(*Z*)-6,9-Epoxynon-5-enoic Acid: a Simple Model which Mimics the Unusual Hydrolytic Lability of Prostacyclin

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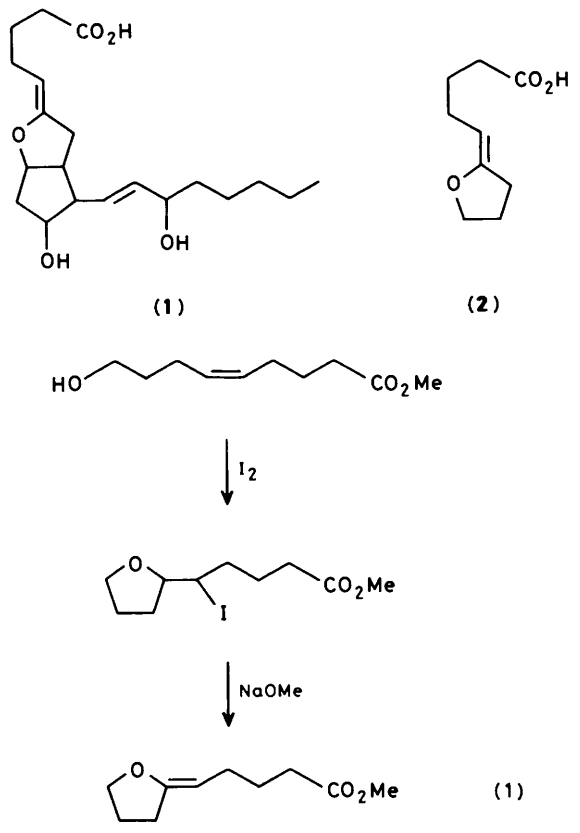
Evidence supporting the hypothesis that hydrolysis of the vinyl ether group of prostacyclin, accelerated by its carboxylic acid function operating in the carboxylate form, is responsible for the unusual hydrolytic lability of this substance is provided by the remarkably similar behaviour of (*Z*)-6,9-epoxynon-5-enoic acid; the latter is a simple model of prostacyclin which contains all of the structural features needed for this destabilization mechanism to function.

Prostacyclin (**1**) is a naturally occurring icosanoid with remarkable anti-blood-clotting properties[1] and an unfortunately great hydrolytic lability.[2] The hypothesis has been advanced that this lability is due to an unusually rapid hydrolysis of prostacyclin's vinyl ether functional group which is accelerated 100-fold by the molecule's carboxylic acid group acting in the carboxylate form.[3] We have obtained additional evidence supporting this idea by examining the hydrolysis of (*Z*)-6,9-epoxynon-5-enoic acid, (**2**); this substance is a simple model of prostacyclin which, according to this hypothesis, contains all of the structural features required for the unusual hydrolytic lability.

We prepared (**2**) by adapting a method used for the synthesis of prostacyclin itself. This involved the iodine-



induced ring closure[4] of (*Z*)-9-hydroxynon-5-enoic acid methyl ester followed by treatment with sodium methoxide to eliminate hydrogen iodide, equation (1);[5] saponification of the ester product then gave the free acid (**2**).† The (*Z*)-9-hydroxynon-5-enoic acid methyl ester required for this purpose was made by esterifying the acid obtained from treatment of 4-hydroxybutanal with the Wittig reagent derived from 5-bromopentanoic acid.[6]

We measured rates of hydrolysis of (**2**) and its methyl ester in dilute $HClO_4$ solutions and in $CNCH_2CO_2H$, HCO_2H, $MeCO_2H$, Me_2AsO_2H, and $H_2PO_4^-$ buffers by monitoring the decrease in vinyl ether double bond absorbance in the range 210—230 nm. The hydrolysis of both substrates followed first-order kinetics accurately, and observed first-order rate constants for catalysis by H_3O^+ obtained from the $HClO_4$ solutions and by extrapolating the buffer solution data to zero buffer concentration provided the rate profiles shown in Figure 1. The data for the ester give a straight line of unit slope, indicating an uncomplicated case of straightforward catalysis by H_3O^+. The data for the acid, on the other hand, show two linear regions of unit slope, one at high $[H^+]$ with rate constants similar to those for hydrolysis of the ester and another at low $[H^+]$ with rate constants two orders of magnitude greater.

This is very much like the behaviour of prostacyclin.[3] The data in that case were interpreted in terms of separate hydronium-ion catalysed hydrolyses of the carboxylic acid and carboxylate forms of the substrate, as in Scheme 1. The present data also conform well to such a reaction model; least squares analysis gives the reaction parameters shown in Table 1.

† Satisfactory spectral and analytical data were obtained for all new compounds.

