Chemical Stability of a Prostacyclin Analogue Due to the Absence of Intramolecular Catalysis

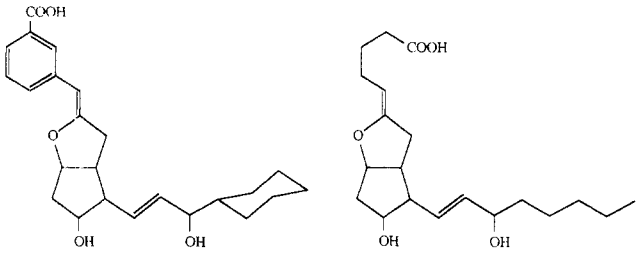
Nils-Åke Bergman* and Torbjörn Halvarsson

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

Received October 14, 1987

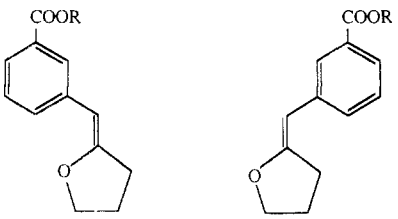
Kinetic investigation of (*Z*)-1-(3-carboxyphenyl)-2,5-epoxypent-1-ene (**3a**), a model compound of the physiologically active prostacyclin analogue taprostene (pINN) (**1**), has revealed that the chemical stability reported for this analogue is due both to conjugation between the aromatic ring and the labile vinyl ether function and to the inability of the carboxylic acid function to act as an efficient electrostatic or intramolecular acid catalyst in the hydrolysis of the vinyl ether group of the molecule. The isomer (*E*)-1-(3-carboxyphenyl)-2,5-epoxypent-1-ene (**4a**) shows the same kinetic behavior as **3a**.

The physiologically active prostacyclin analogue taprostene (pINN) (**1**) is reported to have a high chemical stability due to conjugation between the aromatic ring and the vinyl ether function,[1] which shows great hydrolytic lability in prostacyclin (**2**).[2] We can now present evidence that absence of intramolecular catalysis is also an important factor for the stability of 1.



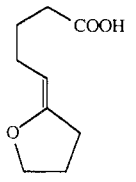
1 2

By examining the hydrolysis of (*Z*)-1-(3-carboxyphenyl)-2,5-epoxypent-1-ene (**3a**), a simple model compound of **1**, we found a kinetic behavior different from that reported for prostacyclin.[3] The rate acceleration found for both **3a** and its *E* isomer **4a** upon ionization is only a factor 2, compared to 99 found for prostacyclin.



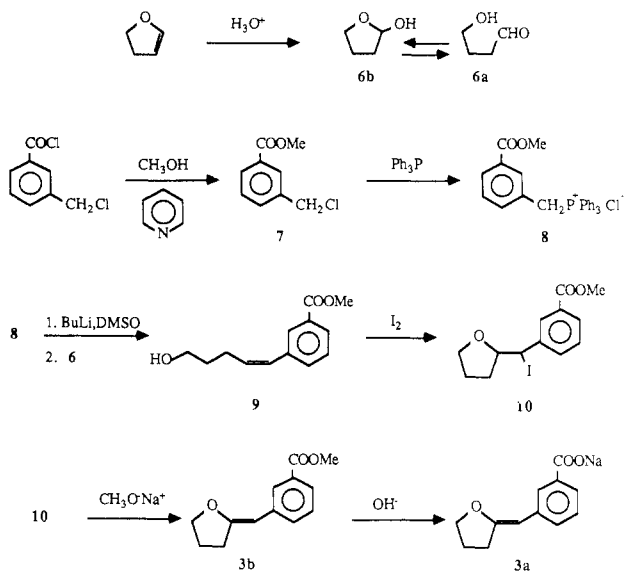
3a R=H, Na 4a R=H, Na
3b R=CH_3 4b R=CH_3

That simple model compounds such as **3** can be used to probe the reactivity of the full compound has been shown by Bergman et al. by the kinetic investigation of **5**, a simple model compound of prostacyclin.[4]



5

Scheme I



The synthesis of the *Z* isomer (**3a**) and the *E* isomer (**4a**) of 1-(3-carboxyphenyl)-2,5-epoxypent-1-ene and their corresponding methyl esters, **3b** and **4b**, respectively, is outlined in Scheme I; it consists essentially of steps that are similar to ones used in the synthesis of prostacyclin[5] and its analogue **1**.[6]

Experimental Section

^{1}H NMR spectra were recorded on a Bruker WH 270 instrument or a Varian XL 400, and chemical shifts are given in ppm downfield from Me_4Si. Mass spectra were obtained with a Finnigan 1020 mass spectrometer. UV spectra were recorded on a Varian Cary 210 UV spectrophotometer. Semipreparative HPLC was performed with a Waters Associates system consisting of a Waters M-45 solvent delivery system, a Waters U6K injector, an R-sil silica column (10-μm particles, 4.6 mm (i.d.) × 25 cm), and a Waters R-401 differential refractometer or with a Varian system consisting of a Varian Vista 5500 liquid chromatograph, a Varian UV-200 detector, a Rheodyne manual loop injector, a Varian Series 600 data system, and a Varian MicroPak column SI-10 (8 mm (i.d.) × 30 cm).

