Large Rate Enhancement for the Hydrolysis of a Four-membered Ring Phosphonamidate

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Unlike β-lactams a four-membered cyclic 1,2-azaphosphetidine shows enhanced hydrolytic reactivity compared with an acyclic analogue; the cyclic phosphonamidate **3** undergoes hydroxide-ion catalysed hydrolysis in water with endocyclic P–N fission; a corresponding acyclic derivative hydrolyses with P–O fission in basic solution, the rate difference between the cyclic and acyclic structures for P–N fission is greater than 5×10^8.

Thermodynamically strained four-membered cyclic β-lactams do not show a corresponding kinetic effect in the rates of their ring opening reactions.[1] The rate of alkaline hydrolysis of the β-lactam **1** is only 3 fold greater than that of **2** despite the strain energy of about 120 kJ mol^{-1} in the four-membered ring.[2] Breaking the C–N bond in these strained ring structures appears to be a relatively difficult process.[3]

The four-membered cyclic phosphonamidate **3** contains a four-coordinate phosphorus with a C–P–N bond angle of 81°,[4] the small bond angle about phosphorus allowing for the longer bonds between it and adjacent atoms.[5] Hydrolysis occurs rapidly in water with exclusive endocyclic P–N fission to generate the corresponding ring opened amino phosphonate **4**, easily identified by NMR in D_2O, in particular the ^1H–C–N–^{31}P coupling disappears upon P–N fission. Deuterium is slowly incorporated in the CH adjacent to the carbonyl group, which indicates that hydrolysis does not occur by a carbanion promoted dissociative pathway. The rate of hydrolysis above pH 8 is first-order in hydroxide and shows a second-order rate constant k_{OH} of 5.97×10^3 dm^3 mol^{-1} s^{-1} determined spectrophotometrically at 30 °C in water. A corresponding acyclic phosphonamidate **5** undergoes hydroxide-ion catalysed hydrolysis with P–O fission to liberate ethanol and with a second-order rate constant of 1.8×10^{-5} dm^3 mol^{-1} s^{-1}. Given P–N fission in the cyclic derivative but P–O fission in the acyclic system, the rate enhancement for P—N fission in the four-membered ring is greater than 5×10^8, a contrast to the hydrolysis of β-lactams and amides.

It has long been known that five-membered cyclic phosphate esters, *e.g.* ethylene phosphate, hydrolyse much faster than their acyclic analogues, although whether this is due to release of strain or difference in solvation energy remains controversial.[6]

For reactions which proceed through an unstable intermediate and for which the breakdown of the intermediate to products is rate-limiting [eqn. (1)], there are limits to the rate enhancement to be expected by lowering the activation energy of the second step (Fig. 1). The steady-state rate expression for the pseudo first order rate constant k_{obs} is given by eqn. (2). If the reaction conditions or reactant structures are

$$A + B \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} I \xrightarrow{k_2} \text{products} \quad (1)$$

$$k_{obs} = \frac{k_1 k_2}{k_{-1} + k_2} = \frac{k_1 (k_2/k_{-1})}{1 + (k_2/k_{-1})} \quad (2)$$

changed such that the rate limiting step is changed without modifying the value of k_1, then the maximum rate enhancement depends on the ratio of k_{-1}/k_2. For the hydroxide-ion catalysed hydrolysis of amides, it appears that the transition state energies for formation and breakdown of the tetrahedral intermediate are similar *i.e.* k_{-1} and k_2 are of similar magnitude.[7] The rate enhancement to be achieved by lowering the activation energy of the second step, k_2, is therefore limited. Although this probably accounts for the small rate difference between the hydrolysis of amides (rls k_2) and β-lactams (rls k_1), the ring opening of four-membered rings in azetidines does appear to be a relatively and expectedly difficult process.[3]

The large rate enhancement observed between the phosphonamidate **5** and 1,2-azaphosphetidine **3** is therefore indicative of a large ratio of k_{-1} to k_2 for phosphonamidate hydrolysis. It is also interesting to note that unlike the hydrolysis of five-membered phosphorous derivatives,[8] there is not a significant bond angle change around P on going from the four-membered reactant **3** to the trigonal-bipyramidal intermediate, **6**.

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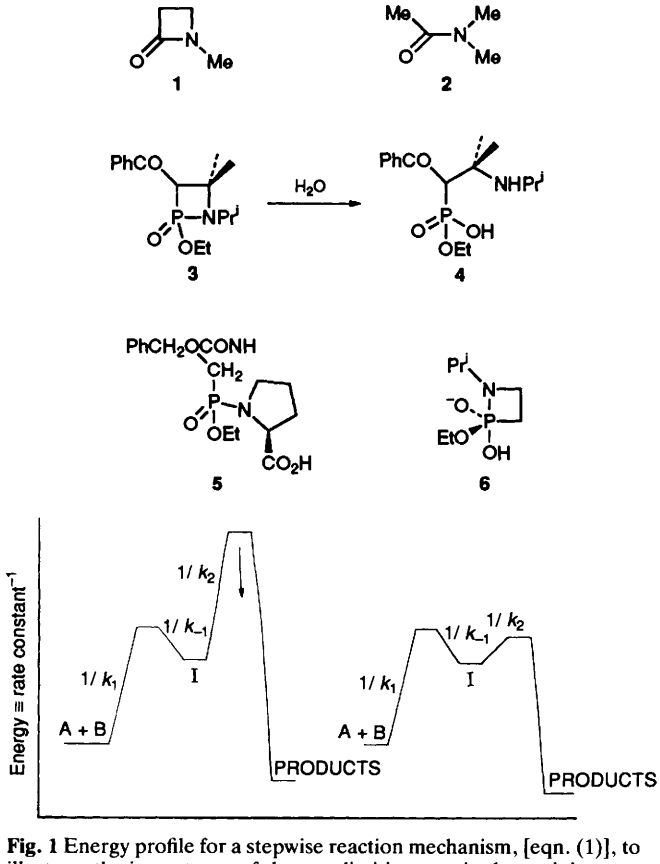

Fig. 1 Energy profile for a stepwise reaction mechanism, [eqn. (1)], to illustrate the importance of the rate-limiting step in determining rate enhancements

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