Solution Chemistry of the *syn*- and *anti*-Tetrahydrodiol Epoxides, the *syn*- and *anti*-Tetrahydrodimethoxy Epoxides, and the 1,2- and 1,4-Tetrahydro Epoxides of Naphthalene

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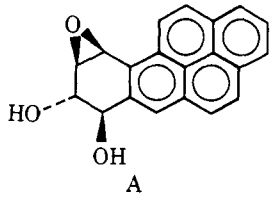
Abstract: The hydrolyses of the *syn*- and *anti*-tetrahydrodiol epoxides (**1** and **2**), the *syn*- and *anti*-tetrahydrodimethoxy epoxides (**3** and **4**), and the 1,2- and 1,4-tetrahydro epoxides (**5** and **6**) of naphthalene occur by both hydronium ion (k_H) and water (k_0) catalysis. Consideration of the various values of k_H and k_0 for **1–4** in H_2O and in 75% dioxane–water suggests that there is no kinetic assistance from an internal hydrogen bond in the solvolysis of **1**. Rather, the values of the various rate constants reflect solely the conformation of the hydroxyl and methoxyl substituents. The large difference in the value of k_H in water for **5** relative to **1–4** is suggested to arise mainly from the pK_a of protonated **5**. From the dependence of the second-order rate constants for nucleophilic attack of β-mercaptoethanol anion upon the concentration of water in dioxane–water mixed solvents, it is concluded that assistance by internal hydrogen bonding to nucleophilic attack on **1** is absent in water but becomes apparent on decrease in the protic nature of the solvent. With the exception of H_3PO_4 and $H_2PO_4^-$ *no* buffer catalysis of solvolysis of **1, 2,** or **5** was observed. The catalysis of the hydrolysis of **1, 2,** and **5** by both H_3PO_4 and $H_2PO_4^-$ is suggested to be general acid in nature based on a study of the products obtained from **5**. Of the epoxides in this study only **5** is subject to nucleophilic attack by chloride and bromide ion. Neither an A-1 nor an A-2 mechanism entirely accounts for the kinetic and product studies with **5** and several suggestions are proposed.

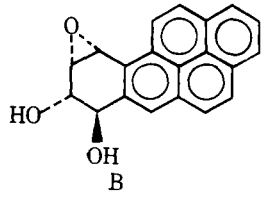
Introduction

Polycyclic aromatic hydrocarbons (PAHs) are oxidatively metabolized by the combined action of the cytochrome P-450 system and the enzyme epoxide hydrase.[1] Many workers have been able to show covalent binding of PAHs to nucleic acids both in vivo[2] and in vitro.[3] It was believed for some time that the K-region epoxides were the metabolites responsible for PAH carcinogenic activity.[4] It had been shown that K-region oxides of carcinogenic PAHs bind to cellular macromolecules to a greater extent than the parent hydrocarbons or possible phenolic metabolites and that they were also more potent in transforming hamster and mouse cell cultures than the parent hydrocarbon.[5,6] With this in mind many studies were undertaken to elaborate the chemistry of both K- and non-K-region arene oxides.[7] With the advent of high-pressure liquid chromatography[8] it has been possible to establish the presence of additional metabolites and the study of these substances has suggested that the ultimate carcinogenic metabolites of PAHs are the tetrahydrodiol epoxides,[9] although the effectiveness of the K-region epoxides as carcinogenic agents cannot be negated. Though the tetrahydrodiol bay region epoxides of PAHs are the most mutagenic,[10] the bay region tetrahydro epoxides are in several cases almost as mutagenic.[11]

In spite of the many published studies of the biological activity (see above) of the tetrahydrodiol and tetrahydro epoxides there is still little known about their chemical reactivity and the mechanisms of their reactions (see Discussion). It has been proposed that the reactivity of the epoxide moiety of 7β,8α-dihydroxy-9β,10β-epoxy-7,8,9,10-tetrahydrobenzo[*a*]pyrene (A, syn isomer) is increased through formation

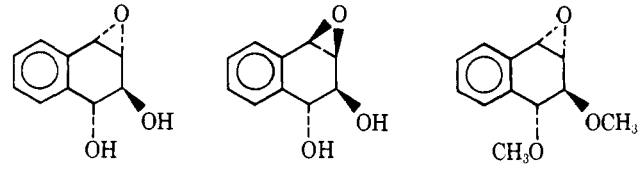


A



B

of an internal hydrogen bond with the 7-OH group. Similar intramolecular hydrogen bonding is not possible with 7β,8α-dihydroxy-9α,10α-epoxy-7,8,9,10-tetrahydrobenzo[*a*]pyrene (B, anti isomer).[12] Like differences in the ability to form an intramolecular hydrogen bond were proposed for the *syn*- and *anti*-tetrahydrodiols of naphthalene (**1** and **2**, respectively).[12b,13] We report herein an investigation of the pH and buffer dependence of solvolysis and nucleophilic attack[14] upon the compounds **1–6.**



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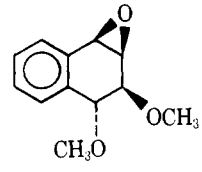

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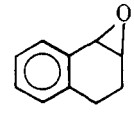

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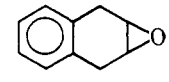

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Experimental Section

General. Melting points are uncorrected. Infrared (IR) spectra were recorded on a Perkin-Elmer 337 or 137 spectrophotometer. Nuclear magnetic resonance (NMR) spectra were obtained on a Varian T-60 or XL-100 instrument (60 MHz unless otherwise stated); chemical shifts are reported as parts per million (ppm) downfield from tetramethylsilane (Me_4Si) in δ units. The data are reported in the order chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, d × d = double of doublets, etc.), coupling constant, and number of protons. Mass spectra were taken on an Associated Electrical Industries MS-902 mass spectrometer using a direct insertion probe (see Acknowledgment). Ultraviolet (UV) spectra were recorded on Cary spectrophotometers and pHs determined on a Radiometer Model 26 pH meter. For those kinetic studies in which $NaClO_4$ was employed to maintain constant μ the calomel electrode was insulated from the titration cell by a $NaClO_4$ flowing junction.[15] All product studies were determined by high-pressure

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liquid chromatography (LC) using an Altex model 100 solvent metering system with a 5-μ, RP-8 (Spectro Physics) reverse phase column (4.6 × 250 nm) at room temperature. A Schoeffel SF 7700 spectroflow detector was used in conjunction with a recorder and a Varian CDC 101 integrator.

Materials. *All synthetic reactions were run under nitrogen.* Most solvents were distilled before use: benzene from calcium hydride, tetrahydrofuran from sodium benzophenone ketyl, dioxane first heated over KOH, then distilled from sodium metal, and then frozen until use. β-Mercaptoethanol was freshly distilled before use and stored under nitrogen. (All kinetic solutions were prepared fresh on each day of use.) The perchloric acid was from an unopened bottle (Mallinckrodt) and stock solutions were titrated with standard KOH to determine the concentration. Metal-free solutions of 1.0 M KCl, 1.0 M $NaClO_4$, and 1.0 M KBr were prepared by extraction with dithizone in CCl_4.[16] All buffer acids and bases and EDTA were commercially available and were employed without further purification. Thick layer chromatography was performed with Analtec 1000-μ silica gel GF plates. All water for kinetic studies was deionized and double glass distilled.

***trans*-1,2-Dibenzoyloxy-1,2,3,4-tetrahydronaphthalene (7).** A solution of iodine (25.4 g, 0.1 mol) in 250 mL of dry benzene was added dropwise over 20 min to silver benzoate (45.8 g, 0.2 mol, prepared by the method of Halperin et al.[17]) in 200 mL of dry benzene. To the resulting thick, yellow suspension there was then added over a period of 5 min 1,2-dihydronaphthalene (13 g, 0.1 mol, Aldrich, technical grade, freshly distilled) in 50 mL of dry benzene. After 8 h of reflux, the cooled reaction mixture was filtered and the precipitate washed well with benzene. The solvent was washed with 2 N sodium carbonate, saturated sodium bicarbonate, water, and brine and dried over magnesium sulfate. Evaporation of the solvent gave 32 g of crude product as an off-white solid which was recrystallized from benzene–methanol (1/10) to give 29.5 g of **7** (79%): mp 140–142 °C; NMR ($CDCl_3$) δ 7.82–8.12 (m, 4 H), 7.05–7.54 (m, 10 H), 6.50 (d, $J_{1,2}$ = 6 Hz, H_1), 5.38–5.72 (m, H_2), 3.07 (t, $J_{3,4}$ = 6 Hz, 2 H, benzylic), 2.07–2.54 (m, 2 H); mass spectrum *m/e* 250 (loss of $C_7H_6O_2$), 222, 219, 145, 128, 115, 105. Calcd for $C_{17}H_{14}O_2$ (loss of $C_7H_6O_2$), 250.099; obsd, 250.100.

