(*S*)-4-Methyl-2,2-dibutyl-1,3,2-dioxastannolane, Enantiomerically Pure Compound (1b). ^{13}C NMR: CHCH₃, 20.91; CHMe, 68.27; CH₂CHMe, 69.33; (CH₂)$_\alpha$, 22.99, 22.87; (CH₂)$_\beta$, 27.58, 27.49; (CH₂)$_\gamma$, 27.00, 26.93; (CH₃)$_\delta$, 13.58. ^{119}Sn NMR: –165.

4-Phenyl-2,2-dibutyl-1,3,2-dioxastannolane, Racemic Compound (2a). ^{13}C NMR: Ph, C$_{ipso}$, 143.56; C$_{o,m}$, 128.31, 126.89; C$_p$, 127.64; CHPh, 76.02; CH₂CHPh, 69.30; (CH₂)$_\alpha$, 22.88; (CH₂)$_\beta$, 27.56; (CH₂)$_\gamma$, 27.07, 26.96; (CH₃)$_\delta$, 13.71. ^{119}Sn NMR: –153.

(*S*)-4-Phenyl-2,2-dibutyl-1,3,2-dioxastannolane, Enantiomerically Pure Compound (2b). ^{13}C NMR: Ph, C$_{ipso}$, 143.48; C$_{o,m}$, 128.32, 126.91; C$_p$, 127.67; CHPh, 75.96; CH₂CHPh, 69.43; (CH₂)$_\alpha$, 22.95, 22.63; (CH₂)$_\beta$, 27.56; (CH₂)$_\gamma$, 27.05, 26.98; (CH₃)$_\delta$, 13.71. ^{119}Sn NMR: –153.

4,4-Dimethyl-2,2-dibutyl-1,3,2-dioxastannolane (3). ^{13}C NMR: (CH₃)₂, 28.06; CMe₂, 70.45; CH₂CMe₂, 72.73; (CH₂)$_\alpha$, 22.72; (CH₂)$_\beta$, 27.36; (CH₂)$_\gamma$, 26.92; (CH₃)$_\delta$, 13.52. ^{119}Sn NMR: –121.

4-Phenyl-4-methyl-2,2-dibutyl-1,3,2-dioxastannolane (4). The racemic compound was prepared from a commercial diol (Janssen, >98%; mp 44–45 °C), purified by crystallization; the 42% ee sample was prepared from an enriched diol, obtained following a known procedure:[20] mp 93–95 °C. ^{13}C NMR: Ph, C$_{ipso}$, 149.17; C$_{o,m}$, 127.91, 125.35; C$_p$, 126.35; CPhMe, 74.48; CH₂CPhMe, 71.78; (CH₂)$_\alpha$, 21.97, 21.69, 21.27, 21.08; (CH₂)$_\beta$, 27.50, 27.29; (CH₂)$_\gamma$, 26.98; (CH₃)$_\delta$, 13.61. [119]Sn

NMR: –115.6. ^{1}H NMR: Ph, 7.0–7.5 (m); CH₂, 3.5 (AB, m); CH₃, 1.4 (s); Bu, 0.7–1.6 (m).

meso-4,5-Dicarbomethoxy-2,2-dibutyl-1,3,2-dioxastannolane (5). The compound was prepared from *meso*-dimethyl tartrate, obtained by esterification with methanol of commercial *meso*-tartaric acid hydrate (Janssen, 99%; mp 146–148 °C): mp 195–196 °C dec. ^{13}C NMR: CO₂CH₃, 51.73; CO₂Me, 172.60; CHCO₂Me, 74.49; (CH₂)$_\alpha$, 26.31, 25.19; (CH₂)$_\beta$, 27.30, 27.24; (CH₂)$_\gamma$, 26.87; (CH₃)$_\delta$, 13.54. ^{1}H NMR: CO₂CH₃, 3.7 (s); CHCO₂Me, 4.55 (s); Bu, 0.8–1.8 (m).

Supplementary Material Available: DNMR spectra for compounds 1–5 (Figures S1–S9) and the appendix to ref 12 (11 pages). Ordering information is given on any current masthead page.

---

(20) Eliel, E. L.; Freeman, J. P. *J. Am. Chem. Soc.* **1952**, *74*, 923.

