Effect of Ring Substituent on the Stability of the Epoxide Derived from Phenyl Vinyl Ether

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Received December 14, 1988

Ring-substituted and unsubstituted phenoxyoxiranes were synthesized from phenyl vinyl ether derivatives by perbenzoic acid oxidation in CHCl₃. The epoxides isolated from the reaction mixture were stable in aprotic solvents. On the other hand, all of the epoxides decomposed rapidly to glycolaldehyde and the corresponding phenol in 0.1 M phosphate buffer, pH 7.4, at 37°C. Under these conditions, the hydrolytic decomposition followed first-order kinetics. Phenoxyoxiranes with an electron-withdrawing substituent in the benzene ring were relatively stable under aqueous conditions. The rate of decomposition was well correlated with the Hammett constant (σ) of the substituent in the benzene ring.

Keywords: epoxide; phenoxyoxirane; vinyl ether; hydrolysis; stability; epoxidation; Hammett constant

It is well-known that metabolically formed epoxides play a key role in the toxicity of olefins and arenes, and that the reactivity of the epoxides with biological nucleophiles is a critical factor in cell necrosis, mutagenesis, and carcinogenesis. Although vinyl ethers are widely used in the chemical industry, there are few reports on their toxicity. Vinyl ether is metabolized to glycolaldehyde and alcohol or phenol via epoxide, a postulated unstable intermediate, by monooxygenase systems. No work has been done on the synthesis of oxiranes with a mono-alkoxy or aryloxy substituent, and the participation of the epoxide in the toxicity of vinyl ether remains uncertain.

We have found that short-lived epoxides of 4-nitrophenyl vinyl ether and umbelliferyl vinyl ether were formed in a microsomal incubation mixture. From this evidence, we postulated that oxiranes substituted with a phenoxy residue are more stable than those with an alkoxyl residue.

We attempted to synthesize a series of phenoxyoxiranes with a substituent in the benzene ring and to compare the effects of various substituents on the stability of the epoxides as model chemicals from a toxicological point of view.

Ring-substituted phenyl vinyl ethers were epoxidized with perbenzoic acid (PBA) in CDCl₃, and the reactions were followed by proton nuclear magnetic resonance (¹H-NMR) spectrometry. Oxirane proton signals of all epoxides (1–9) were detected in the reaction mixture (Table I). The signals of 1 and 2, however, rapidly disappeared. The signals of 10 and 11 were detected instead of those of 1 and 2. These results showed that 1 and 2 reacted easily with benzoic acid (BA) to form the oxirane ring-opened products (Chart 1). Other epoxides (3–9) were isolated by alumina column chromatography from large-scale reaction mixtures. The final preparation of 2 contained about 20% of the substrate as an impurity. Compound 2 was stable in aprotic solvents, but further purification was not successful. We also attempted to synthesize 1, but it could not be isolated from the reaction mixture because it decomposed rapidly during the alumina column chromatography. Though epoxidation of ethyl vinyl ether with PBA was monitored by ¹H-NMR spectrometry, no significant oxirane proton signal was observed. The reaction product was isolated by high-performance liquid chromatography (HPLC) and proved to be the benzoate (12), an oxirane ring-opened product (Chart 1). These results are consistent with the report of Adams et al.⁰ that epoxides of alkyl vinyl ethers are generally too unstable to be synthesized and isolated from an aqueous medium.

The hydrolytic decomposition of epoxides (2–9) to glycolaldehyde and the corresponding phenol proceeded

<table>
<thead>
<tr>
<th>Compd. No.</th>
<th>Substituent</th>
<th>δ (ppm)</th>
<th>J (Hz)</th>
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<tr>
<td>1</td>
<td>4-CH₃</td>
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<tr>
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<td>4-Cl</td>
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<td>3.05</td>
</tr>
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<td>5</td>
<td>4-COCH₃</td>
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</tr>
<tr>
<td>8</td>
<td>3-NO₂</td>
<td>2.95</td>
<td>3.11</td>
</tr>
<tr>
<td>9</td>
<td>4-NO₂</td>
<td>2.97</td>
<td>3.12</td>
</tr>
</tbody>
</table>

Table I. ¹H-NMR Data for the Epoxides Derived from Ring-Substituted Phenyl Vinyl Ethers

*Chemical shifts (δ) were expressed in ppm from the signal of TMS, an internal standard. Oxirane proton: Ha, trans; Hb, cis; Hc, gem.

