$= I_A/I$ and $F_B = I_B/I$). The observed efficiency for reaction of A or B will be the true rearrangement quantum yield (i.e., the ϕ^0's) multiplied by the fraction of light reaching that state:

$$\phi_A = \phi_A^0 F_A \quad (8a)$$

$$\phi_B = \phi_B^0 F_B \quad (8b)$$

Rearranging gives expressions for the true quantum yields:

$$\phi_A^0 = \phi_A/F_A \quad (9a)$$

$$\phi_B^0 = \phi_B/F_B \quad (9b)$$

An upper limit on the magnitude of the quantities in eq 9 exists since by definition, the quantum yield of a nonchain unimolecular process cannot exceed 1.0:

$$\phi_A^0 \leq 1.0 \quad (10a)$$

$$\phi_B^0 \leq 1.0 \quad (10b)$$

and therefore

$$\phi_A/F_A \leq 1.0 \quad (11a)$$

$$\phi_B/F_B \leq 1.0 \quad (11b)$$

Thus a lower limit on F_A and F_B is obtained by simple cross-multiplication:

$$\phi_A \leq F_A \quad (12a)$$

$$\phi_B \leq F_B \quad (12b)$$

This result is entirely reasonable, since at least as much excitation must reach each group as is utilized in its reaction.

An upper limit on the magnitudes of F_A and F_B results from the fact that the total fraction of light in A and B cannot exceed 1.0:

$$F_A + F_B \leq 1.0 \quad (13)$$

and thus by simple subtraction:

$$F_A \leq (1 - F_B) \quad (14a)$$

$$F_B \leq (1 - F_A) \quad (14b)$$

Now, if each side of eq 12b is subtracted from 1.0, and each side of eq 12a is subtracted from 1.0, the inequalities 15 are obtained:

$$(1 - F_B) \leq (1 - \phi_B) \quad (15a)$$

$$(1 - F_A) \leq (1 - \phi_A) \quad (15b)$$

With reference to eq 14a and 15a, it is clear that since F_A is less than $(1 - F_B)$, and $(1 - F_B)$ is itself less than $(1 - \phi_B(\text{obs}))$, F_A must also be less than $(1 - \phi_B(\text{obs}))$. Equations 14b and 15b give a similar result for F_B, and thus upper limits may be placed as follow:

$$F_A \leq (1 - \phi_B) \quad (16a)$$

$$F_B \leq (1 - \phi_A) \quad (16b)$$

In this way eq 12 and 16 place limits on the fraction of excitation reaching each of excited states A and B.

Registry No. 7, 118890-23-6; 8, 91879-84-4; 9, 118868-36-3; 11a, 118868-35-2; 12, 118868-37-4; 13, 118868-38-5; 14, 118868-39-6; 15, 118868-40-9; 17, 118868-41-0; 18, 118868-42-1; 19, 118868-43-2; 20, 118868-44-3; $Eu(FOD)_3$, 17631-68-4; methyl vinyl ketone, 78-94-4; 6-α-naphthyl-3-methoxy-2-cyclohexenone, 98585-94-5; 2-bromonaphthalene, 580-13-2; methyl 2-β-naphthylethanoate, 2876-71-3; 1-bromonaphthalene, 90-11-9.

Supplementary Material Available: ORTEP drawings and tables of positional parameters, interatomic distances, bond angles, and temperature factors for compounds 15, 17, 18, 19, and 20 and tables of conditions and HPLC results for quantum yield determinations of 7 (39 pages). Ordering information is given on any current masthead page.

Hydrolysis of the Vinyl Ether Functional Group in a Model for Prostacyclin in Which the Carboxyl Group Has Been Replaced by a Pyridine Ring

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The hydrolysis of the vinyl ether functional group in the three isomeric compounds (*Z*,*E*)-2-methoxy-6-(2-pyridyl)hex-2-ene (3 and 4) and 2-methoxy-6-(2-pyridyl)hex-1-ene (5) has been studied in hydrochloric acid solutions and acetic acid and biphosphate ion buffer solutions. The rate constant ratio for the hydronium ion catalysis of the neutral and positive forms of the substrates are 45.7, 44.9 and 15.7, respectively. The rate accelerations are interpreted in terms of intramolecular general acid catalysis and the results are discussed in relation to the suggested mechanism for hydrolysis of prostacyclin.

The unusual high hydrolytic lability of prostacyclin (1)[1] has been traced to its carboxylic acid functional group acting in ionized form.[2] Two mechanistic alternatives, illustrated in Scheme I, have been discussed for the hydrolysis reaction of prostacyclin.[2-4]

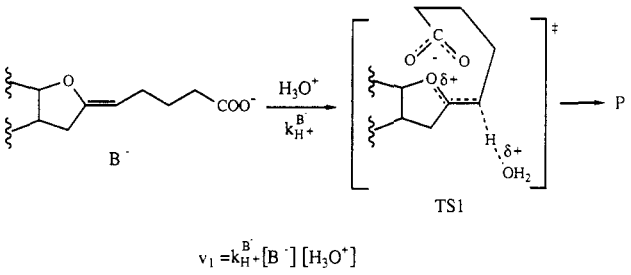
Mechanism 1 is an electrostatic catalysis[5] by the carboxylate ion during intermolecular protonation. The negative charge on the carboxylate group can stabilize the developing positive charge on the vinyl ether function in the transition state, TS1. In mechanism 2, there is a rapid

(1) Cho, M. J.; Allen, M. A. *Prostaglandins* **1978**, *15*, 943.
(2) Chiang, Y.; Cho, M. J.; Euser, B. A.; Kresge, A. J. *J. Am. Chem. Soc.* **1986**, *108*, 4192.
(3) Bergman, N.-Å.; Chiang, Y.; Jansson, M.; Kresge, A. J.; Yin, Y. *J. Org. Chem.* **1987**, *52*, 4449.
(4) Bergman, N.-Å.; Jansson, M.; Chiang, Y.; Kresge, A. J. *J. Org. Chem.* **1988**, *53*, 2544.
(5) This is strictly speaking a field effect but the term electrostatic catalysis has been kept here as this terminology has been used in related work.[2-4] The inductive effect is probably negligible in the present system.

