. L. *J. Am. Chem. Soc.* **1982**, *104*, 1658.

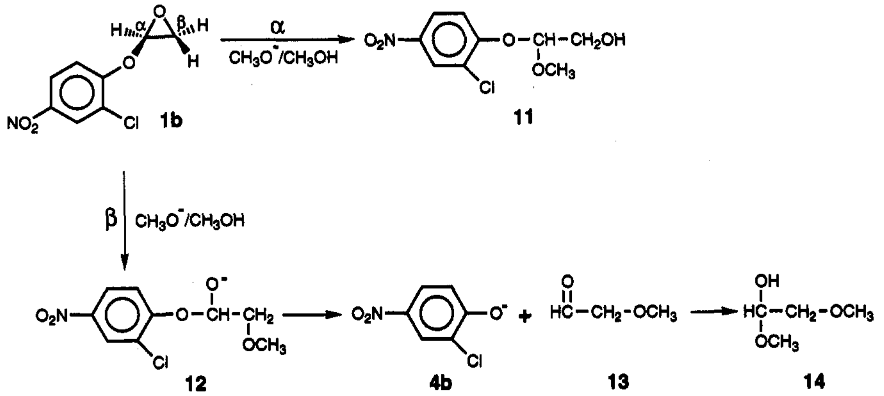
[11] Jones, T. C.; Thornton, E. R. *J. Am. Chem. Soc.* **1967**, *89*, 4863.

[12] (a) Whalen, D. L.; Ross, A. R. *J. Am. Chem. Soc.* **1976**, *98*, 7859. (b) Whalen, D. L.; Ross, A. M.; Dansette, P. M.; Jerina, D. M. *J. Am. Chem. Soc.* **1977**, *99*, 5672. (c) Becker, A. R.; Janusz, J. M.; Bruice, T. C. *J. Am. Chem. Soc.* **1979**, *101*, 5679.

Scheme 2



Scheme 3



dependent reaction. At sufficiently high pH this reaction pathway becomes insignificant relative to direct reaction of water and hydroxide ion with the epoxide, and a change in the reaction pathway occurs. A similar mechanism would be expected for the present reaction if attack of chloride ion occurred at the α-acetal carbon to give **7**. Reaction of neutral **7** to form **4** and **5** is expected to occur via a first-order, pH-independent cleavage of the C–Cl bond of **7** to produce an aryloxonium ion and chloride ion, followed by addition of water to the aryloxonium ion to yield an unstable hemiacetal **3** which is converted to **4** and **5**. At low pH this reaction sequence should occur faster than reclosure of **7** to epoxide, and thus attack of chloride ion on the epoxide should be rate-determining. As the pH of the solution is raised, the second-order reaction of hydroxide ion with **7** to regenerate epoxide **1** and chloride ion should compete with the first-order solvolysis of **7** to form **4** and **5**, since chlorohydrins generally close very rapidly to form epoxides at pH > *ca.* 9.[13,14] Thus, if **7** is an intermediate in the reactions of **1a** and **1b** with chloride ion, a changeover in rate-limiting step from attack of chloride ion on the epoxide to solvolysis of **7** would be expected to occur upon increasing the pH above *ca.* 9, and this change would give rise to a complex pH–rate profile.[10,12]

On the other hand, reaction of chloride ion at the β-methylene carbon to give **9** would not be expected to undergo any pH-dependent change in rate-determining step and hence should give rise to a relatively simple pH–rate profile. The hydrolysis of hemiacetals is markedly catalyzed by hydroxide ion,[9c] and therefore the rate of conversion of hemiacetal **9** to products **4** and **10** should be rapid relative to reclosure of the epoxide ring throughout the pH region above neutrality.[9c] Thus, a pH-dependent change in rate-limiting step from chloride ion attack to solvolysis of **9** is not expected. The simple pH–rate profiles for reactions of **1a** and **1b** in KCl solutions are hence consistent with β-attack and the products formed.

