described for Table II, entry 1, to give the product **6a**, 0.55 g (47%), as a colorless solid, identical in all respects with the product prepared from **2a**.

1-[2-(Methoxycarbonyl)ethyl]-3-[2-[4-(2-methoxyphenyl)piperazin-1-yl]ethyl]thieno[3,4-*d*]pyrimidine-2,4-dione (7).[3] Thienopyrimidine **2b** (0.77 g, 2 mmol) was treated with methyl acrylate (0.2 mL, 2 mmol) in DMF (15 mL) at room temperature for 24 h. The resultant solution was worked up as described for **3a** and **4a** to give the product, 0.93 g (99%), as a colorless solid: mp 140-141 °C;[3] IR (KBr) 2820, 1700, 1655, 1580, and 1500 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.6-3.2 (m, 12 H), 3.67 (s, 3 H), 3.83 (s, 3 H), 4.03-4.33 (m, 4 H), 6.73 (d, J = 3 Hz, 1 H), 6.83-7.0 (m, 4 H), and 8.25 (d, J = 3 Hz, 1 H). Anal. Calcd for $C_{23}H_{28}N_4O_5S$: C, 58.45; H, 5.97; N, 11.86. Found: C, 58.21; H, 6.08; N, 11.89.

Acknowledgment. We thank Dr. M. L. Cotter for analytical support and especially Dr. D. Graden and Ms. Madeleine Cozine for ^1H NMR and COSY experiments. We thank Ms. Deborah Loughney for calculations using MOPAC. Mr. Douglas Alves-Santana determined HRMS data. We also thank Dr. J. Hinkle for discussions during the course of regio- and stereochemical assignments of the Diels-Alder adducts. Lastly, we thank Mr. Jerry Roberts for preparations of intermediates for this work.

Evidence for Intramolecular Electrostatic Catalysis as a Possible Mechanism in the Hydrolysis of Vinyl Ethers in Aqueous Solution

Torbjörn Halvarsson† and Nils-Åke Bergman*,‡

Department of Organic Chemistry, AB Hässle, S-431 83 Mölndal, Sweden, and Department of Organic Chemistry, University of Göteborg, S-412 96 Göteborg, Sweden

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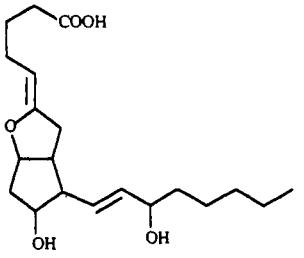
The hydrolysis of the vinyl ether functional group in 2-methoxybicyclo[2.2.2]oct-2-ene-1-carboxylic acid (**2**) has been found to be catalyzed by intramolecular electrostatic catalysis by the carboxylate ion of the substrate.[1] The rate constant ratios of the charged and the neutral form of the substrate are 32.3 and 31.2 for catalysis by hydronium ion and acetic acid, respectively. This is in contrast to ratios that have been found for vinyl ethers hydrolyzed by intramolecular general-acid catalysis, where large rate ratios for catalysis by hydronium ion but small rate ratios, normally a factor 2, when catalyzed by acetic acid are observed. The solvent isotope effect, 3.4 ± 0.5, is close to what has been predicted for electrostatic catalysis in the hydrolysis of prostacyclin (**1**).

Electrostatic catalysis has been discussed as a possible mechanism in enzymatic reactions and also in the hydrolysis of the vinyl ether function of prostacyclin (**1**). However, electrostatic interactions are small in aqueous solution, and it is therefore difficult to unambigiously detect electrostatic catalysis with small molecules in that medium. All evidence presented in the kinetic investigations of prostacyclin[2] and different model compounds for prostacyclin[3-5] are in favor of intramolecular general-acid catalysis as the mechanism in the hydrolysis of the vinyl ether function.

