Solvolysis of Organic Phosphates. III1) 3-Pyridyl and 8-Quinolyl Phosphates in Spontaneous Reaction2)

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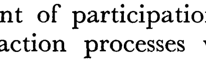
The spontaneous hydrolysis of 3-pyridyl and 8-quinolyl phosphates was investigated at 60, 70, and 80°C over the $-\log[H^+]$ range from 1 to 7 in aqueous media with an ionic strength of 0.10. The reactions followed apparent first-order kinetics with respect to the unreacted phosphate species, and the maximum rate was observed around $-\log[H^+]=2.5$. Reactive species of each phosphate in hydrolysis were the neutral zwitterion and the monoanion, the former being found to be more labile. In a moderately acidic region ($-\log[H^+]<2.0$), an apparent enhancement of the reaction rate was detected for both phosphates, which was attributed to the acid catalysis acting on the zwitterion species. The activation enthalpy for hydrolysis of the zwitterion and the monoanion falls near 30 kcal mol^{-1}. This is consistent with the reaction mechanism expected for hydrolysis of ordinary monoalkyl or monoaryl phosphate, in which the P–O bond cleavage takes place. The activation entropy data also provide an evidence for the unimolecular nature of the transition state. The kinetic solvent isotope effect k^{H_2O}/k^{D_2O} for the hydrolysis of both phosphates falls near unity. The isotope effect in this magnitude is consistent with the intramolecular proton-transfer mechanism. The results are, therefore, consistent with a mechanism for the hydrolysis of the zwitterion species of 8-quinolyl phosphate in which the quinolinium group donates a proton intramolecularly to the leaving ester oxygen atom in the transition state.

In an earlier study3) dealing with the hydrolysis of pyridylmethyl phosphates in the presence and the absence of metal ions, we elucidated the correlation between reaction rate and structural specificity of the leaving alcohol group of the phosphates. As a result, the extent of participation of the pyridyl nitrogen in their reaction processes was discussed. The neutral zwitterion form of 2-pyridylmethyl phosphate **1** was found to be more labile than the corresponding monoanion species **2**. The profound reactivity of the former was attributed to the unique intramolecular proton-transfer mechanism, in which the pyridinium group donates a proton to the leaving ester-oxygen in the transition state. In the hydrolysis reactions of 3- and 4-pyridylmethyl phosphates no such unique behavior was detected.



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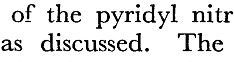

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In the present work, the spontaneous hydrolysis of 3-pyridyl and 8-quinolyl phosphates has been investigated in conjunction with kinetic solvent isotope effect as well as activation entropy and enthalpy effects. The former phosphate has no pyridinium proton available for an intramolecular proton-transfer mechanism, while the latter has a structural analogy to 2-pyridylmethyl phosphate. It is expected that some aspects, such as an intramolecular proton-transfer mechanism, participation of a water molecule in the transition state, and the electronic effect of the hetero-aromatic nitrogen on reactivity may be clarified.

Experimental

Materials. Preparation and purification of 2-pyridylmethyl phosphate have been described previously.4) 3-Pyridyl and 8-quinolyl phosphates were prepared by the reaction of 3-pyridinol and oxine respectively with phosphorous oxychloride, and purified by the column chromatographic technique with cation exchange resin. Detailed synthetic methods and purification procedures have been described elsewhere.5) Heavy water was obtained from Mallinckrodt Chemical Works (99.8%, Deuter AR), and from E. Merck Ag. Darmstadt (99.75%, Uvasol^R) and used without furhter purification. Use of either of these reagents gave no noticeable difference in reaction kinetics. Sodium deuteroxide solution (0.1 N) was obtained by diluting 40% concentrated sodium deuteroxide (G.R.) purchased from Merck with deuterium oxide. Deuteroperchloric acid (0.1 N) was prepared by diluting 60% aqueous solution with deuterium oxide. Other solution in deuterium oxide were prepared directly by dissolving the anhydrous compounds. Other materials were of analytical grade and used without any particular purification.

Apparatus. The reaction vessel used for kinetic and potentiometric measurements was the same as that designed and use for the reactions of pyridylmethyl phosphates.3) Electrodes used for pH measurements in kinetic runs were a set of glass electrode HG-6005 and reference electrode HC-605 of TOA Electronics, Ltd., Tokyo, or a set of Beckman glass electrode No. 39099 and Beckman reference electrode No. 39402. When the Beckman electrodes were adopted, a Beckman SS-2 pH meter was used in place of TOA HM-5A. Both of these pH meters were incorporated with TOA pH-stat HS-1B and TOA EPR-2T recorder in order to maintain pH-value constant during each run.

