Reactions of α-Chloro Epoxides. 1. Hydrolysis of 1,3-Dichloropropene Oxide

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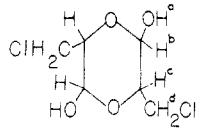
A reinvestigation of the hydrolysis of 1,3-dichloropropene oxide (1) is reported. In contrast to a previous report, the hydrolysis product is 2-hydroxy-3-chloropropanal (4), which dimerizes to 2,5-dihydroxy-3,6-bis(chloromethyl)-1,4-dioxane (5). The α-chloroacrylaldehyde (2) originally reported as the hydrolysis product is derived from the primary thermal isomerization product 2,3-dichloropropanal (3).

In a recent paper Kline, Solomon, and Van Duuren studied the hydrolysis and thermolysis of several α-chloro epoxides, including *cis*- and *trans*-1,3-dichloropropene oxide (**1a** and **1b**, respectively).[1] They reported that both **1a** and **1b** afford α-chloroacrylaldehyde (**2**) upon hydrolysis in pH 7.4 buffer at 37 °C with pseudo- first-order rate constants (k_H) determined to be 2.4×10^{-3} and 2.3×10^{-3} min^{-1}, respectively. They also indicated that thermolysis of **1b** at 200 °C in xylene affords **2** and 2,3-dichloropropanal (**3**) with a measured rate constant (k_i) of 6.1×10^{-3} min^{-1}. No yields of **2** or **3** were given for either the hydrolysis or thermolysis experiments.

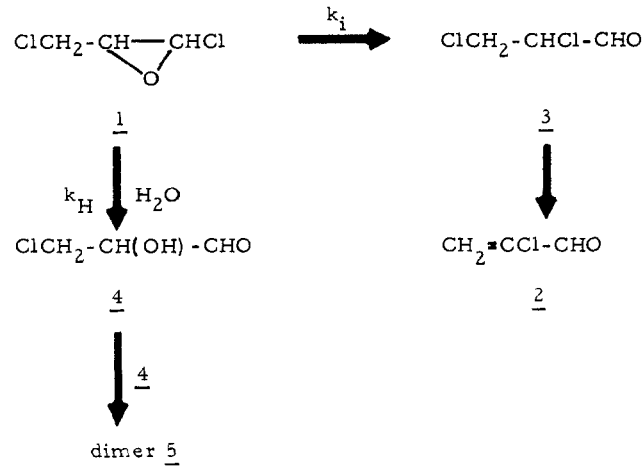
The results of Kline et al.[1] are not entirely consistent with those obtained in our laboratory. Thus, we report herein a more complete study of the reactions of **1a** and **1b** (50% each) in aqueous buffer. Reactions of **1a** are the same as the cis and trans mixture. We conducted our experiment at 20 °C rather than 37 °C to discern between hydrolysis and thermolysis products. A 3.88×10^{-3} M solution of **1a** and **1b** in a 50% THF–pH 7.4 phosphate buffer was stirred for 168 h, at which time no epoxide starting material remained. The rate of disappearance of **1a** and **1b** under these conditions was measured by the method of Barbin et al.[2] and calculated to a half-life of 800 min. Upon workup the reaction afforded a 52% yield of **3** and **2** in trace amounts. The "true" hydrolysis product 2-hydroxy-3-chloropropanal (**4**) could not be isolated in pure form because of its propensity to dimerize to 2,5-dihydroxy-3,6-bis(chloromethyl)-1,4-dioxane (**5**). The yield of **5**, after silica gel chromatography, was 20%. Control reaction with aldehyde **3** showed that it is not a source of **5**.