Reactions of 1a and 1b with HO⁻ and CH₃O⁻. The second-order reactions of **1a** and **1b** with hydroxide ion or their spontaneous reactions with water could also occur by addition of solvent to either the acetal (α) or the methylene (β) carbons of the oxirane ring. Addition of hydroxide ion to either oxirane carbon atom will yield the same α-hydroxy hemiacetal intermediate **3**, which will dissociate to phenol and aldehyde products **4** and **5**. Thus, the regiochemistry of addition of hydroxide ion to **1** cannot be determined by product studies in the absence of isotopic labeling. However, methoxide ion may be used as a model for hydroxide ion in order to identify the site of nucleophilic attack. Pseudo-first-order rate constants for the reaction of **1b** in 1–200 mM sodium methoxide in methanol are linearly dependent on the concentration of sodium methoxide with a slope of 4.2×10^{-2} M^{-1} s^{-1}, corresponding to the second-order rate constant for methoxide ion attack, and an intercept of $(9.3 \pm 0.6) \times 10^{-5}$ s^{-1}, corresponding to the rate constant for reaction of **1b** with methanol in the absence of methoxide ion. To determine the regiochemistry of addition of methoxide ion, the product mixture from reaction of **1b** with 0.5 M CD_3ONa in CD_3OD was analyzed by ^1H NMR spectroscopy. If CD_3O^- were to add to the acetal carbon of **1b**, an acetal product **11** (Scheme 3) will be formed that should be stable to the reaction conditions. If CD_3O^- adds to the methylene carbon of **1b**, an unstable hemiacetal anion **12** will be formed that should rapidly dissociate to 2-chloro-4-nitrophenoxide ion and methoxyacetaldehyde. The ^1H NMR spectrum of the product mixture showed resonances identical to those of authentic samples of sodium 2-chloro-4-nitrophenoxide and the hemiacetal from methoxyacetaldehyde and methanol (**14**) in CD_3OD. No other signals

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(13) Hydroxide-induced ring closure of indene chlorohydrin to indene oxide becomes rapid relative to its first-order solvolysis at pH > 9: cf. ref 12a.

(14) Frost, A. A.; Pearson, R. G. *Kinetics and Mechanism*, 2nd ed.; John Wiley & Sons, Inc.: New York, 1961; Chapter 12 and references cited therein.

were present that could be assigned to an acetal with structure **11**. Within experimental error, therefore, methoxide ion in methanol adds exclusively to the methylene carbon of **1b**. Thus, it is likely that hydroxide ion in water also adds at this position.

Further support for the proposal that hydroxide ion adds to the methylene carbons of **1a** and **1b** is provided by the kinetic data summarized in Table 1. Attack of hydroxide ion at the benzyl carbon of substituted styrene oxides is retarded by electron-withdrawing substituents (Hammett $\rho = -0.9$),[15] whereas attack of hydroxide ion on the β-methylene carbon of styrene oxides is slightly accelerated by electron-withdrawing substituents ($\rho = +0.2$).[15] The same substituent effects should operate in the addition of nucleophiles to substituted phenoxyethylene oxides. Therefore, if hydroxide ion were to add to the acetal carbon of phenoxyethylene oxides, k_{OH} for reaction of **1b** should be smaller than k_{OH} for reaction of **1a**, whereas if attack took place at the methylene carbon the reverse should be true. Since k_{OH} is in fact larger for **1b** than for **1a**, relative reactivities of these two substrates are consistent with attack of hydroxide ion primarily at the methylene carbon. The fact that methoxide, chloride, and hydroxide ions add mainly to the β-methylene carbons of **1a** and **1b** parallels the observation that in S_N2 reactions of styrene oxides with electron-withdrawing substituents, nucleophiles add primarily at the β-methylene carbons.[15,16] Our observation that nucleophiles add at the methylene carbons of **1a** and **1b** is in contrast to those of published studies[7a] on the base-catalyzed methanolysis of several aliphatic epoxy ethers, where nucleophilic attack occurs at the acetal carbons.

Reactions of 1a–c with H_2O. The pH-independent reactions of **1a** and **1b** (in the absence of chloride ion) can involve nucleophilic attack of water at either the acetal carbon or methylene carbon. If attack occurs at the acetal carbon then substituent effects on the rate for reaction of water with **1a** and **1b** should parallel those for attack of water at the α-benzyl (retarded by electron-withdrawing substituents; $\rho^+ = -2.0$)[15] rather than to the β-methylene carbon of aryl-substituted styrene oxides. Although ρ for attack of water at the β-carbon of styrene oxides is not known, it is presumably positive, similar to ρ's for attack of hydroxide ion[15] and amines.[16] The electron-withdrawing chloro substituent in **1b** slightly increases its rate of pH-independent hydrolysis (k_o; Table 1) relative to **1a**, consistent with predominant addition of water to the β-methylene carbons of **1a** and **1b**.