0022-3263/89/1954-2137$01.50/0

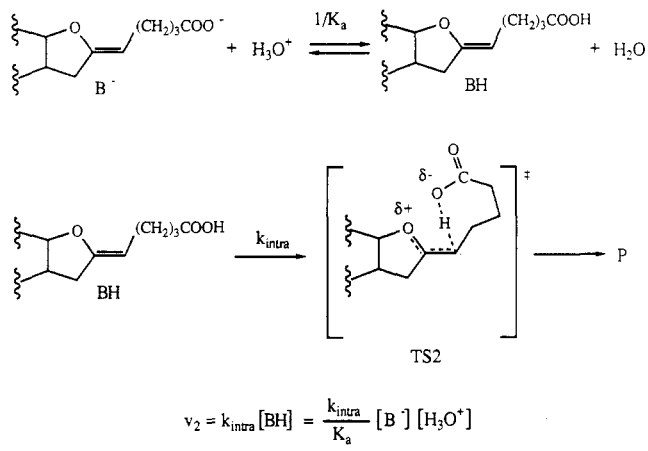
Scheme I

Mechanism 1:



$$v_1 = k_{H^+}^{B^-}[B^-][H_3O^+]$$

Mechanism 2:



$$v_2 = k_{intra}[BH] = \frac{k_{intra}}{K_a}[B^-][H_3O^+]$$

acid–base preequilibrium forming the corresponding acid of the substrate followed by a rate-determining intramolecular protonation, TS2. These two mechanisms are kinetically equivalent and not easily separated by simple kinetic considerations. Solvent isotope effect measurements on prostacyclin[2] as well as on the model compound (**2**)[3] and studies[4] of the corresponding *E* isomer of **2** have shown that mechanism 2 is the most probable one.

In the present investigation we have used substrates (**3**, **4**, and **5**) that are positively charged in their acid forms and neutral in their corresponding base forms (Chart I). Thus, mechanism 1 is eliminated since no negative charge is present to stabilize the developing positive charge on the vinyl ether function during intermolecular protonation.

The synthesis of compounds **3**, **4**, and **5** is outlined in Scheme II.

Experimental Section

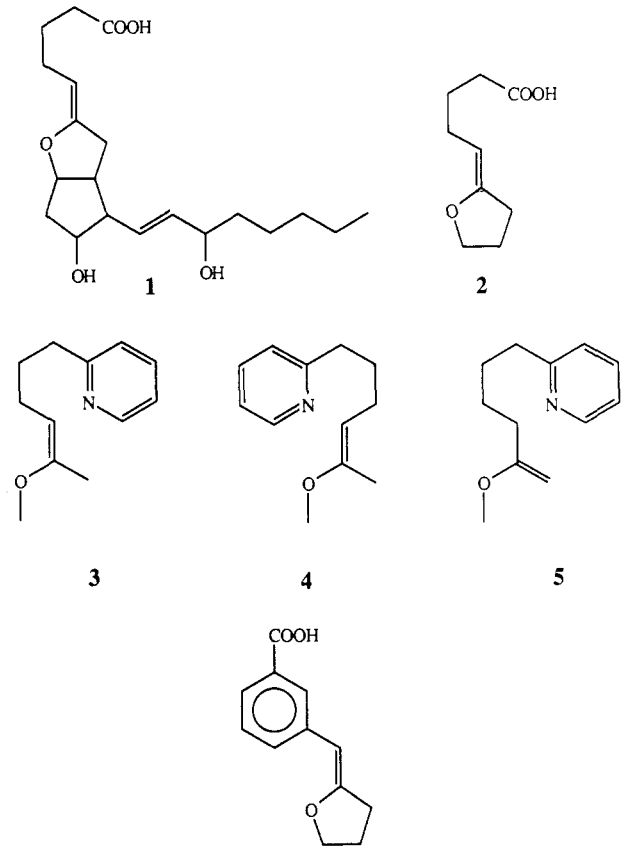
^{1}H NMR spectra were recorded on a Bruker WH 270 instrument or a Varian XL 400 instrument with a modified transmitter and computer system. Chemical shifts are given in ppm downfield from Me_4Si. Mass analyses were obtained with a Finnigan MAT 90 spectrometer. UV spectra were recorded on a Varian CARY 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, a R-sil^R silica column (10-μm particles, 4.6 mm (i.d.) × 25 cm), and a Waters R-401 differential refractometer.

Synthetic Procedure. 2,2-Dimethoxy-5-chloropentane (6). Freshly distilled 5-chloro-2-pentanone (40 mL, 0.35 mol) was mixed with 80 mL (0.73 mol) of trimethyl orthoformate and 0.1 g of *p*-toluenesulfonic acid in 100 mL of methanol and then refluxed for 5.5 h. The sulfonic acid was then neutralized by adding 1 mL of triethylamine. The solvent was removed under reduced pressure and the residue was taken up in ether and washed with water and saturated $NaHCO_3$ and dried ($MgSO_4$). The solution was concentrated and the residue was distilled in vacuo, giving **6** as a colorless liquid (53.9 g, 92%). Examination with ^{1}H NMR showed that the product contained ~8% starting material. A fraction of the product was dissolved in ether and shaken with saturated $NaHSO_3$ to remove unreacted ketone, but this procedure increased the amount of ketone.

