Intramolecular Electrostatic Catalysis in the Hydrolysis of a Bicyclic Vinyl Ether

Torbjörn Halvarsson and Nils-Åke Bergman*

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

Intramolecular electrostatic catalysis by a carboxylate ion has been observed in the hydrolysis of 2-methoxybicyclo[2.2.2]oct-2-ene-1-carboxylic acid in aqueous buffer solutions.

Intramolecular electrostatic catalysis has been discussed as a possible mechanism in the hydrolysis of the vinyl ether function of prostacyclin (**1**). However, all evidence presented in the kinetic investigations of prostacyclin[1] and different model compounds for prostacyclin[2—4] is in favour of intramolecular general-acid catalysis as the mechanism. In fact it has been concluded that electrostatic stabilization of a developing α-oxocarbonium ion by an internal carboxylate group is not significant.[5]

We can now present evidence that electrostatic catalysis is a possible mechanism in the hydrolysis of vinyl ethers. By examining the hydrolysis of 2-methoxybicyclo[2.2.2]oct-2-ene-1-carboxylic acid (**2a**), a vinyl ether compound in which intramolecular general-acid catalysis is impossible due to the rigid carbon framework, we obtained a considerable rate increase upon ionization of the carboxylic acid group.

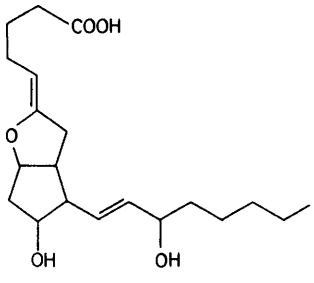
The methyl ester (**2c**) was prepared by *O*-alkylation of the enolate of the known ketone (**3**),[6] using potassium hydride as the base and dimethyl sulphate as the alkylating agent. The vinyl ether compound was purified by semi-preparative h.p.l.c. on a Si-10 silica column with n-hexane and triethylamine (97:3 v/v) as the mobile phase. Satisfactory spectral and analytical data were obtained. Saponification of the methyl ester gave pure sodium salt (**2b**). No intermediate acylal could be detected in the hydrolysis of (**2b**), and the only hydrolysis product isolated is the carboxylic acid of (**3**).

Rates of hydrolysis of (**2a**, **b**, and **c**) were measured by monitoring the decrease in absorbance of the vinyl ether double bond at 212—215 nm. Measurements were made in aqueous HCl solutions and in aqueous HCO_2H, $MeCO_2H$, and $H_2PO_4^-$ buffer solutions. The decrease in absorbance followed first-order kinetics accurately. The rate profiles shown in Figure 1 are obtained from observed first-order rate constants for catalysis by H_3O^+ in HCl solutions, extrapolating the buffer rate constants to zero buffer concentration. The data for the ester show a linear dependence of unit slope of log k_{obs} *vs.* $-\log [H^+]$, indicating an uncomplicated catalysis by H_3O^+. In the plot of the data for the acid two linear portions can be seen. This is similar to what has been found for prostacyclin, and can be interpreted in terms of separate hydronium ion-catalysed hydrolysis of the unionized and ionized forms of the substrate.[1] Rate and dissociation constants obtained by a least-squares analysis are shown in Table 1.

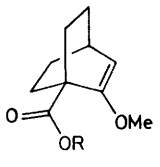
Table 1. Reaction parameters for the hydrolysis of 2-methoxybicyclo[2.2.2]oct-2-ene-1-carboxylic acid (**2a**) and its corresponding methyl ester (**2c**) in aqueous solution at 25 °C, ionic strength 0.10 M.[a]

pK_a[b]	4.45 ± 0.05
k_{H^+} (ester)/dm^3 mol^{-1} s^{-1}	17.7 ± 0.2
k_{H^+}/dm^3 mol^{-1} s^{-1}[c]	23.0 ± 1.4
k'_{H^+}/dm^3 mol^{-1} s^{-1}[d]	742 ± 101
Rate increase (k'_{H^+}/k_{H^+})	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.



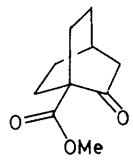
(1)



(**2a**); R = H

(**2b**); R = Na

(**2c**); R = Me



(**3**)

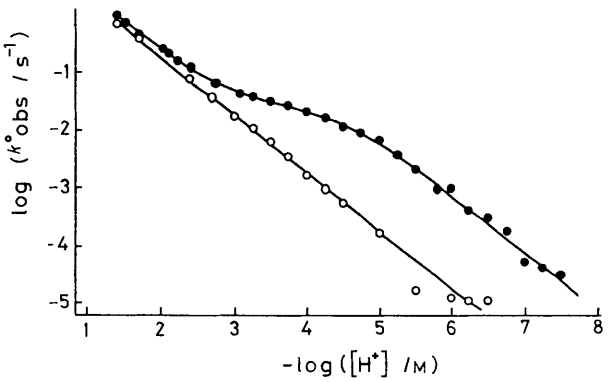


Figure 1. Rate profiles for hydrolysis of 2-methoxybicyclo[2.2.2]oct-2-ene-1-carboxylic acid (**2a**) (●) and its methyl ester (**2c**) (○) in aqueous solution at 25.0 ± 0.1 °C. Ionic strength 0.10 M.

The magnitude of the rate constant ratio, $k'_{H+}/k_{H+} = 32.3$, reveals that intramolecular electrostatic catalysis is a possible mechanism in the hydrolysis of vinyl ethers. The carboxylate ion in (**2b**) is in proximity to the developing positive charge on the vinyl ether function and is thus in a favourable position for electrostatic stabilization. Intramolecular general-acid catalysis is impossible in this molecule since the carboxylic acid group in (**2a**) cannot reach the vinyl ether carbon to be protonated. Electrostatic catalysis should be significant for all kinds of buffer acids. This is nicely borne out by our observation that $k'_{MeCO_2H}/k_{MeCO_2H} = 31.2$ for hydrolysis of (**2**). The results obtained in the present investigation do not contradict the conclusions from the investigations of prostacyclin and related model compounds. Both intramolecular general-acid catalysis and electrostatic catalysis are possible mechanisms in the hydrolysis of prostacyclin but apparently the most effective mechanism is intramolecular general-acid catalysis.

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