Chart 1

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stoichiometrically in 0.1 M phosphate buffer, pH 7.4, at 37 °C. The hydrolysis might be initiated by protonation of the oxirane oxygen followed by nucleophilic attack of water. The glycol hemiacetals formed by the hydrolysis of oxiranes are very unstable, as is the glycol of 2-chloroethylene oxide,10 and are decomposed rapidly to phenols and glycolaldehyde (Chart 2). Therefore, the amount of epoxide hydrolyzed in the medium is equivalent to that of the phenol formed. The hydrolytic decomposition of epoxides (2–9) in 0.1 M phosphate buffer, pH 7.4, at 37 °C was followed continuously by measuring the absorbance change due to the formation of the corresponding phenol. All of the epoxides decomposed according to first-order kinetics. Half lives calculated for 2, 3, 4, 5, 6, 7, 8, and 9 were 0.6, 2.1, 1.3, 3.9, 3.6, 4.8, 4.6, and 4.6 min, respectively. The rates of hydrolysis were well correlated with the Hammett constants8 of the substituent in the benzene ring (Fig. 1). The instability of 1 could also be interpreted in terms of the Hammett constant of the 4-CH3 substituent.

The attack of water on phenoxyoxiranes may occur at the oxirane α-carbon because BA and MeOH were found to attack that carbon (Charts 1 and 2). It has been reported that substituted alkoxyoxirane reacted with a nucleophile at the α-carbon attached to the alkoxy residue,9–13 and that the regioselectivity of the nucleophilic attack is related to the conjugative electron release from the alkoxy oxygen atom, which promotes an incipient positive charge on the α-carbon.10 Conjugative electron release from the phenoxo oxygen atom is also known to accelerate the acid-catalyzed decomposition of ring-substituted phenyl vinyl ether.12 These results indicate that an electron-withdrawing substituent in the benzene ring of phenoxyoxirane decreases the conjugative electron release and stabilizes the oxirane ring from nucleophilic attack. Thus, the observed correlation between the Hammett constant and the stability of substituted phenoxyoxiranes can be well explained.

The oxirane ring opening of the unstable vinyl ether epoxide formed in biological systems would be caused by nucleophilic attack of biological constituents such as glutathione, protein, or deoxyribonucleic acid (DNA) bases as well as water. These reactions are responsible for toxic effects such as cell death and mutagenesis by vinyl ethers. Because of their variety of reactivities, vinyl ether epoxides are useful as model chemicals for toxicological studies of substituted ethylene oxides. We will report on the relationship between structure and mutagenicity on vinyl ethers and their epoxides elsewhere.

Experimental

1H-NMR spectra were recorded on JEOL JNM-FX90Q and JNM-GX400 NMR spectrometers with tetramethylsilane (TMS) as an internal standard, mass spectra (MS) and high-resolution MS (High MS) on a JEOL JMS-DX300 mass spectrometer, and ultraviolet (UV) spectra on a Shimadzu UV-160 spectrophotometer. HPLC was carried out on a Shimadzu LC-5A apparatus equipped with a silica column (LiChrosorb Si 60, 5 μ, 4 × 250 mm) and a JASCO UVIDEC-100 UV spectrophotometer (254 nm). The column was eluted at a flow rate of 2.0 ml/min with a solvent mixture of n-hexane-2-propanol.