Kinetic Measurements. The reaction rate was determined by measuring the amount of inorganic orthophosphate liberated in the course of reaction. When an aqueous system was investigated, the experimental technique generally followed the procedure described previously.2) When the

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1) Contribution No. 211 from the Department of Organic Synthesis, Faculty of Engineering, Kyushu University.

2) Preliminary communication: Y. Murakami, J. Sunamoto, and H. Sadamori, *Chem. Commun.*, **1969**, 983.

3) Y. Murakami and M. Takagi, *J. Amer. Chem. Soc.*, **91**, 5130 (1969).

4) Y. Murakami, M. Takagi, and H. Nishi, This Bulletin, **39**, 1197 (1966).

5) Y. Murakami, J. Sunamoto, H. Sadamori, H. Kondo, and M. Takagi, *ibid.*, **43**, 2518 (1970).

reaction was carried out in deuterium oxide, the solution was made up initially to 35 m*l* in total volume and a 1.00-m*l* sample was drawn out from the vessel by a syringe at an appropriate time interval.

pD Measurements. The pH-meter was first calibrated with two standard aqueous buffer solutions, phthalate and phosphate buffers, and then potentiometric titration of deuteroperchloric acid with sodium deuteroxide of known concentration was carried out at a given temperature and a constant ionic strength. The difference (ΔpD) between the negative logarithm of a real concentration of deuterium ion, established by the titration of deuteroperchloric acid with sodium deuteroxide, and the apparent pH-meter reading is represented by the equation:

$$\Delta\text{pD} = -\log[\text{D}^+] - \text{“pH-meter reading”}$$

For example, at an ionic strength of 0.10 (KNO_3) and 70°C, ΔpD was determined to be 0.276. It was assumed that the ΔpD value was valid at the same temperature and ionic strength over the whole pD range studied. In this way, $-\log[D^+]$ values were established from pH-meter readings. Before determining ΔpD, the electrodes used were pre-equilibrated in deuterium oxide for 2 days or more. In each run, thereafter, the electrode system was conveniently checked with 0.05 M potassium biphthalate in deuterium oxide. The pH-meter reading of this reference solution corresponds to 4.21 in pD value at 70°C, 4.32 at 80°C, and 4.30 at 90°C.

Determination of Acid Dissociation Constants. The acid dissociation constants of 3-pyridyl and 8-quinolyl phosphates in aqueous solution at low temperature (25°C) were determined by titrating 2.0×10^{-3} M solution of the phosphates with a standard alkaline solution according to standard procedures. However, the acid dissociation constants obtained by this method at higher temperatures, especially the second one (K_{H_2A}), were suspected to involve a little uncertainty. The possible errors can be caused by trace hydrolysis of the phosphates during the course of measurements. Thus, under these circumstances as well as in the runs in heavy water at elevated temperatures, the kinetic (or dynamic) acid dissociation constants of each ionic species were evaluated by means of the equation:

$$k_0 = k_{H_2A}X_{H_2A} + k_{HA}X_{HA} + k_AX_A \tag{1}$$

where k_0 is the over-all rate constant and *k*s stand for the specific rate constants of ionic species suffixed to them; H_2A, HA, and A refer to neutral, monoanionic, and dianionic species of the phosphate, respectively. Mole fraction *X* of each ionic species is related to the corresponding acid dissociation constant in terms of the following relationships:

$$T_E = [H_3A] + [H_2A] + [HA] + [A]$$

$$[H_3A] = \frac{[A]}{K_{H_3A}K_{H_2A}K_{HA}}[H^+]^3$$

$$[H_2A] = \frac{[A]}{K_{H_2A}K_{HA}}[H^+]^2$$

$$[HA] = \frac{[A]}{K_{HA}}[H^+]$$

*K*s are acid dissociation constants of various ionic species suffixed to them, and T_E is the total phosphate concentration. In spite of the above general expression for reaction rate, the dianionic species of the present phosphates, as well as those of the pyridylmethyl phosphates,[3] were not reactive in the spontaneous hydrolysis. Thus, we could eliminate the last term in the right side of Eq. (1). The first approximation of the remaining four constants K_{H_2A}, K_{HA}, k_{H_2A}, and k_{HA} were carried out by solving the corresponding matrix of four rows and four columns, based on the data obtained in a pH range 3.0—6.0. The calculation was then iterated with the use of these evaluated four constants as a starting set until the best fit of the calculated values to the observed over-all rate constants was attained over the appropriate pH range studied ($-\log[H^+]=2.5$—7.0). All the calculation processes were programmed by means of Kyushu Daigaku Fortran and carried out on a FACOM 230-60 electronic computer of the Computer Center of Kyushu University.

