

means that the ^3H -labeling experiments are not especially useful as a measure of H exchange or inversion, a result we perhaps should have foreseen.

While this work was in progress, Fastrez and co-workers⁴⁰ and Mensi and Isied⁴⁹ have published results which suggest complete or major epimerization in the chelated amino acid during coupling. Our recent results show that this can be minimized. For example, the $(\Delta)\text{Co}(\text{S})\text{LeuOMe} + \text{AlaOMe}$ coupling in Me_2SO gives 40% epimerization under certain conditions whereas the $(\Lambda)\text{Co}(\text{S})\text{LeuOMe}$ diastereomer gives <1%. Similar discriminations are shown by other amino acid combinations.

Summary and Prognosis

Where do we go from here? The ability of coordinated H_2O and HO^- to promote the hydrolysis of esters

(49) Mensi, N.; Isied, S. S. *Inorg. Chem.* 1986, 25, 147.

and amides over and above that available to the directly activated substrate has obvious implications to metalloenzymes. This has already been suggested for some, but it will be difficult to demonstrate unequivocally in the in vivo situation. Modern spectroscopic methods together with low-temperature X-ray investigations offer some promise, but in the absence of direct verification it is important to establish with certainty such alternatives in labile "model" systems. So far, such studies have lacked originality and leave much in doubt; kinetic information alone is not sufficient. The $\text{Co}(\text{III})$ ester method for synthesizing small peptides offers some new opportunities, not the least of which is the orange color imparted to the coupled product, but the accompanying epimerization at asymmetric C centers will need to be carefully documented before the method can be considered alongside the more conventional organic routes.

Registry No. Cobalt(III), 22541-63-5.

Unusual Reactivity of Prostacyclin: Rational Drug Design through Physical Organic Chemistry[†]

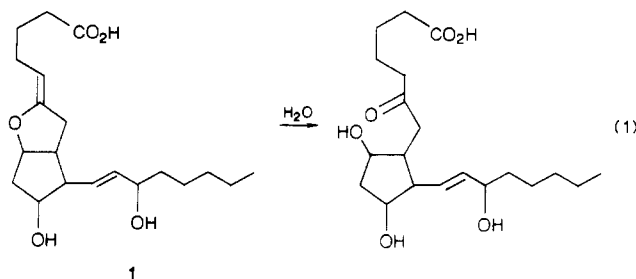
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Prostacyclin, 1, a naturally occurring bioregulator discovered just over 10 years ago,¹ has remarkable physiological properties: it is the most potent inhibitor of blood-clot formation known.² This gives it tremendous potential as a therapeutic agent for the treatment of heart attack and stroke and also as an anticlotting factor to confer noncoagulant properties upon polymeric materials used to manufacture vascular prosthetic devices such as heart valves and blood vessel replacements. Unfortunately, prostacyclin is also very unstable: its lifetime at physiological pH is only 3 min, which drastically limits its biomedical applications.

It was determined early in the short history of prostacyclin that this instability is due to hydrolysis of the molecule's vinyl ether functional group (eq 1).³

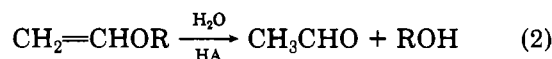


Jerry Kresge received his undergraduate education at Cornell University and did graduate work at the University of Illinois. After postdoctoral research at University College, London, Purdue, and M.I.T., he joined the staff of Brookhaven National Laboratory. In 1960 he moved to the Illinois Institute of Technology and in 1974 took up his present position at the University of Toronto.

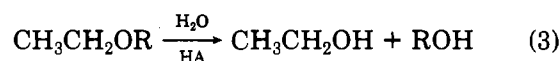
That discovery aroused our attention, for we had been studying the hydrolysis of vinyl ethers in considerable detail. Our interest in vinyl ether hydrolysis originally, and for some time thereafter, was purely theoretical: the process provided a good example of what was then a rare reaction type, rate-determining proton transfer from catalyzing acid to substrate, and we were using it to learn as much as possible about the proton-transfer process. We never thought that our work might have a practical application, but it has. Through our knowledge of vinyl ether hydrolysis, we have been able to contribute to the chemistry of prostacyclin and to suggest ways in which its instability might be overcome. This Account describes that work.

