Participation of Neighbouring Groups in the Hydrolysis of 3-Hydroxy-2-pyridylmethyl Phosphate

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Summary The reactive species in the hydrolysis of 3-hydroxy-2-pyridylmethyl phosphate are the neutral zwitterion, the monoanion, and the dianion, of which the last species is the most labile; the intramolecular catalytic effect of the hydroxy-group is much greater than that of the pyridinium group, and causes a unique rate enhancement.

IN our studies on the hydrolysis reactions of heteroaromatic phosphates, we have reported evidence for an intramolecular general acid catalysis, which results in a marked rate enhancement, in the hydrolysis of 2-pyridylmethyl[1] and 8-quinolyl phosphate.[2] This specific effect, due to the participation of neighbouring groups, appears to aid the transfer of a proton to the ester oxygen at which bond cleavage takes place. We now report on the significant intramolecular catalytic effect of the hydroxy-group in the spontaneous hydrolysis of 3-hydroxy-2-pyridylmethyl phosphate (I).[3] This work also clarifies which neighbouring group, the 1-pyridinium or the 3-hydroxy-group, has the greater intramolecular catalytic effect in this hydrolysis.

The spontaneous hydrolysis of (I) was carried out at 60, 70, and 80° in aqueous media with an ionic strength of 0·10 ($NaClO_4$ or KNO_3) over the pH range 1·0—10·0. The pH *vs.* rate profiles are shown in the Figure; the reaction followed apparent first-order kinetics. The acid dissociation processes shown in Scheme 1 may be reasonably assigned to (I). The specific rate constants and the acid

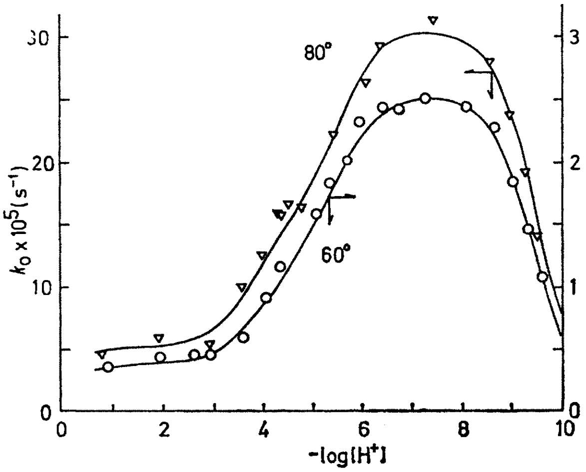
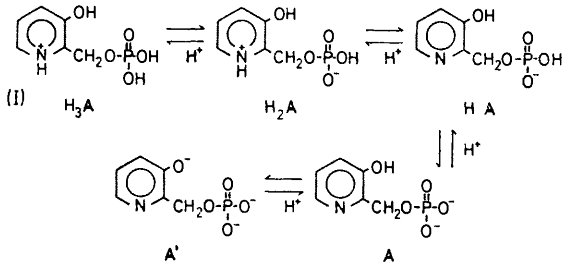


FIGURE. *The* pH vs. *rate profiles for the hydrolysis of 3-hydroxy-2-pyridylmethyl phosphate at* $\mu = 0·1$; ○ *and* ▽, ***experimental*** *points at 60 and 80°, respectively. Solid lines* ***are theoretical*** *curves calculated from values listed in Tables 1* ***and 2 by*** *using equation 1.*

TABLE 1. *Specific rate constants*[a] *and activation parameters for the spontaneous hydrolysis reactions of 3-hydroxy-2-pyridylmethyl phosphate at* 60 *and* 80°, *and* μ = 0·1

Species	T (°)	$k_{H^+} \times 10^4$ ($M^{-1}\,s^{-1}$)	$k \times 10^5$ (s^{-1})	E (kcal mol^{-1})	$\Delta H^{\ddagger}$ (kcal mol^{-1})	$\Delta S^{\ddagger}$ (e.u.)
Zwitterion	60	0·534		25·1	24·4	−5
(H_3A)	80	4·58				
Zwitterion	60		0·376	30·6	29·9	+6
(H_2A)	80		5·16			
Monoanion	60		1·17	30·4	29·7	+8
(HA)	80		15·7			
Dianion	60		2·52	29·1	28·5	+6
(A)	80		30·5			

[a] Calculated by the aid of dynamic acid dissociation constants listed in Table 2.