Replacement of the strongly electron-withdrawing nitro group (**1a**) by a phenyl group (**1c**) should markedly retard k_o for β-attack by water. In fact, k_o for **1c** is *increased* by a factor of approximately 11 relative to **1a**. We suggest that this result may be due to a change in mechanism from β-attack at the methylene (for **1a,b**) to α-attack at the acetal carbon (for **1c**). An analogous change in mechanism has been documented for attack of benyzylamine on styrene oxides[16] from predominant attack at the methylene carbon (positive Hammett slope) to predominant attack at the benzyl carbon (negative Hammett slope), as the phenyl substituent becomes more electron-donating.

The Acid-Catalyzed Reaction: Comparison of Reactivities of 1a–c with Those of Styrene Oxides. We were particularly interested in a comparison of the reactivities in acid of the phenoxyethylene oxides with the analogous styrene oxides because an ether substituent directly bonded to the α-carbon atom that is presumably the site of epoxide C–O cleavage in acid was expected to have a large effect on the reactivity of **1a** and **1b**. Resonance electron donation by the ether oxygen should markedly stabilize the transition states for acid-catalyzed cleavage of **1a** and **1b** relative to their styrene oxide analogs. Acid-catalyzed hydrolysis of **1a** (Table 1) is *ca.* 6200 times faster than that of 4-nitrostyrene oxide,[15] consistent with additional stabilization of the α-oxocarbonium ion from **1a** relative to the benzylic carbocation that results from benzyl C–O cleavage[17] of 4-nitrostyrene oxide.

The relative reactivities of **1a** and **1b** under acidic conditions are reversed relative to their reactivities under neutral or basic conditions. Thus, the pH–rate profiles for **1a** and **1b** cross at low pH (Figure 1). The reversal in direction of the substituent effect at low pH, such that an inductive electron-withdrawing chloro group in the *ortho* position of **1b** produces an approximately 9-fold decrease in k_H for this compound relative to **1a**, is consistent with the interpretation that the regioselectivity of epoxide ring opening changes for the reaction with acid, relative to the reactions with water and hydroxide ion, and occurs at the α carbon atom. Analogously, the rates of acid-catalyzed hydrolysis[15] and methanolysis[17a] of aryl-substituted styrene oxides, which involve benzyl C–O bond cleavage, are retarded by electron-withdrawing substituents and accelerated by electron-donating substituents (negative Hammett ρ values).

To provide further support for a mechanism involving rate-limiting epoxide cleavage at the α-carbon, analogous to the acid catalysis of styrene oxides, we investigated the reactivity of (4-phenylphenoxy)ethylene oxide (**1c**) in order to provide a clearer indication of the sensitivity to substituent effects of phenoxyethylene oxide hydrolysis in acid. As expected, **1c** reacts more rapidly (57-fold) than styrene oxide and also 73-fold faster than **1a**. The Hammett ρ^+ value for hydronium ion catalyzed hydrolysis of substituted styrene oxides is -4.2.[15] Although a comparable value for acid-catalyzed α-opening of phenoxyethylene oxides is unavailable, a Hammett ρ value that is at least -1.7, and may be even more negative, is expected for this reaction.[18] A ρ value between -2 and -4 is also within the range expected for substituent effects of the nondeparting RO group in the hydronium ion-catalyzed hydrolysis of simple acetals.[20] Use of $\rho = -2$ and

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(15) Blumenstein, J. J.; Ukachukwu, V. C.; Mohan, R. S.; Whalen, D. L. *J. Org. Chem.* **1993**, *58*, 924.

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

(17) (a) Biggs, J.; Chapman, N. B.; Finch, A. F.; Wray, V. *J. Chem. Soc. B* **1971**, 55. (b) Hanzlik, R. P.; Westkaemper, R. B. *J. Am. Chem. Soc.* **1980**, *102*, 2464. (c) Jacober, S. P.; Hanzlik, R. P. *J. Am. Chem. Soc.* **1986**, *108*, 1594.

(18) In the styrene oxides the substituted benzene ring is directly bonded to the reacting carbon atom, whereas in the phenoxyethylene oxides this ring is attached to the epoxide carbon atom through an oxygen link, which should attenuate the substituent effect. The magnitude of the fall-off factor for transmission of inductive substituent effects on log k (or log K) by a methylene group is about 2–3.[19] Use of a fall-off factor of 2.5 results in a predicted ρ value of $-4.2/2.5$ or -1.7 for acid hydrolysis of the phenoxyethylene oxides. Since oxygen but not $-CH_2-$ is capable of direct resonance interaction with electron-withdrawing *ortho* or *para* substituents, the ether linkage in **1a-c** may transmit such substituent effects more effectively than a methylene group. Thus, the calculated ρ value for the phenoxyethylene oxides represents a limit and could in fact be more negative.