Synthetic Procedure. 4-Hydroxybutanal (6).[7] 2,3-Dihydrofuran (5.0 mL, 66.3 mmol) was added to 25 mL of 0.2 M HCl with stirring and cooling on an ice bath. After 15 min a

(1) Flohé, L.; Böhlke, H.; Frankus, E.; Kim, S.-M. A.; Lintz, W.; Loschen, G.; Michel, G.; Müller, B.; Schneider, J.; Seipp, U.; Vollenberg, W.; Wilsmann, K. *Arzneim.-Forsch.* **1983**, *33*(II), 1240.
(2) Cho, M. J.; Allen, M. A. *Prostaglandins* **1978**, *15*, 943.
(3) Chiang, Y.; Cho, M. J.; Euser, B. A.; Kresge, A. J. *J. Am. Chem. Soc.* **1986**, *108*, 4192.
(4) (a) Bergman, N.-Å.; Chiang, Y.; Jansson, M.; Kresge, A. J.; Ya, Y. *J. Chem. Soc., Chem. Commun.* **1986**, 1366. (b) Bergman, N.-Å.; Chiang, Y.; Jansson, M.; Kresge, A. J.; Yin, Y. *J. Org. Chem.* **1987**, *52*, 4449.
(5) (a) Johnson, R. A.; Lincoln, F. H.; Nidy, E. G.; Schneider, W. P.; Thompson, J. L.; Axen, U. *J. Am. Chem. Soc.* **1978**, *100*, 7690. (b) Whittaker, N. *Tetrahedron Lett.* **1977**, 2805.
(6) Seipp, U.; Vollenberg, W.; Michel, G.; Müller, B. German Patent DE 3029 984 (Grünenthal GmbH), Feb 18, 1982.
(7) Paul, R.; Fluchaire, M.; Collardeau, G. *Bull. Soc. Chim. Fr.* **1950**, 668.

0022-3263/88/1953-2548$01.50/0

homogeneous solution was obtained. Stirring was continued at room temperature for 45 min. The aqueous phase was extracted eight times with CH_2Cl_2, 125 mL altogether. The combined organic phases were washed with saturated $NaHCO_3$ and dried ($MgSO_4$). After removal of the solvent a colorless liquid (5.25 g, 90%) was obtained. The crude product was used without further purification. Distillation of **6** leads to partial polymerization. 4-Hydroxybutanal (**6a**) exists in an equilibrium with the cyclic hemiacetal, i.e., 2-hydroxytetrahydrofuran (**6b**). **6**: ^{1}H NMR ($CDCl_3$) δ 1.8–2.0 (m), 2.46–2.52 (td, J = 7, 2 Hz), 3.38–3.46 (dt, J = 10, 6 Hz), 3.65–3.73 (dt, J = 10, 6 Hz), 3.83–3.88 (t, J = 6 Hz), 5.07–5.09 (dd, J = 4, 1 Hz), 9.76–9.77 (t, J = 2 Hz).

Methyl 3-(Chloromethyl)benzoate (7). 3-(Chloromethyl)-benzoyl chloride (50 mL, 0.35 mol) was added over a period of 1 h to a solution of 28.5 mL (0.35 mol) of pyridine in 100 mL of anhydrous methanol with cooling in an ice bath. The reaction mixture was then refluxed for 4 h and the solvent removed under reduced pressure. The residue was taken up in 60 mL of ether, washed with 0.5 M HCl three times, water, and saturated $NaHCO_3$, and dried ($MgSO_4$). The solution was concentrated in a rotary evaporator and the residue was distilled in vacuo, giving **7** as a colorless liquid (60.0 g, 92%): bp 68 °C/0.7 mmHg; n^{21}_D 1.5401; ^{1}H NMR ($CDCl_3$) δ 3.92 (s, 3 H), 4.61 (s, 2 H), 7.41–7.47 (t, 1 H, J = 8 Hz), 7.57–7.60 (d, 1 H, J = 8 Hz), 7.97–8.01 (d, 1 H, J = 8 Hz), 8.06 (s, 1 H).

Anal. Calcd for $C_9H_9ClO_2$: C, 58.6; H, 4.9. Found: C, 59.0; H, 4.9.

Triphenylphosphonium Salt of Methyl 3-(Chloromethyl)benzoate (8). Methyl 3-(chloromethyl)benzoate (**7**) (5.56 g, 30.0 mmol) and 23.61 g (90 mmol) of triphenylphosphine were refluxed in 60 mL of xylene for 24 h. The precipitated phosphonium salt was filtered off and washed several times with ether to remove excess triphenylphosphine. After drying in vacuo, the white salt (12.4 g, 93%) was stored in a desiccator **8**: mp 218.5–219.5 °C; ^{1}H NMR (DMSO-d_6) δ 3.76 (s, 3 H), 5.26–5.30 (d, 2 H, J_{P-CH_2} = 16 Hz), 7.25–7.95 (19 H, aromatic).

1-(3-Carboxyphenyl)-5-hydroxypent-1-ene Methyl Ester (9). The Wittig reaction was carried out under a nitrogen atmosphere. Butyllithium in hexane (20 mL, 32 mmol) was added in small portions to 25 mL of anhydrous DMSO during magnetic stirring. After 5 min a solution of 14.3 g (32 mmol) of **8** in 50 mL of anhydrous DMSO was added in one portion. The reaction solution turned immediately red. After 15 min **6** (2.8 g, 32 mmol) was added to the ylide solution and the red color slowly changed to orange. The reaction mixture was allowed to stand overnight and then the bulk of DMSO was distilled off in vacuo at 30–35 °C. The residue was taken up in ether and water. The ether solution was washed with water twice and with brine once and dried ($CaSO_4$). The bulk of $Ph_3P{=}O$ was precipitated by adding cold (0 °C) hexane and then filtered off. The solvent was removed at reduced pressure and the residue was chromatographed on silica using ethyl acetate/hexane (1:1) as eluent to give 2.55 g (36%) of alkene product as a 45/55 Z/E mixture. An attempt to distill the alkene mixture was not successful. The two isomers were separated on HPLC using (hexane + 0.5% 2-propanol)/ethyl acetate (90:10) as the mobile phase. The Z isomer was eluted first, with the separation factor α = 1.2.