Vinyl Ether Hydrolysis

The hydrolysis of vinyl ethers (eq 2) bears some sim-



ilarity to the hydrolysis of saturated ethers (eq 3). Both



[†]Dedicated to Prof. Nelson J. Leonard on the occasion of his 70th birthday.

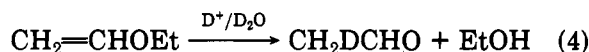
(1) Moncada, S.; Gryglewski, R.; Bunting, S.; Vane, J. R. *Nature (London)* 1976, 263, 663-665.

(2) For recent reviews of the physiological and chemical properties of prostacyclin, see: Bartmann, W.; Beck, G. *Angew. Chem., Int. Ed. Engl.* 1982, 21, 751-764. Nelson, N. A.; Kelly, R. C.; Johnson, R. A. *Chem. Eng. News* 1982, 60(30), 30-44.

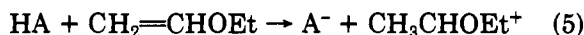
(3) Cho, M. J.; Allen, M. A. *Prostaglandins* 1978, 15, 943-954.

reactions are catalyzed by acids and not by bases, and both give alcohol products. There are, however, important differences, chief among which is reactivity. Vinyl ethers hydrolyze readily, whereas saturated ethers are fairly inert. Ethyl vinyl ether, for example, undergoes hydrolysis 10^{13} times faster than diethyl ether.⁴ Vinyl ethers, of course, have an additional functional group, the carbon-carbon double bond, which could provide an additional seat of reaction, and an early examination of the effect of structure on reaction rate did in fact reveal a pattern of reactivity consistent with electrophilic addition to the vinyl ether double bond.⁵

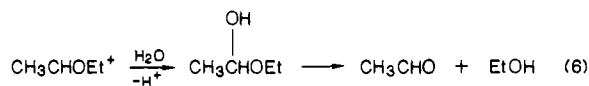
Some of the first detailed studies of the mechanism of vinyl ether hydrolysis were conducted by Fife⁶ and by Salomaa and his students.⁷ These investigators found that the reaction is catalyzed by undissociated acids as well as by the hydronium ion and that it gives an appreciable hydronium ion isotope effect in the normal direction, $k_{\text{H}_3\text{O}^+}/k_{\text{D}_3\text{O}^+} > 1$. We began our own work on vinyl ether hydrolysis at about the same time⁸ and also found general acid catalysis and substantial kinetic isotope effects. In addition, we learned that, when the hydrolysis of ethyl vinyl ether is conducted in D_2O , only one deuterium atom appears in the acetaldehyde product (eq 4) and that the rate of appearance of product is equal to the rate of disappearance of starting material.



These observations imply that electrophilic addition of a proton to the vinyl group is rate-determining and nonreversible, and they require that no intermediate be built up in significant amount during the course of the reaction. This is consistent with a mechanism whose first step is slow proton transfer from the catalyst to the substrate (eq 5). That is then followed by rapid



hydration of the alkoxy carbocation thus formed and further fast decomposition of the ensuing hemiacetal (eq 6). We have recently measured the rate of acid-



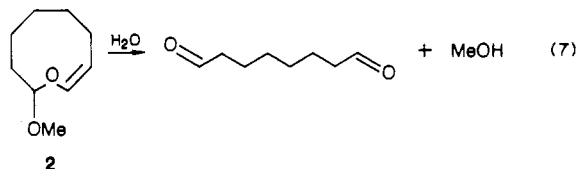
catalyzed decomposition of acetaldehyde ethyl hemiacetyl directly and have found that it is 2 orders of magnitude more rapid than the hydrolysis of ethyl vinyl ether.⁹