4-Bromo-*trans*-1,2-dibenzoyloxy-1,2,3,4-tetrahydronaphthalene (8). To the dibenzoate **7** (20 g, 53.8 mmol) dissolved in 400 mL of carbon tetrachloride there were added 9.8 g of succinimide (55 mmol, recrystallized from water) and ~100 mg of benzoyl peroxide and the stirred reaction mixture was slowly heated. An exothermic reaction began and the mixture came to reflux. The reaction mixture was maintained at reflux for 20 min, cooled, and filtered and the solvent evaporated to give 20.8 g (85%) of **8** as a tan solid; NMR ($CDCl_3$) δ 7.78–8.11 (m, 4 H), 7.07–7.62 (m, 10 H), 6.48–6.74 (m, 1 H), 5.78–6.21 (m, 1 H), 5.36–5.70 (m, 1 H), 2.47–3.05 (m, 2 H).

A portion of the crude product was recrystallized from benzene–hexane to give powdery, white crystals of mp 158–160 °C which appear to be a single isomer:[18] NMR ($CDCl_3$) δ 7.77–8.13 (m, 4 H), 7.10–7.60 (m, 10 H), 6.64 (d, $J_{1,2}$ = 7.8 Hz, H_1), 5.75–6.21 (m, H_2), 5.56 (t, $J_{3,4}$ = 4.0 Hz, H_4), 2.54–2.94 (m, 2 H, $H_{3\alpha}$ and $H_{3\beta}$); mass spectrum *m/e* 330 (loss of $C_7H_5O_2$), 328, 247, 144, 128, 122, 115, 105, 77. Calcd for $C_{17}H_{13}O_2Br$ (loss of $C_7H_7O_2$), 328.001; obsd, 328.001.

***trans*-1,2-Dibenzoyloxy-1,2-dihydronaphthalene (9).** 1,5-Diazabicyclo[4.3.0]nonane (11.2 g, 90 mmol) in 100 mL of dry THF was added dropwise to **8** (23.4 g, 51.9 mmol) in 250 mL of dry THF at 0 °C. The reaction mixture was stirred for 8 h at 0 °C and 12 h at room temperature. Most of the solvent was evaporated and 350 mL of ethyl acetate was added. The organic phase was washed twice with 0.1 N HCl, dilute sodium bicarbonate, and brine and was dried over magnesium sulfate. The purple solution was boiled with activated carbon, filtered, and evaporated. The crude product was purified by column chromatography on silica gel with ethyl acetate. The solvent was evaporated to give a very pale blue solid which was crushed into a fine powder, washed with cold methanol–ether (1/1), and then recrystallized from hexane–ether to give 12 g (63%) of **9**: mp 126.5–128.5 °C; NMR (100 MHz, acetone-d_6) δ 7.80–8.26 (m, 4 H), 7.16–7.80 (m, 10 H), 6.85 (d, $J_{3,4}$ = 9.5, $J_{2,4}$ = 1.0 Hz, H_4), 6.65 (d, $J_{1,2}$ = 7.5 Hz, H_1), 6.26 (d × d, $J_{2,3}$ = 3.7 Hz, H_3), 6.10 (m, H_2); mass spectrum *m/e* 248 (loss of $C_7H_6O_2$), 128, 105. High-resolution mass spectroscopy showed a molecular weight of 248.0858 corresponding to a molecular formula of $C_{17}H_{12}O_2$ with an error of 0.0021 amu. This represents the molecular ion minus benzoic acid.

***trans*-1,2-Dihydroxy-1,2-dihydronaphthalene (10).** The dibenzoate **9** (5 g, 13.5 mmol) was dissolved in 400 mL of methanol–THF (1/1), cooled to 0 °C, when sodium hydroxide (60 mL of 1 N, 60 mmol) was added in four portions over 5 min and the reaction mixture stirred for 2 h at room temperature. Most of the solvent was evaporated, 50 mL of water was added, and the aqueous phase was extracted twice with ether and once with ethyl acetate. The combined extracts were washed with water and brine and dried over magnesium sulfate. The solvent was evaporated and the crude product recrystallized from benzene to give 1.8 g of **10** (82%). The NMR spectrum was consistent with that of Jeffrey et al.[19]

(±)-1β,2α-Dihydroxy-3β,4β-epoxy-1,2,3,4-tetrahydronaphthalene (1). Since the procedure of Yagi et al.[20] did not yield **1** in our hands, it was modified as follows. *N*-Bromoacetamide (435 mg, 15 mmol, recrystallized from methylene chloride–hexane (6/1)) was added in two portions to a solution of **10** (500 mg, 3.08 mmol) in 50 mL of THF/water (3/1) at 0 °C. One drop of 1 N HCl was added and the reaction mixture was stirred for 1 h. Most of the THF was evaporated, 40 mL of ethyl acetate was added, and the layers were separated. The aqueous layer was extracted twice with ethyl acetate and the combined extracts were washed with brine and dried over magnesium sulfate. Evaporation of the solvent gave a yellow-orange oil which was triturated with cold ethyl acetate (−23 °C, dry ice/CCl_4). The crystals were collected and washed with hexane. A second crop was obtained by evaporation of solvents and trituration. A total of 400 mg (50%) of **11** was obtained, mp 153–155 °C. The NMR was consistent with that of Yagi et al.[12b] Under nitrogen the bromotriol prepared above (300 mg, 1.16 mmol) was dissolved in 25 mL of dry THF and the solution was cooled to 0 °C. Potassium *tert*-butoxide (135 mg, 1.20 mmol) was added in two portions over 5 min and the reaction mixture was stirred for 1 h. The mixture was poured through a pad of silica gel using ether, then ethyl acetate. The solvent was evaporated and the crude, pale yellow syrup was purified by thick layer chromatography on silica gel with ether as eluent (R_f 0.35). The product was extracted from the silica gel by repeated washing with ether and ethyl acetate. The solvent was evaporated to yield 190 mg of **1** (92%) as a near-colorless syrup; NMR consistent with that of Yagi et al.;[12b] mass spectrum *m/e* 178 (parent), 160, 132, 131, 119, 103, 91.

(±)-1β,2α-Dihydroxy-3α,4α-epoxy-1,2,3,4-tetrahydronaphthalene (2). The procedure of Yagi et al. was followed.[20] Further purification by recrystallization from $CHCl_3$–CH_3OH yielded white crystals, mp 157–158 °C.

(±)-1β,2α-Dimethoxy-3α,4α-epoxy-1,2,3,4-tetrahydronaphthalene (4). Sodium hydride (67 mg of a 50% oil dispersion, 1.39 mmol) was placed in a dry three-neck flask and was washed with three portions of pentane. Dry THF (10 mL) was added and the mixture was heated to 50 °C. Methyl iodide (238 mg, 1.68 mmol) was added followed by the dropwise addition of **2** (100 mg, 0.56 mmol) in 5 mL of dry THF. The reaction was maintained at 45–50 °C for 15 min. More methyl iodide (~200 mg) was added and the reaction mixture stirred for another 10 min. After cooling, water was carefully added dropwise until no solid remained. The layers were separated and the aqueous layer was extracted twice with ether. The combined extracts were washed with water and brine and dried over magnesium sulfate. The solvent was evaporated and the crude product purified by thick layer chromatography on silica gel with ether–hexane (1/1) as eluent (R_f 0.42) to give 86.6 mg of **4** (75%) as a colorless oil: NMR (100 MHz, acetone-d_6) δ 7.23–7.55 (m, 4 H), 4.30 (d, $J_{1,2}$ = 8.8 Hz, H_1), 3.98 (d, $J_{3,4}$ = 4.4 Hz, H_4), 3.80 (d × d, $J_{2,3}$ = 1.0 Hz, H_3), 3.68 (s, 3 H), 3.63 (s, 3 H), 3.64 (d × d, H_2); UV (H_2O) maxima at 273, 267, 261, 255 (sh) nm; mass spectrum *m/e* 206, 148,[21] 131, 115, 91. High-resolution mass spectroscopy showed a molecular weight of 206.0952 corresponding to a molecular formula of $C_{12}H_{14}O_3$ with an error of 0.0009 amu.