Z isomer of **9**: ^{1}H NMR ($CDCl_3$) δ 1.32–1.35 (t, 1 H, OH), 1.70–1.78 (m, 2 H), 2.40–2.45 (q, 2 H, $CH_2C{=}$), 3.66–3.70 (q, 2 H, CH_2OH), 3.92 (s, 3 H, $COOCH_3$), 5.72–5.78 (m, 1 H, $C{=}CHCH_2$), 6.46–6.49 (d, 1 H, $C{=}CHAr$, J = 12 Hz), 7.39–7.42 (t, 1 H), 7.46–7.48 (d, 1 H), 7.88–7.91 (d, 1 H), 7.95 (s, 1 H); ^{13}C NMR ($CDCl_3$) 167.1 (COOR), 137.7, 133.2, 133.1, 130.0, 129.8, 128.5, 128.2, and 127.6 (aromatic and olefinic), 62.3 (CH_2OH), 52.1 (OCH_3), 32.7 (CH_2), 24.8 (CH_2); MS m/e (relative intensity) 50 (16.4), 51 (32.8), 59 (80.3), 63 (21.3), 65 (10.4), 73 (15.3), 74 (12.0), 76 (15.3), 77 (29.0), 91 (68.8), 103 (19.1), 105 (18.6), 115 (88.5), 116 (31.2), 117 (16.9), 127 (19.1), 128 (71.6), 129 (43.2), 131 (51.4), 141 (12.6), 142 (23.0), 143 (100), 144 (17.5); UV (CH_3CN) λ_{max} 225 (ϵ 26 260), 250 (shoulder, ϵ 10 200), 292 nm (ϵ 960); IR (film) 3400 (OH), 3000 (=CH), 1715 (C=O), 1280 cm^{-1} (ester).

Anal. Calcd for $C_{13}H_{16}O_3$: C, 70.9; H, 7.3. Found: C, 69.9; H, 7.4.

E isomer of **9**: ^{1}H NMR ($CDCl_3$) δ 1.31–1.33 (t, 1 H, OH), 1.72–1.82 (m, 2 H), 2.30–2.38 (q, 2 H, $CH_2C{=}$), 3.69–3.75 (q, 2 H, CH_2OH), 3.92 (s, 3 H, $COOCH_3$), 6.26–6.37 (dt, 1 H, $C{=}CHCH_2$, J = 16, 7 Hz), 6.43–6.49 (d, 1 H, $C{=}CHAr$, J = 16 Hz), 7.33–7.39 (t, 1 H), 7.49–7.53 (d, 1 H), 7.84–7.88 (d, 1 H), 8.02 (s, 1 H); ^{13}C NMR ($CDCl_3$) 167.1 (COOR), 137.9, 131.5, 130.3 (two carbons), 129.4, 128.5, 127.9, and 127.0 (aromatic and olefinic), 62.3 (CH_2OH), 52.1 (OCH_3), 32.1 (CH_2), 29.3 (CH_2); MS m/e (relative intensity) 51 (21.7), 53 (13.6), 55 (14.9), 57 (11.5), 59 (68.1), 63 (19.6), 65 (17.0), 66 (11.0), 71 (21.7), 73 (23.0), 76 (12.8), 77 (32.3), 89 (21.7), 91 (74.9), 103 (23.4), 105 (24.3), 115 (92.3), 116 (38.3), 117 (23.0), 127 (25.1), 128 (87.2), 129 (48.1), 130 (13.6), 131 (47.2), 141 (11.1), 142 (17.4), 143 (100), 144 (17.4), 149 (17.9), 155 (12.8), 187 (11.5), 188 (11.9), 189 (10.6), 220 (10.6) M$^+$; UV (CH_3CN) λ_{max} 227 (ϵ 29 770), 255 (ϵ 14 470), 301 nm (ϵ 1300); IR (film) 3370 (OH), 1715 (C=O), 1285 (ester), 960 cm^{-1} (=CH).

Anal. Calcd for $C_{13}H_{16}O_3$: C, 70.9; H, 7.3. Found: C, 70.7; H, 7.5.

1-(3-Carboxyphenyl)-2,5-epoxy-1-iodopentane Methyl Ester (10). A Z/E mixture of **9** (0.37 g, 1.68 mmol) was dissolved in 5 mL of CH_2Cl_2 and added to 20 mL of saturated $NaHCO_3$. A solution of 0.47 g (1.85 mmol) of iodine in 15 mL of CH_2Cl_2 was added dropwise to the two-phase system during a period of 2.5 h at 0 °C. The reaction mixture was stirred at 0 °C for 12 h. Sodium thiosulfate (pentahydrate) was added at room temperature until a colorless solution was obtained. The two phases were separated, and the organic solution was washed with water and brine, dried ($MgSO_4$), and concentrated in vacuo. The crude slightly yellow product (0.58 g) was used immediately without further purification. The iodo compound is not stable and turns black in a week. According to NMR, the product consisted of the diastereomeric mixture of **10** (70%) and unreacted starting material. The ^{1}H NMR spectrum of the diastereomeric mixture is complex, and signals have not been fully assigned. ^{1}H NMR ($CDCl_3$) δ 1.52–1.66 (br d), 1.82–2.06 (m), 2.24–2.46 (m), 2.67–2.76 (br d), 3.63–3.76 (td), 3.91 (s), 3.92 (s), 3.83–4.07 (m), 4.13–4.27 (m), 4.47–4.51 (d), 5.04–5.09 (t), 7.35–7.70 (2 H, aromatic), 7.85–8.10 (2 H, aromatic).