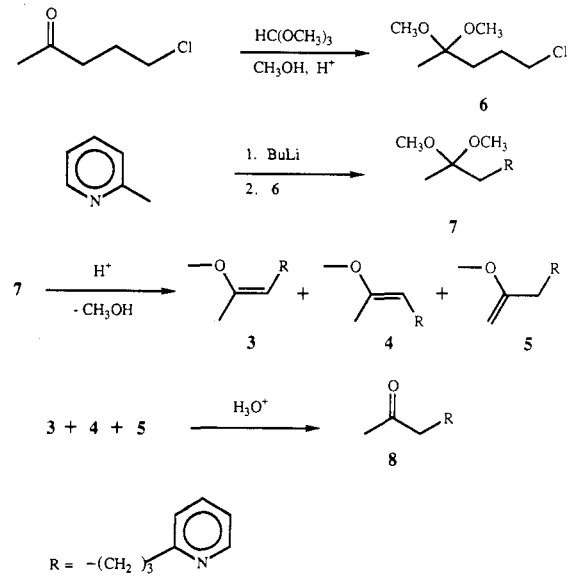
6: bp 76–79 °C/18 mmHg; ^{1}H NMR ($CDCl_3$) δ 1.27 (s, 3 H), 1.72–1.85 (m, 4 H), 3.18 (s, 6 H), 3.53–3.57 (t, 2 H, J = 6 Hz); IR (film, cm^{-1}) 2820, 1120, 1100, 1075, and 1050.

2,2-Dimethoxy-6-(2-pyridyl)hexane (7). The reaction was carried out under a nitrogen atmosphere, using the method described by Beumel et al. for formation of 2-picolyllithium[6] and the procedure described by Jones and Law for addition of 2-picolyllithium to halo acetals.[7] Thus, 100 mL of 1.6 M butyl-

Chart I



Scheme II



(6) Beumel, D. F., Jr.; Smith, W. N.; Rybalka, B. *Synthesis* **1974**, 43.

lithium in hexane was added to a solution of 15.8 mL (0.16 mol) of freshly distilled 2-picoline in 100 mL of anhydrous THF during a period of 30 min at −15 to −17 °C. After 1 h at room temperature, 13.3 g (0.08 mol) of **6** was added in 10 min to the dark red solution. The reaction mixture was stirred at room temperature for 10 h. Lithium chloride precipitated during the reaction. Aqueous NH_3 (5%) saturated with NH_4Cl was added slowly until the red color disappeared. The phases were separated and the organic phase dried ($MgSO_4$) and concentrated in vacuo. The residue was distilled in vacuo, giving **7** (11.2 g, 62.5%) as a slightly yellow liquid.

7: bp 86–92 °C/0.7 mmHg; ^1H NMR (C_6D_6) δ 1.18 (s, 3 H, CH_3C), 1.34–1.43 (m, 2 H, $C(OCH_3)_2CH_2CH_2$), 1.64–1.69 (m, 2 H, $C(OCH_3)_2CH_2$) 1.72–1.81 (quint, 2 H, J = 8 Hz, CH_2CH_2-pyr), 2.73–2.77 (t, 2 H, J = 8 Hz, CH_2-pyr), 3.03 (s, 6 H, OCH_3), 6.59–6.62 (dd, 1 H, J = 8 and 5 Hz, pyr 5-H), 6.71–6.73 (d, 1 H, J = 8 Hz, pyr 3-H), 7.02–7.06 (td, 1 H, J = 8 and 2 Hz, pyr 4-H), 8.49–8.51 (d br, 1 H, J = 5 Hz, pyr 6-H); ^{13}C NMR (C_6D_6) δ 21.2 (CH_3), 24.3 (CH_2), 30.3 (CH_2), 36.9 (CH_2), 38.6 (CH_2), 47.7 (OCH_3), 101.6 ($C(OMe)_2$), 120.8 (pyr C-5), 122.5 (pyr C-3), 135.6 (pyr C-4), 149.7 (pyr C-6), 162.6 (pyr C-2); IR (film, cm^{-1}) 3050, 2990, 2900, 2860, 2820, 1585, 1560, 1470, 1430, 1370, 1300, 1265, 1240, 1190, 1170, 1145, 1120, 1105, 1085, 1050, 990, 845, and 745; UV (0.10 M KCl in H_2O) δ_{max} 256 (shoulder ε 4000), 261 (ε 4600), 267 nm (shoulder ε 3500).

Anal. Calcd for $C_{13}H_{21}NO_2$: C, 69.9; H, 9.5; N, 6.3. Found: C, 70.0; H, 9.4; N, 6.4.

(*Z*)- and (*E*)-2-Methoxy-6-(2-pyridyl)hex-2-ene and 2-Methoxy-6-(2-pyridyl)hex-1-ene (3, 4, and 5, respectively). 2,2-Dimethoxy-6-(2-pyridyl)hexane (**7**) (11.2 g, 50 mmol) and 50 mg of *p*-toluenesulfonic acid were heated with an oil bath (110–130 °C) under reduced pressure (170–200 mmHg) until no more methanol distilled off, 5 h. The brown residue was then distilled in vacuo, giving a mixture of **3**, **4**, and **5** (7.9 g, 82%) as a colorless liquid. According to ^1H NMR, the product composition was 8, 47 and 45% of **3**, **4**, and **5**, respectively. The three isomers were separated on HPLC with hexane/triethylamine (98:2) as mobile phase and were eluted in the order **5**, **4**, and **3** with **3** as a shoulder on the tail of **4**. The α value between **5** and **4** was 1.32 and between **4** and **3** 1.19. Since **3** elutes on the tail of **4**, it was not possible to obtain **3** with only one separation.