Synthesis and Kinetic Studies of a Simple Prostacyclin Model

Nils-Åke Bergman* and Marie Jansson

Department of Organic Chemistry, Chalmers University of Technology and University of Göteborg, S-412 96 Göteborg, Sweden

Yvonne Chiang, A. Jerry Kresge, and Ya Yin

Department of Chemistry, University of Toronto, Toronto, Ontario M5S 1A1, Canada

A simple prostacyclin model, (*Z*)-6,9-epoxynon-5-enoic acid, has been synthesized, and the rate of hydrolysis of the vinyl ether functional group of it and its methyl ester has been measured by monitoring UV spectral changes over the pH range 1–8 at 25.0 ± 0.1 °C and total ionic strength 0.1 M. The measurements show that (*Z*)-6,9-epoxynon-5-enoic acid is 82 times more reactive than its methyl ester at high pH when the carboxylic acid group is in an ionized form. The present results indicate that the simple model closely mimics the behavior of prostacyclin.

Introduction

Prostacyclin (1), a recently discovered prostaglandin,[1] is an extremely potent inhibitor of blood coagulation. This

1
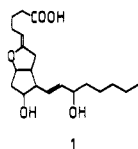
makes it a very interesting compound, but its usefulness as a therapeutic agent in the treatment of thrombosis is severely limited by its great hydrolytic lability. The half-life of prostacyclin in aqueous solution at physiological pH is only 3 min.[2] Prostacyclin, like other vinyl ethers, undergoes acid-catalyzed hydrolysis in aqueous solution.

Kinetic experiments have been carried out on prostacyclin and its methyl ester.[2,3] These measurements show that prostacyclin is 104 times more reactive than its methyl ester at high pH. The difference in reactivity decreases with increasing acid concentration and disappears at pH 1–2. The difference in reactivity at high pH indicates that the hydrolysis rate is accelerated when the carboxylic acid group is in an ionized form. It has been suggested that this acceleration might be due to electrostatic stabilization or to intramolecular general acid catalysis.[3] Solvent isotope effect measurements support the latter alternative.[3b]

In order to explore the mechanistic details of the hydrolysis of prostacyclin further, we have started an investigation of model compounds. By use of a model with a simpler structure we hope to be able to carry out the necessary structural modifications needed to elucidate

---

(1) Moncada, S.; Gryglewski, R.; Bunting, S.; Vane, J. R. *Nature (London)* **1976**, *263*, 663.
(2) Cho, M. J.; Allen, M. A. *Prostaglandins* **1978**, *15*, 943.

(3) (a) Kresge, A. J.; Chiang, Y.; Cho, M. J. *J. Chem. Soc., Chem. Commun.* **1979**, 129. (b) Chiang, Y.; Cho, M. J.; Euser, B. A.; Kresge, A. J. *J. Am. Chem. Soc.* **1986**, *108*, 4192.

Scheme I

different mechanistic details. The results from our investigation of the first model compound (*Z*)-6,9-epoxynon-5-enoic acid (**2a**) and its methyl ester (**2b**) are presented in the present paper, which is a full description of work communicated in a preliminary form.[4]

2a R = H
2b R = CH₃

The synthesis of (*Z*)-6,9-epoxynon-5-enoic acid and its methyl ester is outlined in Scheme I; it consists essentially of steps which are similar to ones used in the synthesis of prostacyclin itself.

Experimental Section

^{1}H NMR spectra were recorded on a Bruker WH 270 instrument, and chemical shifts are given in ppm downfield from Me$_4$Si. Isolation of products involved flash chromatography on silica gel according to ref 5. Mass spectra were obtained with a Finnigan 1020 mass spectrometer and a ZAB-HF mass spectrometer.

Synthetic Procedures. (*Z*)-9-Hydroxynon-5-enoic Acid (5). 4-Hydroxybutanal (3) was prepared from 2,3-dihydrofuran.[6] 2,3-Dihydrofuran (20 mL, 0.265 mol) was added dropwise to 50 mL of 0.8 M HCl with stirring and ice bath cooling. After 5–10 min the mixture was neutralized by adding a 1 M NaOH solution. The resulting mixture was extracted with diethyl ether, the ether was removed, and the residue was distilled at reduced pressure, bp 19 °C (0.5 mmHg): yield, 5.4 g (23%) of a colorless oil.

The phosphonium bromide salt of 5-bromopentanoic acid (4) was prepared according to ref 7. A mixture of 10.60 g (59 mmol) of 4 and 15.48 g (59 mmol) of triphenylphosphine was heated under reflux in 100 mL of acetonitrile for 24 h. The resulting salt was recrystallized from acetonitrile, washed with ether, and dried in vacuum: yield, 14.8 g (56%); ^{1}H NMR (CDCl₃) δ 1.69–1.77 (m, 2 H), 1.90–1.98 (m, 2 H), 2.73–2.78 (t, 2 H, *J* = 7 Hz), 3.61–3.72 (m, 2 H), 7.67–7.83 (m, 15 H).