It follows from these studies that the lability of vinyl ethers to acid-catalyzed hydrolysis results from the ease with which the initial double-bond protonation step (eq 5) takes place, and this in turn must be due to the strong stabilizing influence of the alkoxy group on the carbocation product of this reaction step. This stabilizing effect is very powerful indeed; for example, the rate of protonation by H_3O^+ of the double bond in ethyl vinyl ether is 10^{15} times greater than that of the cor-

responding reaction of ethylene!¹⁰

An Apparent Mechanistic Exception

Following these early studies, we¹¹ and others¹²⁻¹⁵ conducted a number of additional investigations of vinyl ether hydrolysis, which has provided more mechanistic information. All of this evidence, with but one exception, is consistent with the now generally accepted reaction scheme of eq 5 and 6. The single exception occurs in the hydrolysis of 9-methoxyoxacyclonon-2-ene, **2** (eq 7).¹⁶



In hydrochloric acid solutions, this substance behaves in accord with eq 5 and 6, giving a substantial hydronium ion isotope effect in the normal direction. In acetic acid buffers, however, it behaves in an unexpected fashion: buffer catalysis becomes saturated and the isotope effect turns inverse ($k_{\text{H}_3\text{O}^+}/k_{\text{D}_3\text{O}^+} < 1$). Inverse hydronium ion isotope effects are indicative of rapid and reversible proton transfer from catalyst to substrate,¹⁷ and reversible substrate protonation, if followed by a slow step not involving another proton transfer, would give specific hydrogen ion rather than general acid catalysis.¹⁸ The unusual behavior of 9-

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(7) Salomaa, P.; Kankaanpera, A.; Lajunen, M. *Acta Chem. Scand.* 1966, 20, 1790-1801. Salomaa, P.; Kankaanpera, A. *Acta Chem. Scand.* 1966, 20, 1802-1810.

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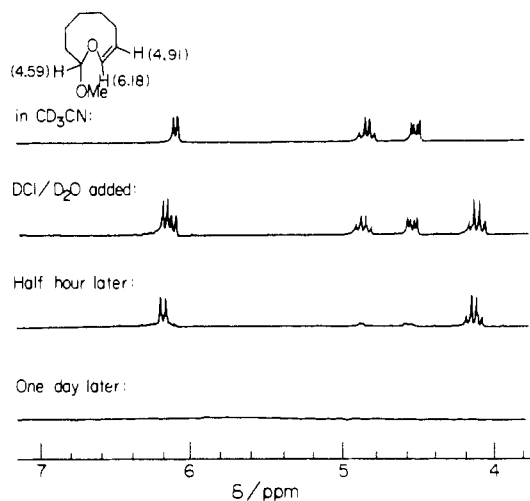


Figure 1. ^1H NMR spectral changes occurring during the hydrolysis of 9-methoxyoxacyclonon-2-ene in aqueous (D_2O) acetonitrile solution.

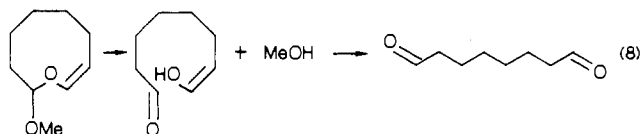
methoxyoxacyclonon-2-ene was therefore interpreted in terms of a change in rate-determining step: it was inferred that carbon protonation had become reversible and some subsequent step, perhaps hydration of the alkoxy carbocation, was now rate-determining. Such a change in reaction mechanism in acetic acid buffers might not be unreasonable, for the acetate ion present in these buffers, being basic, could remove a proton from the carbocation thereby rendering carbon protonation reversible.

We have recently found, however, that this is not the case and that the process being observed is not even reaction of the vinyl ether group.¹⁹ The hydrolysis of 9-methoxyoxacyclonon-2-ene can be monitored by following the decrease in UV absorbance at $\lambda \cong 215$ nm which is characteristic of carbon-carbon double bonds bearing oxygen substituents. Careful examination of this absorbance change reveals that the usual exponential decrease is preceded by a somewhat faster and considerably smaller increase. This biphasic process is accompanied by corresponding changes in the NMR spectra of hydrolysis reaction mixtures. As Figure 1 shows, upon the addition of aqueous acid to an acetonitrile solution of 9-methoxyoxacyclonon-2-ene, the original set of vinyl proton signals is replaced by a new vinyl group resonance; this new resonance then also disappears, leaving this region of the spectrum bare. Similar changes occur with wholly aqueous solutions, and these are accompanied by the appearance of signals attributable to aldehyde and aldehyde hydrate protons.