By synthesizing a vinyl ether compound in which electrostatic stabilization of the developing oxocarbonium ion is achieved, and where, at the same time, intramolecular general-acid catalysis is excluded, it has been possible to demonstrate that electrostatic catalysis is a possible mechanism in the hydrolysis of vinyl ethers even in aqueous solution. Thus, with the compound 2-methoxybicyclo[2.2.2]oct-2-ene-1-carboxylic acid (**2**), we still obtained a considerable rate increase upon ionization of the carboxylic acid group. The only possible explanation for this behavior is that the vinyl ether function is hydrolyzed through intramolecular electrostatic catalysis during intermolecular protonation.

Experimental Section

^1H NMR spectra were recorded on a Varian XL 400 instrument with a modified transmitter and computer system. Chemical shifts are given in ppm downfield from Me_4Si. Semipreparative HPLC was performed with a Waters Associates System consisting of a Waters M-45 solvent delivery system, a Waters U6K injector, a



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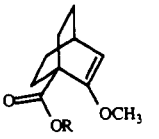
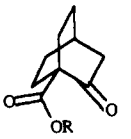


2 R=H, Na
3 R=CH_3



4 R=CH_3
5 R=H

R-sil silica column (10 μm particles, 4.6 mm (i.d.) × 25 cm) and a Waters R-401 differential refractometer.

Synthetic Procedure. The bicyclic vinyl ether **3** was synthesized from the known ketone **4**[6] by O-alkylation of the enolate formed from **4** using potassium hydride as the base. Ketone **4** was synthesized from crotonaldehyde and dimethylamine in 11 steps using the procedures described in refs 6-8. Ketone **4** is also the product formed in the hydrolysis of the vinyl ether **3**.

Methyl 2-oxobicyclo[2.2.2]octane-1-carboxylate (4): mp (from hexane) 63.6-64.1 °C (lit.[6] mp 62.5-64.5 °C); NMR (C_6D_6) ^1H δ 1.05-1.22 (m, 4 H), 1.42-1.48 (quint, 1 H, J = 3 Hz, >C*H*CH_2C=O), 1.51-1.64 (m, 2 H), 1.84-1.87 (dd, 2 H, J = 3 and

† AB Hässle.
‡ University of Göteborg.

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1 Hz, CH_2C=O), 2.09–2.23 (m, 2 H), and 3.45 ppm (s, 3 H, $COOCH_3$); ^{13}C δ 24.6 (2 CH_2), 26.0 (2 CH_2), 27.9 (CH), 44.1 (>$CHCH_2C$=O), 51.6 ($COOCH_3$), 54.3 ($CCOOCH_3$), 172.0 ($COOCH_3$), and 209.1 ppm (>C=O).

Methyl 2-Methoxybicyclo[2.2.2]oct-2-ene-1-carboxylate (3). A solution of 1.86 g (10.2 mmol) of 4 in 35 mL of anhydrous DMF was added to 490 mg (12.2 mmol) of KH in an N_2 atmosphere. When the evolution of gas had ceased (~10 min), alkylation was achieved by the addition of 1.25 mL (13.2 mmol) of dimethyl sulfate. The reaction mixture was stirred at room temperature for 2 h and was then poured into 150 mL of water and extracted with 3 × 50 mL of hexane. The hexane solution was washed with saturated $NaHCO_3$ and brine, dried ($MgSO_4$), and concentrated in vacuo to yield a yellow liquid (2.17 g), with 3 as the major product. A small part of the product mixture was dissolved in 20 mL of hexane containing 0.5% of triethylamine, passed through a 3-mL BondElut cyanopropyl column and then separated on HPLC using hexane + 0.5% triethylamine as the mobile phase. The purified vinyl ether 3, was used in kinetic experiments, for spectral analysis, and to prepare the sodium salt of 2.