A Wittig reaction between 4-hydroxybutanal and the phosphonium bromide salt of 4 gave 5. All apparatus was thoroughly dried by heating at 120 °C for 18 h, and the reaction was carried out under a nitrogen atmosphere. Butyllithium in hexane (36 mL, 72 mmol) was first added dropwise to 20 mL of dry dimethyl sulfoxide with stirring and ice bath cooling, and then the phosphonium bromide salt of 4 (15.1 g, 35 mmol) dissolved in 40 mL of dry dimethyl sulfoxide was added to this mixture. After being

stirred for 15 min at room temperature, the reaction mixture was cooled again, 5.86 g (35 mmol) of 4-hydroxybutanal was added, and stirring was continued overnight.

Dimethyl sulfoxide was then removed by distillation at reduced pressure, and the brown residue was dissolved in a mixture of 70 mL of water and 70 mL of toluene. The layers were separated, and the aqueous portion was washed with 3 × 40 mL of toluene. Hydrochloric acid (8 mL, 3 M) was then added to the water phase, and the acidified mixture was extracted with diethyl ether. The ether extract was washed twice with NaCl solution and was dried (MgSO₄), and the ether was removed in vacuo to yield 3.0 g of a yellow oil. This product was used without further purification.

(*Z*)-9-Hydroxynon-5-enoic Acid Methyl Ester (6). (*Z*)-9-Hydroxynon-5-enoic acid (3.0 g) was dissolved in 55 mL of methanol, a few crystals of *p*-toluenesulfonic acid were added, and the mixture was heated under reflux for 5 h. After this the methanol solvent was removed by evaporation, and the residue was dissolved in diethyl ether and water. The ether phase was then extracted twice with NaCl solution and was dried (MgSO₄), and the ether was removed in vacuo. The residue was flash chromatographed on silica gel with ethyl acetate/hexane (1/1) as eluent: yield, 1.2 g (18% based on the amount of 4-hydroxybutanal used) of a colorless oil; ^{1}H NMR (CDCl₃) δ 1.62–1.72 (m, 4 H), 2.08–2.13 (m, 4 H), 2.29–2.35 (t, 2 H, *J* = 7 Hz), 3.62–3.67 (t, 2 H, *J* = 6 Hz), 3.67 (s, 3 H), 5.38–5.41 (m, 2 H).

6,9-Epoxy-5-iodononanoic Acid Methyl Ester (7). 6,9-Epoxy-5-iodononanoic acid methyl ester was prepared from (*Z*)-9-hydroxynon-5-enoic acid methyl ester by a procedure similar to the one in ref 8 and 9. A 6% aqueous solution of sodium hydrogen carbonate (120 mL) was added to a solution of 1.2 g (6.4 mmol) of (*Z*)-9-hydroxynon-5-enoic acid methyl ester in 115 mL of methylene chloride. This mixture was stirred and cooled in an ice bath, while a solution of 1.8 g of iodine in 90 mL of methylene chloride was added dropwise over a period of 6 h. Stirring was then continued overnight. To the resulting mixture was added an aqueous sodium thiosulfate solution, and the methylene chloride phase was separated, washed with water, and dried (MgSO₄). Removal of the methylene chloride in vacuo and flash chromatography of the residue on silica gel with ethyl acetate/hexane (1/1) as eluent gave 1.2 g (60%) of a colorless oil: ^{1}H NMR (CDCl₃) δ 1.63–2.13 (m, 8 H), 2.35 (td, 2 H, *J* = 7 and 2 Hz), 3.67 (s, 3 H), 3.67–3.75 (m, 1 H), 3.78–3.87 (m, 1 H), 3.93–4.01 (m, 1 H), 4.04–4.15 (m, 1 H).

(*Z*)-6,9-Epoxynon-5-enoic Acid Methyl Ester (2b). The vinyl ether function was generated by elimination of hydrogen iodide from (*Z*)-6,9-epoxy-5-iodononanoic acid methyl ester by a procedure similar to the one in ref 9. A sodium methoxide solution was added to a solution of 250 mg of 7 in 1.4 mL of absolute methanol. (The methoxide solution was prepared under nitrogen by dissolving 0.3 g of sodium in 3.7 mL of absolute methanol.) This reaction mixture was allowed to stand for 14 h at room temperature in a gas-tight vial. The methanol was then evaporated at room temperature, the residue was dissolved in diethyl ether, and the ether layer was washed once with a buffer solution (pH 5) and twice with water and was dried (MgSO₄ + Na₂CO₃). Upon removal of the ether, 98.7 mg of a light yellow oil was obtained.