Synthesis of Epoxides. Phenoxyoxirane (2) and ring-substituted phenoxyoxiranes (3, 5–9) were synthesized as follows by modifications of the previously reported method for the synthesis of 9. A ring-substituted phenyl vinyl ether5–16 (0.6 mmol) dissolved in anhydrous CHCl3 (1.0 ml) was added to a CHCl3 solution (0.5 ml) of PBA5 (0.7 mmol). The reaction mixture was kept at room temperature for 1–2 h until the substrate was consumed. In the case of the synthesis of 2 and 4, the reaction was terminated at 3 and 10 min, respectively. After dilution with CH2Cl2 (1.5 ml), the mixture was passed through an alumina column (10 × 30 mm) packed with C6H6–CHCl3 (1:1), in order to remove organic acids and polar products. By evaporation of the solvents from the unadsorbed fraction, the corresponding epoxide was isolated as an amorphous solid or oily liquid. The purity of the epoxides was confirmed by 1H-NMR spectrum to be over 95%, 3-Chlorophenoxyoxirane (3): 10% yield. UVλmax(hexane) nm (log ε): 278.4 (3.04), 271.2 (3.08), MS m/z: 170 (M+1), 141 (M’ – CHO), 111 (C6H4Cl). High MS m/z: 170.040 (M+), Caled for C9H7ClO2: 170.0135. 4-Chlorophenoxyoxirane (4): 10% yield. UVλmax(hexane) nm (log ε): 278.6 (3.10), 277.4 (3.15), 224.0 (4.41), MS m/z: 170 (M+1), 141 (M’ – CHO), 111 (C6H4Cl). High MS m/z: 170.0135 (M+), Caled for C9H7ClO2: 170.0135. 4-Acetylphenoxyoxirane (5): 25% yield. UVλmax(hexane) nm (log ε): 256.4 (4.22), MS m/z: 178 (M’+), 163 (M’ – CH3). High MS m/z: 178.0628 (M+), Caled for C9H7ClO2: 178.0630. 3-Cyanophenoxyoxirane (6): 26% yield. UVλmax(hexane) nm (log ε): 290.4 (3.29), 282.6 (3.33), 226.8 (4.00), MS m/z: 161 (M’+), 132 (M’ – CHO), 102
(C$_2$H$_5$CN). High MS m/z: 161.0468 (M$^+$, Caled for C$_2$H$_5$NO$_2$: 161.0477). 4-Cyanophenoxime (7): 30% yield. UV $\lambda_{max}$ nm (log $\varepsilon$): 238.2 (4.29). MS m/z: 161 (M$^+$), 132 (M$^+$ - CH$_3$), 102 (C$_2$H$_5$CN$^+$). High MS m/z: 161.0486 (M$^+$, Caled for C$_2$H$_5$NO$_2$: 161.0477). 3-Nitrophenoxyamine (8): 29% yield. UV $\lambda_{max}$ nm (log $\varepsilon$): 301.6 (3.25), 256.4 (3.82). MS m/z: 181 (M$^+$), 152 (M$^+$ - CH$_3$). High MS m/z: 181.0380 (M$^+$, Caled for C$_2$H$_5$NO$_2$: 181.0375). 4-Nitrophenoxyamine (9): 3% yield. UV $\lambda_{max}$ nm (log $\varepsilon$): 287.5 (3.99). MS m/z: 181 (M$^+$), 152 (M$^+$ - CH$_3$). High MS m/z: 181.0380 (M$^+$, Caled for C$_2$H$_5$NO$_2$: 181.0375).