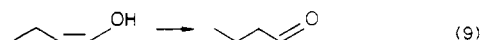
These observations show that the process being monitored cannot be hydrolysis of the vinyl ether functional group of 9-methoxyoxacyclonon-2-ene, for that process would give simple loss of the original vinyl group signals without intermediate formation of a new set. Initial hydrolysis of the molecule's acetal function, on the other hand, would produce an enol with a different vinyl group (eq 8). Enols, moreover, are known to have vinyl proton NMR signals which differ from those of the corresponding vinyl ethers in the way shown by Figure 1.²⁰

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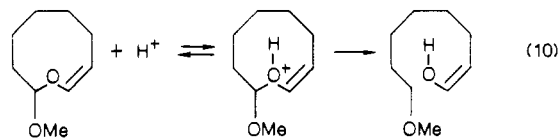


The second step of this biphasic hydrolysis of 9-methoxyoxacyclonon-2-ene must then be ketonization of the enol intermediate. Such a proposal would have been considered an unreasonable suggestion in 1971 when this hydrolysis reaction was first examined, for simple enols were regarded then as being very unstable substances which tautomerize to their keto isomers very rapidly. Since then, however, we²¹ and others²² have shown that the acid-catalyzed ketonization of some enols can be a slow process, easily observed by conventional kinetic techniques. We have found, moreover, that ketonization of *cis*-butenol (eq 9), a good model for



the enol of eq 8, proceeds with the hydronium ion rate constant $k_{\text{H}^+} = 6.1 \pm 0.1 \text{ M}^{-1} \text{ s}^{-1}$, which agrees well with the rate constant $k_{\text{H}^+} = 6.8 \pm 0.5 \text{ M}^{-1} \text{ s}^{-1}$ that may be obtained for ketonization of the enol intermediate of eq 8 from the slower exponential decays of biphasic UV absorption changes.

Fitting these biphasic absorption changes to a double-exponential function provides a rate constant, $k_{\text{H}^+} = 15 \pm 1 \text{ M}^{-1} \text{ s}^{-1}$, for the first stage of the reaction sequence of eq 8. This result shows that, in dilute mineral acid solutions, hydrolysis of the acetal group of 9-methoxyoxacyclonon-2-ene is twice as fast as ketonization of the enol intermediate. Ketone formation of enols, however, is strongly buffer catalyzed,^{21,22a} whereas the hydrolysis of simple acetals is not.²³ In buffer solutions, therefore, ketonization will speed up as the buffer concentration is raised, but acetal hydrolysis will not. Eventually, acetal hydrolysis will become the slower, rate-determining process, with ketonization occurring as an unobservable subsequent fast reaction, and this will give the appearance of buffer catalysis saturation. Because acetal hydrolysis is a pre-equilibrium proton transfer process (eq 10), this change will also produce an inverse hydronium ion isotope effect.



Our reinvestigation of the hydrolysis of 9-methoxyoxacyclonon-2-ene has thus shown that this substance

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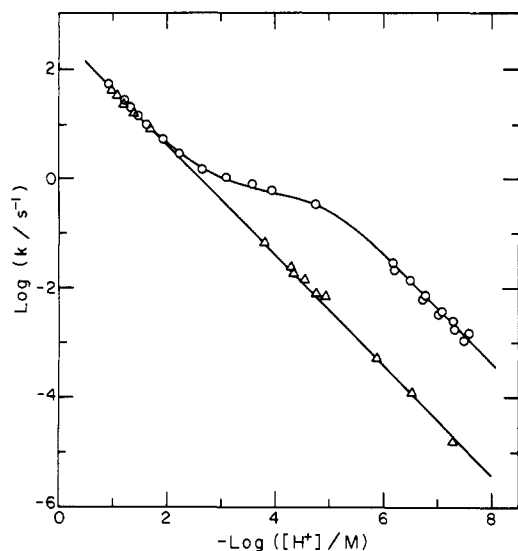
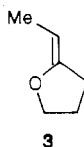


Figure 2. Rate profile for the hydrolysis of the vinyl ether functional group of prostacyclin (O) and its methyl ester (Δ) in aqueous solution at 25 °C.

does not undergo vinyl ether hydrolysis in buffer solutions by a reversible carbon protonation reaction mechanism. Consequently, there are now no exceptions to the rate-determining proton-transfer reaction scheme of eq 5 and 6 for the hydrolysis of simple vinyl ethers.