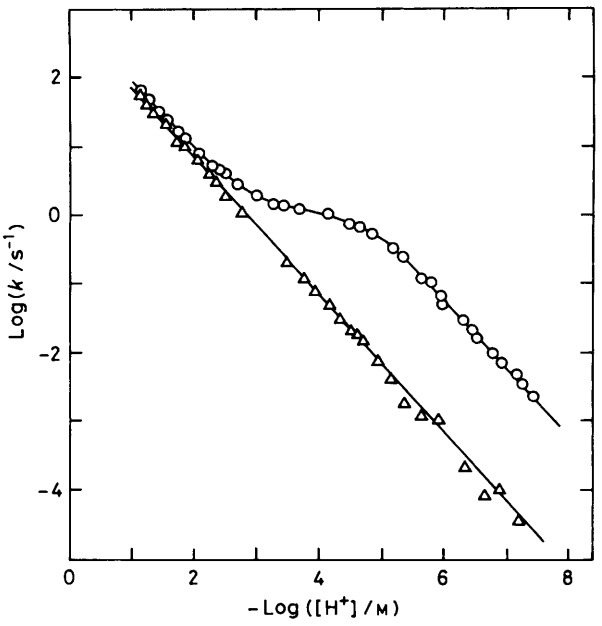
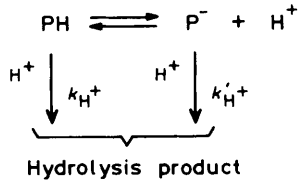


Figure 1. Rate profile for the hydrolysis of (**2**), ○, and its methyl ester, △, in aqueous solution at 25 °C; ionic strength = 0.10 M.



Scheme 1

Table 1. Reaction parameters for the hydrolysis of (*Z*)-6,9-epoxynon-5-enoic acid (**2**) and prostacyclin (**1**) in aqueous solution at 25 °C, ionic strength = 0.10 M.

Parameter	(*Z*)-6,9-Epoxynon-5-enoic acid[a]	Prostacyclin[a,b]
pK_a[c]	4.90 ± 0.13	5.03 ± 0.15
k_{H^+}/mol^{-1} dm^3 s^{-1}[d]	753 ± 6	439 ± 4
k'_{H^+}/mol^{-1} dm^3 s^{-1}[e]	57 300 ± 2000	43 600 ± 900
k_{H^+}(ester)/mol^{-1} dm^3 s^{-1}	692 ± 7	418 ± 5
Acceleration (k'_{H^+}/k_{H^+})[d,e]	76 ± 3	99 ± 2

[a] The uncertainties cited are standard deviations derived from statistical analysis of the data; they do not include possible systematic errors. [b] Ref. 7. [c] Acidity constant at zero ionic strength estimated using activity coefficients recommended by Bates (ref. 8). [d] Rate constant for hydrolysis of substrate in carboxylic acid form. [e] Rate constant for hydrolysis of substrate in carboxylate form.

These results indicate that the simple model (**2**) mimics the behaviour of prostacyclin closely. The pK_a's of the two substances are identical and the hydrolysis reaction accelerations shown by the carboxylate over the carboxylic acid forms of the substrates are comparable. The rate constants themselves for the model are from 30 to 70% greater than the corresponding ones for prostacyclin, but this may be because one face of the vinyl ether group of prostacyclin is shielded by the *cis*-fusion of its two five-membered rings whereas both faces of this group in the model are accessible to catalyst attack.

This model, however, does not inhibit blood platelet aggregation. Thus, although its hydrolytic reactivity is quite similar to prostacyclin's, its physiological activity is not.

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References

1 S. Moncada, R. Gryglewski, S. Bunting, and J. R. Vane, *Nature*, 1976, **263**, 663. For reviews of the physiological and chemical properties of prostacyclin, see W. Bartmann and G. Beck, *Angew. Chem., Int. Ed. Engl.*, 1982, **21**, 751; N. A. Nelson, R. C. Kelly, and R. A. Johnson, *Chem. Eng. News*, August 16th, 1982, p. 30.

2 M. J. Cho and M. A. Allen, *Prostaglandins*, 1978, **15**, 943.

3 Y. Chiang, and A. J. Kresge, and M. J. Cho, *J. Chem. Soc., Chem. Commun.*, 1979, 129.

4 R. A. Johnson, F. H. Lincoln, J. L. Thompson, E. G. Nidy, S. A. Mizsak, and U. Axen, *J. Am. Chem. Soc.*, 1977, **99**, 4184; R. A. Johnson, F. H. Lincoln, E. G. Nidy, W. P. Schneider, J. L. Thompson, and U. Axen, *ibid.*, 1978, **100**, 7690; K. C. Nicolaou, W. E. Barnette, G. P. Gasic, R. L. Magolda, and W. J. Sipio, *J. Chem. Soc., Chem. Commun.*, 1977, 630.

5 N. Whittaker, *Tetrahedron Lett.*, 1977, 2805.

6 E. J. Corey, N. M. Weinshenker, T. K. Schaaf, and W. Huber, *J. Am. Chem. Soc.*, 1969, **91**, 5675; R. Greenwald, M. Chaykovsky, and E. J. Corey, *J. Org. Chem.*, 1963, **28**, 1128.

7 Y. Chiang, M. J. Cho, B. A. Euser, and A. J. Kresge, *J. Am. Chem. Soc.*, 1986, **108**, 4192.

8 R. G. Bates, 'Determination of pH. Theory and Practice,' Wiley, New York, 1973, p. 49.