5

A CH_2Cl_2 solution of **4**, initially contaminated with small amounts of **5**, exhibits an IR carbonyl stretch at 1730 cm^{-1}. Upon standing overnight at 20 °C this band completely disappears and a white solid forms. A KBr disc of **5** exhibits intense bands at 3450 (OH) and 845 (CCl) cm^{-1}, but no carbonyl absorption at 1730. The ^1H NMR (Me_2SO-d_6) shows no aldehydic proton but does contain an exchangeable doublet at δ 6.73 (J_{ab} = 5.1 Hz) assigned to the hydroxyl proton (H_a), a doublet of doublets assigned to the C-2 proton H_b at δ 4.90 (J_{ab} = 5.1 Hz, J_{bc} = 1.3 Hz) which collapses to a doublet (J_{bc} = 1.3 Hz) upon addition of D_2O, a triplet of doublets at δ 4.12 (J_{cd} = 6.2 Hz, J_{bc} = 1.3 Hz) which is unchanged by the addition of D_2O and is asigned to the C-3 proton (H_c), and a multiplet centered at δ 3.38 assigned to the nonequivalent methylene protons (H_d). The extremely intense band at 3450 cm^{-1} suggests intramolecular hydrogen bonding which would require **5** to be in a twist-boat form. Unfortunately the poor solubility of **5** in nonpolar solvents prevents confirmation of structure by IR or NMR dilution studies. The fully decoupled ^{13}C NMR (Me_2SO-d_6) of **5** shows resonances at δ 43.44 (CH_2Cl), 68.36 (C-3), and 88.46 (C-2).

Scheme I



The electron-ionization mass spectrum of **5** did not show a molecular ion, although peaks were observed at *m/e* 137.0006 (59%, $C_4H_6ClO_3$), 109.0029 (43%, $C_3H_6ClO_2$), and 78.9917 (100%, C_2H_4ClO) attributed to the ions resulting from the possible ring fragmentations. A small peak at *m/e* 107.9967 (2%, $C_3H_5ClO_2$) was observed and is consistent with structure **4**. The chemical-ionization mass spectrum exhibits a base peak at *m/e* 109, resulting from protonated monomer **4**, as well as an intense peak (65%) at *m/e* 91 corresponding to $4H^+ - H_2O$. **4** was characterized by treating the reaction solution with pentafluorophenylhydrazine (**6**) in ethanol. As anticipated, because of dehydrochlorination, the product from this derivatization was identical with that obtained from authentic pyruvaldehyde. The yield of pyruvaldehyde bis(pentafluorophenylhydrazone) (**7**) was 33% after correcting for recovery based on reactions with authentic pyruvaldehyde. Derivatization of **2** with **6** yielded only 4% of the bishydrazone **7**.

Aldehyde **2**, reported to be the hydrolysis product of **1a** and **1b**, is actually formed by a thermal rearrangement pathway (see Scheme I).[3] We assume that the rate of

(1) S. A. Kline, J. J. Solomon and B. L. Van Duuren, *J. Org. Chem.*, **43**, 3596 (1978).

(2) A. Barbin, H. Bresil, A. Croisy, P. Jacquignon, C. Malaveille, R. Montesano, and H. Bartsch, *Biochem. Biophys. Res. Commun.*, **67**, 596 (1975).

(3) R. N. McDonald and T. E. Tabor, *J. Am. Chem. Soc.*, **89**, 6573 (1967).

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formation of rearrangement product **3** is greatly accelerated in the polar aqueous solvent, as compared to the rate measured in xylene. Recently McDonald and Cousins have reported that the rate of thermolysis for a series of α-chlorostyrene oxides is accelerated by a factor of 180 in nitrobenzene relative to CCl_4.[4] Since the kinetic measurements reported by Kline et al.[1] were based on the assumption that the disappearance of **1a** and **1b** was directly proportional to the formation of hydrolysis product, the reported k_H are incorrect, in that they actually represent the rate of isomerization (k_i) in aqueous solution. Differentation between k_i and k_H is extremely important since k_H can be used to relate the electrophilicity of the chloro epoxides to their observed carcinogenic and mutagenic activity.[5] In contrast to that reported by Kline et al., the initial hydrolysis products of vinyl chloride oxide, *cis*- and *trans*-1-chloropropene oxide, trichloroethylene oxide, and tetrachloroethylene oxides are glycolaldehyde, α-hydroxypropionaldehyde, 1,1,2-trichloro-1,2-propanediol, and oxalyl chloride, respectively.[6-8] We conclude that the "hydrolysis" rate constants reported by Kline et al. include a large isomerization component.

Experimental Section

Melting points are uncorrected. Spectra were obtained on Beckmann IR-9 (IR), Varian HA-100 and CFT-20 (^1H and ^{13}C NMR), and AEI MS-9 (mass spectrum) spectrometers. GLC analyses were carried out on a Varian 3700, using 6 ft × 2 mm glass columns and a flow rate of 30 mL of N_2/min.

cis- and *trans*-1,3-dichloropropene oxide (**1a** and **1b**) were synthesized by the method of Kline et al.[1] Approximately 25% of **1b** was present in **1a**. In addition 10% of 1,3-dichlorobenzene, identified by GLC, ^1H NMR, ^{13}C NMR, and mass spectrometry, was formed during the synthesis and removed by a second distillation.