Results

Acid Dissociation Constants. As mentioned in the experimental section, acid dissociation constants at elevated temperatures were evaluated by potentiometric method and/or by kinetic method. They are listed in Table 1, along with the values previously reported for 2-pyridylmethyl phosphate.[3]

TABLE 1. ACID DISSOCIATION CONSTANTS OF 8-QUINOLYL, 3-PYRIDYL, AND 2-PYRIDYLMETHYL PHOSPHATES AT VARIOUS TEMPERATURES AND $\mu=0.10$ (KNO_3)

Temp. °C	pK_{H_2A}	pK_{HA}
	8-Quinolyl phosphate	
25	4.17[a]	6.42[a]
80	4.16[a]	6.29[a]
80	4.09[b]	6.24[b]
80	4.05[c]	6.50[c]
	3-Pyridyl phosphate	
25	3.86[a]	5.64[a]
50	3.85[a]	5.62[a]
70	3.87[b]	5.76[b]
70	4.28[c]	5.71[c]
	2-Pyridylmethyl phosphate	
25	4.42[d]	6.29[d]
80	4.15[d]	6.54[d]
90	4.03[b]	6.46[b]
90	4.46[c]	6.46[c]

a) Determined by potentiometric titration.
b) Estimated by kinetic method using Eq. (1).
c) Estimated by kinetic method using Eq. (1) in deuterium oxide.
d) Reported previously[3] (determined by potentiometric titration).

Spontaneous Hydrolysis in Aqueous Media. 3-Pyridyl and 8-quinolyl phosphates were hydrolyzed at 60, 70, and 80°C in aqueous media for which an ionic strength was maintained at 0.10. The reactions followed apparent first-order kinetics with respect to the total concentration of the unreacted phosphate. The over-all rate constants, k_{obs}, thus obtained are listed in Table 2, together with the results in deuterium oxide as well as those for 2-pyridylmethyl phosphate in deuterium oxide.

The pH-rate profiles for 8-quinolyl, 3-pyridyl, and 2-pyridylmethyl phosphates are shown in Figs. 1, 2, and 3, respectively, along with the corresponding pD-rate profiles.

For the hydrolysis of 3-pyridyl phosphate, there is a narrow plateau on its experimental pH-rate profile

TABLE 2. APPARENT FIRST-ORDER RATE CONSTANTS FOR THE SPONTANEOUS HYDROLYSIS OF 8-QUINOLYL, 3-PYRIDYL, AND 2-PYRIDYLMETHYL PHOSPHATES AT $\mu=0.10$

$-\log [H^+]$[a]	Temp. °C	$k_{obs}\times 10^5$ sec^{-1}	Supporting electrolyte
	8-Quinolyl phosphate		
1.04	80	8.55	$HClO_4$
1.05	80	8.51	$HClO_4$
1.51	80	7.64	$HClO_4-NaClO_4$
1.52	80	7.07	$HClO_4-NaClO_4$
2.02	80	7.81	$HClO_4-NaClO_4$
2.04	80	7.52	$HClO_4-NaClO_4$
2.33	80	7.93	$HClO_4-NaClO_4$
2.97	80	7.53	$HClO_4-NaClO_4$
3.47	80	7.26	$NaClO_4$
3.53	80	7.18	$NaClO_4$
3.91	80	6.36	KNO_3
4.37	80	6.53	KNO_3
5.00	80	4.36	KNO_3
5.62	80	3.22	KNO_3
6.31	80	1.94	KNO_3
2.01	70	2.11	$HClO_4-NaClO_4$
4.31	70	1.42	KNO_3
2.00	60	0.717	$HClO_4-NaClO_4$
4.39	60	0.397	KNO_3
2.44[c]	80	7.36[d]	$DClO_4-KNO_3$
3.88[c]	80	7.71[d]	KNO_3
4.38[b,c]	80	6.34[d]	KNO_3
6.05[c]	80	3.61[d]	KNO_3
	3-Pyridyl phosphate		
1.02	70	9.00	$HClO_4$
1.03	70	8.83	$HClO_4$
1.42	70	7.75	$HClO_4-NaClO_4$
1.49	70	7.86	$HClO_4-NaClO_4$
2.00	70	7.72	$HClO_4-NaClO_4$
2.01	70	7.72	$HClO_4-NaClO_4$
2.37	70	7.39	$HClO_4-NaClO_4$
2.41	70	7.44	$HClO_4-NaClO_4$
3.06	70	6.97	$NaClO_4$
3.08	70	6.83	$NaClO_4$
3.31	70	6.44	$NaClO_4$
3.32	70	6.39	$NaClO_4$
3.82	70	4.92	KNO_3
3.83	70	4.67	$NaClO_4$
4.25	70	3.28	KNO_3
4.31	70	3.36	KNO_3
4.79	70	2.33	KNO_3
4.80	70	2.31	KNO_3
5.20	70	1.72	KNO_3
5.31	70	1.75	KNO_3
5.64	70	1.19	KNO_3
5.65	70	1.14	KNO_3
6.20	70	0.580	KNO_3
2.05	80	22.9	$HClO_4-NaClO_4$
4.52	80	8.58	$NaClO_4$
2.00	60	2.17	$HClO_4$
4.59	60	0.667	$NaClO_4$
2.08[c]	80	8.53[d]	$DClO_4$
3.66[c]	80	6.33[d]	KNO_3
4.31[c]	80	4.78[d]	KNO_3
5.33[c]	80	2.22[d]	KNO_3
6.63[c]	80	0.294[d]	KNO_3
	2-Pyridylmethyl phosphate		
2.23[c]	90	2.82[d]	$DClO_4-KNO_3$
3.80[c]	90	2.55[d]	KNO_3
4.36[c]	90	2.19[d]	KNO_3
6.95[c]	90	0.358[d]	KNO_3