3: NMR (C_6D_6) ^1H δ 1.24–1.38 (m, 4 H, two CH_2 next to CH bridgehead carbon), 1.58–1.67 (m, 2 H), 2.09–2.19 (m, 2 H), 2.36–2.43 (m, 1 H, bridgehead carbon CH), 3.13 (s, 3 H, HC=$COCH_3$), 3.51 (s, 3 H, $COOCH_3$), and 4.67–4.70 ppm (d, 1 H, J = 7 Hz, CH_3OC=CH); ^{13}C δ 27.2 (2 CH_2), 29.7 (2 CH_2), 30.3 (CH bridgehead carbon), 47.5 (bridgehead carbon $CCOOCH_3$), 51.4 and 54.3 ($COOCH_3$ and CH_3OC=), 96.1 (CH=$COCH_3$), 159.5 (CH=$COCH_3$), and 173.4 ppm ($COOCH_3$). Anal. Calcd for $C_{11}H_{16}O_3$: C, 67.3; H, 8.2. Found: C, 67.5; H, 8.3 (hygroscopic).

Sodium 2-Methoxybicyclo[2.2.2]oct-2-ene-1-carboxylate (2). A solution of 11.3 mg of 3 in 4.5 mL of methanol was mixed with 0.5 mL of 0.5 M NaOH and left at room temperature for several days. The solution was evaporated to dryness. Water (5 mL) was added, and the aqueous solution was extracted with ether twice to remove any remaining ester. This basic solution of 2 was used in the kinetic investigation.

2-Oxobicyclo[2.2.2]octane-1-carboxylic Acid (5). The sodium salt of 2 (44 μmol) was dissolved in 25 mL of biphosphate buffer solution, –log [H^+] = 6.00. After 1.5 half-lives (150 s), the reaction solution was extracted rapidly with 50 mL of hexane, in order to isolate any acylal formed. The organic phase was dried ($MgSO_4$) and evaporated. No acylal was obtained. The aqueous phase was left at room temperature for 70 min (~40 half-lives) and then acidified with 2 M aqueous HCl. The solution was extracted with ether three times, and the organic solution was dried ($MgSO_4$) and concentrated giving 5 as a crystalline residue. The residue was identical with that obtained by hydrolysis of the methyl ester 4 according to ^1H NMR, and the carbonyl peak was detected by ^{13}C NMR.[10] 5: NMR (C_6D_6) ^1H δ 0.93–1.01 (m, 2 H), 1.05–1.11 (m, 2 H), 1.35–1.38 (quint, 1 H), 1.61–1.68 (m, 2 H), 1.75–1.77 (dd, 2 H), and 1.81–1.88 ppm (tm, 2 H); ^{13}C δ 24.3 (2 CH_2), 26.1 (2 CH_2), 27.7 (CH), 43.9 (>$CHCH_2C$=O), 53.0 ($CCOOH$), 176.5 (COOH), and 211.9 ppm (C=O).

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 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 210–215 nm for at least 3 half-lives. The kinetic measurements were made with a Varian CARY 210 spectrophotometer equipped with a Hi-Tech Scientific SFA-11 Rapid Kinetics Accessory. The buffer solutions and the UV cells were thermostatted at 25.0 ± 0.1 °C. The kinetic data conformed well to the first-order rate law.

Results

The kinetic measurements were performed in dilute hydrochloric acid solutions and in formic acid, acetic acid, and biphosphate ion buffer solutions. Solvent isotope effects were obtained in D_2O with biphosphate ion buffer solutions. The ionic strength in all solutions was maintained at 0.10 M with KCl. The rate data are summarized in Tables S1–S5.[10]

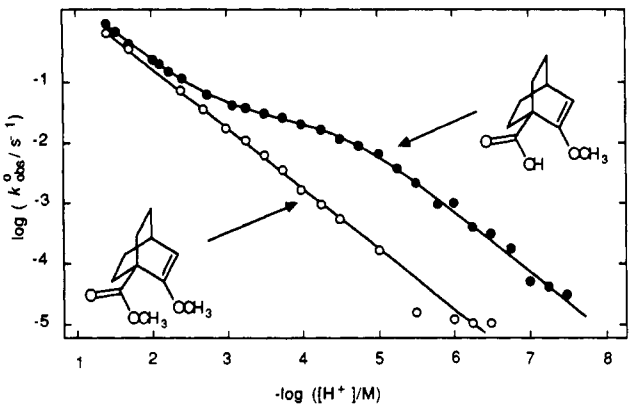
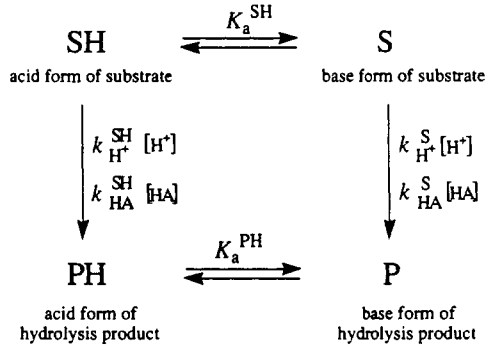