1-(3-Carboxyphenyl)-2,5-epoxypent-1-ene Methyl Ester (3b and 4b). The crude iodo compound **10** (0.58 g) was dissolved in 5 mL of anhydrous methanol under a nitrogen atmosphere. A sodium methoxide solution (10 mL, 0.87 M) obtained by dissolving 0.2 g of sodium in 10 mL of anhydrous methanol was slowly added while cooling on an ice bath. The reaction mixture was left at room temperature overnight. Solid $NaHCO_3$ was added to neutralize excess base. After 30 min of stirring, the solvent was removed under reduced pressure. The residue was extracted three times with ether. The ether solutions were combined and then washed twice with saturated $NaHCO_3$ and once with brine. The remaining residue was taken up in ether and quickly washed with buffer, pH 4. The ether phase was separated and washed twice with saturated $NaHCO_3$ and with brine and then combined with the other ether solution. After drying (Na_2CO_3 + $MgSO_4$), the solvent was removed under reduced pressure, giving 0.27 g of a slightly yellow oil. The crude product was chromatographed on a silica column using ether/hexane/triethylamine (10:89:1) as mobile phase, giving one large (0.25 g) and one small (0.02 g) fraction of a colorless oil. The main fraction was shown by ^{1}H NMR to consist of three compounds: the Z and the E isomers of the vinyl ether product, **3b** (33%) and **4b** (22%), respectively, and a third, not identified compound (45%), calculated from the integrals of the methyl ester peaks. The unidentified compound is presently under investigation. A part of the product mixture was separated on a semipreparative HPLC column, with (hexane + 1% triethylamine)/CH_2Cl_2 (95:5) as mobile phase, for analysis and kinetic experiments. The three compounds are eluted in the order Z isomer, E isomer, and unknown, with the separation factor α = 1.1. The vinyl ethers polymerize to a yellow oil but not or only slowly when stored as dilute solutions in methanol, deuteriated benzene, or hexane containing 0.5% triethylamine. Distillation of the crude product leads to extensive polymerization, and the distillate obtained is less pure than before distillation.

3b: mp 54.6–56.1 °C; ^{1}H NMR (C_6D_6) δ 1.16–1.25 (m, 2 H), 2.08–2.14 (td, 2 H, J = 8, 1 Hz), 3.51 (s, 3 H), 3.62–3.67 (t, 2 H, J = 7 Hz), 5.15 (d, 1 H, J = 1 Hz), 7.17–7.23 (t, 1 H, J = 8 Hz), 7.86–7.89 (d, 1 H, J = 8 Hz), 7.97–8.00 (d, 1 H, J = 8 Hz), 8.70 (s, 1 H); ^{13}C (C_6D_6) 167.3 (COOR), 158.7 (OC=), 138.2, 131.7, 130.9, 128.8, 128.5, and 126.0 (aromatic), 96.7 (ArC=), 72.2 (OCH_2), 51.5 (OCH_3), 31.1 (CH_2), 24.0 (CH_2); MS m/e (relative intensity) 51

(11.0), 63 (20.5), 77 (24.4), 89 (43.3), 91 (19.7), 103 (27.6), 117 (15.0), 128 (12.6), 129 (13.4), 131 (59.8), 133 (39.4), 145 (47.2), 176 (86.6), 187 (21.3), 218 (100) M^+, 219 (13.4); UV (4% MeOH in water) λ_{max} 240 (ϵ 20 100), 274 (ϵ 17 200), 318 nm (ϵ 1650).

4b: ^1H NMR (C_6D_6) δ 1.23–1.33 (m, 2 H), 2.26–2.32 (td, 2 H, J = 8, 2 Hz), 3.52 (s, 3 H), 3.54–3.57 (t, 2 H, J = 7 Hz), 6.13 (s, 1 H), 7.05–7.12 (m, 2 H), 7.93–7.96 (d, 1 H, J = 7 Hz), 8.16 (s, 1 H); ^{13}C (C_6D_6) 167.1 (COOR), 160.9 (OC=), 139.0, 131.7, 131.0, and 125.8 (aromatic, two signals are hidden under the benzene peak), 98.6 (ArC=), 69.3 (OCH_2), 51.6 (OCH_3), 28.5 (CH_2), 25.0 (CH_2); MS m/e (relative intensity) 63 (17.4), 89 (23.0), 131 (36.2), 133 (28.8), 145 (30.2), 149 (12.7), 176 (77.7), 187 (16.6), 218 (100) M^+, 219 (12.6); UV (H_2O) λ_{max} 242 (ϵ 23 100), 272 nm (ϵ 17 900).

Alternative Route to 3b and 4b. **3b** and **4b** were also prepared from **10** by stirring **10** with 3 equiv of DBU (dried over molecular sieves) in toluene (1.2 mL/100 mg) for 24 h at room temperature. The hydrochloride of DBU precipitated during the reaction. After removal of solvent, the residue was taken up in ether and chromatographed on a silica column to remove salt and excess DBU. The yield of product mixture was the same as with methoxide as the base. When commercial DBU was used without prior drying over molecular sieves, no reaction occurred.