Semipreparative HPLC (high-performance liquid chromatography) was used in the purification of the (*Z*)-6,9-epoxynon-5-enoic acid methyl ester. Chromatography was performed with a Waters Associates System consisting of a Waters M-45 solvent delivery system, a Waters U6K injector, a R-sil^R silica column (10-μm particles, 4.6 mm (i.d.) × 25 cm), and a Waters R-401 differential refractometer. The solvent system was 3% triethylamine in hexane: yield, 46 mg (31%); ^{1}H NMR (C₆D₆) δ 1.30–1.42 (m, 2 H), 1.75–1.87 (m, 2 H), 2.06–2.14 (m, 2 H), 2.23–2.36 (m, 4 H), 3.34 (s, 3 H), 3.65 (t, 2 H, *J* = 7 Hz), 4.12–4.19 (m, 1 H); MS, *m/e* (relative intensity) 55 (100), 56 (12.5), 67 (10.9), 69 (20.0), 81 (14.5), 82 (10.1), 84 (27.6), 97 (90.5), 110 (25.6), 111 (15.7), 184 (12.3) [all peaks smaller than 10% of the base peak are omitted]; HRMS, calcd for C₁₀H₁₆O₃ 184.1098, found 184.1091. Anal. Calcd for C₁₀H₁₆O₃: C, 65.2; H, 8.8; O, 26.1. Found: C, 65.0; H, 8.6; O, 26.2.

(4) Bergman, N.-Å.; Chiang, Y.; Jansson, M.; Kresge, A. J.; Yin, Y. *J. Chem. Soc., Chem. Commun.* **1986**, 1366.

(5) Kühler, T.; Lindsten, G. R. *J. Org. Chem.* **1983**, *48*, 3589.

(6) Paul, R.; Fluchaire, M.; Collardeau, G. *Bull. Soc. Chim. Fr.* **1950**, 668.

(7) Corey, E. J.; Weinschenker, N. M.; Schaaf, T. K.; Huber, W. *J. Am. Chem. Soc.* **1969**, *91*, 5675.

(8) Johnson, R. A.; Lincoln, F. H.; Nicly, E. G.; Schneider, P.; Thompson, J. L; Axen, U. *J. Am. Chem. Soc.* **1978**, *100*, 7690.

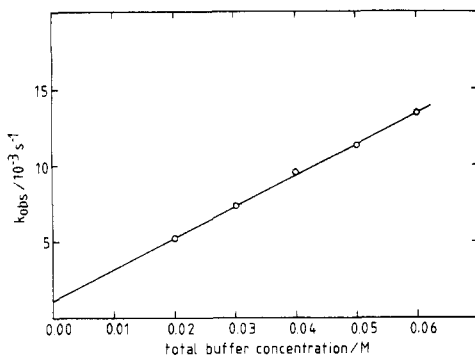(9) Whittaker, N. *Tetrahedron Lett.* **1977**, 2805.

Figure 1. The hydrolysis of (Z)-6,9-epoxynon-5-enoic acid methyl ester in phosphate buffer (pH 5.98) at 25.0 ± 0.1 °C and I = 0.1 M.

(Z)-6,9-Epoxynon-5-enoic Acid Sodium Salt (2c). Saponification of (Z)-6,9-epoxynon-5-enoic acid methyl ester gave (Z)-6,9-epoxynon-5-enoic acid sodium salt under conditions similar to the ones in ref 8 and 9.

Kinetic Procedure. The buffer solutions were prepared from commercially obtained buffer components, all A.R. grade, and constant ionic strength was maintained by using KCl or NaCl. pH measurements were made with a Beckman Model 3560 digital pH meter equipped with a Beckman combination electrode 39501.

The slow kinetic measurements were carried out on a Varian CARY 210 UV spectrophotometer, interfaced with an Apple II computer or on a Varian CARY 118 spectrophotometer. The fast kinetic measurements were carried out with Nortech SF-3A or Durrum-Gibson stopped-flow spectrophotometers. The buffer solutions and the UV cells were thermostated at 25.0 ± 0.1 °C.