a) Variation was maintained within ±0.02 unless otherwise stated.
b) Variation was maintained within ±0.04.
c) Value of $-\log [D^+]$ in deuterium oxide solution.
d) A reference electrode with calomel internal element which was placed in a bridge solution consisting of saturated potassium chloride solution was used.

in the pH region 2—3, where the major fraction of the phosphate is in the neutral zwitterion form. A similar observation was made for the hydrolysis of 8-quinolyl phosphate. Thus, we may propose that the neutral zwitterion and the monoanionic species of these phosphates are reactive as was confirmed to be the case for pyridylmethyl phosphates. To evaluate the specific rate constants for these reactive ionic species, fractional molar concentrations of various ionic species of each substrate were calculated by the aid of acid dissociation constsnts listed in Table 1. The following equation can be used for the calculation of the specific rate constants for these active species.

$$k_{obs} = k_{H_2A}X_{H_2A} + k_{HA}X_{HA}$$

where k_{obs} refers to the observed over-all rate constant. On the other hand, employment of Eq. (1) results in a simultaneous evaluation of rate constants and acid dissociation constants as mentioned in the previous section. The results are listed in Table 3.

In a moderately acidic region ($-\log[H^+]<2.0$), a good linear relationship between $k_{obs}-(k_{H_2A}X_{H_2A}+k_{HA}X_{HA})$ and the stoichiometric concentration of hydrogen ion exists for both phosphates. From the slope of the straight line, we tentatively estimated a specific rate constant for acid-catalyzed reaction, K_{H^+}: 8-quinolyl phosphate, $k_{H^+}=4.79\times 10^{-4}\text{M}^{-1}\text{sec}^{-1}$ at 80°C; 3-pyridyl phosphate, $k_{H^+}=5.00\times 10^{-4}\text{M}^{-1}\text{sec}^{-1}$ at 70°C.

Activation Parameters. Activation parameters for the hydrolysis of 8-quinolyl and 3-pyridyl phosphates are listed in Table 4. They were evaluated from the specific rate constants for the hydrolysis reactions of the neutral and monoanionic species (Table 3).

Discussion

In general, organic phosphates are polybasic acids and various ionic species with different degree of protonation exist in solution. The reactivity of these ionic species varies from one species to another, depending upon the structural property of the leaving alcohol group. In a series of solvolysis studies of

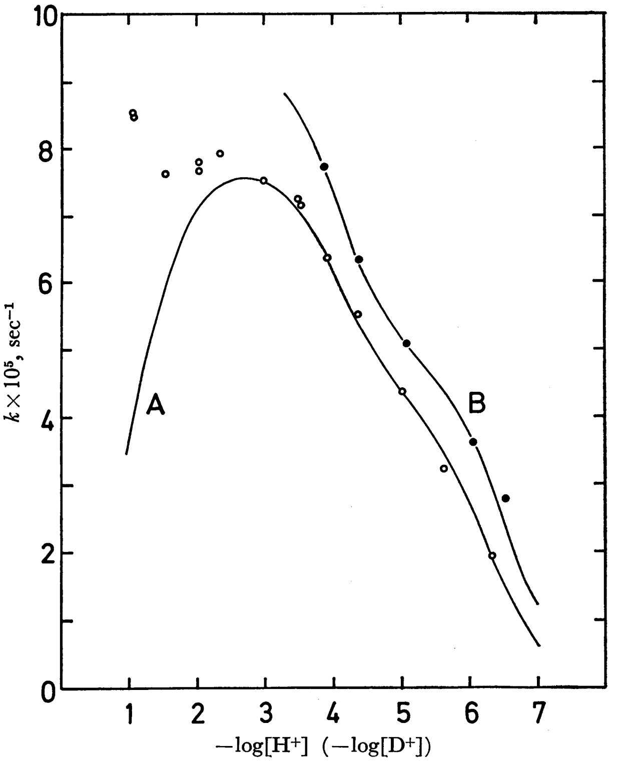


Fig. 1. Rate profiles for the spontaneous hydrolysis of 8-quinolyl phosphate in water (curve A) and in deuterium oxide (curve B) at 80°C and μ=0.10.

