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

Tomomichi SONE,* Masakazu ISOBE, and Eigo TAKABATAKE

Department of Toxicology, Faculty of Pharmaceutical Sciences, Setsunan University, 45-1 Nagaotoge-cho, Hirakata, Osaka 573-01, Japan.
Received December 14, 1988

Ring-substituted and unsubstituted phenoxyoxiranes were synthesized from phenyl vinyl ether derivatives by perbenzoic acid oxidation in $CHCl_3$. 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[1-3] 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[4] and umbelliferyl vinyl ether[5] 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 alkoxy 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 $CDCl_3$ and the reactions were followed by proton nuclear magnetic resonance (^{1}H-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 ^{1}H-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.*[6] 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 I. ^{1}H-NMR Data for the Epoxides Derived from Ring-Substituted Phenyl Vinyl Ethers

Compd. No.	Substituent (X)	δ (ppm)			J (Hz)		
		H_a	H_b	H_c	J_{ab}	J_{bc}	J_{ac}
1	4-CH_3	2.85	3.04	5.03	4.19	1.32	2.43
2	H	2.86	3.05	5.07	4.19	1.32	2.43
3	3-Cl	2.89	3.06	5.07	4.19	1.11	2.43
4	4-Cl	2.88	3.05	5.04	4.19	1.11	2.43
5	4-$COCH_3$	2.92	3.09	5.14	4.19	1.32	2.42
6	3-CN	2.93	3.08	5.10	4.19	1.11	2.42
7	4-CN	2.94	3.09	5.13	4.19	1.11	2.43
8	3-NO_2	2.95	3.11	5.16	4.19	1.10	2.43
9	4-NO_2	2.97	3.12	5.18	4.18	1.23	2.46

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

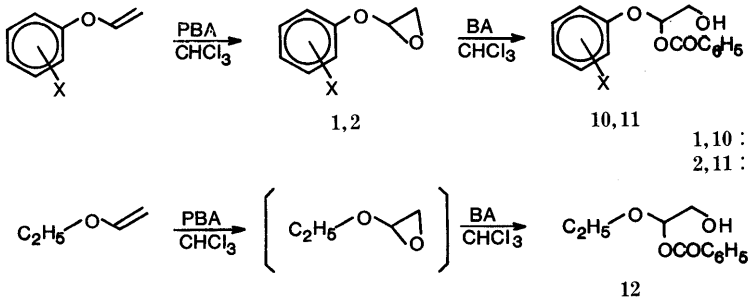

Chart 1

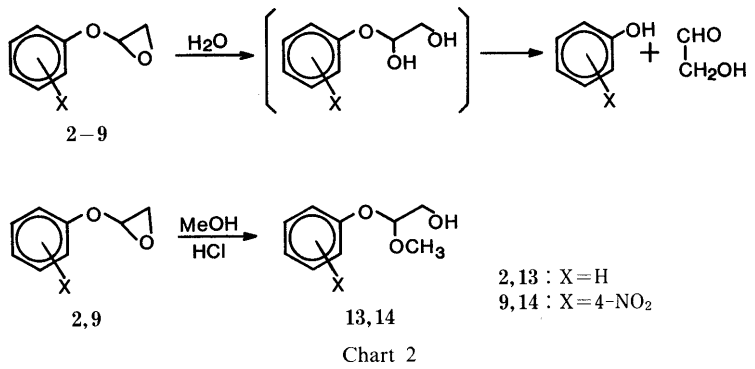

Chart 2

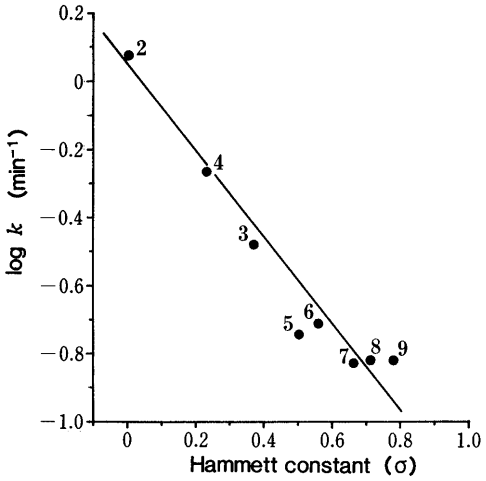

Fig. 1. Correlation between Rate Constant of the Hydrolysis and Hammett Constant of the Substituent in the Benzene Ring of Phenoxyoxiranes