Prostacyclin

The event that drew us into prostacyclin research was an early kinetic study of its hydrolysis reaction conducted by scientists at the Upjohn Co., mainly for the purpose of determining conditions under which this substance might be stored in aqueous solution.³ That study, performed over the pH range 6–10, produced a rate constant, $k_{H^+} = 37\,000\text{ M}^{-1}\text{ s}^{-1}$, which we recognized as being anomalously large. Enough was then already known of the effect of structure on vinyl ether reactivity to provide a good estimate of the rate constant for hydrolysis of any simple vinyl ether, and the hydronium ion catalytic coefficient for (*Z*)-2-ethylidene-tetrahydrofuran, **3**, a reasonable model for the vinyl ether

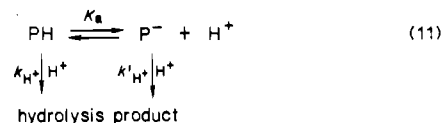


group of prostacyclin, had in fact been measured: $k_{H^+} = 635\text{ M}^{-1}\text{ s}^{-1}$.²⁴ Prostacyclin was thus some 2 orders of magnitude more reactive than it should be.

Working with samples of prostacyclin and its methyl ester provided by Upjohn, we constructed the rate profile shown in Figure 2.²⁵ This revealed that prostacyclin shows its unusual reactivity only at high pH. In mineral acid solutions of concentration down to about 0.01 M, it gives a rate constant, $k_{H^+} = 439\text{ M}^{-1}\text{ s}^{-1}$, which is normal for a vinyl ether of this structure and is also similar to the rate constant for hydrolysis of the vinyl ether group of prostacyclin methyl ester, $k_{H^+} = 418\text{ M}^{-1}\text{ s}^{-1}$. At higher pH, however, observed

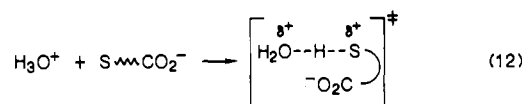
first-order rate constants for prostacyclin hydrolysis fail to drop in proportion to $[H^+]$; instead, they pass through a region where they are nearly constant and then, beyond a point which corresponds to the expected pK_a of the carboxylic acid group of prostacyclin, they drop again giving a new bimolecular rate constant 2 orders of magnitude larger than that which operates in the low-pH region. The methyl ester, on the other hand, continues to hydrolyze with the same bimolecular rate constant over the entire pH range investigated.

This behavior suggests that prostacyclin expresses its extra reactivity only when it exists in the carboxylate form. The kinetic data do in fact give a good fit to the rate law for a kinetic scheme (eq 11) based upon this

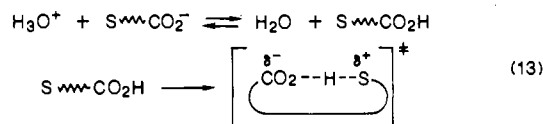


hypothesis. (In this scheme, PH represents prostacyclin in the carboxylic acid form and P^- , the carboxylate form.) Least-squares analysis gives a value of the acid ionization constant K_a which corresponds to $pK_a = 5.0$, a reasonable value for a carboxylic acid of this structure, and the catalytic coefficient $k'_{H^+} = 43\,600\text{ M}^{-1}\text{ s}^{-1}$ for hydrolysis of the vinyl ether group of the carboxylate form. This rate constant is 99 times that for hydrolysis of prostacyclin in the carboxylic acid form.

How does the carboxylate group accelerate the rate of hydrolysis? Two mechanisms come readily to mind. One of these, shown in eq 12, involves electrostatic



stabilization of the transition state of this reaction through an energy-lowering interaction between the carboxylate group and the positive charge being generated on the substrate; electrostatic effects of this kind have been observed in other vinyl ether hydrolysis reactions.²⁶ The second mechanism, shown in eq 13,



involves protonation of the carboxylate group to give the carboxylic acid form followed by intramolecular proton transfer from this acid to the vinyl ether group. Intramolecular reactions are generally more favorable than their intermolecular counterparts,²⁷ and intramolecular general acid catalysis of this kind should produce a rate acceleration.

