Acid-catalysed Hydrolysis of Prostacyclin: Origin of the Unused Lability

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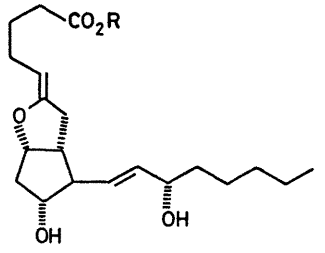
Summary The extra lability (89×) of prostacyclin towards acid-catalysed hydrolysis of its vinyl ether functional group in aqueous solution at 25 °C is traced to the carboxylic acid residue of this molecule operating in its ionized form, either as an electrostatic catalyst or, upon prior protonation, as an intramolecular general acid catalyst.

PROSTACYCLIN, a newly discovered[1] prostaglandin, is an extremely potent inhibitor of blood coagulation.[2] Its usefulness as a therapeutic agent in the treatment of thrombosis, however, is severely limited by its great hydrolytic lability: its half-life in aqueous solution at physiological pH is only *ca.* 3—4 min.



(1)

It was recognized that this lability probably originates from the vinyl ether group in the molecule (**1**, R = H); it is well known that vinyl ethers undergo acid-catalysed hydrolysis in aqueous solution and that the reactions are rapid even under weakly acidic conditions.[3] This was confirmed recently by an investigation of the kinetics of prostacyclin hydrolysis.[4] That study, however, revealed that prostacyclin is unusually reactive even as a vinyl ether; the specific rate for its hydrolysis catalysed by H^+, determined at pH 6—10, was some two orders of magnitude greater than that for similarly substituted simple vinyl ether analogues. We have now traced this enhanced reactivity to the carboxylic acid group also present in the prostacyclin molecule (**1**, R = H).

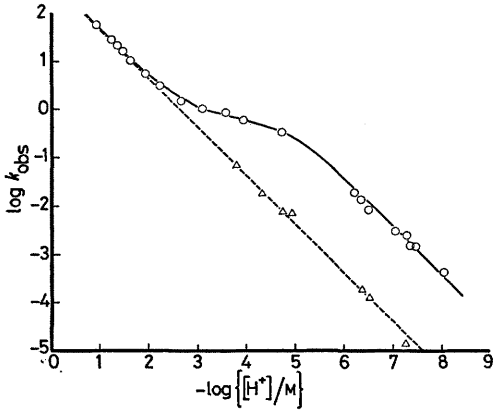
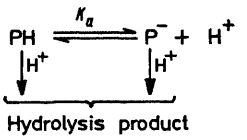


FIGURE. Rate profile for the hydrolysis of prostacyclin (○) and its methyl ester (△) in aqueous solution at 25 °C, μ = 0·1 M.

The Figure shows the rate profile for the hydrolysis of prostacyclin (**1**, R = H) and its methyl ester (**1**, R = Me), obtained by determining first-order rate constants, k_{obs}, in dilute HCl solutions and in carboxylic acid, ammonium ion, and phosphonate anion buffers; general acid catalysis was observed in the buffer solutions, and the values of k_{obs} shown in the Figure refer to zero buffer concentration. It may be seen that, at low acidities ($[H^+] = 10^{-6}$—10^{-8} M), prostacyclin is nearly two orders of magnitude (89×) more reactive than its methyl ester: $k_{H^+} = (3{\cdot}76 \pm 0{\cdot}07) \times 10^4$ and $(4{\cdot}25 \pm 0{\cdot}37) \times 10^2$ l mol^{-1} s^{-1}, respectively. This difference, however, does not persist to higher acid concentrations. There is a break in the linear dependence of k_{obs} upon $[H^+]$ for prostacyclin, and the new value of k_{H^+} which the system takes up at $[H^+] = 0{\cdot}1$—$0{\cdot}01$ M, $k_{H^+} = (4{\cdot}39 \pm 0{\cdot}05) \times 10^2$ l mol^{-1} s^{-1}, is indistinguishable from that of the methyl ester. The data are consistent with the model of the Scheme, and least squares analysis gives $pK_a = 4{\cdot}78 \pm 0{\cdot}07$. This is an entirely reasonable value for the carboxylic acid residue of prostacyclin, and the



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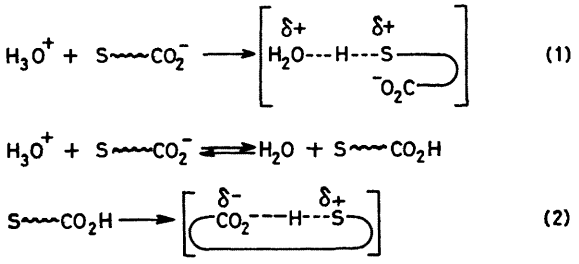
values of k_{H^+} for the ester as well as for prostacyclin at high acidities are also completely consistent with the structure of the vinyl ether group in these molecules.

These results indicate that the hydrolysis of prostacyclin is normal at acid concentrations sufficiently high to keep the carboxylic acid group in un-ionized form. Ionization of this group, however, produces a marked acceleration of the hydrolysis rate. This acceleration might be produced by electrostatic stabilization of the hydrolysis transition state, through coulombic interaction between the carboxylate anion and the positive charge being generated on the substrate [equation (1)].[5] Alternatively, it could be the result of intramolecular general acid catalysis by the un-ionized carboxylic acid group formed through prior reaction of the ionized substrate with H_3O^+ [equation (2)].



Similar explanations have been advanced for an analogous, though somewhat smaller, rate acceleration found previously in the hydrolysis of another vinyl ether containing a carboxylic acid functional group.[6] There, as here, the available information was insufficient to permit a mechanistic assignment. We hope, however, that by examining the effects of charged and neutral catalysts upon this reaction, we shall be able to make a choice.

We thank the Natural Sciences Engineering and Research Council Canada (formerly National Research Council of Canada) for financial support.

(*Received, 5th October* 1978; *Com.* 1069.)

[1] S. Moncada, R. Gryglewski, S. Bunting, and J. R. Vane, *Nature*, 1976, **263**, 663.
[2] For a recent review of the chemical and biological properties of prostacyclin, see K. C. Nicolaou, G. P. Gasic, and W. E. Barnette, *Angew Chem. Internat. Edn.*, 1978, **17**, 293.
[3] A. J. Kresge and W. K. Chwang, *J. Amer. Chem. Soc.*, 1978, **100**, 1249, and references cited therein.
[4] M. J. Cho and M. A. Allen, *Prostaglandins*, 1978, **15**, 943.
[5] A. J. Kresge and Y. Chiang, *J. Amer. Chem. Soc.*, 1973, **95**, 803; W. K. Chwang, R. Eliason, and A. J. Kresge, *ibid.*, 1977, **99**, 805.
[6] G. M. Loudon and D. E. Ryono, *J. Amer. Chem. Soc.*, 1976, **98**, 1900.