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,[7] 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 constants[8] 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-CH_3 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,[9-11] 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 phenoxy 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

^{1}H-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-IV 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**.[4] A ring-substituted phenyl vinyl ether[13-16] (0.6 mmol) dissolved in anhydrous $CHCl_3$ (1.0 ml) was added to a $CHCl_3$ solution (0.5 ml) of PBA[17] (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 C_6H_6 (1.5 ml), the mixture was passed through an alumina column (10 × 30 mm) packed with C_6H_6–$CHCl_3$ (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 ^{1}H-NMR spectrometry to be over 95%. 3-Chlorophenoxyoxirane (**3**): 10% yield. UV $\lambda_{max}^{n\text{-hexane}}$ nm (log ε): 278.4 (3.04), 271.2 (3.08). MS *m/z*: 170 (M^+), 141 (M^+.−CHO), 111 ($C_6H_4Cl^+$). High MS *m/z*: 170.0140 (M^+, Calcd for $C_8H_7ClO_2$: 170.0135). 4-Chlorophenoxyoxirane (**4**): 10% yield. UV $\lambda_{max}^{n\text{-hexane}}$ nm (log ε): 284.6 (3.10), 277.4 (3.15), 224.0 (4.11). MS *m/z*: 170 (M^+), 141 (M^+ −CHO), 111 ($C_6H_4Cl^+$). High MS *m/z*: 170.0135 (M^+, Calcd for $C_8H_7ClO_2$: 170.0135). 4-Acetylphenoxyoxirane (**5**): 25% yield. UV $\lambda_{max}^{n\text{-hexane}}$ nm (log ε): 256.4 (4.22). MS *m/z*: 178 (M^+), 163 ($M^+ - CH_3$). High MS *m/z*: 178.0628 (M^+, Calcd for $C_{10}H_{10}O_3$: 178.0630). 3-Cyanophenoxyoxirane (**6**): 26% yield. UV $\lambda_{max}^{n\text{-hexane}}$ nm (log ε): 290.4 (3.29), 282.6 (3.33), 226.8 (4.00). MS *m/z*: 161 (M^+), 132 (M^+ −CHO), 102

($C_6H_4CN^+$). High MS *m/z*: 161.0468 (M^+, Calcd for $C_9H_7NO_2$: 161.0477). 4-Cyanophenoxyoxirane (**7**): 30% yield. UV $\lambda_{max}^{n\text{-hexane}}$ nm (log ε): 238.2 (4.29). MS *m/z*: 161 (M^+), 132 ($M^+ - CHO$), 102 ($C_6H_4CN^+$). High MS *m/z*: 161.0486 (M^+, Calcd for $C_9H_7NO_2$: 161.0477). 3-Nitrophenoxyoxirane (**8**): 29% yield. UV $\lambda_{max}^{n\text{-hexane}}$ nm (log ε): 303.6 (3.25), 256.4 (3.82). MS *m/z*: 181 (M^+), 152 ($M^+ - CHO$). High MS *m/z*: 181.0380 (M^+, Calcd for $C_8H_7NO_4$: 181.0375). 4-Nitrophenoxyoxirane (**9**): 30% yield. UV $\lambda_{max}^{n\text{-hexane}}$ nm (log ε): 287.5 (3.99). MS *m/z*: 181 (M^+), 152 ($M^+ - CHO$). High MS *m/z*: 181.0380 (M^+, Calcd for $C_8H_7NO_4$: 181.0375). ^{1}H-NMR data for **3**—**9** are shown in Table I. The purity of **2** was about 80% because of contamination with the unreacted substrate.