3: ^1H NMR (C_6D_6) δ 1.57 (s, 3 H, CH_3C=), 1.90–1.98 (quint, 2 H, J = 7.3–7.8 Hz, $CH_2CH_2CH_2$), 2.28–2.34 (quart, 2 H, J = 7.3 Hz, CH_2CH=), 2.84–2.88 (t, 2 H, J = 7.7 Hz, CH_2-pyr), 3.16 (s, 3 H, CH_3O), 4.42–4.46 (t, 1 H, J = 7.3 Hz, CH=), 6.58–6.61 (dd, 1 H, J = 7.6 and 4.9 Hz, pyr 5-H), 6.75–6.77 (d, 1 H, J = 7.6 Hz, pyr 3-H), 7.00–7.05 (td, 1 H, J = 7.6 and 1.9 Hz, pyr 4-H), 8.50–8.52 (d br, 1 H, J = 4.8 Hz, pyr 6-H); ^{13}C NMR (C_6D_6) 162.9 (pyr C-2), 151.4 (OC=), 149.7 (pyr C-6), 135.6 (pyr C-4), 122.6 (pyr C-3), 120.7 (pyr C-5), 108.1 (CH_2HC=), 55.0 (CH_3O), 38.4 (CH_2-pyr), 30.5 ($CH_2CH_2CH_2$), 24.9 (CH_2C=), 17.4 (CH_3C=).

4: ^1H NMR (C_6D_6) δ 1.74 (s 3 H, CH_3C=), 1.85–1.93 (quint, 2 H, J = 7.4 Hz, $CH_2CH_2CH_2$), 1.99–2.05 (quart, 2 H, J = 7.3 Hz, CH_2CH=), 2.78–2.82 (t, 2 H, J = 7.5 Hz, CH_2-pyr), 3.21 (s, 3 H, CH_3O), 4.28–4.32 (t, 1 H, J = 7.2 Hz, CH_2CH=), 6.60–6.64 (dd, 1 H, J = 7.5 and 4.8 Hz, pyr 5-H), 6.76–6.78 (d, 1 H, J = 7.8 Hz, pyr 3-H), 7.04–7.08 (td, 1 H, J = 7.6 and 1.9 Hz, pyr 4-H), 8.51–8.53 (d br, 1 H, J = 4.8 Hz, pyr 6-H); ^{13}C NMR (C_6D_6) 162.7 (pyr C-2), 154.0 (OC=), 149.7 (pyr C-6), 135.6 (pyr C-4), 122.6 (pyr C-3), 120.8 (pyr C-5), 96.0 (CH_2C=), 53.6 (CH_3O), 38.0 (CH_2-pyr), 31.1 ($CH_2CH_2CH_2$), 26.9 (CH_2C=), 16.3 (CH_3C=); MS, M^+ calcd for $C_{12}H_{17}NO$ 191.1310, found 191.1445; IR (film, cm^{-1}) 3060, 3000, 2940, 2850, 1665, 1585, 1560, 1470, 1430, 1390, 1210, 1150, 1135, 1100, 1080, 1045, 990, 815, 750, and 595.

5: ^1H NMR (C_6D_6) δ 1.56–1.64 (m, 2 H, $=CCH_2CH_2$), 1.75–1.83 (m, 2 H, CH_2CH_2-pyr), 2.13–2.17 (t, 2 H, J = 7.4 Hz, CH_2C=), 2.72–2.76 (t, 2 H, J = 7.6 Hz, CH_2-pyr), 3.19 (s, 3 H, CH_3O), 3.81–3.82 and 3.89–3.90 (two doublets of each, 1 H, J = 2 Hz, $OC=CH_2$), 6.57–6.61 (ddd, 1 H, J = 7.5, 4.8, and 1.2 Hz, pyr 5-H), 6.69–6.71 (d, 1 H, J = 7.8 Hz, pyr 3-H), 7.00–7.05 (td, 1 H, J = 7.6 and 1.9 Hz, pyr 4-H), 8.48–8.50 (d br, 1 H, J = 4.8 Hz, pyr 6-H); ^{13}C NMR (C_6D_6) 164.4 ($OC=CH_2$), 162.6 (pyr C-2), 149.6 (pyr C-6), 135.6 (pyr C-4), 122.5 (pyr C-3), 120.7 (pyr C-5), 80.5 ($C=CH_2$), 54.3 (CH_3O), 38.4 (CH_2-pyr), 35.2 (CH_2), 29.4 (CH_2), 27.4 (CH_2); MS, M^+ calcd for $C_{12}H_{17}NO$ 191.1310, found 191.1456; IR (film, cm^{-1}) 3110, 3050, 3000, 2940, 2850, 1645, 1585, 1560, 1470, 1430, 1305, 1275, 1230, 1190, 1145, 1130, 1100, 1075, 1045, 1030, 990, 925, 795, 760, 745, 625, and 595.

Anal. (for isomeric mixture). Calcd for $C_{12}H_{17}NO$: C, 75.4; H, 9.0; N, 7.3. Found: C, 75.0; H, 9.2; N, 7.4.