(19) Ehrenson, S. *Progr. Phys. Org. Chem.* **1964**, *2*, 195. Wells, P. R. *Linear Free Energy Relationships*; Academic Press: New York, 1968; p 39.

σ values of −0.01 and 0.78 for the 4-phenyl and 4-nitro substituents, respectively,[21] predicts a 38-fold faster rate (k_H) for **1c** relative to **1a**, which is about half the difference observed experimentally. Since the predicted ρ represents a limit and the substituent effect could in fact be larger, the somewhat greater than calculated rate difference between **1a** and **1c** is not surprising. Thus, the magnitude of the substituent effect observed for **1a** *vs* **1c** supports the conclusion that **1a–c** hydrolyze in acid via the same mechanism and rate-determining step as the well-studied[15,17] styrene oxides. It is worth noting that the rate enhancement observed for **1a** *vs* 4-nitrostyrene oxide (~6200-fold) is much larger than that for **1c** *vs* styrene oxide (57-fold); this difference presumably results from different sensitivities to substituent effects (different Hammett slopes) for the styrene oxides *vs* the phenoxyethylene oxides.

Summary

Phenoxyethylene oxides **1a** and **1b** react in water solutions by acid-catalyzed, spontaneous, and hydroxide-catalyzed reactions. It is proposed that the acid-catalyzed hydrolysis of **1a–1c** occurs with epoxide ring opening at the acetal carbon atom via a transition state in which the positive charge is stabilized by the resonance effect of the aryloxy group. These results are similar to published results on the acid-catalyzed methanolysis of other epoxy ethers.[7] An enhanced reactivity of **1a** and **1b** in water solutions containing potassium chloride at pH *ca.* 5–12 is attributed to facile nucleophilic attack of chloride ion on the methylene carbon of the oxirane substrates. Rate and product studies indicate that the reactions of **1a** and **1b** with water, hydroxide ion, and chloride ion in water and methoxide ion in methanol occur by nucleophilic attack at the methylene carbon of the substrate. In reactions of nucleophiles with **1a** and **1b**, the strongly electron-withdrawing nitro group in the *para* position stabilizes formation of an incipient oxyanion on the carbon adjacent to the phenoxy group, thus favoring β-attack.

Experimental Section

Materials and Methods. Unless otherwise indicated, reagents were purchased from commercial suppliers and used without further purification. Dioxane was distilled from sodium metal prior to use. Methanol was treated with magnesium metal turnings and distilled. Solutions of sodium methoxide in methanol were prepared by addition of sodium metal to dry methanol. ^{1}H NMR spectra were recorded at either 80 MHz or at 300 MHz, and chemical shifts are reported relative to internal tetramethylsilane as standard.

Synthesis of Phenoxyethylene Oxides (1a–1c). Phenoxyethylene oxides (**1a**, **1b**) were obtained by direct, peracid oxidation of the corresponding vinyl ethers.[22,23] Purified *m*-chloroperoxybenzoic acid (10 mmol) was added to an equivalent amount of either (4-nitrophenoxy)ethylene or (2-chloro-4-nitrophenoxy)ethylene in methylene chloride (75 mL). The reaction mixtures were stirred at rt for 24 h. The reaction mixtures were cooled to 0 °C, and the precipitated *m*-chlorobenzoic acid was removed by filtration. Ethyl acetate (100 mL) was added, and the solutions were extracted twice with 5% sodium sulfite and dried over sodium sulfate. Solvents were removed under reduced pressure, and the resulting solids were crystallized from methylene chloride/hexane.

The yield of (4-nitrophenoxy)ethylene oxide (**1a**) was 83%: mp 85–87 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.97 (dd, $H_{\beta 1}$), 3.12 (dd, $H_{\beta 2}$), 5.16 (dd, H_α) with $J_{\beta 1,\beta 2} = 4.1$ Hz, $J_{\beta 1,\alpha} = 2.4$ Hz, $J_{\beta 2,\alpha} = 0.8$ Hz, δ 7.18 (d, H_2 and H_6) and 8.25 (d, H_3 and H_5) with $J_{2,3/4,5} = 9.3$ Hz. Anal. Calcd for $C_8H_7NO_4$: C, 53.04; H, 3.90; N, 7.73. Found: C, 52.93; H, 3.93; N, 7.63.