(*Z*)-1-(3-Carboxyphenyl)-2,5-epoxypent-1-ene Sodium Salt (3a). Saponification of **3b** was made under conditions similar to those of ref 5. Thus, 3.7 mg of pure **3b** was dissolved in 0.2 mL of MeOH, and 0.4 mL of a NaOH (0.5 M) solution was added. After 24 h at room temperature, the solution was diluted with 0.2 mL of MeOH. This solution was used in the kinetic experiments.

(*E*)-1-(3-Carboxyphenyl)-2,5-epoxypent-1-ene Sodium Salt (4a). Saponification of **4b** was performed as above, giving a solution that was used in the kinetic experiments.

Kinetic Procedure. All buffer solutions were prepared from commercially available chemicals of the A.R. grade using deionized water that had been distilled. Hydronium ion concentrations were calculated with activity coefficients recommended by Bates.[8]

Rates of hydrolysis of all compounds were measured by monitoring the decrease in absorbance of the conjugated vinyl ether double bond at 270–274 nm. The hydrolysis reaction was followed for 3–5 half-lives. The kinetic measurements were made with either a Varian Cary 210 spectrophotometer or a Durrum-Gibson stopped-flow spectrophotometer. The UV cells and the buffer solutions were thermostated at 25.0 ± 0.1 °C. The substrate concentration in the cell was 10^{-4}–10^{-5} M. The kinetic data conformed well to the first-order rate law, and observed rate constants were evaluated according to ref 4b.

Results

Rates of hydrolysis of the vinyl ether function of the *Z* and *E* isomers of 1-(3-carboxyphenyl)-2,5-epoxypent-1-ene and their corresponding methyl esters were determined in dilute perchloric acid and hydrochloric acid solutions and formic acid, acetic acid, and biphosphate ion buffer solutions. Ionic strength was maintained at 0.10 M with KCl. The data are summarized in Tables S1–S8.[9]

The observed pseudo-first-order rate constant for both the carboxylic acid and the methyl ester of the *Z* and *E* isomers is given by eq 1. The buffer-independent part,

$$k_{obsd} = k^\circ_{obsd} + k^{app}_{HA}[HA] \quad (1)$$

k°_{obsd}, at a given pH is obtained by extrapolating the contribution from the buffer acid to zero buffer concentration.[10] A typical buffer plot is shown in Figure 1. Catalysis by base could not be observed. For the methyl

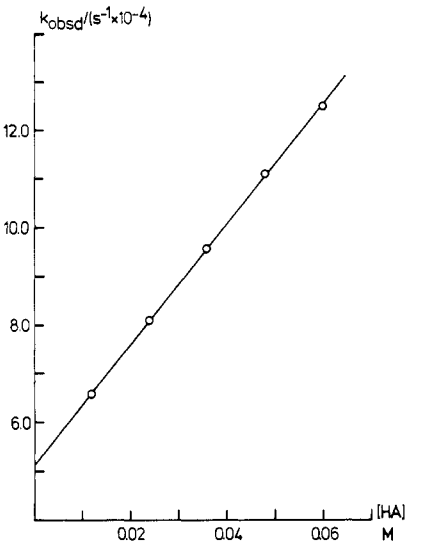
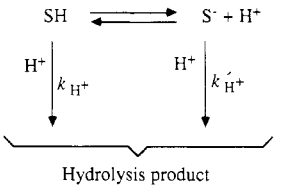


Figure 1. Hydrolysis of (*Z*)-1-(3-carboxyphenyl)-2,5-epoxypent-1-ene (**3a**) in acetic acid buffer solution, $[HA]/[A^-] = 1.51$, at 25 °C.

Scheme II



ester of the two isomers, the buffer-independent part is given by

$$k^\circ_{obsd} = k_{H^+}[H^+] \quad (2)$$

with no contribution from the solvent.

Measurements on the methyl ester of the *Z* isomer (**3b**) (Tables S3 and S4) and the methyl ester of the *E* isomer (**4b**) (Tables S7 and S8) gave $k_{H^+} = 6.32 \pm 0.00\ M^{-1}\ s^{-1}$ and $k_{H^+} = 4.10 \pm 0.00\ M^{-1}\ s^{-1}$, respectively.

In the case of the carboxylic acid form of the *Z* and *E* isomers, the hydrolysis of the vinyl ether function shows a somewhat more complicated pattern. Both the neutral and ionized forms of the carboxylic acid substrates are hydrolyzed by hydronium ion and buffer acids but with different magnitudes of the corresponding rate constants. This is illustrated in Scheme II and is valid for both isomers. According to this scheme, the buffer-independent part of the observed rate constant is given by

$$k^\circ_{obsd} = \frac{[H^+]}{1 + [H^+]/K_a} k_{H^+}([H^+]/K_a + k'_{H^+}/k_{H^+}) \quad (3)$$

and the contribution from the buffer acid is given by

$$k^{app}_{HA} = \frac{k_{HA}}{1 + [H^+]/K_a}([H^+]/K_a + k'_{HA}/k_{HA}) \quad (4)$$

A nonlinear least-squares fit of eq 3 to the experimental data for the *Z* isomer (Tables S1 and S2) and for the *E* isomer (Tables S5 and S6) gave the results shown in Table I.

A similar fit of eq 4 to the experimental data gave the rate acceleration upon ionization of substrate acid for catalysis by buffer acid, i.e., k'_{HA}/k_{HA}. The reaction parameters for the hydrolysis of **3** and **4**, together with a comparison between the rate accelerations obtained for catalysis by buffer acid and that obtained for catalysis by

(8) Bates, R. G. *Determination of pH. Theory and Practice*; Wiley: New York, 1973; p 49.