Figure 1. Rate profiles for hydrolysis of 2-methoxybicyclo-[2.2.2]oct-2-one-1-carboxylic acid (2) and its methyl ester (3) in aqueous solution at 25.0 ± 0.1 °C. Ionic strength 0.10 M.

Scheme I



The rate profiles obtained for

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

the hydrolysis of 2 and 3 are shown in Figure 1. In the case of the methyl ester 3 the experimental data conformed well to the expression given in eq 2.

$$k^\circ_{obs} = k_{H^+}[H_3O^+] \quad (2)$$

The hydrolysis of the vinyl ether function in 2 does not show a linear dependence of k°_{obs} against [H_3O^+]. This is explained by different magnitudes on the hydrolysis rate constants for the acid form and the base form of 2, i.e. $k_{H^+}^{SH} \neq k_{H^+}^{S}$ (Scheme I). In the base form of the bicyclic compound 2, the carboxylate ion is in proximity to the developing positive charge on the vinyl-ether function. The resulting electrostatic interaction between the opposite charges is the reason for the different magnitudes on the hydrolysis rate constants. This is illustrated in Scheme I where catalysis by buffer acids has been taken into account, too. In contrast to prostacyclin[2] and model compounds of prostacyclin[3,4] intramolecular protonation on the β-carbon of the vinyl ether function is for steric reasons inhibited.

The acid form of 2 is hydrolyzed by an intermolecular protonation by hydronium ion or a general acid, HA, with the rate constant $k_{H^+}^{SH}$ and k_{HA}^{SH}, respectively. The base form of 2 is hydrolyzed by intermolecular protonation with the rate constants $k_{H^+}^{S}$ and k_{HA}^{S}.

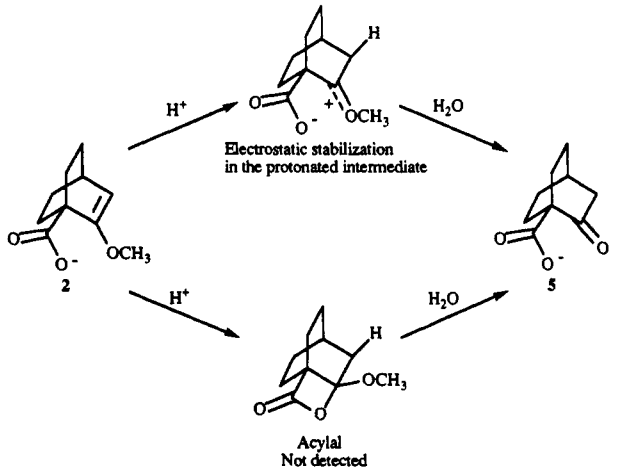
(9) Bates, R. G. *Determination of pH. Theory and Practice*; 2nd ed.; Wiley: New York, 1973; p 49.
(10) Supplementary material; see paragraph at end of this paper.

Table I. Reaction Parameters for the Hydrolysis of 2-Methoxybicyclo[2.2.2]oct-2-ene-1-carboxylic Acid (2) and Its Corresponding Methyl Ester (3) in Aqueous Solution at 25 °C, Ionic Strength 0.10 M[a]

pK_a^{SH} [b]	4.45 ± 0.05
k_{H^+} (ester), M^{-1} s^{-1}	17.7 ± 0.2
$k_{H^+}^{SH}$, M^{-1} s^{-1} [c]	23.0 ± 1.4
k'_{H^+}, M^{-1} s^{-1} [d]	742 ± 101
rate increase ($k'_{H^+}/k_{H^+}^{SH}$)	32.3 ± 2.4

[a] The uncertainties cited are standard deviations derived from statistical analysis of the data; they do not include possible systematic errors. [b] Acid dissociation constant at 0.10 M ionic strength. [c] Rate constant for hydrolysis of substrate in its acid form. [d] Rate constant for hydrolysis of substrate in its base form. $k'_{H^+} = k_{H^+}^{S}$.