The yield of (2-chloro-4-nitrophenoxy)ethylene oxide (**1b**) was 72%: mp 74–75 °C; ^{1}H NMR (300 MHz, acetone-d_6) δ 3.05 (dd, $H_{\beta 1}$), 3.15 (dd, $H_{\beta 2}$), 5.58 (dd, H_α) with $J_{\beta 1,\beta 2} = 4.2$ Hz, $J_{\beta 1,\alpha} = 2.2$ Hz, $J_{\beta 2,\alpha} = 1.0$ Hz, δ 7.58 (d, H_6) with $J_{5,6} = 7.6$ Hz and 8.26–8.36 (m, H_3 and H_5). Anal. Calcd for $C_8H_6ClNO_4$: C, 44.56; H, 2.81; N, 6.50; Cl, 16.45. Found: C, 44.88; H, 3.01; N, 6.52; Cl, 16.62.

(4-Phenylphenoxy)ethylene oxide (**1c**) was obtained by oxidation of the corresponding vinyl ether with dimethyldioxirane.[24] To a solution of (4-phenylphenoxy)ethylene (50 mg)[25] in dry ice cooled acetone (5 mL) was added dimethyldioxirane (20 mL of ~0.4 M solution in acetone). The reaction mixture was allowed to stand at rt for 30 min. After removal of solvent, NMR indicated the product was esentially pure (4-phenylphenoxy)ethylene oxide (50 mg, quantitative yield): mp 103–104 °C (colorless powder from ether/petroleum ether); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.91 (dd, $H_{\beta 1}$), 3.09 (dd, $H_{\beta 2}$), 5.13 (dd, H_α) with $J_{\beta 1,\beta 2} = 4.2$ Hz, $J_{\beta 1,\alpha} = 2.5$ Hz, $J_{\beta 2,\alpha} = 1.0$ Hz, δ 7.10–7.6 (m, 9H_{ar}); HRMS calcd for $C_{14}H_{12}O_2$ 212.0838, found 212.0837. Anal. Calcd for $C_{14}H_{12}O_2$: C, 79.23; H, 5.70. Found: C, 79.09; H, 5.79. For all three epoxides, values of $J_{\beta,\alpha}$ are somewhat smaller than the values of $J_{cis} = 4.1$ Hz and $J_{trans} = 2.6$ Hz for 4-methoxystyrene oxide that were assigned on the basis of deuterium substitution[26] at the β position trans to the substituted phenyl ring and much smaller than the analogous coupling constants (J_{cis} and J_{trans} 8–10 and 4–6 Hz, respectively) for cyclopropanes.[27] Consistent with the relative magnitudes ($J_{cis} > J_{trans}$) observed in both the latter systems, we assign the resonance that occurs at higher field and exhibits the larger value of $J_{\beta,\alpha}$ to the proton ($H_{\beta 1}$) that is cis to H_α and trans to the phenoxy substituent.

Kinetics of Hydrolysis. The rates of reaction of **1a** in a series of buffer solutions of constant buffer ratio and pH but varying buffer concentrations (generally between 0 and 0.10 M), with ionic strength held constant at 1.0 M with added KCl, were determined. These rate constants were extrapolated to zero buffer concentration to obtain the rate constant for reaction of **1a** at a given pH in the absence of buffer. Buffers used for this purpose were acetic acid, phosphate, Tris, and carbonate. Buffer reagents were not used for pH control in solutions of pH < 3 and > 11. Low concentrations of buffer (*ca.* 10^{-3} M) were present for pH control in solutions used for generating pH–rate profiles for the reactions of **1b** in 1.0 M KCl and 0.1 M $NaClO_4$ solutions and for reaction of **1a** in 0.1 M $NaClO_4$ solutions. For kinetic determinations in solutions with pH > 6, 5 μL of a stock solution containing 5 mg of **1a** or **1b** in 1.0 mL of dioxane was added to 3.0 mL of reaction solution in a cuvette in the thermostated cell compartment (25.0 ± 0.2 °C) of a UV–vis spectrophotometer. Reactions of **1a** at pH > 6 and of **1b** at pH > 4 were monitored at 400 nm by following the appearance of 4-nitrophenolate or 2-chloro-4-nitrophenolate ion, respectively. Reactions of **1a** at pH < 6 and of **1b** at pH < 4 were monitored at 270 nm and 317 nm, respectively. For kinetic determinations in solutions with pH < *ca.* 6, increasing volumes of the reactant stock solution up to *ca.* 25 μL were required to observe a sufficient absorbance