The curves were calculated from the experimemtal data by means of Eq. (1) with the following constant: aqueous system, pK_{H_3A}=1.0, pK_{H_2A}=4.09, and pK_{HA}=6.24; k_{H_3A}= 0 sec^{-1}, k_{H_2A}=7.84×10^{-5}sec^{-1}, and k_{HA}=4.19×10^{-5}sec^{-1}: deuterium oxide system, pK_{H_2A}=4.05 and pK_{HA}=6.50; k_{H_2A}=9.65×10^{-5}sec^{-1} and k_{HA}=4.83×10^{-5}sec^{-1}.

TABLE 3. FIRST-ORDER RATE CONSTANTS FOR THE HYDROLYSIS REACTIONS OF THE NEUTRAL AND THE MONOANIONIC SPECIES AT μ=0.10[a)]

Temp. °C	$k_{H_2A}\times10^5$ sec^{-1}	$k_{HA}\times10^5$ sec^{-1}
	8-Quinolyl phosphate	
80	7.97(7.84)	3.97 (4.19)
70	2.33	0.794
60	0.794	0.175
80	(9.65)[b)]	(4.83)[b)]
	3-Pyridyl phosphate	
80	25.0	5.75
70	7.69(7.63)	2.08 (1.92)
60	2.28	0.417
70	(7.21)[b)]	(2.70)[b)]
	2-Pyridylmethyl phosphate	
90	2.33(2.31)	0.414(0.458)
90	(2.78)[b)]	(1.44)[b)]

a) Numbers in parentheses are the values calculated by means of acid dissociation constants obtained from kinetic data.

b) In deuterium oxide.

phosphate esters containing pyridine moieties, the hydrolysis behavior of 3-pyridyl and 8-quinolyl phosphates has been investigated. Four kinds of ionic species have to be taken into consideration for each phosphate in the course of investigating hydrolysis mechanisms. 3-

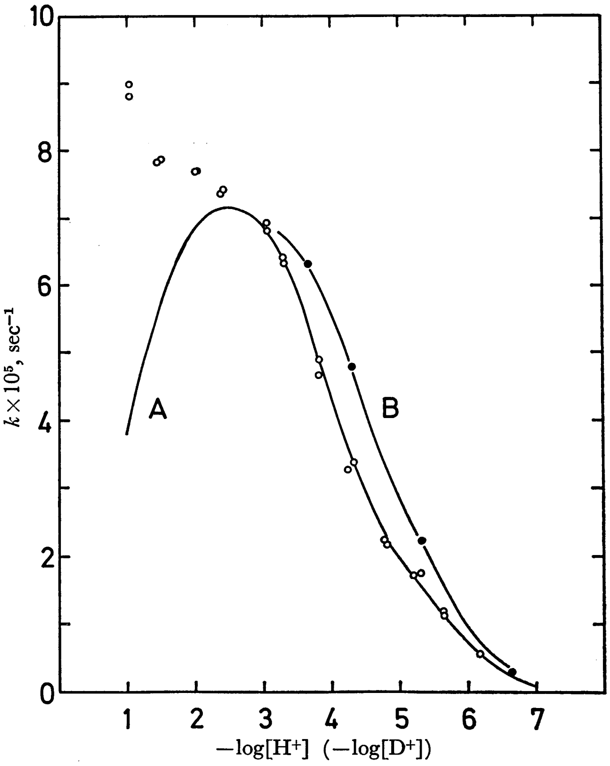


Fig. 2. Rate profiles for the spontaneous hydrolysis of 3-pyridyl phosphate in water (curve A) and in deuterium oxide (curve B) at 70°C and μ=0.10.

The curves were calculated from the experimental data by the aid of Eq. (1) with the following constants: aqueous system, pK_{H_3A}=1.0, pK_{H_2A}=3.87, and pK_{HA}=5.76; k_{H_3A}= 0 sec^{-1}, k_{H_2A}=7.63×10^{-5}sec^{-1}, and k_{HA}=1.92×10^{-5}sec^{-1}: deuterium oxide system, pK_{H_2A}=4.28 and pK_{HA}=5.71; k_{H_2A}=7.21×10^{-5}sec^{-1} and k_{HA}=2.70×10^{-5}sec^{-1}.