Structural Assignment of 3 and 4. The structures of **3** and **4** were confirmed by measuring the difference nuclear Overhauser effect. An irradiation of the methoxy group resulted in an enhancement in the signal of the vinyl proton in **4** but no observable effect in **3**. An irradiation of the methyl group in **3** gave an enhancement in the signal for the vinyl proton in **3**. The relative ^{13}C chemical shifts of the two carbon atoms in the vinyl ether double bond in **3** and **4** are also in agreement with those reported for the *Z* and *E* isomers of prostacyclin.[8]

6-(2-Pyridyl)hexan-2-one (8). A mixture of the vinyl ether isomers **3**,**4**, and **5**, 1.00 g (5.2 mmol), was dissolved in 10 mL of methanol and 53 mL of a 0.10 M aqueous HCl solution. After being stirred at room temperature for 20 min, the reaction mixture was made basic by the addition of 0.8 g of Na_2CO_3. The reaction mixture was extracted 3 times with CH_2Cl_2 and the combined organic extracts was dried ($MgSO_4$) and evaporated, giving a quantitative yield of **8** as a colorless liquid (0.93 g).

8: ^1H NMR (C_6D_6) δ 1.45–1.49 (m, 2 H, $O=CCH_2CH_2$), 1.62 (s, 3 H, CH_3C=O), 1.60–1.68 (m, 2 H, pyr-CH_2CH_2), 1.91–1.95 (t, 2 H, J = 7.3 Hz, CH_2C=O), 2.65–2.69 (t, 2 H, J = 7.5 Hz, CH_2-pyr), 6.63–6.67 (ddd, 1 H, J = 7.5, 4.9, and 1.1 Hz, pyr 5-H), 6.73–6.76 (d, 1 H, J = 7.3 Hz, pyr 3-H), 7.07–7.12 (td, 1 H, J = 7.6 and 1.9 Hz, pyr 4-H), 8.47–8.49 (br d, 1 H, J = 4.9 Hz, pyr 6-H); ^{13}C NMR (C_6D_6) 206.2 (C=O), 162.3 (pyr C-2), 149.5 (pyr C-6), 135.7 (pyr C-4), 122.6 (pyr C-3) and 120.9 (pyr C-5), 43.1 (CH_2C=O), 38.2 (CH_2-pyr), 29.3 (two carbons, CH_3CO and a CH_2) and 23.6 (CH_2); MS, M^+ calcd for $C_{11}H_{15}NO$ 177.1154, found 177.1278; IR (film cm^{-1}) 3050, 3000, 2930, 2850, 1705 (C=O), 1585, 1560, 1470, 1430, 1355, 1295, 1220, 1160, 1150, 1050, 990, 750, and 720; UV (1% CH_3CN in 0.01 M aqueous NaOH) λ_{max} 268 (ε 2940) 261 (ε 4000), and 256 nm (shoulder ε 3440), λ_{min} 226 nm (ε 600); (1% CH_3CN in 0.10 M HCl) λ_{max} 263 nm (ε 7800), λ_{min} 224 nm (ε 90).

Kinetic Procedure. All buffer solutions were prepared from the best available grades of commercial chemicals using deionized water that had been distilled. Hydronium ion concentrations in the buffer solutions were calculated by using activity coefficients recommended by Bates.[9] In the hydrochloric acid solutions the hydronium ion concentrations were determined by titration.

Rates of hydrolysis of all compounds were determined spectrophotometrically, by monitoring the decrease in absorbance of the vinyl ether double bond at 212–220 nm for 3–5 half-lives. The kinetic measurements were made with a Varian CARY 210 spectrophotometer using a Hi-Tech Scientific SFA-11 Rapid Kinetics Accessory to follow the hydrolysis reaction in hydrochloric acid. The buffer solutions and the UV cells 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 3.

Acid dissociation constants at 0.10 M ionic strength of the pyridine groups of all compounds were determined spectrophotometrically according to the method by Albert and Serjeant.[10] The analytical wavelength used was 250 nm where no change in absorbance due to the hydrolysis reaction could be observed.

Results

Rates of hydrolysis of the vinyl ether function of the three isomeric compounds **3**, **4**, and **5** were determined in hydrochloric acid solutions and acetic acid and biphosphate ion buffer solutions. The ionic strength was

(7) Jones, G.; Law, H. D. *J. Chem. Soc.* **1958**, 3631.

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

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

(10) Albert, A.; Serjeant, E. P. *The Determination of Ionization Constants. A Laboratory Manual*; Chapman and Hall: London, 1971.

Table I. Reaction Parameters for the Hydrolysis of (*Z*)- and (*E*)-2-Methoxy-6-(2-pyridyl)hex-2-ene and 2-Methoxy-6-(2-pyridyl)hex-1-ene (3, 4, and 5, Respectively) and Prostacyclin (1) in Aqueous Solution at 25 °C, Ionic Strength = 0.10 M

parameter	2-methoxy-6-(2-pyridyl)hex-2-ene[a]		2-methoxy-6-(2-pyridyl)hex-1-ene[a] (5)	prostacyclin[a,b] (1)
	Z isomer (3)	*E* isomer (4)		
pK_a[c]	5.89 ± 0.02	5.85 ± 0.04	5.85 ± 0.07	5.03 ± 0.15
k_{H^+}/mol^{-1} dm^3 s^{-1}[d]	77.84 ± 1.70	12.76 ± 0.38	115.7 ± 5.0	439 ± 4
k'_{H^+}/mol^{-1} dm^3 s^{-1}[e]	3560 ± 190	573.2 ± 43.9	1821 ± 200	43 600 ± 900
acceleration (k'_{H^+}/k_{H^+})	45.7 ± 1.4	44.9 ± 2.1	15.7 ± 1.0	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 2. [c] Acidity constant at zero ionic strength estimated by using activity coefficients recommended by Bates.[9] Activity coefficients for the pyridinium ions are assumed to be the same as for 2-methylpyridine (0.79) calculated from data in ref 12. [d] Rate constant for hydrolysis of substrate in its acid form. [e] Rate constant for hydrolysis of substrate in its base form.

maintained at 0.10 M with KCl. The rate data are summarized in Tables S1–S6.[11]

At a given pH the observed pseudo-first-order rate constant for all substrates is given by eq 1.