Scheme II



The rate of disappearance of the substrate is given by eq 3. Using the acid dissociation constant, K_a^{SH}, for the

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

equilibrium between SH and S, and since $[SH]_{tot} = [SH] + [S]$, eq 3 may be rearranged to eq 4. The expression

$$-\frac{d[SH]_{tot}}{dt} = \left\{\frac{[H^+]}{1 + [H^+]/K_a^{SH}}k_{H^+}^{SH}([H^+]/K_a^{SH} + k_{H^+}^{S}/k_{H^+}^{SH}) + \frac{1}{1 + [H^+]/K_a^{SH}}k_{HA}^{SH}([H^+]/K_a^{SH} + k_{HA}^{S}/k_{HA}^{SH})[HA]\right\}[SH]_{tot} \quad (4)$$

within brackets is equivalent to the observed rate constant, k_{obs}, and consists of a buffer independent part given by eq 5 and the contribution from the buffer acid, $k_{HA}^{app}[HA]$, where k_{HA}^{app} is given by eq 6. The pH–rate profile for

$$k^{\circ}_{obs} = \frac{[H^+]}{1 + [H^+]/K_a^{SH}}k_{H^+}^{SH}([H^+]/K_a^{SH} + k_{H^+}^{S}/k_{H^+}^{SH}) \quad (5)$$

$$k_{HA}^{app} = \frac{1}{1 + [H^+]/K_a^{SH}}k_{HA}^{SH}([H^+]/K_a^{SH} + k_{HA}^{S}/k_{HA}^{SH}) \quad (6)$$

2 was obtained from a nonlinear least-squares fit of eq 5 to the experimental data. The parameters obtained are given in Table I.

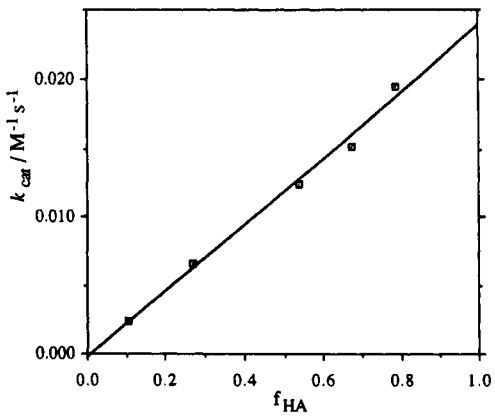


Figure 2. Plot of the buffer rate constant, k_{cat}, vs the fraction of buffer acid, f_{HA}, for hydrolysis of methyl 2-methoxybicyclo-[2.2.2]oct-2-ene-1-carboxylate (3) in acetic acid buffer solutions at 25 °C and 0.10 M ionic strength. The line was obtained by fitting eq 7 to the experimental data.

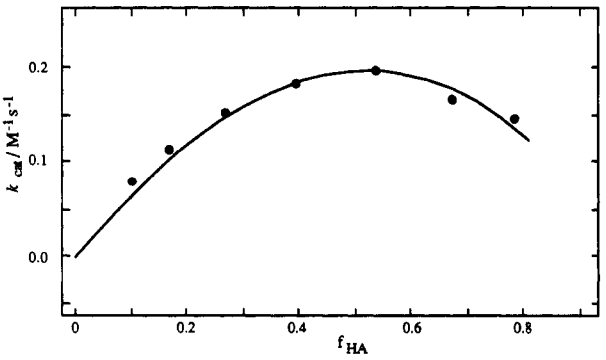


Figure 3. Plot of the buffer rate constant, k_{cat}, vs the fraction of buffer acid, f_{HA}, for hydrolysis of 2-methoxybicyclo[2.2.2]-oct-2-ene-1-carboxylic acid (2) in acetic acid buffer solutions at 25 °C and 0.10 M ionic strength. The line was obtained by fitting eq 9 to the experimental data with the assumption that $k_{HA}^{SH} = k_{HA}^{ester} = 0.024$.