(±)-1β,2α-Dimethoxy-3β,4β-epoxy-1,2,3,4-tetrahydronaphthalene (3). When the above procedure for preparation of the isomeric dimethoxy epoxide **4** was applied in the present case low and nonreproducible yields of **3** were obtained. The reaction mixture turned brown and numerous products were formed even when the reaction was run at 0 °C. A modified procedure was therefore used. In a drybox, ca. 0.5 mL of a 25% oil dispersion of potassium hydride was pipetted into a Schlenk tube and washed three times with 5 mL of ether. While still wet with solvent, the potassium hydride was washed into a three-neck flask with 5 mL of ether. Dry THF (5 mL) and methyl iodide (100 mg, 0.71 mmol) were added and the mixture was cooled to −78 °C. The diol epoxide **1** (42 mg, 0.236 mmol) in 5 mL of dry

THF was added dropwise over 15 min. The reaction mixture was maintained at −78 °C for 6 h and was allowed to warm to room temperature overnight. Water (10 mL) was carefully added dropwise and the layers were separated. The aqueous layer was extracted twice with ether and once with ethyl acetate. The combined extracts were washed with water and brine and were dried over magnesium sulfate. The solvent was evaporated and the crude product purified by thick layer chromatography on silica gel with ether–hexane (1/1) as eluent (R_f 0.32) to give 17.6 mg of **3** (36%) as a white, crystalline solid: mp 115.7–117.0 °C; NMR (100 MHz, acetone-d_6) 7.28–7.68 (m, 4 H), 4.38 (d × d, $J_{1,2}$ = 2.8, $J_{1,3}$ = 1.8 Hz, H_1), 4.00 (d × d, $J_{2,3}$ = 2.5 Hz, H_2), 3.89 (d, $J_{3,4}$ = 4.0 Hz, H_4), 3.72 (m, H_3), 3.48 (s, 3 H), 3.43 (s, 3 H); mass spectrum *m/e* 206 (parent), 174, 131, 114, 103, 91. High-resolution mass spectroscopy showed a molecular weight of 206.093 409 corresponding to a molecular formula of $C_{12}H_{14}O_3$ with an error of 0.000 879 amu.

1,2-Epoxy-1,2,3,4-tetrahydronaphthalene (5). This compound was prepared in 70% yield after distillation, bp 50–52 °C (6 mm) (bp 85 °C, 1 mm[22]), by the action of *m*-chloroperoxybenzoic acid (Aldrich, 85%) on 1,2-dihydronaphthalene (Aldrich, technical grade, freshly distilled) in methylene chloride at 0 °C. Further purification was realized by column chromatography on silica gel with hexane–ether (9/1) as eluent (R_f 0.59) in hexane–ether (7/3); NMR ($CDCl_3$) δ 6.90–7.38 (m, 4 H), 3.46–3.80 (m, 2 H), 1.35–2.90 (m, 4 H); mass spectrum *m/e* 146 (parent), 104, 91. Calcd for $C_{10}H_{10}O$, 146.073; obsd, 146.073.

2,3-Epoxy-1,2,3,4-tetrahydronaphthalene (6). The procedure for preparation of **5** was followed. 1,4-Dihydronaphthalene (2.6 g, 20 mmol, ICN Pharmaceuticals) was used after distillation. By NMR the starting material was composed of 1,4-dihydronaphthalene (~65%), 1,2-dihydronaphthalene (~10%), and tetralin (~25%). The product was readily purified by thick layer chromatography on silica gel with hexane–ether (9/1) as eluent (R_f 0.31). Extraction gave 1.5 g (79%) of **6** as a pale yellow solid, mp 41–43 °C (lit.[23] 43–43.5 °C).

***trans*-1,2-Dihydroxy-1,2,3,4-tetrahydronaphthalene (12).** *trans*-1,2-Dibenzoyloxy-1,2,3,4-tetrahydronaphthalene (**7**) was cleaved by sodium methoxide (Aldrich) in THF–methanol at 0 °C. The crude product was obtained as a tan solid and recrystallized from chloroform to give 300 mg (68%) of **12** as white needles, mp 115–115.5 °C (lit.[24] 112 °C).

***cis*-1,2-Dihydroxy-1,2,3,4-tetrahydronaphthalene (13).** Woodward reaction[23] on 1,2-dihydronaphthalene (Aldrich, technical grade, freshly distilled) yielded the crude monoacetate diol. This was reduced by $LiAlH_4$ in ether to yield the crude diol and then recrystallized from benzene to give 750 mg (46%) of **13** as feathery, white needles, mp 101.5–102.5 °C (lit.[24] 101 °C).

***trans*-2,3-Dihydroxy-1,2,3,4-tetrahydronaphthalene (15) (via 14).** The procedure outlined above for the preparation of **7** (Prevost reaction) was followed. From the Prevost reaction of 1,4-dihydronaphthalene (500 mg, 3.85 mmol, ICN Pharmaceuticals, ~65% pure) 875 mg (~90%) of *trans*-2,3-dibenzoyloxy-1,2,3,4-tetrahydronaphthalene (**14**) was isolated as an off-white solid after purification by column chromatography on silica gel with hexane–ether (3/1) as eluent: NMR ($CDCl_3$) δ 7.86–8.11 (m, 4 H), 7.07–7.57 (m, 10 H), 5.50–5.80 (m, 2 H), 2.85–3.78 (m, 4 H). The trans dibenzoate was hydrolyzed with NaOH–THF–MeOH as described previously for the preparation of **10**. The crude product (321 mg, 86%), was recrystallized from benzene to give 279 mg of **15** as white plates: mp 126–128 °C (lit.[26] 135–136 °C);[27] NMR (CD_3OD) δ 7.05 (s, br, 4 H) 3.64–3.96 (m, 2 H), 2.68–3.10 (m, 4 H); mass spectrum *m/e* 164 (parent), 146, 131, 117, 104, 91.

***cis*-2,3-Dihydroxy-1,2,3,4-tetrahydronaphthalene (16).** The procedure outlined for the preparation of **13** was followed. The crude product, obtained in 42% yield as an off-white solid, was recrystallized from ethyl acetate to give pure diol (**16**) as white needles, mp 122–122.6 °C (lit.[28] 124–125 °C).

pK_a Determinations. The pK_a of β-mercaptoethanol was determined at each dioxane concentration by a computer fit of the absorbance (263 nm) at constant pH values to the equation for the ionization of a monoprotic acid. All pK_as were determined in the pH-stat cell designed for the Cary 15 spectrophotometer.[27] Correction factors were first determined for the glass electrode by making up standard solutions of known hydronium ion concentration for each concentration of dioxane and then determining the pH meter reading. It was found that subtraction of 0.08 from the pH meter reading provided the pH in both 25 and 50% dioxane–H_2O (v/v). pH measurements in 75% dioxane–H_2O were somewhat erratic (see Kinetic Measurements below).

Kinetic Measurements. The kinetic measurement for all reactions carried out in the absence of buffers (pH–rate profiles at 30 °C, μ = 1.0 with KCl, KBr, or $NaClO_4$,[16] and temperature studies, μ = 1.0 with KCl) were obtained in a pH-stat cell designed for the Cary 15 spectrophotometer.[29] Generally 200 μL of a 2×10^{-2} M epoxide stock solution in ethanol (stored at 0 °C) was added to 20.0 mL of a temperature preequilibrated solution (final concentration of epoxide ~2×10^{-4} M) at the desired pH and the disappearance of epoxide was followed with respect to time. All solutions >pH 7.5 had a positive pressure of nitrogen above them to minimize CO_2 absorption. Buffer dilutions with phosphate were typically carried out at five serial dilutions at five or more pHs (for **1** and **5** pHs varied from 5.0 to 6.0 while for **2** it ranged from 3.7 to 4.9; see Results) employing ~10^{-4} M EDTA (pH agreement was ±0.02 at each pH). Generally 50 μL of stock epoxide was added to each of five cuvettes containing 2.0 mL of the respective buffer (0.5–0.05 M) at the desired pH, preequilibrated at 30 °C. The λ_{max} values (nm) monitored for each compound in this study are as follows: **1**, 272; **2**, 269; **3**, 272.5; **4**, 273.2; **5**, 271; **6**, 271.