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

The buffer-independent part, k°_{obsd}, is obtained by extrapolating the contribution from the buffer acid to zero buffer concentration. Catalysis by base was negligible.

The data for hydrolysis of the vinyl ether function of the substrates does not show a linear dependence of k°_{obsd} against $[H^+]$. The rate profile for compound **3** is shown in Figure 1.

The reason for this curvature is that both the acid form and the corresponding base form of the pyridine substrates are hydrolyzed by hydronium ion but with different magnitudes of the corresponding rate constants. There is also a possibility for the acid forms of the substrates to undergo an intramolecular protonation of the vinyl ether function with the rate constant k_{intra}. This is illustrated in Scheme III where catalysis by buffer acids has been taken into account, too. S stands for the neutral form and SH^+ for the pyridinium form of the substrate. Scheme III is valid for all three isomers. According to this scheme, the rate of disappearance of the substrate is given by eq 2.

$$-\frac{d[SH^+]_{tot}}{dt} = (k_{intra} + k_{H^+}^{SH^+}[H^+] + k_{HA}^{SH^+}[HA])[SH^+] + (k_{H^+}^{S}[H^+] + k_{HA}^{S}[HA])[S] \quad (2)$$

Using the acid dissociation constant, K_a, for the equilibrium between SH^+ and S and since $[SH^+]_{tot} = [SH^+] + [S]$, eq 2 can be rearranged to eq 3. The expression

$$-\frac{d[SH^+]_{tot}}{dt} = \left[\frac{[H^+]}{1+[H^+]/K_a}(k_{intra}/K_a + k_{H^+}^{S} + k_{H^+}^{SH^+}[H^+]/K_a) + \frac{1}{1+[H^+]/K_a}(k_{HA}^{SH^+}[H^+]/K_a + k_{HA}^{S})[HA]\right][SH^+]_{tot} \quad (3)$$

within the brackets is equivalent to the observed rate constant, k_{obsd}, and consists of the buffer-independent part given by eq 4

$$k^\circ_{obsd} = \frac{[H^+]}{1+[H^+]/K_a}(k_{intra}/K_a + k_{H^+}^{S} + k_{H^+}^{SH^+}[H^+]/K_a) \quad (4)$$

(11) Supplementary material; see paragraph at the end of this paper.

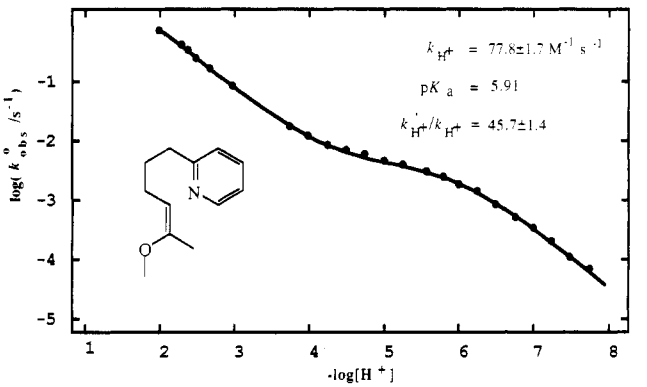
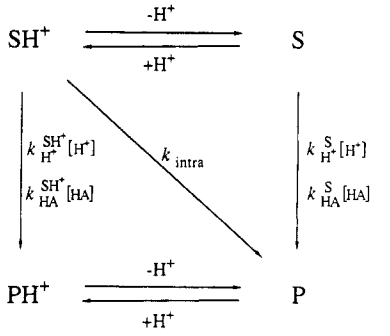


Figure 1. Rate profile for (*Z*)-2-methoxy-6-(2-pyridyl)hex-2-ene (3) in aqueous solution at 25.0 ± 0.1 °C.

Scheme III



and the contribution from the buffer acid, $k_{HA}^{app}[HA]$, where k_{HA}^{app} is given by eq 5.

$$k_{HA}^{app} = \frac{1}{1+[H^+]/K_a}(k_{HA}^{SH^+}[H^+]/K_a + k_{HA}^{S}) \quad (5)$$

The two terms k_{intra}/K_a and $k^S_{H^+}$ in eq 4 can be considered as the contributions from hydronium ion catalyzed hydrolysis of the substrates in their neutral forms (cf. Scheme I).

$$k'_{H^+} = k_{intra}/K_a + k_{H^+}^{S} \quad (6)$$

If k'_{H^+} is defined as the sum of these contributions (eq 6), a combination of eq 4 and 6 gives eq 7 after rearrangement.

$$k^\circ_{obsd} = \frac{[H^+]}{1+[H^+]/K_a}k_{H^+}^{SH^+}([H^+]/K_a + k'_{H^+}/k_{H^+}^{SH^+}) \quad (7)$$

A nonlinear least-squares fit of eq 7 to the experimental data for **3** (Tables S1–S2), for **4** (Tables S3–S4), and for **5** (Tables S5–S6) gave the ratio of the rate constants for the hydrolysis reaction of the neutral and pyridinium forms

Table II. Reaction Parameters for the Hydrolysis of (*Z*)- and (*E*)-2-Methoxy-6-(2-pyridyl)hex-2-ene (3 and 4) and 2-Methoxy-6-(2-pyridyl)hex-1-ene (5) in Aqueous Acetic Acid Buffer Solutions at 25 °C, Ionic Strength = 0.10 M

parameter	2-methoxy-6-(2-pyridyl)hex-2-ene[a]		2-methoxy-6-(2-pyridyl)hex-1-ene[a] (5)
	Z isomer (3)	*E* isomer (4)	
$k_{HA}^{SH^+}$/mol^{-1} dm^3 s^{-1} [b]	0.179 ± 0.004	0.0253 ± 0.0005	0.273 ± 0.006
k_{HA}^{S}/mol^{-1} dm^3 s^{-1} [c]	0.419 ± 0.027	0.0418 ± 0.0038	0.485 ± 0.048
acceleration ($k_{HA}^{S}/k_{HA}^{SH^+}$)	2.35 ± 0.15	1.66 ± 0.12	1.78 ± 0.14

[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 its acid form. [c] Rate constant for hydrolysis of substrate in its base form.