We have been able to distinguish between these two mechanisms on several grounds, one of which involves solvent isotope effects. The mechanisms differ in the respect that, at the transition state of the electrostatic scheme (eq 12), proton transfer from the hydronium ion is under way and the two nonreacting bonds of H_3O^+ are in the process of becoming bonds of a water mole-

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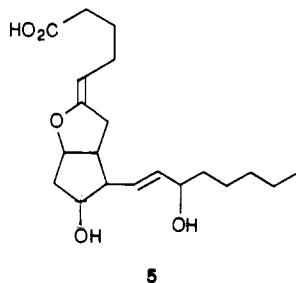
Table I.
Reaction Parameters for the Hydrolysis of Prostacyclin
and Two Simple Models in Aqueous Solution at 25 °C
(Ionic Strength 0.10 M)

parameter	prostacyclin	6,9-epoxynon-5-enoic acid	
		Z isomer	E isomer
pK_a	5.0	4.9	4.9
$k_{H^+}/M^{-1} s^{-1}$	439	745	242
$k'_{H^+}/M^{-1} s^{-1}$	43600	60900	17800
$k_{H^+}(\text{ester})/M^{-1} s^{-1}$	418	703	228
k'_{H^+}/k_{H^+}	99	82	73

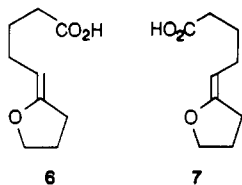
of the same magnitude if intramolecular catalysis is operating.

On the other hand, similar extra reactivities for E and Z isomers should not be observed if the electrostatic stabilization mechanism is operating. This is because the positive charge being generated on the substrate in the rate-determining transition state of a vinyl ether hydrolysis reaction is delocalized onto the ether oxygen atom, and since this atom lies off to one side of the double-bond system, it will not be equally accessible to carboxylate groups attached to either side of the double bond.

In order to apply a mechanistic test based upon this difference, we needed to examine unnatural or (*E*)-prostacyclin, **5**. This material had been made in con-



nection with several early syntheses of prostacyclin itself,³⁴ but the substance is unstable and samples were no longer available. Synthesizing (*E*)-prostacyclin ourselves presented a daunting prospect, but if our ideas concerning prostacyclin's extra reactivity were correct, we did not need the bottom half of the prostacyclin molecule: the upper five-membered ring with its exocyclic double bond and methylene chain carrying a carboxylic acid group were all that was required for operation of either the electrostatic stabilization or the intramolecular catalysis mechanism. We therefore set out to prepare (*Z*)- and (*E*)-6,9-epoxynon-5-enoic acids, **6** and **7**, for the purpose of using these substances as simple prostacyclin models, and we accomplished these syntheses by adopting methods which had been used for prostacyclin itself.



(34) Corey, E. J.; Keck, G. E.; Székely, I. *J. Am. Chem. Soc.* **1977**, *99*, 2006–2008. Johnson, R. A.; Lincoln, F. H.; Thompson, J. L.; Nidy, E. G.; Mazsak, S. A.; Axen, U. *J. Am. Chem. Soc.* **1977**, *99*, 4182–4184. De, B.; Andersen, N. H.; Ippolito, R. M.; Wilson, C. H.; Johnson, W. D. *Prostaglandins* **1980**, *19*, 221–247.

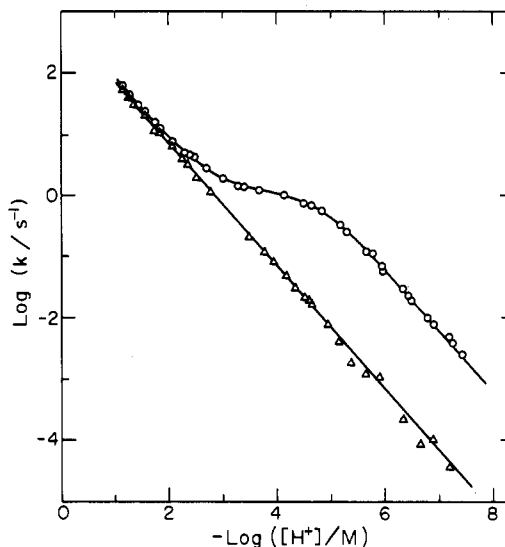


Figure 4. Rate profile for hydrolysis of the vinyl ether group of the simple prostacyclin model, (*Z*)-6,9-epoxynon-5-enoic acid (O), and its methyl ester (Δ) in aqueous solution at 25 °C.