The hydrolysis reaction was followed by monitoring the decrease of the absorbance at 230 or 220 nm for the methyl ester and the sodium salt, respectively. The reaction was followed for at least 2–3 half-lives and showed first-order kinetics.

Analysis of Data. The rate data were analyzed by fitting absorbance and time values to eq 1, where A_0, A_t, and A_∞ are the

$$A_t = A_\infty - (A_\infty - A_0)e^{-k_{obsd}t} \tag{1}$$

initial, intermediate, and final absorbances, k_{obsd} is the first-order rate constant, and t is the time. A multiple-linear-regression program[10] was used to obtain values of k_{obsd}, A_0, and A_∞.

Activity coefficients needed to calculate hydrogen concentrations from measured pH's were estimated by using the Debye–Hückel expression shown as eq 2,[11] where f_i is the activity coefficient, A is a constant (0.512 at 25 °C), z is the charge, and I is the ionic strength.

$$-\log f_i = Az^2I^{0.5}/(1 + I^{0.5}) - 0.1z^2I \tag{2}$$

Results and Discussion

At a given pH the observed pseudo-first-order rate constants for both the ester and the carboxylic acid obeyed the rate law given as eq 3, where $[Buf]_{tot} = [HA] + [A^-]$;

$$k_{obsd} = k_{obsd}° + k_{cat.}[Buf]_{tot} \tag{3}$$

HA is the buffer conjugate acid and A^- is the buffer conjugate base. A typical plot is shown in Figure 1, and the data are summarized in Tables S1–S4.[12] The rate constant $k_{cat.}$ can be divided into contributions from HA as well as from A^- according to eq 4, where $f_{HA} = [HA]/[Buf]_{tot}$,

$$k_{cat.} = k_{HA}{}^{app}f_{HA} + k_{A^-}{}^{app}f_{A^-} =$$
$$(k_{HA}{}^{app} - k_{A^-}{}^{app})f_{HA} + k_{A^-}{}^{app} \tag{4}$$

(10) Varian CARY 219/210 Software Series, Master Kinetic Storage Program and Advanced Order Kinetic Calculations Program.

(11) Perrin, D. D.; Dempsey, B. *Buffers for pH and Metal Ion Control*; Chapman and Hall Ltd: London, 1974.

(12) Supplementary material. See paragraph at the end of this paper regarding availability.
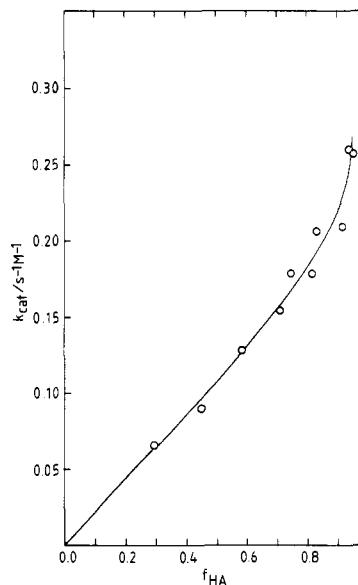
Figure 2. Plot of the rate constant $(k_{cat.})$ vs. the fraction of the buffer acid (f_{HA}) for (Z)-6,9-epoxynon-5-enoic acid methyl ester in phosphate buffers at 25.0 ± 0.1 °C and I = 0.1 M. For the solid curve, see the text.
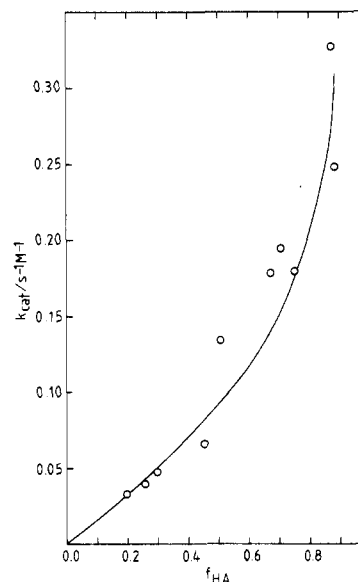
Figure 3. Plot of the rate constant $(k_{cat.})$ vs. the fraction of the buffer acid (f_{HA}) for (Z)-6,9-epoxynon-5-enoic acid sodium salt in phosphate buffers at 25.0 ± 0.1 °C and I = 0.1 M. For the solid curve, see the text.

$k_{HA}{}^{app}$ is the contribution from the buffer acid to the catalysis constant, and $k_{A^-}{}^{app}$ is the contribution from the buffer conjugate base to the catalysis constant.