The reactions with β-mercaptoethanol in water were followed under the pseudo-first-order conditions [S_T] ≫ [epox] in argon degassed Thunberg cuvettes for three thiol dilutions at each of three pHs. Once the thiol anion was established to be the only nucleophile present, all subsequent kinetics in water–dioxane were performed at only one pH. In 75% aqueous dioxane (due to very small absorbance changes) reactions were conducted pseudo first order in epoxide (i.e., [epox] ≫ [S_T]) observing the disappearance of thiol at 250 nm. The 0, 25, and 50% dioxane solutions were 0.1 M in $KHCO_3$–K_2CO_3 (μ = 1.0, KCl). The 75% dioxane was 0.04 M in the same buffer system (μ = 0.10, KCl). Owing to the erratic behavior of the glass electrode, a large quantity of buffer in 75% dioxane was made up and this same stock solution was used for the studies of **1–4**. Thus, although the pH in this solvent system is not accurately known, accurate comparisons of thiol attack are still possible by comparing the ratio of rate constants at the various dioxane concentrations.

All kinetic reactions were found to be first order to 4 or more half-lives. Pseudo-first-order rate constants for all reactions were calculated by least-squares analysis of plots of $\ln (A_\infty - A_0)/(A_\infty - A_t)$ vs. time on a Hewlett-Packard 9825A calculator with a 9862A plotter.

Activation Parameters. The effect of temperature on the rate of acid-catalyzed ring opening of the six epoxides in this study was determined from 40 to 70 °C in 10 °C increments under the same conditions employed for the pH-stat work using 1.0 M KCl. Temperatures were obtained with a calibrated NBS thermometer.

Product Studies. Extinction coefficients were determined for authentic samples of **12, 13, 15, 16,** and α- and β-tetralone at a flow rate of 0.40 mL/min at each methanol–water composition used for the LC separation. The products from **5** were determined immediately after completion of the runs at pH 3.12 in $HClO_4$, 3.27 in HCl, 5.15 (0.5 M NaH_2PO_4–Na_2HPO_4 buffer), and 7.06 (0.10 M Tris-Tris-HCl buffer). The products from **5** in the spontaneous region of the pH–rate profile were obtained from reactions allowed to proceed to only ca. 3 half-lives (for reasons of suspected product instability) under the following conditions: pH 9.67 (0.10 M $KHCO_3$–K_2CO_2 buffer) and 10.20 (0.10 M $NaHCO_3$–Na_2CO_3 buffer). For the three acidic pHs 35% aqueous methanol was used as the mobile phase while 60% aqueous methanol was employed for the remaining pHs. For **6** product studies were determined in only 1.0 M HCl and 1.0 M $HClO_4$ using 35% aqueous methanol as the mobile phase. During the time course of the product study all products with the exception of β-tetralone were stable to the pHs to which they were subjected.

Results

A plot of the logarithm of the observed pseudo-first-order rate constant (k_{obsd}) at 30 °C vs. pH in 1.0 M KCl for compounds **1–6** and 1.0 M $NaClO_4$ for **2** and **5** accurately follow the rate expression

$$k_{obsd} = k_H a_H + k_0 \quad (1)$$

where a_H is the hydrogen ion activity as determined by the glass electrode. The rate constants k_H and k_0 refer to the hy-

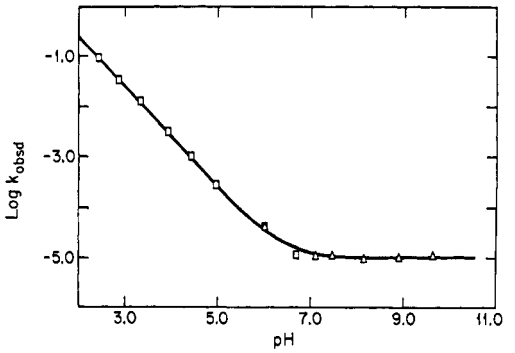

Figure 1. Plot of log k_{obsd} vs. pH for disappearance of **2** at 30 °C, μ = 1.0. The line was generated from eq 1. The squares represent data obtained from a pH-stat while the triangles represent data employing buffers.

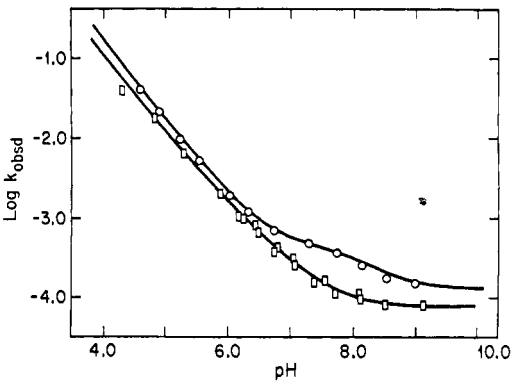

Figure 2. Plot of log k_{obsd} vs. pH for disappearance of **5** at 30 °C, μ = 1.0. The line was generated from eq 2. The squares represent data obtained in KCl while the circles represent data obtained in KBr.

dronium ion catalyzed and pH-independent ring-opening processes, respectively. These values are shown in Table I. A theoretical line generated from eq 1 is shown for **2** in Figure 1. The value of k_0 for **6** was obtained by monitoring its concentration once a day for a period of 6 weeks.

The pH dependence of the solvolysis of **5** in 1.0 M KCl and 1.0 M KBr was found to be inadequately described by eq 1. Scheme I (which is very similar to that proposed by Whalen and co-workers for the chloride ion effect on indene oxide[30] and phenanthrene 9,10-oxide[31]) adequately accounts for the kinetic data in either KCl or KBr. Steady-state approximations for **18** and **19** yield the rate expression

$$k_{obsd} = k_H a_H + k_0 + \frac{k_1[X]}{1 + (k_{-1}K_{a_2}/k_2 a_H)} \qquad (2)$$

where $k_H = k_r/K_{a_1}$ (K_{a_1} is the acid dissociation constant of protonated epoxide and k_r is the rate constant for opening of protonated epoxide) and K_{a_2} is the acid dissociation constant of halohydrin (**19**). Equation 2 was used to generate the theoretical lines shown in Figure 2 and the rate constants displayed in Table II. At low pHs $k_H a_H$ is the dominant term (slope of −1 in the pH vs. log k_{obsd} profile). As the pH increases $k_1[X]$ becomes competitive with $k_H a_H$ until it dominates (pH 7–8.5 for Br^-, pH 6.5–7.5 for Cl^-). As the pH continues to increase the equilibrium between **18** and **19** shifts toward **18** so that the spontaneous pathway is dominant yielding the plateau at pH >9. At these pHs any **18** which is formed returns to **5** by the pathway represented by k_{-1}.