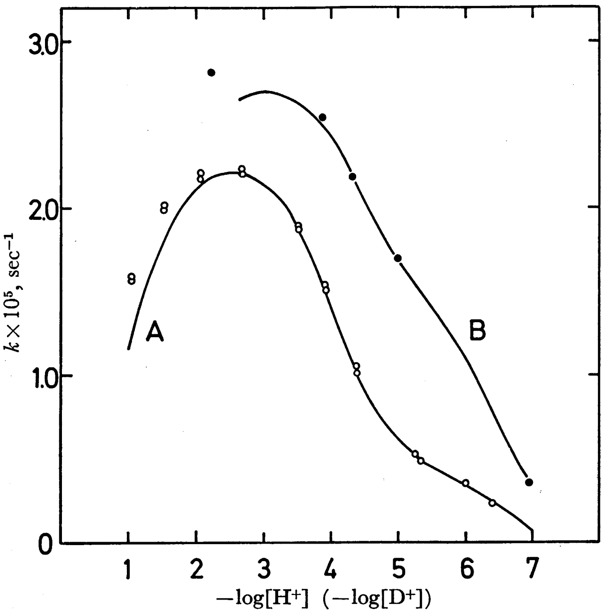


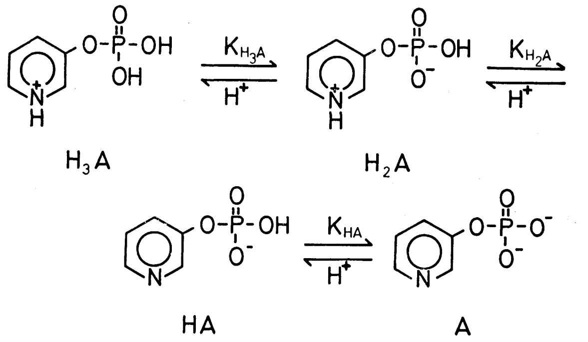
Fig. 3. Rate profiles for the spontaneous hydrolysis of 2-pyridylmethyl phosphate in water (curve A, experimental data were from our previous work[3)]) and in deuterium oxide (curve B) at 90°C and μ=0.10.

The curves were calculated from the data by means of Eq. (1) with the following constants: aqueous system; pK_{H_3A}=1.0, pK_{H_2A}=4.03, and pK_{HA}=6.46; k_{H_3A}=0 sec^{-1}, k_{H_2A}=2.33×10^{-5}sec^{-1}, and k_{HA}=0.458×10^{-5}sec^{-1}: deuterium oxide system, pK_{H_2A}=4.46 and pK_{HA}=6.46; k_{H_2A}= 2.78×10^{-5}sec^{-1} and k_{HA}=1.45×10^{-5}sec^{-1}.

TABLE 4. ACTIVATION PARAMETERS FOR THE SPONTANEOUS HYDROLYSIS REACTIONS OF 8-QUINOLYL AND 3-PYRIDYL PHOSPHATES

Phosphate	Neutral species			Monoanionic species		
	E kcal mol^{-1}	$\Delta H^{\ddagger}$ a) kcal mol^{-1}	$\Delta S^{\ddagger}$ a) e.u.	E kcal mol^{-1}	$\Delta H^{\ddagger}$ a) kcal mol^{-1}	$\Delta S^{\ddagger}$ a) e.u.
8-Quinolyl	27.0	26.3	+3	36.5	35.8	+22
3-Pyridyl	28.0	27.3	+2	30.7	30.0	+7

a) Value at 70°C.



Scheme 1

Pyridyl phosphate affords, for example, four ionic species of different protonation degree due to the dissociation process shown in Scheme 1. Throughout this study we refer H_3A to the monocationic form, H_2A to the neutral zwitterion, and HA to the monoanionic form. Both H_2A and HA, however, involve the monoanionic phosphate group.

Hydrolysis of Neutral Zwitterion Species. In the kinetic and mechanistic studies of hydrolysis of the pyridylmethyl phosphates,[3] the species involving a monoanionic phosphate moiety, zwitterion form (H_2A) and monoanionic form (HA), were confirmed to be reactive toward hydrolysis, although the corresponding acidic hydrolysis did not proceed to any detectable extent in the pH range studied. In addition, irrespective of the phosphate species, the activation energies for the hydrolysis of zwitterion forms were approximately 30 kcal mol^{-1} and the corresponding Arrhenius' A values were in the same order of magnitude as other ordinary alkyl phosphates.[3] Thus, we proposed that the zwitterion species of the pyridylmethyl phosphates follow the same hydrolytic pathway, accompanied with the P–O bond cleavage, as expected for the monoanionic form of an ordinary alkyl phosphate. The reactivity of the zwitterion was much greater than that of the corresponding monoionic species. This trend was marked for 2-pyridylmethyl phosphate; 2.5 times as large as those for its 3- and 4-isomers in terms of the rate ratio k_{H_2A}/k_{HA} as listed in Table 3. This facile hydrolytic tendency of the zwitterion species of 2-pyridylmethyl phosphate was explained in terms of interamolecular proton-transfer mechanism.