A plot of $k_{cat.}$ vs. f_{HA} gives $k_{A^-}{}^{app}$ as the intercept and $k_{HA}{}^{app}$ from the slope. The meaning of $k_{HA}{}^{app}$ will be discussed below.

For acetate buffers this holds for both the ester and the carboxylic acid form of the model giving straight lines with the intercepts equal to zero, indicating no catalysis from the buffer conjugate base.

The corresponding plots for phosphate buffers for both the ester and the carboxylic acid (Figures 2 and 3) are curved. The possible reasons for curvature in such plots will be discussed below.

According to Figures 2 and 3, it is, however, quite reasonable that the intercepts, and hence $k_{A^-}{}^{app}$ are equal to
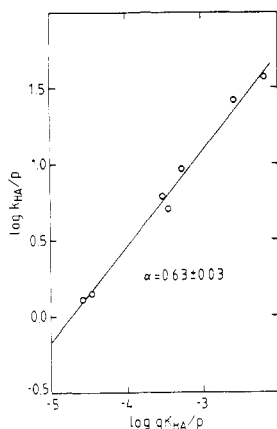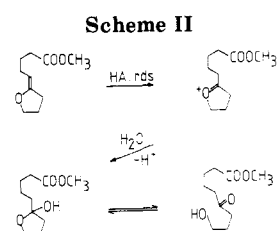
Figure 4. Brønsted relation for the hydrolysis of (Z)-6,9-epoxynon-5-enoic acid methyl ester at 25.0 ± 0.1 °C and $I = 0.04$ M. The catalysts were cyanoacetic, chloroacetic, methoxyacetic, formic, glycolic, acetic, and propionic acids.

Scheme II

zero for the ester and the carboxylic acid.

This mean that

$$k_{\text{cat.}} = k_{\text{HA}}{}^{\text{app}} f_{\text{HA}} = k_{\text{HA}}{}^{\text{app}} \frac{[\text{HA}]}{[\text{Buf}]_{\text{tot}}} \qquad (5)$$

and

$$k_{\text{obsd}} = k_{\text{obsd}}{}^{\circ} + k_{\text{HA}}{}^{\text{app}}[\text{HA}] \qquad (6)$$

The reaction of the methyl ester will be treated first. Since general acid catalysis is observed (Figure 1) with a Brønsted $\alpha = 0.63$ (Figure 4, Table S5[12]), the most probable mechanism is a rate-determining protonation (Scheme II).

The buffer independent part of eq 6 for the methyl ester should be equal to $k_{\text{H}^+}[\text{H}^+]$, and the average value of k_{H^+} obtained from all of the buffers 697 ± 10, is in good agreement with the result obtained directly in HClO_4 solutions, $k_{\text{H}^+} = 703 \pm 12$ M^{-1} s^{-1} (Table S3[12]).

A plot of log $k_{\text{obsd}}{}^{\circ}$ vs. -log $[\text{H}^+]$ should give a straight line with the slope equal to -1. This is also the case which can be seen from Figure 5.

Hydrolysis of (Z)-6,9-epoxynon-5-enoic acid in the carboxylic acid form shows a more complicated picture. A contracted reaction mechanism consistent with the experimental data is given in Scheme III. For such a system the observed rate constant at a given pH is given by eq 7, in which k_Ψ and k'_Ψ are pseudo-first order rate constants

$$k_{\text{obsd}} = \frac{[\text{H}^+]}{[\text{H}^+] + K_{\text{a}}} \left(k_\Psi + \frac{k'_\Psi}{[\text{H}^+]} K_{\text{a}} \right) \qquad (7)$$

and K_{a} is the equilibrium constant for the dissociation of the acid. Since the reaction shows general acid catalysis with no contribution from the buffer conjugate base, the two pseudo-first-order rate constants (assuming negligible
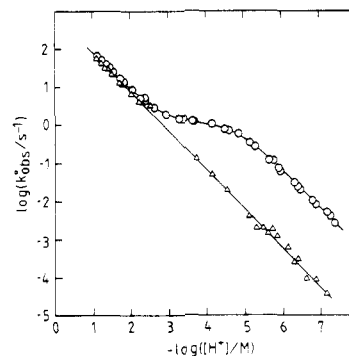
Figure 5. Rate profile for (Z)-6,9-epoxynon-5-enoic acid (O) and its methyl ester (△) in aqueous solution at 25.0 ± 0.1 °C and $I = 0.1$ M.