(9) Supplementary material; see paragraph at end of paper regarding availability.

(10) In formic acid buffers, with buffer ratios $[HA]/[A^-] > 0.4$, and acetic acid buffers, with buffer ratios >2.5, $[H^+]$ is not constant along a dilution series with constant stoichiometric buffer ratio. This buffer failure has been corrected for by adjusting observed rate constants according to ref 11. These adjustments never amounted to more than a few percent of k_{obsd}.

Table I. Reaction Parameters for the Hydrolysis of (*Z*)-(3a) and (*E*)-1-(3-Carboxyphenyl)-2,5-epoxypent-1-ene (4a) and Prostacyclin (2) in Aqueous Solution at 25 °C (Ionic Strength = 0.10 M)

parameter	1-(3-carboxyphenyl)-2,5-epoxypent-1-ene[a]		
	Z isomer (3a)	*E* isomer (4a)	prostacyclin[a,b]
pK_a[c]	4.30 ± 0.10	4.21 ± 0.15	5.03 ± 0.15
k_{H^+}/(mol^{-1} dm^3 s^{-1})[d]	6.71 ± 0.20	4.33 ± 0.10	439 ± 4
k'_{H^+}/(mol^{-1} dm^3 s^{-1})[e]	15.25 ± 1.11	9.03 ± 0.65	43600 ± 900
acceleration (k'_{H^+}/k_{H^+})	2.27 ± 0.10	2.09 ± 0.10	99 ± 2

[a] The uncertainties cited are standard deviations derived from statistical analysis of the data; they do not include possible systematic errors. [b] Reference 3. [c] Acidity constant a zero ionic strength estimated with activity coefficients recommended by Bates.[8] [d] Rate constant for hydrolysis of substrate in carboxylic acid form. [e] Rate constant for hydrolysis of substrate in carboxylate form.

Table II. Reaction Parameters for the Hydrolysis of (*Z*)-(3a) and (*E*)-1-(3-Carboxyphenyl)-2,5-epoxypent-1-ene (4a) and Their Corresponding Methyl Esters (3b and 4b) in Aqueous Buffer Solutions at 25 °C (Ionic Strength = 0.10 M)

parameter	substrate	buffer acid[a]	
		HCOOH	CH_3COOH
k_{HA}/(mol^{-1} dm^3 s^{-1})[b]	3a	0.0439 ± 0.0017	0.00926 ± 0.00036
	4a	0.0331 ± 0.0022	0.00906 ± 0.00016
k'_{HA}/(mol^{-1} dm^3 s^{-1})[c]	3a	0.0435 ± 0.0105	0.0141 ± 0.0013
	4a	0.0445 ± 0.0106	0.0106 ± 0.0004
k_{HA}(ester)/(mol^{-1} dm^3 s^{-1})[d]	3b	0.0410 ± 0.0026	0.00946 ± 0.00026
	4b	0.0326 ± 0.0004	0.00830 ± 0.00020
acceleration (k'_{HA}/k_{HA})	3a	0.99 ± 0.20	1.52 ± 0.08
	4a	1.34 ± 0.23	1.17 ± 0.03
(k'_{H^+}/k_{H^+})[e]	3a	2.27 ± 0.10[f]	
	4a	2.09 ± 0.10[f]	

[a] The uncertainties cited are standard deviations derived from statistical analysis of the data; they do not include possible systematic errors. [b] Rate constant for hydrolysis of substrate in carboxylic acid form. [c] Rate constant for hydrolysis of substrate in carboxylate form. [d] Mean values. [e] From Table I. [f] H_3O^+.

hydronium ion, are shown in Table II.

Discussion

The rate profiles shown in Figure 2 are obtained from observed first-order rate constants for catalysis by H_3O^+ in $HClO_4$ and HCl solutions and by extrapolating the observed rate constants to zero buffer concentration. The data for the methyl esters of both the *Z* and the *E* isomers show a linear dependence of unit slope of log $k°_{obsd}$ against −log [H^+], indicating an uncomplicated catalysis by H_3O^+. In each rate profile of the two isomeric acid substrates two linear portions can be seen: one at −log [H^+] $\lesssim$ 3 and one at −log [H^+] $\gtrsim$ 5. This is similar to what has been found for prostacyclin and can be interpreted in terms of separate hydronium ion catalyzed hydrolysis of the un-ionized and the ionized forms of the substrates, as in Scheme II.[3]

As can be seen in Figure 2 and from the results in Table I, the *Z* isomers are approximately 1.5 times more reactive than the corresponding forms of the *E* isomers. This rate difference is normal for isomers of vinyl ethers,[12] and the same magnitude is observed for the *Z* and *E* isomers of the model compound (5) of prostacyclin.[13]