The same mechanistic argument can be applied to the elucidation of the facile hydrolysis of H_2A species of 8-quinolyl phosphate in the light of its structural analogy to 2-pyridylmethyl phosphate, activation parameters, and kinetic solvent isotope effect. First, the zwitterion species of 8-quinolyl phosphate has a quinolinium proton at a suitable position for attacking the ester-oxygen atom. The phosphate moiety is constrained more effectively in the neighborhood of nitrogen due to the quinolyl ring structure than expected in 2-pyridylmethyl phosphate. The proton is, therefore, readily transferred in the transition state to the oxygen atom. The activation parameters listed in Table 4 may further qualify for this similarity of the hydrolytic pathway among the zwitterion species of 2-pyridylmethyl and 8-quinolyl phosphates. The activation energy for the H_2A species of 8-quinolyl phosphate is very close to that for the corresponding species of 2-pyridylmethyl phosphate; the former is 27.0 kcal mol^{-1} and the latter is 28.2 kcal mol^{-1}, respectively. This equality must be attributed to the similarity in their hydrolytic pathways. Also, the small and positive entropy of activation for the H_2A species of 8-quinolyl phosphate, +3, is consistent with the unimolecular nature of the transition state, and rules out the possibility of participation of a water molecule. Similar observation has been made in many hydrolysis reactions of the monoanionic phosphate species; *e.g.*, in the hydrolysis of glucose-6-,[6] isopropyl,[7] and nitrophenyl phosphates.[8]

TABLE 5. KINETIC SOLVENT ISOTOPE EFFECT IN HYDROLYSIS REACTIONS OF SOME ORGANIC PHOSPHATES CONTAINING AN ACIDIC GROUP

Species	k^{H_2O}/k^{D_2O}	Reference
8-Quinolyl phosphate zwitterion	0.81	a)
8-Quinolyl phosphate monoanion	0.87	a)
3-Pyridyl phosphate zwitterion	1.06	a)
3-Pyridyl phosphate monoanion	0.71	a)
2-Pyridylmethyl phosphate zwitterion	0.84	a)
2-Pyridylmethyl phosphate monoanion	0.32	a)
Salicyl phosphate dianion	0.96	10
Methyl phosphate monoanion	0.87	b)

a) This work.
b) C.A. Bunton. D. R. Llewellyn, K. G. Oldham, and C. A. Vernon, *J. Chem. Soc.*, **1958**, 3574.

Further additional evidence for the intramolecular proton-transfer mechanism is provided for the neutral zwitterion species of both 8-quinolyl and 2-pyridylmethyl phosphates in terms of the kientic solvent isotope effect as listed in Table 5. As suggested by Westheimer[9] the deuterium oxide solvent isotope effect (k^H/k^D)

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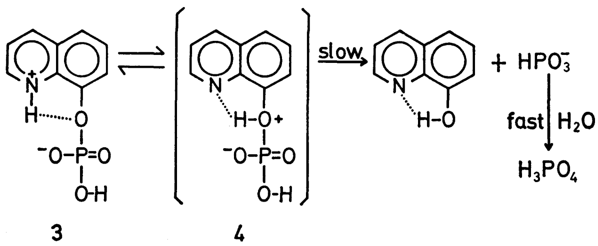
[6] Ch. Degani and M. Halmann, *J. Amer. Chem. Soc.*, **88**, 4075 (1967).

[7] L. Kugel and M. Halmann, *J. Org. Chem.*, **32**, 642 (1967).

[8] C. A. Bunton, E. J. Fendler, E. Humeres, and K. Yang, *J. Org. Chem.*. **32**, 2806 (1967).

[9] F. H. Westheimer, *Chem. Rev.*, **61**, 265 (1961).