Scheme III
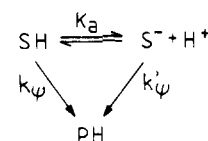
SH = (Z)-6,9-epoxynon-5-enoic acid
S⁻ = the carboxylate anion of
(Z)-6,9-epoxynon-5-enoic acid
PH = the hydrolysis product

contribution from water as a general acid) could be written as shown in eq 8 and 9.

$$k_\Psi = k_{\text{H}^+}[\text{H}^+] + k_{\text{HA}}[\text{HA}] \qquad (8)$$

$$k'_\Psi = k'_{\text{H}^+}[\text{H}^+] + k'_{\text{HA}}[\text{HA}] \qquad (9)$$

Insertion of eq 8 and 9 into eq 7 and rearranging gives

$$k_{\text{obsd}} = \frac{[\text{H}^+]}{[\text{H}^+] + K_{\text{a}}}(k_{\text{H}^+}[\text{H}^+] + k'_{\text{H}^+}K_{\text{a}}) +$$

$$\frac{[\text{HA}]}{[\text{H}^+] + K_{\text{a}}}(k_{\text{HA}}[\text{H}^+] + k'_{\text{HA}}K_{\text{a}}) \quad (10)$$

A comparison with eq 6 gives

$$k_{\text{obsd}}{}^{\circ} = \frac{[\text{H}^+]}{[\text{H}^+] + K_{\text{a}}}(k_{\text{H}^+}[\text{H}^+] + k'_{\text{H}^+}K_{\text{a}}) \qquad (11)$$

$$k_{\text{HA}}{}^{\text{app}} = \frac{k_{\text{HA}}[\text{H}^+] + k'_{\text{HA}}K_{\text{a}}}{[\text{H}^+] + K_{\text{a}}} \qquad (12)$$

The buffer dependent term of eq 10 gives $k_{\text{HA}}{}^{\text{app}}$ according to eq 12.

As mentioned above, the plots of $k_{\text{cat.}}$ vs. f_{HA} for the ester (Figure 2) and the acid (Figure 3) show pronounced curvature. In the case of the acid this can be explained in the following way

$$k_{\text{cat.}} = f_{\text{HA}}k_{\text{HA}}{}^{\text{app}} = f_{\text{HA}}\frac{k_{\text{HA}}[\text{H}^+] + k'_{\text{HA}}K_{\text{a}}}{[\text{H}^+] + K_{\text{a}}} \qquad (13)$$

Insofar as $k_{\text{HA}} \neq k'_{\text{HA}}$ the rate constant $k_{\text{cat.}}$ will depend on $[\text{H}^+]$ and the simple relation $k_{\text{cat.}} = f_{\text{HA}}k_{\text{HA}}$ will not hold. This situation will give rise to a nonlinear plot of $k_{\text{cat.}}$ vs. f_{HA} for the acid (Figure 3). However, this explanation cannot be valid in the case of the ester, for which K_{a} vanishes and eq 13 reduces to $k_{\text{cat.}} = f_{\text{HA}}k_{\text{HA}}$.

Another possible explanation, valid for the ester as well as the acid, is that H_3PO_4 is a very efficient catalyst so that even at high pH it can contribute to the rate law.[13,14]

Chart I

TS 1   TS 2
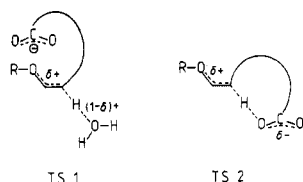
In the case of the ester, this possibly leads to eq 14, where $K_1 = [H_2PO_4^-][H^+]/[H_3PO_4]$ which shows that the

$$k_{cat.} = (k_{H_2PO_4^-} + k_{H_3PO_4}[H^+]/K_1)f_{H_2PO_4^-} \quad (14)$$

rate constant $k_{cat.}$ will be dependent on $[H^+]$. A similar but more complicated expression applies to the acid, and the simple relation $k_{cat.} = f_{HA}k_{HA}$ will hold neither for the acid nor for the methyl ester.

The experimental points have been fitted to the above expression for the ester and the corresponding more complicated one for the acid. The theoretical curves are given in Figures 2 and 3.

In Figure 5, log $k_{obsd}°$ vs. −log $[H^+]$ has also been plotted for the acid.