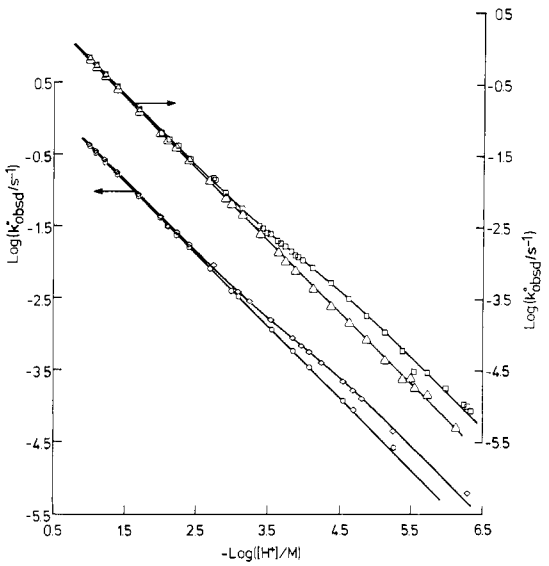


Figure 2. Rate profiles for hydrolysis of (*Z*)-1-(3-carboxyphenyl)-2,5-epoxypent-1-ene (**3a**) (□), the methyl ester of **3a** (**3b**), (△), (*E*)-1-(3-carboxyphenyl)-2,5-epoxypent-1-ene (**4a**) (◇), and the methyl ester of **4a** (**4b**) (○) in aqueous solution at 25 °C. log ($k°_{obsd}$/s^{-1}) values for the *Z* isomers are shown on the right ordinate, offset one log unit from the left ordinate for the *E* isomers.

In the case of **5** it was found that $k_{H^+}(\mathbf{5})/k_{H^+}$(prostacyclin) = 1.7 and $k'_{H^+}(\mathbf{5})/k'_{H^+}$(prostacyclin) = 1.4.[4] This was interpreted as due to that one face of the vinyl ether group of prostacyclin is shielded by the cis fusion of its two five-membered rings. If the same is assumed to be valid in the present case, it could be estimated that $k'_{H^+}(1)$ = 10.9 M^{-1} s^{-1} and $k_{H^+}(1)$ = 3.9 M^{-1} s^{-1}. One could thus estimate that the carboxylate form of **1** should be some 4000 times less reactive than the corresponding form of prostacyclin and that the carboxylic acid form of **1** should be only 110 times less reactive than the acid form of prostacyclin. A similar rate difference has been observed by Kresge.[14] In a kinetic investigation of **1** it was found that the carboxylate form of **1** was 3350 times less reactive and that the acid form of **1** was 89 times less reactive than the corresponding forms of prostacyclin. This indicates that the stabilization obtained by conjugation (corresponding to the 89-fold decrease in rate) is only partly responsible for the increased stability of **1** at pH >6 compared to prostacyclin.

The additional stabilization originates from the rigidity of the aromatic ring, which prevents the carboxylic acid function from coming close to any part of the vinyl ether function. The possibility of the carboxylic acid function to act as an efficient electrostatic or an intramolecular acid catalyst is therefore hampered.

The small rate acceleration obtained upon ionization of both the *Z* isomer and the *E* isomer is probably an electrostatic effect. Small electrostatic effects like the present one have been observed in other systems where an effective intramolecular participation is impossible.[15] As can be seen from Table II, the rate acceleration found for catalysis by hydronium ion, k'_{H^+}/k_{H^+}, is clearly larger than the rate ratio obtained for catalysis by neutral carboxylic acids, k'_{HA}/k_{HA}. This is quite natural as the stabilizing effect of

(11) (a) Kresge, A. J.; Chen, H. L.; Chiang, Y.; Murril, E.; Payne, M. A.; Sagatys, D. S. *J. Am. Chem. Soc.* **1971**, *93*, 413. (b) Lin, A. C.; Chiang, Y.; Dahlberg, D. B.; Kresge, A. J. *J. Am. Chem. Soc.* **1983**, *105*, 5380.
(12) (a) Taskinen, E. *Ann. Acad. Sci. Fenn., Ser. A* **1972**, *163*, 1. (b) Kresge, A. J.; Sagatys, D. S.; Chen, H. L. *J. Am. Chem. Soc.* **1977**, *99*, 7228.
(13) Bergman, N.-Å.; Jansson, M.; Chiang, Y.; Kresge, A. J. *J. Org. Chem.*, preceding paper in this issue.
(14) Chiang, Y.; Kresge, A. J.; Seipp, U.; Winter, W. *J. Org. Chem.*, following paper in this issue.
(15) (a) Loudon, G. M.; Smith, C. K.; Zimmerman, S. E. *J. Am. Chem. Soc.* **1974**, *96*, 465. (b) Loudon, G. M.; Ryono, D. E. *J. Am. Chem. Soc.* **1976**, *98*, 1900.

the carboxylate ion should be very pronounced in a reaction with a positively charged catalyst such as H_3O^+. In the reaction between the carboxylate form of **3a** and a neutral catalyst (such as CH_3COOH), this stabilizing effect is of minor importance, in agreement with the observation.

The results obtained for both the *Z* isomer (**3**) and the *E* isomer (**4**) have been confirmed by Kresge in the kinetic investigation of **1** and its *E* isomer, where it was shown that **1** follows the same kinetic pattern that has been found in the present investigation of the model compound of **1**.[14]

Acknowledgment. We express our thanks to Professor A. J. Kresge, University of Toronto, for equipment placed at our disposal during a stay of T.H. at the University of Toronto. We are grateful to the Swedish Natural Science Research Council for financial support of this work.

Supplementary Material Available: Rate data for the hydrolyses of (*Z*)- and (*E*)-1-(3-carboxyphenyl)-2,5-epoxypent-1-ene and the corresponding methyl esters in various solutions (Tables S1–S8) (26 pages). Ordering information is given on any current masthead page.