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(20) Cordes, E. H.; Bull, H. G. *Chem. Rev.* **1974**, *74*, 581. Values of Taft's ρ^* are generally in the range of *ca.* −2 to −4.3 for the effect of substituents on the nondeparting alkoxy group in the hydronium ion-catalyzed hydrolyses of acetals. Correction for a 10% difference between the Hammett and Taft scales[21a] gives estimated ρ values between −1.8 and −3.9 for substituents on a resident aryloxy group.

(21) (a) Ritchie, C. D; Sager, W. F. *Progr. Phys Org. Chem.* **1964**, *2*, 323. (b) Since in the 4-substituted phenoxyethylene oxides the substituent is not in direct conjugation with the carbocationic reaction center, values of σ rather than σ^+ are used.

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(23) Kalabina, A. V.; Dubinskaya, E. I.; Filippova, A. K.; Frolov, Y. L.; Ratovskii, G. V. *Izv. Vysshikh Uchebn. Zavedenii, Khim. i Khim. Tekhnol.* **1964**, *7*, 232; *Chem. Abstr.* **1964**, *61*, 10613b.

(24) Adam, W.; Curci, R.; Edwards, J. O. *Acc. Chem. Res.* **1989**, *22*, 205.

(25) Kalabina, A. V.; Tyukavkina, N. A.; Bardamova, M. I.; Lavrova, A. S. *Zh. Obsch. Khim.* **1961**, *31*, 3222; *Chem. Abstr.* **1962**, *57*, 2114i.

(26) Whalen, D. L. Unpublished data. Cf. Ukachukwu, V. C.; Blumenstein, J. J.; Whalen, D. L. *J. Am. Chem. Soc.* **1986**, *108*, 5039.

(27) Cf. Becker, E. D. *High Resolution NMR*, 2nd ed.; Academic Press: Orlando, FL, 1980; p 95.

change. Pseudo-first-order rate constants were calculated by nonlinear regression analysis of the time course for the reaction. Dependence of these rate constants on pH is shown in Figure 1. Kinetics of the hydrolysis of **1c** were followed at 242 nm after addition of 10 μL of **1c** (3 mg/mL in dioxane) to a cuvette containing 3 mL of aqueous buffer (acetate, MES or Tris, pH 4.3–8.0, ionic strength maintained at 0.1 M with $NaClO_4$) or dilute $HClO_4$ (pH 3.8–4.2). No buffer catalysis was observed at four buffer concentrations between 1 and 4×10^{-3} M, and thus, rate constants measured at constant pH in the presence of these buffer concentrations were averaged.

Kinetics of Methanolysis. Pseudo-first-order rate constants for reaction of **1b** in methanol solutions containing 0–0.2 M sodium methoxide were determined by following the appearance of 2-chloro-4-nitrophenolate ion. No other salt was added in order to maintain constant ionic strength. In a typical determination, 5 μL aliquots of a stock solution containing 5 mg of **1b** in 1.0 mL of dioxane were added to 3.0 mL of sodium methoxide–methanol solution that was temperature-equilibrated at 25.0 ± 0.2 °C, and the reactions were monitored at 400 nm.

Products from Reaction of 1a in D_2O–Dioxane-d_8–KCl Solution. A solution of 5 mg of **1a** in 60 μL of dioxane-d_8 was added to 0.54 mL of 2.0 M KCl in D_2O. The reaction mixture was cloudy at first but cleared after several minutes. The pD of the solution was measured to be 7.7.[28] The reaction solution was stirred for 30 min at rt, and its ^{1}H NMR spectrum was then recorded. In addition to resonances due to solvent there were two aromatic resonances that appeared as doublets at δ 8.18 and 6.70 (J = 9.4), assigned to *p*-nitrophenol. Also present were two triplets at δ 5.31 and 5.14 (88:12 ratio, total integration 1 H, J = 4.4 and 5.1, respectively) and two doublets at δ 3.70 and 3.60 (10:1 ratio, total integration 2 H, J = 4.4 and 5.1, respectively). The major triplet at δ 5.31 and major doublet at δ 3.70 had chemical shifts identical to those of a sample of commercial chloroacetaldehyde. Because of the absence of a resonance at δ 9–10 due to an aldehyde hydrogen and the presence of a triplet a δ 5.3, the actual structure of this material was assigned to be the aldehyde hydrate. The minor triplet and minor doublet possessed chemical shifts identical to those of hydroxyacetaldehyde, obtained by allowing commercial glycoaldehyde dimer to stand in the reaction solution for several days. It was assumed, therefore, that the minor product was hydroxyacetaldehyde hydrate.