With the exception of H_3PO_4 and $H_2PO_4^-$ no general catalysis was observed for the buffers employed in this study (acetic acid, tris(hydroxymethyl)aminomethane (Tris), imidazole, bicarbonate–carbonate, and formic, malonic, succinic, and cacodylic acid). Primary plots of k_{obsd} vs. total phosphate concentration ([P_T]) at constant pH were linear for **1**, **2**, and **5** showing kinetic behavior in accord with the equation

$$k_{obsd} = k_H a_H + k_0 + k_{ga}\frac{a_H}{K_{a_4} + a_H}[P_T] \qquad (3)$$

Scheme I

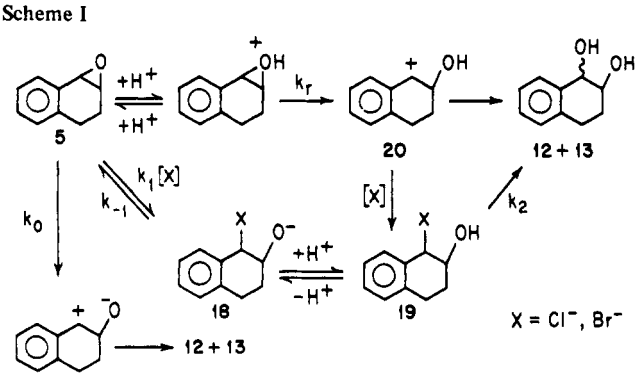

Table I. Rate Constants for the Acid-Catalyzed (k_H, M^{-1} s^{-1}) and Spontaneous (k_0, s^{-1}) Ring Opening of Epoxides (30 °C, Solvent H_2O, μ = 1.0)

epoxide	k_H[a]	k_H[b]	k_0[a] × 10^5	k_0[b] × 10^5
1	6		8.5	
2	40	25	1.1	1.1
3	5		4.0	
4	25		1.1	
5	1200[c]	1250	7.8	3.5
6	0.13	0.020	0.032	

[a] Determined in 1.0 M KCl. [b] Determined in 1.0 M $NaClO_4$. [c] Corrected for chloride effect.[30]

where K_{a_4} refers to the acid dissociation constant of dihydrogen phosphate monoanion. To preclude any chance of Cl^- participation, $NaClO_4$ was used to maintain μ = 1.0 for **5** and μ = 4.0 for **2**. Employing μ = 1.0 ($NaClO_4$ or KCl) with **2** yielded upward curving buffer dilution plots. At ionic strength 4.0 ($NaClO_4$) the contribution to the maintenance of μ by phosphate was decreased (at μ = 1.0 the contribution to μ by phosphate varies from 10 to 100%) and linear buffer dilution plots were obtained for **2**. Assuming only general acid behavior by $H_2PO_4^-$, a plot of the slope from the primary plot vs. $a_H/(K_{a_4} + a_H)$ should yield a linear plot with a slope equal to k_{ga} and a zero intercept. Such plots were far from being linear, suggesting additional kinetic contributions from phosphate. Assuming possible catalysis by H_3PO_4 the equation

$$k_{obsd} = k_H a_H + k_0 + [P_T]\left\{\frac{k_{ga_1}a_H^2 + k_{ga_2}K_{a_3}a_H}{a_H^2 + K_{a_3}a_H + K_{a_3}K_{a_4}}\right\} \qquad (4)$$

can be derived, where K_{a_3} refers to the acid dissociation constant of phosphoric acid and k_{ga_1} and k_{ga_2} the rate constants for catalysis by H_3PO_4 and $H_2PO_4^-$, respectively. From the buffer dilution plots, the primary slope is now given by

$$\text{slope} = \frac{k_{ga_1}a_H^2 + k_{ga_2}K_{a_3}a_H}{a_H^2 + K_{a_3}a_H + K_{a_3}K_{a_4}} \qquad (5)$$

Neglecting a_H^2 in the denominator (due to the pHs used in this study) and rearranging eq 5 leads to

$$\text{slope}/(a_H/(K_{a_4} + a_H)) = \frac{k_{ga_1}a_H}{K_{a_3}} + k_{ga_2} \qquad (6)$$

A plot of the left side of eq 6 vs. a_H (shown for **5** in Figure 3) yields the value of k_{ga_1}/K_{a_3} as slope and k_{ga_2} as intercept (values of k_{ga_1} and k_{ga_2} are given in Table III). A value of 1.6 was used for pK_{a_3}[32] while 6.4 was used for pK_{a_4}.[33] For **2** (μ = 4.0 $NaClO_4$), a value of 1.2 was used for pK_{a_3} while 5.2 was used for pK_{a_4} (determined by half-neutralization).[34]

Table II. Rate Constants for the Reaction of Halide Ion with **5** in Metal-Free Solution at 30 °C, μ = 1.0

	k_H, M^{-1} s^{-1}	k_0, s^{-1}	$k_1[X]$, s^{-1}	$k_{-1}K_a/k_2$, M
chloride	1200	7.5×10^{-5}	$(4.0\text{-}1.3) \times 10^{-4}$ [a]	$(4.0\text{-}0.70) \times 10^{-7}$ [a]
bromide	1600	1.2×10^{-4}	$(3.4\text{-}3.2) \times 10^{-4}$	$(1.3\text{-}1.1) \times 10^{-8}$

[a] Because the chloride pathway represents at most 30% of the reaction pathway (see Figure 2) the higher values of k_1 and kK_{a_2}/k_2 provided fits to eq 2 indistinguishable from the lower values of k_1^{-1} and $k_{-1}K_{a_2}/k_2$.

Table III. Rate Constants for Catalysis of Epoxide Ring Opening by H_3PO_4 (k_{ga_1}, M^{-1} s^{-1}) and $H_2PO_4^-$ (k_{ga_2}, M^{-1} s^{-1}) at 30 °C

epoxide	k_{ga_1}	k_{ga_2}
1[a]	0.48	3.6×10^{-5}
2[b]	1.5	2.8×10^{-4}
5[c]	21	1.0×10^{-3}

[a] Determined at μ = 1.0, KCl. [b] Determined at μ = 4.0, $NaClO_4$. [c] Determined at μ = 1.0, $NaClO_4$.

The nucleophilic reaction of β-mercaptoethanol anion with all six compounds in this study follows the rate law

$$k_{obsd} = k_s \frac{K_{a_5}}{K_{a_5} + a_H} [S_T] \quad (7)$$

where $[S_T]$ = total thiol concentration and K_{a_5} = acid dissociation constant of β-mercaptoethanol (determined to be 9.23, μ = 1.0, KCl at 30 °C). Plots of k_{obsd} vs. $K_{a_5}/(K_{a_5} + a_H)$ were linear showing increasing slopes with increasing pHs, all with zero intercepts (indicating the absence of contribution by other kinetic terms). The k_s and k_H rate constants for **1–4** and the pK_a for β-mercaptoethanol were also determined as a function of dioxane concentration (Table IV). The ratios of k_H and k_s for **1** vs. **2** and **3** vs. **4** as a function of dioxane concentration are presented in Table V.

Activation energies for acid-catalyzed solvolysis of **1–6** were obtained from Arrhenius plots of ln k vs. $1/K$. The values of $E_a^{\ddagger}$ and $\Delta S^{\ddagger}$ at 30 °C (corr coeff of ln k vs. $1/K \geq 0.999$) are provided in Table VI.

The results of the product studies for solvolysis of **5** under six separate conditions are indicated in Table VII. It is to be noted that the product ratio of **12:13** is 94:6 in phosphate buffer at pH 5.15. Employing the rate constants in Table III it may be calculated that for this experiment reaction of **5** with H_3PO_4 and $H_2PO_4^-$ accounts for 31 and 4%, respectively, of the total reaction while acid-catalyzed solvolysis accounts for the remainder. However, the same product ratio was observed at pH 3.12 with $HClO_4$ where only acid catalysis is in effect. This suggests a common intermediate for H_3O^+, H_3PO_4, and $H_2PO_4^-$ catalysis. In addition it was found that at most 2–3% of β-tetralone is formed by the spontaneous ring opening pathway. At all pHs trans diol (**12**) predominates over the cis isomer (**13**). Product studies were determined for **6** only under acidic conditions since it lacks reactivity at high pH values. Employing either 1.0 M HCl or 1.0 M $HClO_4$ the only detectable product from **6** by LC was the trans diol **15.** Based on the initial epoxide concentration, 98 ± 2% of **15** was detected in $HClO_4$ while only 23 ± 2% was found in HCl.