SCHEME 1

dissociation constants at elevated temperatures were calculated from the kinetic data using equations 1 and 2; the results are summarized in Tables 1 and 2.

TABLE 2. *Acid dissociation constants of 3-hydroxy-2-pyridylmethyl phosphate at* 25, 60, *and* 80° *and* μ = 0·1

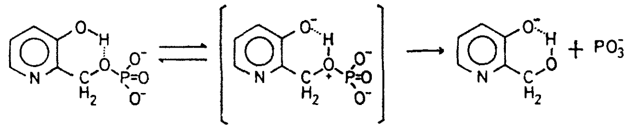
		Temp.	
pK_a	25° [a]	60° [b]	80° [b]
pK_{H_3A}	—	1·16	1·00
pK_{H_2A}	4·54	3·88	3·80
pK_{HA}	5·75	5·48	5·55
pK_{OH}	9·67	9·48	9·51

[a] Obtained by means of potentiometric titration.
[b] Estimated kinetically using equation 1.

$$k_0 T_A = k_{H^+}[H^+][H_2A] + k_{H_2A}[H_2A] + k_{HA}[HA] + k_A[A] \qquad (1)$$

$$T_A = [H_3A] + [H_2A] + [HA] + [A] + [A'] \qquad (2)$$

where k_0 is the overall rate constant and k_{H^+} refers to the specific rate constant for the acid catalysis, while k_{H_2A}, k_{HA}, and k_A are the specific rate constants for the hydrolysis of the neutral zwitterion, the monoanion, and the dianion, respectively; T_A stands for the total concentration of the phosphate species. When the first term on the right hand side of equation 1 was replaced for the hydrolysis of the monocationic species (H_3A), calculation of the specific rate constant and the corresponding activation parameters for this reaction yielded anomalous values, thus excluding this possibility. In the present case, the neutral zwitterion and monoanionic forms are relatively less reactive in the various ionic species, in contrast to the case of 2-pyridylmethyl and 8-quinolyl phosphate. The most reactive species is the dianionic species, which has one proton exclusively on the hydroxy-group. The absolute value of the specific rate constant for the neutral zwitterion of 3-hydroxy-2-pyridylmethyl phosphate is, however, *ca.* 3× and 29× as large as those for 8-quinolyl phosphate and 2-pyridylmethyl phosphate, respectively. The monoanionic species of the present phosphate was also found to hydrolyse *ca.* 100× faster than that of 2-pyridylmethyl phosphate. Therefore, the substitution of a hydroxy-group in the 3-position of 2-pyridylmethyl phosphate results in a large enhancement of the hydrolysis rates of the zwitterion and the monoanionic species. In the former species either the pyridinium or the hydroxy-proton is transferred to the ester oxygen in the transition state, while in the latter species it is the phosphate or hydroxy-proton. The extremely large rate enhancement for the monoanionic species over the zwitterion suggests that the intramolecular participation of the 3-hydroxy-group takes place in the transition state of hydrolysis. The dianionic species of (I), which is the most labile towards hydrolysis, is considered to pass through the reaction steps shown in Scheme 2, in agreement with the activation parameters listed in Table 1. The favourable formation of the activated complex is thought to be due to two factors: (i) sterically favoured ring-formation which involves the proton to be transferred, and (ii) large electron density at the ester oxygen due to the completely ionized phosphate moiety, both factors aiding the proton acceptability of the ester oxygen.



SCHEME 2.

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[1] Y. Murakami and M. Takagi, *J. Amer. Chem. Soc.*, 1969, **91**, 5130.

[2] Y. Murakami, J. Sunamoto, and H. Sadamori, *Chem. Comm.*, 1969, 983; Y. Murakami and J. Sunamoto, submitted for publication in *J. Amer. Chem. Soc.*

[3] For detailed synthetic procedure, see, Y. Murakami, J. Sunamoto, H. Sadamori, H. Kondo, and M. Takagi, *Bull. Chem. Soc. Japan*, 1970, **43**, 2518.