Table III. Reaction Parameters for the Hydrolysis of the Base Forms of (*Z*)- and (*E*)-2-Methoxy-6-(2-pyridyl)hex-2-ene and 2-Methoxy-6-(2-pyridyl)hex-1-ene (3, 4, and 5, Respectively) in Aqueous Solution at 25 °C, Ionic Strength = 0.10 M[a]

parameter	2-methoxy-6-(2-pyridyl)hex-2-ene		2-methoxy-6-(2-pyridyl)hex-1-ene (5)
	Z isomer (3)	*E* isomer (4)	
k_{intra}/K_a/mol^{-1} dm^3 s^{-1} [b]	3404	548	1591
$k_{H^+}^{S}$/mol^{-1} dm^3 s^{-1} [c]	155.7	25.5	231.4
extent of intramolecular reaction, % [d]	95.6	95.6	87.5

[a] The parameters are calculated by using eq 6 and the parameters in Table I with the assumption that $k_{H^+}^{S} = 2k_{H^+}^{SH^+}$ where $k_{H^+}^{SH^+}$ is the rate constant for intermolecular hydrolysis of substrate in its acid form. This constant is equivalent to k_{H^+} in Table I. [b] Rate constant for intramolecular hydrolysis of substrate in its base form. [c] Rate constant for intermolecular hydrolysis of substrate in its base form. [d] Defined as $100 \times (k_{intra}/K_a)/(k_{H^+}^{S} + k_{intra}/K_a)$.

for catalysis by hydronium ion, i.e., $k'_{H^+}/k_{H^+}^{SH^+}$. The results are shown in Table I.

After rearrangement of eq 5 to eq 8, a similar fit of eq

$$k_{HA}^{app} = \frac{k_{HA}^{SH^+}}{1 + [H^+]/K_a}([H^+]/K_a + k_{HA}^{S}/k_{HA}^{SH^+}) \quad (8)$$

8 to the experimental data gave the corresponding ratio for catalysis by buffer acid, i.e. $k_{HA}^{S}/k_{HA}^{SH^+}$. The results are shown in Table II.

The ionization constants for the pyridinium forms of the substrates and for 2-methylpyridine were determined spectrophotometrically at 25 °C and at a constant ionic strength of 0.10 M. Absorbance measurements were made in 0.10 M HCl and 0.005 M NaOH solutions and in six–seven different buffer solutions with –log [H$^+$] = 5.00–6.50. These data are summarized in Table S7.[11] The value obtained for 2-methylpyridine, pK_a = 5.98 ± 0.03, is equal to the value that can be calculated from ref 12. The pK_a values obtained under these conditions are for **2**, pK_a = 5.81 ± 0.06; for **3**, pK_a = 5.81 ± 0.04, and for **4**, pK_a = 5.80 ± 0.05. These values are in good agreement with those obtained from the analysis of the rate data (Table I).

Discussion

The rate constant ratios given in Tables I and II correspond to the ratios k'_{H^+}/k_{H^+} and k'_{HA}/k_{HA} discussed in the kinetic investigation of prostacyclin[2] and the model compounds **2**[3,4] and **9**.[13]

However, the problem with the mechanistic ambiguity in earlier investigations is absent in the present case where the effectiveness of an electrostatic stabilization should be negligible as the negatively charged COO$^-$ group is missing.

This means that the intermolecular protonation should be independent of whether the substrate is in its acid or in its base form and in that case, $k_{H^+}^{S} = k_{H^+}^{SH^+}$ and $k_{HA}^{S} = k_{HA}^{SH^+}$. Thus, eq 6 would be changed to eq 9, and since

$$k'_{H^+} = k_{H^+}^{SH^+} + k_{intra}/K_a \quad (9)$$

$k_{H^+}^{SH^+}$ is experimentally determined in HCl solutions, K_a is determined spectrophotometrically and k'_{H^+} is obtained from the least-squares analysis, it would then be possible to determine the magnitude of k_{intra}. It would also mean that the ratio of the buffer rate constants should be equal to unity and eq 8 would then be simplified to $k_{HA}^{app} = k_{HA}^{SH^+}$. The observed buffer rate constants (k_{HA}^{app}) should thus be constant for all buffer ratios.

Of course, such a theoretical model does not hold in reality and the buffer rate constant ratios obtained were approximately equal to 2, as can be seen in Table II. When it comes to hydronium ion catalysis, the positive charge on the acid form of the substrate may have a repulsive effect on the incoming proton and therefore it is likely that $k_{H^+}^{S} > k_{H^+}^{SH^+}$. In the case of prostacyclin the base form of prostacyclin is negatively charged and may thus have an attractive effect on the incoming proton. These electrostatic effects must be reflected in the energy barriers and in the rate profiles but should not be mixed up with the electrostatic catalysis in Scheme I in which the negative charge takes an active part in the hydrolysis of the vinyl ether function.