Benzene Derived from Oxidation of 4-toly vinyl ether, phenyl vinyl ether, and vinyl ether with PBA were carried out under the same conditions as described above. The reaction mixture was kept at room temperature for 30 min. After dilution with Et$_2$O, the mixture was washed with 5% Na$_2$CO$_3$ and saturated NaCl, and then dried over anhydrous Na$_2$SO$_4$. The solvent was evaporated off and the residue was subjected to HPLC. The benzoxazoles (10, 11, and 12), oxazine ring-opened products, were eluted from the column with a solvent mixture of n-hexane-2-propanol (70:1) at 5.9, 6.1, and 7.7 min, respectively. 10: H$^+$-NMR (CDCl$_3$) 2.05 (1H, t, J = 7.07 Hz, -CH$_2$OH), 2.27 (3H, s, -CH$_3$), 4.01 (2H, dd, J = 4.86, 7.07 Hz, -CH$_2$OH), 6.69 (1H, t, J = 4.86 Hz, -CH$_2$OH), 6.89 - 8.10 (9H, aromatic H), MS m/z: 272 (M$^+$), 165 (M$^+$ - CH$_2$OH), 150 (M$^+$ - C$_2$H$_5$CO$_2$H). High MS m/z: 272.1046 (M$^+$, Caled for C$_8$H$_7$NO$_2$: 272.1049). 11: H$^+$-NMR (CDCl$_3$) 2.07 (1H, t, J = 7.07 Hz, -CH$_2$OH), 4.03 (2H, dd, J = 4.85, 7.07 Hz, -CH$_2$OH), 6.76 (1H, t, J = 4.85 Hz, -CH$_2$OH), 6.96 - 8.11 (10H, aromatic H), MS m/z: 258 (M$^+$), 165 (M$^+$ - H$_2$O), 136 (M$^+$ - C$_2$H$_5$CO$_2$H), 116 (M$^+$ - CO$_2$), 88 (M$^+$ - C$_2$H$_5$CO$_2$H). High MS m/z: 258.0899 (M$^+$, Caled for C$_8$H$_7$O$_2$: 258.0892). 12: H$^+$-NMR (CDCl$_3$) 2.12 (3H, s, -CH$_3$), 3.73 (1H, q, J = 7.02 Hz, -CH$_2$OH), 7.43 - 8.09 (5H, aromatic H), MS m/z: 210 (M$^+$), 192 (M$^+$ - H$_2$O), 165 (M$^+$ - C$_2$H$_5$CO$_2$H). High MS m/z: 210.0895 (M$^+$, Caled for C$_8$H$_7$O$_2$: 210.0892).

Metahalogenation of Ethanol 2 and 9 (0.1 mmol) dissolved in 50 ml of anhydrous tetrahydrofuran (THF) were added to MeOH (1.0 ml) containing 0.1 ml of 1 N HCl. The reaction mixture was kept at room temperature for 30 min. After dilution with Et$_2$O, the mixture was washed with 5% Na$_2$CO$_3$ and saturated NaCl, and then dried over anhydrous Na$_2$SO$_4$. The solvent was evaporated off and the residue was subjected to HPLC. 13 and 14 were eluted from the column with a solvent mixture of n-hexane-2-propanol (40:1) at 5.2 and 13.6 min, respectively. 13: H$^+$-NMR (CDCl$_3$) 2.65 (1H, brs, -CH$_2$OH), 3.45 (3H, s, -CH$_3$), 3.79 (2H, d, J = 5.30 Hz, -CH$_2$OH), 5.22 (1H, t, J = 5.30 Hz, -CH$_2$OH), 6.94 - 7.29 (5H, aromatic H), MS m/z: 168 (M$^+$), 137 (M$^+$ - OH), 74 (M$^+$ - C$_2$H$_5$OH). High MS m/z: 168.0786 (M$^+$, Caled for C$_7$H$_7$O$_2$: 168.0787). 14: H$^+$-NMR (CDCl$_3$) 2.53 (1H, brs, -CH$_2$OH), 3.46 (3H, s, -CH$_3$), 3.87 (2H, d, J = 5.29 Hz, -CH$_2$OH), 3.73 (1H, t, J = 5.29 Hz, -CH$_2$OH), 6.78 - 8.26 (4H, aromatic H), MS m/z: 213 (M$^+$), 182 (M$^+$ - CH$_3$), 74 (M$^+$ - NO$_2$-C$_6$H$_4$OH). High MS m/z: 213.0646 (M$^+$, Caled for C$_8$H$_7$O$_2$: 213.0637).

Stability of Epoxides in an Aqueous Medium An epoxide (about 0.1 µmol) dissolved in THF (50 µl) was added to 0.1 M phosphate buffer, pH 7.4 (3.0 ml), at 37°C and the absorbance change due to the formation of the corresponding phenol from the epoxide was monitored continuously at 276, 282, 288, 290, 300, 304, or 360 nm for 2, 3, 4, 5, 6, 7, or 8, respectively. The hydrolysis of 9 was carried out according to the method described previously. Glycolaldehyde was assayed by the method described in the present paper.

References