No intermediate acylal has been detected in the hydrolysis of 2, and the only hydrolysis product isolated is 5. The hydrolysis route is illustrated in Scheme II. The four-membered ring in the acylal would be severely strained since the bond angles are set by the bicyclic ring.

The catalytic constant, k_{cat}, is obtained as the slope of a plot of the observed pseudo-first-order rate constant against the total buffer concentration, $[HA]_{tot} = [HA] + [A^-]$, at constant hydronium ion concentration. The catalytic constant is given by eq 7 in which $f_{HA} = [HA]/[HA]_{tot}$ is the fraction of buffer acid in the solution, $f_{A^-} = 1 - f_{HA}$, and the rate constants k_{HA}^{app} and $k_{A^-}^{app}$ are the contributions from the buffer acid and the conjugate base to the catalysis constant.

$$k_{cat} = k_{HA}^{app}f_{HA} + k_{A^-}^{app}f_{A^-} = (k_{HA}^{app} - k_{A^-}^{app})f_{HA} + k_{A^-}^{app} \quad (7)$$

The contributions from the buffer acid and the buffer conjugate base for the hydrolysis of 3 in acetate buffer solution were evaluated from Figure 2. A plot of k_{cat} versus the fraction of buffer acid, f_{HA}, gives a straight line with the intercept equal to zero. There is thus no contribution to the catalysis constant from the conjugate base of the buffer species, and eq 7 is simplified to eq 8. In

$$k_{cat} = k_{HA}^{app}f_{HA} \quad (8)$$

the case of the ester 3, k_{HA}^{app} is equal to the buffer acid catalysis constant k_{HA}.

The corresponding plot of k_{cat} vs f_{HA} for 2 is shown in Figure 3. Under the assumption of no contribution from

Table II. Rate Constant Ratios for Catalysis by Acetic Acid and by Hydronium Ion in Hydrolysis of Compounds 2, 6, 7, 8

substrate	k_{HA}^{S}/k_{HA}^{SH}	$k'_{H^+}/k_{H^+}^{SH}$
2	31.2 ± 1.6[a]	32.3 ± 2.4
6[b]	2.1 ± 0.2	82 ± 2
7[c]	2.35 ± 0.15	45.7 ± 1.4
8	1.29[d]	8[e]

[a] Obtained by fitting eq 9 to the experimental data with the assumption that $k_{HA}^{SH} = k_{HA}^{ester} = 0.024$. [b] Reference 4. [c] Reference 5. [d] Calculated from the equation $k_{HA}^{app}([H^+] + K_a) = k_{HA}[H^+] + k'_{HA}K_a$ using the experimental data given in ref 11 as supplementary material. [e] Reference 11.

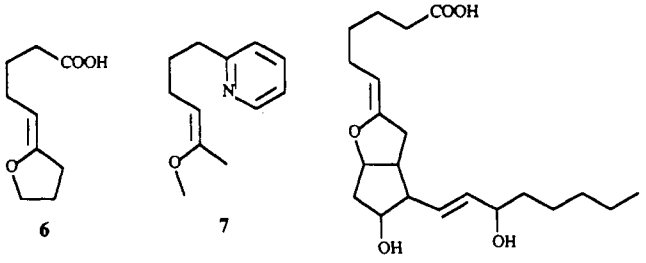
the conjugate base of the buffer species, eq 9 could be derived.

$$k_{cat} = \frac{f_{HA}[k_{HA}^{SH}(K_a^{HA}/K_a^{SH} - k_{HA}^{S}/k_{HA}^{SH})f_{HA} + k_{HA}^{S}]}{1 + (K_a^{HA}/K_a^{SH} - 1)f_{HA}} \quad (9)$$