However, one cannot account for the large differences in reactivity between the base form and the acid form of prostacyclin and the pyridine compounds **3** and **4** as just an electrostatic effect. In the investigation of the model compound **9**, it was found that the carboxylate form of the substrate was only twice as reactive as the corresponding acid form of **9**.[13] This difference in reactivity was attributed to an electrostatic effect since the rigidity of the system prevents the carboxylic acid function from exerting an effective intramolecular catalysis. A magnitude of this size due to ionization of the substrate has been found also for other systems.[14]

It therefore seems reasonable to assume that we have an electrostatic effect of the same magnitude in the pyridine compounds in the present investigation and that $k_{H^+}^{S} = 2k_{H^+}^{SH^+}$.

It is thus possible to obtain a value of k_{intra} by combining this relationship with eq 6. Now it is also possible to calculate to what extent the hydrolysis of the neutral vinyl ether occurs through the intramolecular pathway. At hydronium ion concentrations where [H$^+$] $\ll K_a$, eq 4 is simplified to eq 10.

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$$k^{\circ}_{obsd} = [H^+](k_{intra}/K_a + k_{H^+}{}^S) = [H^+](k_{intra}/K_a + 2k_{H^+}{}^{SH^+}) \quad (10)$$

The values in Table I inserted in eq 6 give the results shown in Table III.

Hydrolysis of **3** and **4** occurs to 95% through the intramolecular pathway. Only 87% of **5** is hydrolyzed through the intramolecular route. If the mechanism for hydrolysis of prostacyclin was electrostatic catalysis, i.e., mechanism 1 in Scheme I, then the extent of intramolecular catalysis for the pyridine compounds in the present investigation would be zero or at least very small. The difference in reactivity between the base form and the acid form of the substrates should be small and only an electrostatic effect similar to the one observed in the investigation of **9**[13] should be obtained. The rate acceleration shown in Table I should thus amount to a factor of approximately 2. This would of course be reflected in the rate profile as a very small change in the intermediate pH region instead of the large change observed (Figure 1). The interpretation of the results obtained in the present investigation clearly supports the existing evidence[2-4] for the mechanism with intramolecular protonation of the vinyl ether double bond, i.e., mechanism 2 in Scheme I.

The rate acceleration obtained for **3** and **4** is only half of that observed for prostacyclin, which might be due to different steric requirements in the intramolecular proton-transfer step from the acid function to the vinyl ether double bond. The extent of intramolecular catalysis will diminish if the proton transfer becomes more difficult and thus the observed rate acceleration will decrease.

The isomer **5** shows a much smaller rate acceleration than those obtained for **3** and **4** (Table I). The reason behind this is probably that, in the case of **5**, the cyclic transition state (including the proton that is transferred) is a nine-membered ring, whereas it is only a seven-membered ring for **3** and **4**. A similar observation has been made by Kresge who obtained a rate acceleration of 8 for hydrolysis of homoprostacyclin where an eight-membered ring is formed in the transition state.[15]

Acknowledgment. We are grateful to the Swedish Natural Science Research Council for financial support.

Supplementary Material Available: Rate data for the hydrolyses of (*Z*)- and (*E*)-2-methoxy-6-(2-pyridyl)hex-2-ene (**3** and **4**) and 2-methoxy-6-(2-pyridyl)hex-1-ene (**5**) in various solutions and equilibrium data from the pK_a measurements (Tables S1-S7) (23 pages). Ordering information is given on any current masthead page.

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Thiophenes as Traps for Benzyne. 2. Cycloaddition and Ene Reactions[1]

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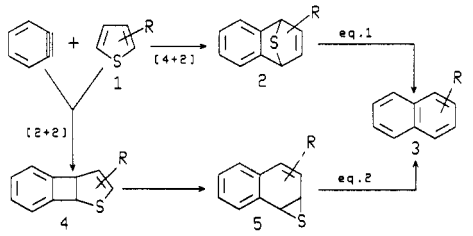
The reactions of 11 mono- and disubstituted thiophenes (**1b-1l**) with benzyne generated from diphenyliodonium 2-carboxylate (**7**) were studied under a standard set of conditions. The major products were naphthalenes (**3**) whose substitution patterns indicated that both [4 + 2] and [2 + 2] cycloaddition occurred, with the former predominating. A significant proportion of [2 + 2] cycloaddition was found only with the 3-halothiophenes **1i** and **1k**, suggesting enamine-like enhancement of the 2π-character of the thiophene. Benzo[*b*]thiophenes (**8**) were found in low yields in several of the reactions, and their substitution patterns suggested a [3 + 2] cycloaddition mechanism involving an intermediate betaine **11**. Ene (**17**) and especially double ene (**18**) products were observed with the alkylthiophenes **1b-d** and **1g**. The halothiophenes **1h-l** underwent substantial carbon-halogen bond cleavage leading to halogenated phenylthiophenes.

Recently we demonstrated that with the proper choice of precursor and reaction conditions benzyne could be induced to react with thiophene (**1**) to give primarily naphthalene (**3**), the product of apparent [4 + 2] cycloaddition to **2** followed by loss of sulfur (eq 1).[2] The present paper describes a more detailed investigation of this reaction as well as several others which lead to additional benzyne + thiophene-derived products.



Of particular interest is the extent to which naphthalene formation involves a stepwise [2 + 2] cycloaddition to **4** followed by rearrangement to **5** and loss of sulfur (eq 2) rather than a concerted [4 + 2] pathway (eq 1). The latter mechanism generally is much preferred in the reactions of benzyne with a wide variety of dienes,[3,4] including the related five-membered heterocycles furan[5] and pyrrole.[6] On the other hand, electron-rich thiophenes can react thermally with electron-deficient alkynes in a predominantly [2 + 2] manner.[7] Furthermore, the five-membered hetaryne, 2,3-didehydrothiophene (**6**), also reacts with appropriately labelled thiophenes to give products that

(1) Taken in part from the Dissertation of D.D.M. submitted in partial fulfillment of the Ph.D. degree at Texas Christian University.

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