Kinetics of Hydrolysis of the Vinyl Ether Functional Group of the Stable, Bioactive Prostacyclin Analogue Taprostene (CG 4203)

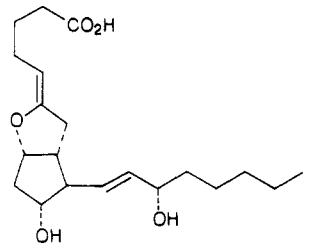
Y. Chiang,[†] A. J. Kresge,*[,†] U. Seipp,[‡] and W. Winter[‡]

Department of Chemistry, University of Toronto, Toronto, Ontario M5S 1A1, Canada, and Grünenthal GmbH, Center of Research, D-5100 Aachen, West Germany

Received October 14, 1987

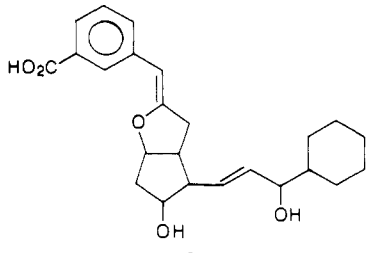
Rates of hydrolysis of the vinyl ether functional groups of the stable, bioactive prostacyclin analogue taprostene [(5*Z*,13*E*,9α,11α,15*S*)-2,3,4-trinor-1,5-*inter*-*m*-phenylene-6,9-epoxy-11,15-dihydroxy-15-cyclohexyl-16,17,18,19,20-pentanor]prosta-5,13-dienoic acid (**2**) (CG 4203), its methyl ester **3**, and its 5*E* isomer **4** were measured in dilute aqueous perchloric acid solutions and also in formic acid, acetic acid, and biphosphate ion buffers at 25 °C, ionic strength = 0.10 M. These data provide rate profiles that show that the two acids, **2** and **4**, are each about 3 times more reactive in their ionized, carboxylate forms than in their carboxylic acid forms. Rate constants for all three substrates are normal for vinyl ethers of this structure, and pK_a's of the acids **2** and **4** are consistent with expectation for aromatic carboxylic acids. The lifetime of **2** at physiological pH is 9 days.

Prostacyclin, **1**, is a naturally occurring bioregulator with remarkable physiological properties: it is the most potent inhibitor of blood-clot formation so far known.[1] Unfortunately, prostacyclin is also very unstable: its lifetime at physiological pH (=7) is only 3 min.[2] We have recently traced this instability to hydrolysis of prostacyclin's vinyl ether group accelerated 100-fold through intramolecular general-acid catalysis by the molecule's carboxylic acid function.[3]



1

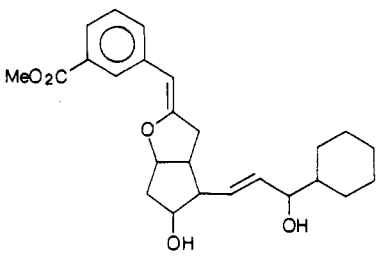
The hydrolysis of vinyl ethers is known to be inhibited by β-phenyl substituents,[4] such as that present in the recently prepared bioactive prostacyclin analogue taprostene, **2** (CG 4203).[5] The carboxylic acid group of this substance, moreover, is situated in a position from which intramolecular catalysis is not possible. This substance should therefore be much more stable than prostacyclin, and a hydrolytic lifetime of 20 days at physiological pH has in fact been predicted for it.[6] We now present evidence that substantiates this prediction.



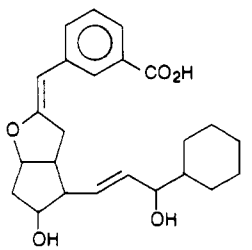
2

Experimental Section

Materials. **2** {[(5*Z*,13*E*,9α,11α,15*S*)-2,3,4-trinor-1,5-*inter*-*m*-phenylene-6,9-epoxy-11,15-dihydroxy-15-cyclohexyl-16,17,18,19,20-pentanor]prosta-5,13-dienoic acid}, its methyl ester (**3**), and its 5*E* isomer (**4**), are substances whose synthesis has been



3



4

[†] University of Toronto.
[‡] Grünenthal GmbH.

(1) For recent reviews of the physiological and chemical properties of prostacyclin, see: Bartman, W.; Beck, G. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 751–764. Nelson, N. A.; Kelly, R. C.; Johnson, R. A. *Chem. Eng. News* **1982**, *60*(30) 30–44.

(2) Cho, M. J.; Allen, M. A. *Prostaglandins* **1978**, *15*, 943–954. Chiang, Y.; Kresge, A. J.; Cho, M. J. *J. Chem. Soc., Chem. Commun.* **1979**, 129–130.

(3) (a) Chiang, Y.; Cho, M. J.; Euser, B. A.; Kresge, A. J. *J. Am. Chem. Soc.* **1986**, *108*, 4192–4196. (b) Bergman, N. A.; Chiang, Y.; Jansson, M.; Kresge, A. J.; Ya, Y. *J. Chem. Soc., Chem. Commun.* **1986**, 1366–1368.

(4) (a) Kresge, A. J.; Chen, H. J. *J. Am. Chem. Soc.* **1972**, *94*, 2818–2822. (b) Chiang, Y.; Kresge, A. J.; Young, C. I. *Can. J. Chem.* **1978**, *56*, 461–464.

(5) Flohé, L.; Bohlke, H.; Frankus, E.; Kim, S.-M.A.; Lintz, W.; Loschen, G.; Michel, G.; Muller, B.; Schneider, J.; Seipp, U.; Vollenberg, W.; Wilsmann, K. *Arzneim.-Forsch.* **1983**, *33*(II), 1240–1248.

(6) Kresge, A. J. *Acc. Chem. Res.* **1987**, *20*, 364–370.

0022-3263/88/1953-2552$01.50/0