Equation 11 can be rearranged to eq 15.

$$k_{obsd}° = \frac{[H^+]}{[H^+]/K_a + 1} k_{H^+}([H^+]/K_a + k'_{H^+}/k_{H^+}) \quad (15)$$

A nonlinear least-squares fit[15] of the experimental data to eq 15 gives[16]

$$K_a = (1.840 \pm 0.077) \times 10^{-5} \text{ M}$$

$$k_{H^+} = 745 \pm 17 \text{ M}^{-1} \text{ s}^{-1}$$

$$k'_{H^+}/k_{H^+} = 82 \pm 2$$

The rate constant k_{H^+} is in good agreement with $k_{H^+} = 768 \pm 10$ M^{-1} s^{-1} obtained from measurements in HClO$_4$ (Table S1[12]). From the ratio $k'_{H^+}/k_{H^+} = 82$ the rate constant $k'_{H^+} = 61100 \pm 2900$ M^{-1} s^{-1} is obtained. This rate constant is the second-order rate constant for hydronium ion catalyzed hydrolysis of S$^-$ (S$^-$ = the carboxylate anion of (Z)-6,9-epoxynon-5-enoic acid) and could be divided into the contributions from the two kinetically equivalent mechanisms 1 and 2 (Chart I).
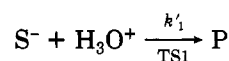
mechanism 1

$$S^- + H_3O^+ \xrightarrow[TS1]{k'_1} P$$

$$v_1 = k'_1[S^-][H_3O^+]$$

mechanism 2

$$S^- + H_3O^+ \underset{1/K_a}{\rightleftharpoons} SH + H_2O$$

$$SH \xrightarrow[TS2]{k'_2} P$$

$$v_2 = k'_2[SH] = (k'_2/K_a)[S^-][H_3O]$$

According to mechanisms 1 and 2 the following are obtained:

$$v = k'_{H^+}[S^-][H_3O^+] = (k'_1 + k'_2/K_a)[S^-][H_3O^+] \quad (16)$$

$$k'_{H^+} = k'_1 + k'_2/K_a \quad (17)$$

The large ratio (82) of the rate constants for the hydrolysis reaction of the ionized and un-ionized form, k'_{H^+}/k_{H^+}, could therefore be interpreted in terms of a large rate constant k'_1 for mechanism 1 or a large rate constant k'_2/K_a for mechanism 2. The role of the carboxylate anion with respect to mechanisms 1 and 2 is presently under investigation.[17]

Conclusion

A comparison between the results from the present investigation (Figure 5) and those for prostacyclin and its methyl ester[3] shows that (Z)-6,9-epoxynon-5-enoic acid is a good model substance for prostacyclin. The rate profiles found in the two investigations are very similar. The large ratio (82) between the rate constants for hydrolysis of the carboxylate form and the carboxylic acid form of the model is very close to the corresponding ratio (99) found for prostacyclin and the pK$_a$ of the carboxylic acid function of the model is 4.74 (I = 0.10 M) compared to 4.89 (I = 0.04 M) for prostacyclin.[3b]

Registry No. 1, 35121-78-9; **2a**, 108428-26-8; **2b**, 108428-27-9; **2c**, 109997-32-2; **3**, 25714-71-0; **4**, 2067-33-6; **5**, 109997-30-0; **6**, 75964-05-5; **7**, 109997-31-1; Ph$_3$P$^+$(CH$_2$)$_4$CO$_2$H·Br$^-$, 17814-85-6; 2,3-dihydrofuran, 1191-99-7; tetrahydrofuran-2-ol, 5371-52-8.

Supplementary Material Available: Tables S1–S5 of rate data for the hydrolyses of (Z)-6,9-epoxynon-5-enoic acid and its methyl ester in various solutions (20 pages). Ordering information is given on any current masthead page.

(13) Loudon, G. M.; Ryono, D. E. *J. Org. Chem.* **1975**, *40*, 3574.

(14) Chiang, Y.; Kresge, A. J.; Lahti, M. O.; Weeks, P. O. *J. Am. Chem. Soc.* **1983**, *105*, 6852. Chiang, Y.; Kresge, A. J.; Van Do, S.; Weebs, D. P. *J. Org. Chem.* **1986**, *51*, 4035.

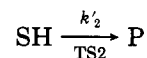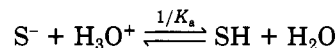(15) Johnson, K. J. *Numerical Methods in Chemistry*; Marcel Dekker: New York, 1980.

(16) These values are slightly different from the ones published in preliminary form,[4] because we have refined our original data.

(17) Bergman, N.-Å.; Jansson, M.; Chiang, Y.; Kresge, A. J., manuscript in preparation.