Benzoate Derived from Epoxide Oxidation reactions of 4-tolyl vinyl ether, phenyl vinyl ether, and ethyl 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_2O, the mixture was washed with 5% Na_2CO_3 and saturated NaCl, and then dried over anhydrous Na_2SO_4. The solvent was evaporated off and the residue was subjected to HPLC. The benzoates (**10**, **11**, and **12**), oxirane 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**: ^{1}H-NMR ($CDCl_3$) δ: 2.05 (1H, t, J=7.07 Hz, –CHCH$_2$OH), 2.27 (3H, s, –CH$_3$), 4.01 (2H, dd, J=4.86, 7.07 Hz, –CHCH$_2$OH), 6.69 (1H, t, J=4.86 Hz, –CHCH$_2$OH), 6.89—8.10 (9H, aromatic H). MS *m/z*: 272 (M^+), 165 ($M^+ - CH_3C_6H_4O$), 150 ($M^+ - C_6H_5CO_2H$). High MS *m/z*: 272.1046 (M^+, Calcd for $C_{16}H_{16}O_4$: 272.1049). **11**: ^{1}H-NMR ($CDCl_3$) δ: 2.07 (1H, t, J=7.07 Hz, –CHCH$_2$OH), 4.03 (2H, dd, J=4.85, 7.07 Hz, –CHCH$_2$OH), 6.76. (1H, t, J=4.85 Hz, –CHCH$_2$OH), 6.96—8.11 (10H, aromatic H). MS *m/z*: 258 (M^+), 165 ($M^+ - C_6H_5O$), 136 ($M^+ - C_6H_5CO_2H$). High MS *m/z*: 258.0899 (M^+, Calcd for $C_{15}H_{14}O_4$: 258.0892). **12**: ^{1}H-NMR ($CDCl_3$) δ: 1.26 (3H, t, J=7.02 Hz, –OCH$_2$CH$_3$), 2.12 (1H, br s, –CHCH$_2$OH), 3.73 (1H, dq, J=7.02, 9.77 Hz, –OCH$_2$CH$_3$), 3.79 (2H, d, J=4.88 Hz, –CHCH$_2$OH), 3.88 (1H, dq, J=7.02, 9.77 Hz, –OCH$_2$CH$_3$), 6.13 (1H, t, J=4.88 Hz, –CHCH$_2$OH), 7.43—8.09 (5H, aromatic H). MS *m/z*: 210 (M^+), 192 ($M^+ - H_2O$), 165 ($M^+ - C_2H_5O$), 88 ($M^+ - C_6H_5CO_2H$). High MS *m/z*: 210.0895 (M^+, Calcd for $C_{11}H_{14}O_4$: 210.0892).

Methanolysis of Epoxide **2** and **9** (0.1 mmol) dissolved in 50 μl 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_2O, the mixture was washed with 5% Na_2CO_3 and saturated NaCl, and then dried over anhydrous Na_2SO_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**: ^{1}H-NMR ($CDCl_3$) δ: 2.65 (1H, br s, –CHCH$_2$OH), 3.45 (3H, s, –CHOCH$_3$), 3.79 (2H, d, J=5.30 Hz, –CHCH$_2$OH), 5.22 (1H, t, J=5.30 Hz, –CHCH$_2$OH), 6.94—7.29 (5H, aromatic H). MS *m/z*: 168 (M^+), 137 ($M^+ - OCH_3$), 74 ($M^+ - C_6H_5OH$). High MS *m/z*: 168.0786 (M^+, Calcd for $C_9H_{12}O_3$: 168.0787). **14**: ^{1}H-NMR ($CDCl_3$) δ: 2.53 (1H, br s, –CHCH$_2$OH), 3.46 (3H, s, –CHOCH$_3$), 3.87 (2H, d, J=5.29 Hz, –CHCH$_2$OH), 5.37 (1H, t, J=5.29 Hz, –CHCH$_2$OH), 7.08—8.26 (4H, aromatic H). MS *m/z*: 213 (M^+), 182 ($M^+ - OCH_3$), 74 ($M^+ - NO_2C_6H_4OH$). High MS *m/z*: 213.0646 (M^+, Calcd for $C_9H_{11}NO_5$: 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, 260, 300, 240, 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.[4] Glycolaldehyde was assayed by the method described in the previous paper.[3]

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