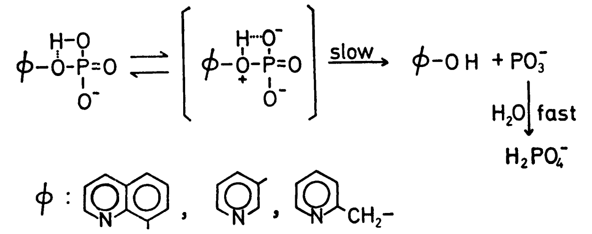
Scheme 2

reaches its maximum when the symmetric transition state is attained. On the other hand, if a transition state becomes asymmetric with respect to the position of a proton, without transfer or complete transfer of a proton to the ester oxygen (**3** or **4** in Scheme 2) in the transition state, the isotope effect $(k^{\mathrm{H}}/k^{\mathrm{D}})$ decreases markedly. A large deuterium oxide isotope effect was observed in none of the reactions including hydrolysis of salicyl phosphate dianion and methyl phosphate monoanion as shown in Table 5. Since the kinetic isotope effects for 8-quinolyl and 2-pyridylmethyl phosphates in their zwitterion forms are smaller than unity, a certain proton-transfer mechanism seems to be engaged in some analogy to A1 and A2 mechanisms. On the other hand, the small entropy of activation must eliminate the possibility of bimolecular process in the transition state. On the basis of the above arguments, the solvolysis mechanism for 8-quinolyl and 2-pyridylmethyl phosphates is closely related to A1 mechanism, even though the proton-transfer would not be as complete as expected in the A1 process. As a result, the most plausible reaction mechanism must involve the pre-equilibrium intramolecular proton-transfer (Scheme 2) in a manner similar to that suggested by Bender and Lawlor for the solvolysis of salicyl phosphate dianion.[10]

On the other hand, the value of deuterium kinetic solvent isotope effect for the zwitterion species of 3-pyridyl phosphate is approximately unity. As the molecular structure indicates, 3-pyridyl phosphate does not possess any proton suitably placed for an intramolecular hydrogen bonding. Such a kinetic isotope effect, therefore, must be attributed to another hydrolytic pathway. The data of activation parameters and of kinetic isotope effect are, however, consistent with the unimolecular and intramolecular proton-transfer mechanism. Thus, the zwitterion of 3-pyridyl phosphate seems to hydrolyze through the transition state similar to those for the monoanionic species as described below.

Hydrolysis of Monoanionic Species. 3-Pyridyl and 2-pyridylmethyl phosphates in their monoanionic forms seem to hydrolyze thourgh the same mechanistic path as proposed for the hydrolysis of methyl phosphate monoanion[11,12] in the light of the activation parameters and the kinetic solvent isotope effects.

The hydrolysis of 8-quinolyl phosphate monoanion provided relatively large activation parameters; a large positive entropy term in particular, $\Delta S^{*}=+22$. So far, such a large positive entropy term for solvolysis reactions does not seem to have been previously reported. We have not obtained any reliable activation parameters for the hydrolysis of 2-pyridylmethyl phosphate monoanion, which is analogous in structure to the 8-quinolyl phosphate monoanion. We are not ready to give a plausible explanation at present for the kinetic entropy effect. In any case, however, both kinetic deuterium oxide solvent isotope effect and activation entropy effect are in favor of unimolecular and intramolecular proton-transfer mechanism (Scheme 3).



Scheme 3

Hydrolysis in Lower pH Region. The hydrolysis rates of 8-quinolyl and 3-pyridyl phosphates increase in the moderately acidic region $(-\log[\mathrm{H}^+]=1.0$—$2.0)$ in proportion to the stoichiometric concentration of acid. This rate enhancement is primarily due to the acid-catalyzed hydrolysis of the neutral zwitterion species. The increase of electron-withdrawing power of the alcohol moiety may cause the deficiency of charge density on the ester oxygen atom, and consequently the electrophilic attack by the hydronium ion would be less favored. Contrary to what would be expected, the zwitterion species of pyridylmethyl phosphates do not undergo acid-catalyzed hydrolysis to any detectable extent in a moderately acidic region. We believe, therefore, that the favorable acid catalysis for 3-pyridyl and 8-quinolyl phosphates is due to electron-withdrawing effect caused by the pyridinium proton, which results in the weakening of P–O bond. Resonance stabilization effect given to the yielded alcohol of phenolic nature may facilitate the hydrolysis reaction.

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[10] M. L. Bender and J. M. Lawlor, *J. Amer. Chem. Soc.*, **85**, 3010 (1963).

[11] C. A. Vernon, *Chem. Soc. (London) Spec. Publ. No.* 8, 17 (1957); C. A. Bunton, D. R. Llewellyn, K. G. Oldham and C. A. Vernon, *J. Chem. Soc.*, **1958**, 3574.

[12] T. C. Bruice and S. J. Benkovic, "Bioorganic Mechanisms," Vol. II, W. A. Benjamin, Inc., New York, N. Y. (1966), Chapter 5.