Discussion

It has been suggested[12] in the case of tetrahydrobenzo[*a*]pyrene diol epoxides that an intramolecular hydrogen bond between the 7-OH and the 9,10-epoxide of A (syn isomer) accounts for its greater spontaneous solvolysis with respect to B (anti isomer). This proposed hydrogen bond has been suggested to cause a decrease in the pK of the protonated oxirane ring of A thus resulting in the smaller value for the acid-catalyzed rate constant (k_H).[35] Support for the steric feasibility of an internal hydrogen bond in A was obtained from NMR

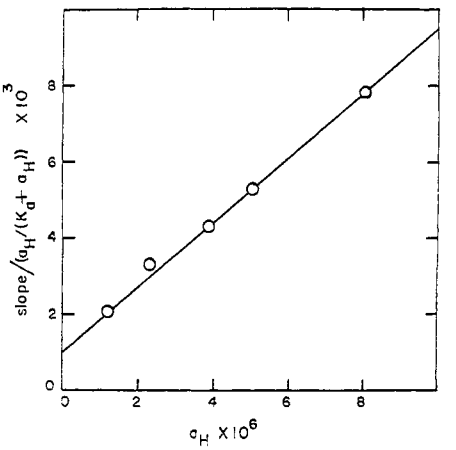

Figure 3. Plot of slope/$(a_H/(K_a + a_H))$ vs. a_H (see text) for reaction of phosphate buffer with **5** at 30 °C, μ = 1.0. The slope is equal to k_{ga_1}/K_{a_3} and the intercept equals k_{ga_2}.

coupling constants (in Me_2SO-d_6) which suggested the trans hydroxyl groups to be in a quasi-diaxial conformation for A and quasi-diequatorial conformation for B.[12b] The naphthalene diol epoxides (**1** and **2**) revealed the same conformational characteristics.[12b,36] We chose the syn and anti dimethoxyl derivatives (**3** and **4**) to test the hydrogen bonding proposal. A methoxyl group has an almost identical electronic effect as that of a hydroxyl group in alkyl systems and, of course, lacks the hydrogen-bonding ability. The NMR data in acetone-d_6[37] (see Experimental Section) show that **3** and **4** have the same conformation as **1** and **2.** The NMR coupling constant for H_1 and H_2 of both **1** and **3** is ~3 Hz, in accord with a diequatorial conformation so the trans hydroxyls and trans methoxyls must be diaxial. The $J_{1,2}$ value for **2** and **4** is ~9 Hz, implying a conformation in which the trans hydroxyl and methoxyl groups are diequatorial. Since the k_H and k_0 rate constants parallel each other so closely for **1** and **3** and for **2** and **4** (Table I) we feel that the differences in reactivity for **1** and **2** are due to conformational differences, not internal hydrogen bonding. The proposed internal hydrogen bond may well be nonexistent in water owing to the competition of water itself for hydrogen bonding to the oxirane ring. For this reason anchimeric assistance by an internal hydrogen bond might only be revealed in kinetic studies by decreasing the protic nature of the solvent. For this purpose we have employed aqueous dioxane solvents. The values of k_H in 75% dioxane (Table IV) all decreased relative to 0% dioxane (Table I). The ratio of rate constants for **1:2** showed little change from that in 0% dioxane. This indicates that even in 75% aqueous dioxane the kinetic importance of an internal hydrogen bond to the value of k_H is negligible. The change in the rate ratio of **3:4** of fivefold amounts to less than 1 kcal and is therefore difficult to attribute to any particular cause. Since the values of k_0 for epoxide ring openings in water are small and are generally greatly depressed on lowering the dielectric constant of the solvent,[7] we were unable to determine them in aqueous dioxane.

The question of internal hydrogen bond assisted nucleophilic attack upon oxirane ring structures has arisen recently in the literature in studies on the antileukemic drug tripdiolide,[38] the

Table IV. Rate Constants for Acid-Catalyzed Ring Opening of (k_H, M^{-1} s^{-1}) and Nucleophilic Attack of β-Mercaptoethanol Anion (k_s, M^{-1} s^{-1}) on Epoxides and pK_as of β-Mercaptoethanol in Water–Dioxane Solvent Mixtures (30 °C)

	k_H	k_s			
(dioxane concn)	(75%[a])	(0[a,c])	(25%[a,c])	(50%[a,c])	(75%[b,d])
pK_a		9.23	10.10[a,c]	10.60[a,c]	11.68[b,d]
epoxide					
1	0.22	0.64	0.85	0.98	3.33
2	1.90	0.51	0.27	0.12	0.18
3	0.052	0.13			0.08
4	0.049	0.62			0.28

[a] μ = 1.0, KCl. [b] μ = 0.10, KCl. [c] Adjusted for pH-meter correction. [d] pH-meter reading (see Experimental Section).

Table V. Ratios of k_s and k_H Rate Constants as a function of the Protic Nature of the Solvent

	vol % dioxane			
	0	25	50	75
		k_s Ratios		
1/2	1.2	3.2	7.9	18.5
3/4	0.20			0.28
		k_H Ratios		
1/2	0.15			0.12
3/4	0.20			1.0

Table VI. Activation Energies[a] and Entropies of Activation[b] at 30 °C for the Acid-Catalyzed Ring Opening of Epoxides, μ = 1.0 (KCl)

	k_H	
epoxide	E_a	$\Delta S^{\ddagger}$
1	18.2	3.2
2	15.4	−2.2
3	19.4	6.7
4	14.6	−5.8
5	15.7	4.6
6	20.7	2.9

[a] kcal/mol. [b] esu.

analeptic drug picrotoxinin,[39] and epoxy steroids.[40] It should be noted that in all of these studies mixed organic–aqueous solvents were used. Examination of the data in Table IV (k_s, 0% dioxane) for attack by β-mercaptoethanol anion in water does not show an enhancement in the rate for nucleophilic attack on **1** relative to either **2, 3,** or **4,** again suggesting no anchimeric assistance by the C-1 hydroxyl group. Assuming trans attack by the thiol anion on **3,** Drieding models suggest that the methoxyl group at C-2 (in a quasi-axial conformation) sterically hinders S_N2 attack on the benzylic carbon of the oxirane ring. This would account for the lower k_s value observed for **3.** Upon increasing the dioxane concentration (see Table V) the values of k_s consistently decrease for **2** while at the same time increase for **1.** A better comparison is available from the data in Table V; the ratio of k_s^3/k_s^4 remains constant in going from 0 to 75% dioxane while the ratio of k_s^1/k_s^2 increases by a factor of 15.[41] Thus, it appears that the ability to form an internal hydrogen bond provides no assistance in the acid-catalyzed (in either 0 or 75% dioxane) or spontaneous (0% dioxane) solvolysis of the oxirane moiety of **1.** However, nucleophilic attack by thiol can benefit from an internal hydrogen bond. The assistance is not very large until the concentration of water as solvent is substantially decreased. Similar results were obtained by Jerina and co-workers[12b] in preliminary studies of nucleophilic attack by *p*-nitrothiophenolate with A, B, **1,** and **2.** They had also found no evidence of anchimeric assistance in A or **1** until the aqueous solvent had been replaced by dry *tert*-butyl alcohol with ca. 5% Me_2SO.

We are unable to explain why the rate constants for the acid-catalyzed solvolysis of **2** and **4** exceed the like constants for **1** and **3** while exactly the reverse is true for the rate constants for spontaneous solvolysis. The difference in the values of k_0 for **1–5** is a factor of 8 (ca. 1 kcal). As stated earlier, a small energy difference is difficult to attribute to a particular factor. The differences in the k_H values between **5** and **1, 2, 3,** or **4** are much larger. We feel that the smaller values of k_H for **1–4** are due mainly to the decrease in pK_a caused by the presence of the electron-withdrawing hydroxyl or methoxyl groups. As pointed out by eq 2, the k_H values we report in Table I are actually equal to k_r/K_{a_1}. Jerina and co-workers in a study comparing the bay-region epoxides of phenanthrene, chrysene, and benzo[*a*]pyrene have suggested stereoelectronic factors[42] as being a major determinant of the greater reactivity toward acid-catalyzed hydrolysis of the tetrahydro epoxides relative to the diol epoxides. They suggested that, owing to the steric interaction at the bay region, the favored conformation for the tetrahydro epoxide was the one which provided for maximum overlap of the aromatic nucleus with the p orbital developing on oxirane ring opening. However, for the diol epoxides the NMR data suggested that the most stable conformation was the one in which the dihedral angle between the developing p orbital and aromatic nucleus was ~60°—a conformation allowing less overlap than the favored one for the tetrahydro epoxides. They therefore suggested that the diol epoxides must either react from the conformation less favorable for maximum p orbital overlap or undergo a prior equilibrium to the less stable conformer before reaction. The fact that no bay region exists for the compounds in this study and yet the rate constant k_H for tetrahydro epoxide **5** exceeds k_H for compounds **1–4** by 30–240-fold suggests that factors other than bay-region enforced stereoelectronic effects are involved. Since the transition state for the spontaneous ring opening must be later than for the acid-catalyzed process,[43] any effects upon the stabilization of the developing carbonium ion should be more strongly felt in the spontaneous pathway. If the stereoelectronic effect is a major factor governing reactivity then the large rate enhancement found for acid-catalyzed solvolysis of tetrahydro epoxides (relative to the diol epoxides) should be even larger in the case of spontaneous solvolysis. This has not been found to be so either in previous studies[42] or in the present study. Jerina has also suggested[42] the "maximum p orbital overlap" argument to account for the ~500-fold difference in the acid-catalyzed rearrangement of benzene oxide (k_H = 32 M^{-1} s^{-2})[44] and cyclohexadiene oxide (k_H = 1.6 × 10^4 M^{-1} s^{-2}).[45] Again, however, the k_0 values do not support his argument (k_0 for benzene oxide is ca. sixfold larger than k_0 for cyclohexadiene oxide).