Products from Reaction of 1b in D_2O–Dioxane-d_8–KCl Solution. A solution of 3.5 mg of **1b** in 60 μL of dioxane-d_8 was added to 0.54 mL of 2.0 M KCl in D_2O as described for **1a** above, and the solution was allowed to stir at rt for 15 min before recording the ^{1}H NMR spectrum. The presence of 2-chloro-4-nitrophenol as one of the products was apparent from resonances at δ 8.38 (H_3, d, J = 3.1 Hz), 8.11 (H_5, dd, J = 3.1, 9.2 Hz) and 6.79 (H_6, d, J = 9.2 Hz). Triplets at δ 5.31 (J = 4.4 Hz) and 5.14 (J = 5.1 Hz), and doublets at δ 3.70 (J = 4.4 Hz) and 3.60 (J = 5.1 Hz) confirmed the presence of both chloroacetaldehyde hydrate and hydroxyacetaldehyde hydrate products, formed in yields of *ca.* 90% and 10%, respectively.

Products from Reaction of 1b in D_2O–Dioxane-d_8 at pD 2.8. To a solution of 4.1 mg of **1b** in 60 μL of dioxane-d_8 was added 0.54 mL of deuterium oxide and a small drop of 0.1 M $HClO_4$ in D_2O. The resulting reaction mixture was cloudy at first but cleared after stirring for 30 min. The pD of the solution was measured to be 2.8.[28] The solution was stirred for 7.5 h, and the ^{1}H NMR spectrum was recorded. In addition to resonances due to 2-chloro-4-nitrophenol, a triplet (1 H, J = 5.1 Hz) at 4.94 and a doublet (2 H, J = 5.1 Hz) at δ 3.40 indicated that hydroxyacetaldehyde hydrate was the only other product. Potassium chloride (80 mg) was added to the product mixture, and the chemical shifts of the triplet and doublet moved to δ 5.14 and 3.60, respectively, the same chemical shifts as those of hydroxyacetaldehyde hydrate in the same solvent.

Products of Methanolysis. Sodium metal (5–7 mg) was added to 0.41 g of methanol-d_4 to produce a solution containing *ca.* 1 M sodium methoxide. The estimated half-life for reaction of **1b** under these conditions is 15 s. A sample of **1b** (5–10 mg) was added, and the ^{1}H NMR spectrum was recorded within approximately 15 min. In addition to resonances due to solvent and at δ 6.49 (H_6, d, J = 9.2 Hz), 7.86 (H_5, dd, J = 9.2, 3.0 Hz), and 8.08 (H_3, d, J = 3.0 Hz), for 2-chloro-4-nitrophenolate ion, there was a single resonance at δ 4.86 that integrated for one hydrogen. This resonance was assigned to the hemiacetal hydrogen in **14**-d_9 ($CD_3OCH(OD)CD_2OCD_3$), derived from attack of methoxide ion at the β-methylene carbon (Scheme 3). Exchange of the methylene hydrogens for deuterium under these highly basic conditions would be expected to be rapid. The hemiacetal hydrogen also slowly underwent exchange under the conditions with a half-life of *ca.* 2 h. Methoxyacetaldehyde hydrate was prepared by stirring a solution of methoxyacetaldehyde dimethyl acetal in water with strongly acidic Amberlite. Fractional distillation of this product mixture followed by collection of an early fraction by gas chromatography yielded a sample containing mostly methoxyacetaldehyde hydrate and water. The ^{1}H NMR spectrum of this sample in methanol-d_4 containing sodium methoxide also contained initially a resonance at δ 4.86, which decreased with time over several hours due to exchange of the hemiacetal hydrogen with solvent.

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(28) The pD of the D_2O solution was calculated by adding 0.4 to the measured pH value: Glasoe, P. K.; Long, F. A. *J. Phys. Chem.* **1960**, *64*, 188.