Hydrolysis of 1a and 1b. A solution of 1.97 g (155 mmol) of **1a**, or a 50–50 mixture of **1a** and **1b**, in 250 mL of 50% THF–0.1 M pH 7.4 phosphate buffer was stirred for 168 h, at which time no epoxide was detected (GLC). A 200-mL aliquot of the aqueous solution was extracted with CH_2Cl_2 (2 × 100 mL). The CH_2Cl_2 layer was concentrated to dryness in vacuo and the residue chromatographed on silicic acid (Bio-Rad Laboratories) with methanol–CH_2Cl_2. The oil obtained afforded a white solid upon standing at room temperature. Additional dimer could be isolated from the aqueous layer by concentration in vacuo and trituration of the residue with CH_2Cl_2, followed by concentration of the CH_2Cl_2. The total yield varied from 13% to 20%: mp 135 °C dec; IR(KBr disk) 3450 (OH) and 845 cm^{-1} (CCl); ^1H NMR (Me_2SO-d_6) δ 3.38 (m, 4 H, Cl-CH_2), 4.12 (t of d, 2 H, $CHCH_2Cl$, J = 6.2 and 1.3 Hz), 4.90 (d of d, 2 H, CH–O, J = 5.1 and 1.3 Hz, collapses to d upon addition of D_2O), 6.73 (d, 2 H, OH, J = 5.1 Hz, exchanges with D_2O); ^{13}C NMR (Me_2SO-d_6) δ 43.44 (CH_2Cl), 68.36 (CCH_2Cl), 88.46 (OCO); mass spectrum (chemical ionization), m/e 109 [$(C_3H_5O_2Cl + H)^+$, 100%], 91 [$(C_3H_3OCl + H)^+$, 65%]; mass spectrum (electron ionization), m/e 137.0006 ($C_4H_6ClO_3$, 59%), 109.0029 ($C_3H_6ClO_2$, 43%), 78.9917 (C_2H_4ClO, 100%).

Anal. Calcd for $C_6H_{10}O_4Cl_2$: C, 33.18; H, 4.65; Cl, 32.68. Found: C, 33.35; H, 4.60; Cl, 32.55.

A 10-mL aliquot of the original aqueous reaction solution was extracted with CH_2Cl_2 and analyzed for **3** by GLC (10% SP-2100 on 100/120 Supelcoport, 50 °C/5 min–5 °C/min to 100 °C). Based on recovery experiments with authentic **3** (K+K Labs), the yield was 52%. The trace amount of **2** present (<1%) was detected by ^1H NMR. **3** has chromatographic and spectroscopic properties identical with those of authentic 2,3-dichloropropanal. Neither **4** or **5** could be detected by GLC.

Derivatization with Pentafluorophenylhydrazine. A 10-mL aliquot of the aqueous reaction solution and 50 mL of 0.05 M pentafluorophenylhydrazine (Aldrich) in ethanol was refluxed for 15 h. The solution was then gently concentrated in vacuo and the residue triturated with 5 mL of THF. The yield of pyruvaldehyde bis(pentafluorophenylhydrazone) (**7**), determined by GLC (3% SE-30 on 80/100 Chromosorb WHP, 220 °C), was 33%. Authentic **3** was treated under identical conditions to yield 4% **7**. Isolated **7** was identical with that obtained from derivatization of authentic pyruvaldehyde: mp 122–123 °C (hexane); ^1H NMR (Me_2SO-d_6) 2.08 (s, 3 H, CH_3), 7.73 (s, 1 H, N=CH), 9.00 and 10.63 (br s, NH's); mass spectrum, m/e 432.0436 (M^+, $C_{15}H_6N_4F_{10}$, 43%), 249.0317 ($C_9H_4N_3F_5$, 63%).

Anal. Calcd for $C_{15}H_6N_4F_{10}$: C, 41.68; H, 1.40; N, 12.96; F, 43.95. Found: C, 41.62; H, 1.34; N, 13.30; F, 43.89.

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Registry No. **1a**, 66826-72-0; **1b**, 66826-73-1; **2**, 683-51-2; **3**, 10140-89-3; **4**, 69519-13-7; **5**, 76429-86-2; **7**, 76429-87-3.

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