Our finding of general acid catalysis by H_3PO_4 at four or more pH units above its pK_a (see Results) is indeed surprising—particularly so since no other buffer acid exhibited reactivity. In both cyclopentadiene oxide[46] and cyclohexadiene oxide[45] general acid catalysis was only detected by $H_2PO_4^-$ and cacodylic acid, although for cyclopentadiene oxide it was not reported whether catalysis by other general acids was

Table VII. Ratio of Products from the Rearrangement of **5** in H_2O at 30 °C, μ = 1.0

region of pH-rate profile	counterion	pH	% **12**	% **13**	% recovery (±2)[a]	% **17** (±2)[b]
	Cl^-	3.27	82	18	94	6
k_H	ClO_4^-	3.12	94	6	100	0
	Cl^-	9.67	85	15	100	0
k_0	ClO_4^-	10.20	100	0	99	1
k_{Cl}[c]	Cl^-	7.06	58	42	97	3
k_P[d]	ClO_4^-	5.15	94	6	95	5

[a] Total percent of **12** and **13** determined by LC based on starting epoxide concentration employing authentic **12** and **13** as standards. [b] Maximum concentration of β-tetralone (**17**) formed, obtained from the difference in starting epoxide concentration and the sum of **12** and **13.** [c] Portion of profile where chloride ion has maximum kinetic effect (see Discussion). [d] 0.5 M total phosphate buffer concentration where 31% of reaction pathway is catalyzed by H_3PO_4 and 4% by H_2PO_4. The remainder is acid catalyzed.

looked for. Loudon and Ryono[32] found enhanced catalysis of the hydrolysis of vinyl ethers by H_3PO_4. In their study the general acid rate constant for H_3PO_4 was found to possess a sixfold positive deviation from the Brønsted plot constructed from the general acid rate constants for carboxylic acids. The approximate value of the Brønsted "α" for **1, 2,** and **5** can be obtained from

$$\alpha = \log (k_{ga_1}/k_{ga_2})/(pK_{a_1} - pK_{a_2}) \quad (8)$$

By drawing Brønsted lines of slope "α" (0.8–0.9 for **1, 2,** and **5**) through the log k_H values for **1, 2,** and **5,** it can be shown by calculation that specific acid catalysis would swamp out any general acid catalysis by buffer acids at the concentrations normally used for kinetic studies (up to 0.5 M). The observation of catalysis by phosphate species must be attributed to a positive deviation of log k_{ga_1} and log k_{ga_2} from the Brønsted line for oxygen acids. Indeed, further studies may show this type of general acid behavior by H_3PO_4 to be a general phenomenon for all oxirane ring openings.

Because of suggestions by Jerina and co-workers[47] that phosphate acts as a nucleophile toward A and B (see Introduction) the products from **5** at pH 5.15 in 0.5 M phosphate buffer (see Results) were determined within a time period of 8 half-lives for solvolysis (ca. 10 min) after the addition of the epoxide to the buffer. The same ratio of **12:13** was found as that obtained at pH 3.12 in the absence of buffer when $HClO_4$ was used as the proton source (μ = 1.0, $NaClO_4$; see Table VII). General acid and specific acid catalysis would be expected to produce the same intermediate (**20** in Scheme I) and therefore the same product ratio. Nucleophilic attack by $H_2PO_4^-$ upon protonated epoxide is kinetically indistinguishable from H_3PO_4 general acid catalysis of solvolysis of neutral epoxide. However, phosphate attack would be expected to produce a trans adduct. It is unlikely that such a trans adduct (which would be required to be formed in 31% yield) could hydrolyze quickly enough to be analyzed as diol. Further, it is highly unlikely that the same ratio of **12:13** would be obtained via specific acid–$H_2PO_4^-$ nucleophilic attack as for general- or specific-acid-catalyzed hydrolysis. In fact, Jerina and co-workers[47] note that only ca. 85% of the expected tetrol product is extractable from water in the solvolysis of A or B in phosphate buffer.[48] The remaining tetrol, which they suggest is tied up as an alkylated phosphate derivative, is recoverable upon heating the aqueous solution to 100 °C for 20 min and reextracting. Clearly the phosphate adducts formed from A and B are quite stable. If similar adducts were formed from **5** under the experimental conditions of this study, >95% diol would not have been recoverable within the time period of our analysis. Because the Brønsted α value (see eq 8) is almost identical for **1, 2,** and **5,** we feel that the behavior expressed by k_{ga_1} for **1** and **2** also represents general acid catalysis by H_3PO_4 rather than nucleophilic attack.

As stated earlier (see Results) the kinetic behavior of **5** in the presence of halide ions follows that first seen for indene oxide[30] and 9,10-phenanthrene oxide.[31] For **2,** no chloride effect was found since identical values of k_0 and almost identical values of k_H (factor of ca. 1.7; see Table I) were obtained in the presence of 1.0 M KCl or $NaClO_4$. We feel that the difference in the k_H values is due to a nonnucleophilic salt effect. In the phosphate buffer studies for **2** obvious counterion effects forced us to employ μ = 4.0 (see Results). The values of k_H and k_0 in Tables I and II indicate that the rate of spontaneous solvolysis of **5** is also subject to a salt effect by various counterions. However, the results in Cl^- and Br^- suggest that **5** is also susceptible to nucleophilic attack by halide ions (see Figure 2).

Whalen suggests that the chlorohydrin formed from indene oxide in the acid region in the presence of NaCl (equivalent to **19** in Scheme I) produces cis and trans diol in ca. the same ratio as that produced from the benzyl cation and hence it must hydrolyze, at least partially, through the benzyl cation (equivalent to **20** in Scheme I). In the tetralin series we find that solvolysis of **5** produces a smaller ratio of **12:13** when $HClO_4$ is replaced by HCl (Table VII). This implies that **19** must solvolyze to produce more cis diol than that provided from the collapse of **20** with water. Likewise, the ratio of **12:13** formed by spontaneous (k_0) hydrolysis changes when $NaClO_4$ is replaced by KCl. In $NaClO_4$ no **13** is formed while in KCl **13** is formed in 15% yield. Upon addition of **5** to 1.0 M KCl at acidic pHs, we observed a rapid upward drift in pH followed by a slower downward drift to ca. the initial pH. The observed increase in pH was directly proportional to the initial concentration of **5** and did not occur when $NaClO_4$ was substituted for KCl. This behavior can be predicted from Scheme I if **19** is formed only slightly faster than it disappears (a condition under which the steady-state derivation used to produce eq 2 is still valid). By converting pHs to the corresponding H_3O^+ concentrations at those values where the increase in pH occurred, calculations show that **19** builds up to 2% of the initial concentration of **5** during the course of the reaction.