A model, of course, is not the real thing, and we were therefore gratified to learn that (*Z*)-6,9-epoxynon-5-enoic acid mimics the hydrolytic behavior of prostacyclin closely.³⁵ As Figure 4 shows, it gives a rate profile very much like that provided by prostacyclin itself (Figure 2). The first two columns of Table I compare the parameters obtained by analyzing these profiles. The pK_a 's of prostacyclin and the model are closely similar, as are also the extra reactivities, k'_{H^+}/k_{H^+} . The rate constants themselves are similar as well, but there is a consistent difference: those for the model are about half again as large as those for prostacyclin. This is probably because the two five-membered rings of prostacyclin are joined in a *cis* fashion, and that places the lower ring in a position where it might obstruct access to one face of the molecule's vinyl ether double bond; the model, of course, since it lacks a second ring, can react with equal ease at either face of its double bond.

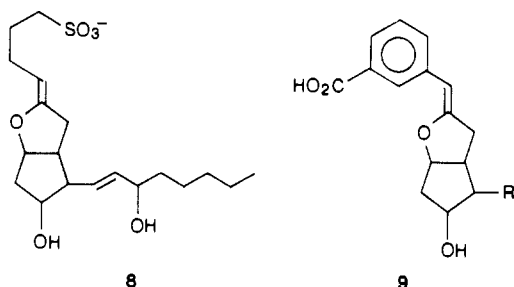
These results show that 6,9-epoxynon-5-enoic acid is a good model for prostacyclin insofar as hydrolysis of its vinyl ether group is concerned and that conclusions reached by studying this model should apply to the hydrolytic reactivity of prostacyclin itself. It is significant, therefore, that the other isomer of the model with *E* stereochemistry shows an extra reactivity comparable to that given by the *Z* isomer (Table I).^{35c} This is the result predicted for the intramolecular catalysis explanation of prostacyclin's extra reactivity, and this test therefore supports the assignment of this mechanism made on the basis of solvent isotope effects.

Although the *Z* and *E* isomers **6** and **7** show comparable extra reactivities, they nevertheless react at different rates. This, plus the fact that they do not interconvert during the course of the vinyl ether hydrolysis reaction, indicates that the carbon protonation step is not reversible. A mechanism such as that proposed for 9-methoxyoxacyclonon-2-ene (**2**) therefore does not operate here.

(35) (a) Bergman, N.-Å.; Chiang, Y.; Jansson, M.; Kresge, A. J.; Ya, Y. *J. Chem. Soc., Chem. Commun.* **1986**, 1366–1368. (b) Bergman, N.-Å.; Jansson, M.; Chiang, Y.; Kresge, A. J.; Yin, Y. *J. Org. Chem.*, in press. (c) Bergman, N.-Å.; Jansson, M.; Chiang, Y.; Kresge, A. J., submitted to *J. Chem. Soc., Perkin Trans. 2*.

Drug Design

Although (*Z*)-6,9-epoxynon-5-enoic acid is a good model for the hydrolytic reactivity of prostacyclin, it has none of prostacyclin's remarkable anti-blood-clotting properties. This shows that the bottom half of the prostacyclin molecule is required for its physiological function. The methyl ester of prostacyclin is not biologically active either, and since prostacyclin's carboxylic acid group is fully ionized at blood pH, this suggests that a negative charge is needed at the top end of the molecule. Our studies have shown that, when this negative charge is supplied by a carboxylate group, protonation of that group followed by intramolecular catalysis shortens the lifetime of prostacyclin by a factor of 10^2 . If, however, the negative charge were to be supplied by a less basic group, such as a sulfonate in sulfoprostacyclin, **8**, a much smaller fraction of the substance would exist in the catalytically active protonated form, and a more stable and possibly biologically active molecule would result.