It clearly shows that when $k_{HA}^{S} \neq k_{HA}^{SH}$, k_{cat} is a nonlinear function of f_{HA}. We have not been able to determine k_{HA}^{S} and k_{HA}^{SH} simultaneously from a nonlinear least-squares fit of eq 9 to experimental data (Table S2). However, using the assumption that $k_{HA}^{SH} = k_{HA}^{ester} = 0.024$ M^{-1} s^{-1} and known values of K_a^{SH} (Table I) and K_a^{HA} enabled us to determine $k_{HA}^{S}/k_{HA}^{SH} = 31.2 \pm 1.6$.

Discussion

In prostacyclin 1,[2] the model compound for prostacyclin 6,[3] the pyridine compound 7,[5] and homoprostacyclin 8,[11] the acid function is attached to a flexible carbon chain. These compounds have all been found to be hydrolyzed through intramolecular protonation.



The rate ratios for catalysis by a buffer acid, i.e. k_{HA}^{S}/k_{HA}^{SH}, found for 6, 7, and 8 are small, a factor of 1 to 2, in contrast to the considerably larger rate ratios obtained for hydronium ion catalysis (Table II). Buffer catalysis for 2 differs markedly from that reported for 6, 7, and 8 as can be seen from Table II. In fact, the buffer rate constant ratio (31.2) for catalysis by acetic acid obtained for 2 is approximately of the same magnitude as the rate constant ratio (32.3) obtained for hydronium ion catalysis.

The observed difference in buffer catalysis is expected. Intramolecular protonation (valid for compounds 6, 7, and 8) can be regarded as specific hydronium ion catalysis and would not show buffer catalysis. The only reason that buffer catalysis is observed for the vinyl ethers listed in Table II is that a fraction of the substrate is hydrolyzed by intermolecular protonation in a parallel pathway. On the other hand, electrostatic stabilization of the developing positive charge would be observed with all acid catalysts. The only differences between the catalyzing acids are attractive or repulsive forces between the carboxylate ion in the substrate and the protonating acid. These forces result in small changes in the rate constant ratios.

This is expected from what is known about electrostatic effects on vinyl ether hydrolysis[12] and also from the work by Ritchie and Hofelich who found a very weak effect of a neighboring anion on the kinetic and thermodynamic stability of a triarylmethyl carbocation.[13] Buffer rate constant ratios may thus be used to differentiate between the two mechanisms.

The exact mechanism by which the carboxylate ion is stabilizing the developing positive charge in the transition state of the reaction of 2 is not that easily determined from the data of only compound 2. However, we assume that it is mainly electrostatic in nature in agreement with the generally accepted view on the relative importance of field and inductive effects.[14]

Since electrostatic catalysis was established for the hydrolysis of 2 it was of interest to measure the solvent isotope effect for this compound. We obtained $k_{H_3O^+}/k_{D_3O^+} = 3.3$, which is close to the value predicted by Kresge for electrostatic catalysis but also to the values generally observed for vinyl ethers in general. However, the result supports the idea that the bicyclic compound is hydrolyzed with a different mechanism than that found for hydrolysis of prostacyclin.

It is now clear that electrostatic catalysis is a possible mechanism in vinyl ether hydrolysis, and it may be of significant magnitude despite the fact that electrostatic effects are expected to be of minor importance in aqueous solution or any environment with a high dielectric constant. In media of lower dielectric constant, electrostatic effects should be more important. This is the case, e.g., in the active sites of enzymes, where the dielectric constant is usually assumed to be lower than in water. Electrostatic effects may therefore be of great importance in enzymatic reactions.[15]

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

Supplementary Material Available: Rate data for the hydrolysis of 2-methoxybicyclo[2.2.2]oct-2-ene-1-carboxylic acid (2) and methyl 2-methoxybicyclo[2.2.2]oct-2-ene-1-carboxylate (3) in various solutions (Tables S1–S5) and the ^{13}C NMR spectrum of 5 (13 pages). Ordering information is given on any current masthead page.

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