At pH 7.06 (maximum effect of chloride) employing Tris buffer, **5** produces **12** and **13** in the ratio 58:42. At this pH 29% of **5** proceeds through the chloride pathway indicating that the chlorohydrin formed must produce more cis than trans diol. The expected product from S_N2 attack of Cl^- on **5** is *trans*-**19.** If diol formation is by S_N2 attack of H_2O on chlorohydrin then *trans*-**19** would be expected to produce cis diol (**13**). By the above assumption chloride attack on **5** at pH 7.06 should account for 29% of **13.** The remaining solvolysis (71%) is by the acid-catalyzed pathway which, according to the results of Table VII (see the product ratio for k_H in HCl), should provide 58% of **12** and 13% of **13.** By the above analysis, at pH 7.06 the chloride and acid-catalyzed pathways should yield **12** and **13** in the ratio of 58:42, respectively, which is in accord with our experimental findings. In the acid-catalyzed pathway **20** would be expected to produce both *cis*- and *trans*-**19** (see Scheme I) and therefore no assessment can be made of the relative rates of trapping of **20** by Cl^- and H_2O. However, we do feel that

20 would produce predominantly *trans*-**19** (owing to the ratio of **12:13** from **20** in $HClO_4$; see Table VII) therefore producing a large amount of **13** when HCl is substituted for $HClO_4$. This is experimentally realized. Although our assumption of S_N2 attack on **19** agrees with the product ratios, we cannot eliminate concurrent S_N1–S_N2 or exclusively S_N1 mechanisms which might fortuitously explain the product ratios.

Substantial amounts of 2-indanone were found by Whelan in the spontaneous rearrangement of indene oxide.[30] It is therefore surprising that little or no β-tetralone (see **17** in Table VII) is produced in the spontaneous rearrangement of **5**. Evidently for **5**, the "NIH" shift is not able to compete with the trapping of the zwitterionic carbonium ion by H_2O or chloride ion.

Controversy still exists as to whether the acid-catalyzed pathway for oxirane ring opening is an A-1 or A-2 mechanism.[49a-d] The results of this study are not entirely consistent with either mechanism. For A-1 or general acid mechanisms we would expect trapping of **20** by H_2O (Scheme I) to produce cis and trans diol (**12** and **13**) in a ratio of ca. 1:1. For an A-2 mechanism we would expect only trans diol. However, the change in the ratio of **12:13** at acidic pHs when $NaClO_4$ is replaced by KCl, even though the k_H rate constant remains invariant, suggests different rate- and product-determining steps and hence an intermediate must be formed. An ion-pair intermediate with either Cl^- or ClO_4^- as the counterion or a borderline A-2 mechanism (bond breaking is further advanced than bond making) may account for our results. Kinetic studies on oxirane ring opening by halogen acids in aqueous solvents have suggested rate-determining formation of ion pairs,[50] while many authors have evoked borderline A-2 mechanisms to account for their results.[49a,b,51]

For the acid-catalyzed oxirane ring opening negative $\Delta S^{\ddagger}$ values have been employed to support an A-2 mechanism. All of the $\Delta S^{\ddagger}$ values in Table VII are ca. zero or slightly positive suggesting an A-1 mechanism. However, the product studies suggest that this is not the case for **5**. Recently Pocker and Ronald[52] have obtained a $\Delta S^{\ddagger}$ of -1.6 ± 0.7 for tetramethylethylene oxide, an epoxide for which their product data suggests an A-2 mechanism. Values of entropies of activation for acid-catalyzed epoxide solvolyses may therefore not be a good criterion for elucidation of mechanisms. It has been suggested[53] that the loss of entropy due to freezing out a water molecule in the transition state in an A-2 mechanism may be compensated for by the gain in rotational entropy upon cleavage of the C–O bond of the oxirane ring. This feature would be dependent upon the extent of C–O bond breaking in the transition state and is thus not easily determinable.

A study of the spontaneous rearrangement of five arene oxides[33] has suggested the involvement of H_2O as an encounter-controlled protonic trapping agent of the intermediate zwitterion, preventing the latter from returning to starting epoxide. In this study the change in the ratio of **12:13** from 100:0 in $NaClO_4$ to 85:15 in KCl (Table VII) for spontaneous solvolysis might at first glance indicate competitive trapping of the zwitterion by Cl^- and H_2O, similar to the trapping of **20** in the acid-catalyzed pathway. The generation of chlorohydrin (with *trans*-**19** expected to predominate) would produce the additional **13** seen when Cl^- was present. However, at the pHs where the product study was carried out (see Table VII), any **18** which is formed from the zwitterion would react by the k_{-1} pathway to regenerate **5** and the percentage of **13** produced would never increase. A mechanism where trapping (protonation) of the zwitterion by H_3O^+ to generate **20** which can then be trapped by Cl^- and H_2O is neither kinetically competent nor in agreement with the product studies. An alternative to Scheme I with H_2O acting to donate a proton to **18** thus forming **19** (in conjunction with H_3O^+, see Scheme I) is in accord with product studies. However by microscopic reversibility HO^- must remove the proton from **19** (to produce **18**) generating an additional kinetic term which is not in accord with that observed experimentally. Although not commented on, the product ratio from indene oxide[30] showed a similar (although smaller[54]) change when KCl was substituted for $NaClO_4$ in the spontaneous pathway. We are unable to explain these anomalous results.

Clearly the behavior of the tetrahydrodiol and tetrahydrodimethoxy epoxides vs. the tetrahydro epoxides toward nucleophilic attack and spontaneous and general-acid-catalyzed oxirane ring opening indicates that all these epoxides have similar solution chemistry. Contrary to previous suggestions, we find the absence of a significant contribution by an internal hydrogen bond in **1** except for nucleophilic attack in organic–aqueous solutions. Of major concern, which we are not able to answer in this study, is whether the same parallels will be found in PAHs which are carcinogens or whether naphthalene represents a unique system.[53]

Acknowledgment. This work was supported by grants from the National Institutes of Health (AM 09171-13) and The American Cancer Society (BC-124). We should like to express our appreciation to Dr. V. P. Williams and Mr. J. Kruse (UCLA) for mass spectral analysis (National Institutes of Health Grant HL-12745).

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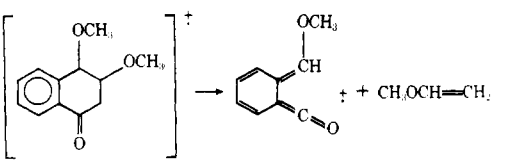

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Oxidation of Amines with Sulfonyl Peroxides. 5. Base-Promoted, Imine-Forming Eliminations in *N*-Benzyl-*O*-arylsulfonylhydroxylamines Produced from Benzylamines and Sulfonyl Peroxides

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Abstract: The reactions of substituted benzylamines with substituted arylsulfonyl peroxides give a series of *O*-sulfonylhydroxylamines, $XC_6H_4CH_2NHOSO_2C_6H_4Y$, which undergo base-induced elimination to the imine. By suitable choice of amine and peroxide, substituent effects on the benzylic position and on the leaving group were determined, kinetic deuterium isotope effects were measured, and activation parameters were obtained for imine-forming elimination. The results are best interpreted in terms of an elimination transition state in which leaving group loss is well ahead of benzylic proton removal. The present results are compared with other imine-forming eliminations and with olefin-forming eliminations. The respective transition states are well-accommodated by utilizing a More O'Ferrall-Jencks diagram to depict bonding changes from one system to another.

Introduction

Olefin-forming 1,2-elimination reactions have been studied extensively, and a rather detailed qualitative understanding of steric and electronic effects on these reactions has evolved.[2] In contrast, if one excludes the acid-catalyzed reactions of carbinolamines,[3] 1,2-eliminations to give carbon–nitrogen double bonds have received very little attention. Nitrogen-substituted amines (haloamines, *N*-tosyloxy derivatives) are known to undergo facile elimination to the imine,[4] and several synthetic procedures for oxidative deamination have attempted to exploit this facility.[5]

Until recently, virtually no mechanistic studies of these systems had been reported. Brauman and Hill reported that *N,N*-difluoroalkylamines undergo elimination in aqueous diglyme, the water being sufficiently basic to promote the elimination (eq 1).[6] Reactivities and activation parameters were presented, but several traditional methods for studying eliminations (substituent effects, isotope effects, etc.) were not included. Oae and Sakurai investigated the formation of imines from *N*-benzoyloxydibenzylamines and weak bases (azide, chloride, and cyanide) in Me_2SO (eq 2).[7] Negligible substituent effects were observed (X = H, *p*-CH_3, *p*-Cl) but a large

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