A long physiological lifetime may also be predicted for the carboxyphenylene analogue of prostacyclin, **9**. With this molecule intramolecular catalysis is sterically impossible, and the phenyl group also exerts an electronic stabilizing effect which protects the substance from attack by external acids. This electronic effect may be estimated from rates of hydrolysis of simple vinyl ethers, and that, coupled with a factor of 100 for loss of intramolecular catalysis, gives this molecule a predicted physiological lifetime of 20 days.

Substances such as **9** do show much improved hydrolytic stability,³³ and they also have some prostacyclin-like physiological activity—but they are not as potent as prostacyclin itself.³⁶

Another tactic which might be used to overcome prostacyclin's unusual instability is to supply it in prodrug form. Although prostacyclin methyl ester is not physiologically active, when tested in vivo or in blood plasma, it quickly develops completely prostacyclin-like activity.³⁷ This presumably is because the ester group is hydrolyzed rapidly by enzymes present in these media. This suggests that other esters whose enzymatic hydrolysis is slower, or indeed other acyl derivatives such as amides, might serve as useful prodrugs which could deliver prostacyclin at convenient, controlled rates.

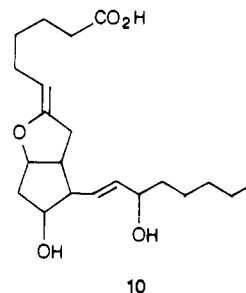
(36) Flohe, L.; Bohlke, H.; Frankus, E.; Kim, S.-M. A.; Lintz, W.; Loschen, G.; Michel, G.; Muller, B.; Schneider, J.; Seipp, U.; Vollenberg, W.; Wilsmann, K. *Arzneim.-Forsch.* **1983**, *9*, 1240-1248.

(37) Moncada, S., private communication.

Homoprostacyclin and Control of Bleeding

The short physiological lifetime of prostacyclin, though it does impose severe restrictions upon biomedical applications, has some beneficial aspects as well. Prostacyclin is produced in the endothelial lining of blood vessels and is released into the blood, where it exists in homeostatic balance with thromboxane, a potent blood-clotting factor.² When a blood vessel is broken, manufacture of prostacyclin becomes impaired at the site of the lesion, and rapid hydrolysis of the remaining prostacyclin quickly lowers its concentration in that region to a level where it can no longer offset the effects of thromboxane. Blood platelet aggregation, which is the first step in clot formation, then takes place, and that stems the flow of blood from the broken vein or artery. If the lifetime of prostacyclin at physiological pH were significantly greater than the 3 min it is, clotting would take place more slowly and significantly more blood would be lost. The short physiological lifetime of prostacyclin would thus appear to be a critical feature of a body mechanism for control of bleeding.

As we have shown, this short lifetime is a direct consequence of intramolecular catalysis of prostacyclin hydrolysis. It is interesting to speculate that natural evolution has given prostacyclin an optimum hydrolysis lifetime by adjusting the length of the carbon chain which joins the carboxylic acid group to the vinyl ether function. Support for this idea comes from studies we have carried out on homoprostacyclin, **10**, supplied to



us by the Ono Pharmaceutical Co. Homoprostacyclin has one carbon atom more than prostacyclin in the chain joining its vinyl ether and carboxylic acid functional groups. This makes it a less efficient intramolecular catalyst: its extra reactivity amounts to only a factor of 8.³⁸ That gives it a physiological lifetime of the order of half an hour, which is too long to be effective in the control of bleeding.

I am grateful to many skilled colleagues who have contributed so much to this research; in particular, the work on simple prostacyclin models could not have been done without the help of Dr. N. Å. Bergman and his students at the Chalmers University of Technology and University of Goteborg in Sweden. I also thank Upjohn, Ono, and Grunenthal for samples and the Natural Sciences and Engineering Research Council of Canada, the donors of the Petroleum Research Fund, administered by the American Chemical Society, and the Swedish Natural Science Research Council for financial support.

Registry No. 1, 35121-78-9.

(38) Chiang, Y., unpublished work.