Solvolysis of Organic Phosphates. IV.[1] 3-Pyridyl and 8-Quinolyl Phosphates as Effected by the Presence of Metal Ions

Yukito MURAKAMI and Junzo SUNAMOTO

Department of Organic Synthesis, Faculty of Engineering, Kyushu University, Hakozaki, Fukuoka

(Received December 26, 1970)

Influence of nickel(II), copper(II), and thorium(IV) ions on the hydrolysis of 3-pyridyl and 8-quinolyl phosphates was investigated at $\mu=0.10$ in a lower pH region. The reaction in the presence of the bivalent metal ions followed apparent first-order kinetics with respect to the phosphates in homogeneous phase. The copper ion showed a positive catalytic effect only on the hydrolysis of 8-quinolyl phosphate, and such effect increased markedly as pH was raised. The nickel ion, however, did not show any significant effect on the hydrolysis of both phosphates. The requisites for effective catalysis of bivalent metals have been postulated previously: *(1) preliminary chelate formation*, and *(2) transitional chelate formation*. Accordingly, complex formation of the present phosphates with copper(II) and nickel(II) was studied by means of potentiometric measurements. The results strongly suggest the importance of (1) for yielding catalytic efficiency. The presence of the thorium ion resulted in a profound acceleration of hydrolysis of both phosphates in a relatively lower temperature range. The reaction rate did not follow the simple kinetic law although the reaction system was kept homogeneous under the present experimental conditions. The complex formation with the phosphate moiety, which would provide effective charge neutralization for the substrate, is most likely the necessary cause for the thorium-catalysis. Plausible reaction mechanisms and the corresponding potential energy correlations were postulated for the present catalysis.

The influence of metal ions on the hydrolysis reactions of phosphate monoesters has been extensively studied up to the present time in connection with the biochemical interest. Among such studies, some efforts have been made by a limited number of research groups to clarify the reaction mechanisms of catalysis which has possibly arisen through the complex-forming interaction of metal ions with organic phosphates in the transition state.

In our previous work,[2,3] the hydrolysis of pyridylmethyl phosphates was investigated in the presence of bivalent and polyvalent metal ions. Of the bivalent metal ions, only the copper ion promoted the hydrolysis rate of 2-pyridylmethyl phosphate to a considerable extent in a moderate pH range. Its presence, however, did not cause any rate enhancement for the hydrolysis of 3- and 4-pyridylmethyl phosphates. We have proposed from these studies[2-4] that the two successive interactions are required for bivalent metals to yield catalytic efficiency: (1) A metal ion must demonstrate a significant chelate-forming affinity for an organic phosphate. Both the neighboring functional group in the leaving alcohol group (*e.g.*, the pyridyl nitrogen for 2-pyridylmethyl phosphate and the carboxyl group for salicyl phosphate) and the phosphate group, in which one of the oxygen atoms may act as a donor atom, may participate in such coordination interaction. This is the requirement of the preliminary chelate formation. (2) A metal ion must demonstrate an appropriate affinity for the ester oxygen in the transition state, so that the chelate ring involving both the neighboring functional group and the ester oxygen is to be formed in the excited state. This affinity can be judged from the chelating tendency of a metal ion with the alcohol, a hydrolysis product. This may be called the requirement of the transitional chelate formation.

Among polyvalent metal ions, the thorium ion accelerated the hydrolysis of pyridylmethyl phosphates, irrespective of the difference in isomeric structures, to a remarkable extent. However, we failed to find a satisfactory explanation for the profound catalysis although the primary interaction with the phosphate moiety seems to result in such rate enhancement.

The present work as well as the subsequent investigations has been designed to accumulate kinetic and mechanistic data for the confirmation of the above requisites established for the bivalent metal catalysis.

We also intend to investigate the role of polyvalent metal ions, particularly the thorium ion, in the hydrolysis reactions from the mechanistic viewpoint. In this work, the hydrolysis of 3-pyridyl and 8-quinolyl phosphates was studied in the presence of copper(II), nickel(II), and thorium(IV) ions in aqueous media at various temperatures. The complex-forming interaction between these metal ions and the phosphates has also been investigated to obtain key information on the catalytic reaction mechanism.

Experimental

Materials. Preparation of 3-pyridyl and 8-quinolyl phosphates has been described in our previous paper.[5] Other materials of analytical grade were commercially obtained and used without further purification. The stock solutions of metal ions were prepared from their nitrate salts. These solutions were standardized by means of the usual chelatometric titration.

Kinetic Measurements. The apparatus and experimental procedures were essentially the same as those employed pre-

---

[1] a) Contribution No. 224 from the Department of Organic Synthesis, Faculty of Engineering, Kyushu University. b) Preliminary communication: Y. Murakami, J. Sunamoto, and H. Sadamori, *J. Chem. Soc., D*, **1969**, 983. c) Part III: Y. Murakami and J. Sunamoto, This Bulletin, **44**, 1939 (1971).

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

[3] Y. Murakami and M. Takagi, This Bulletin, **42**, 3478 (1969).

[4] Y. Murakami, *Nippon Kagaku Zasshi*, **91**, 185 (1970).

[5] Y. Murakami, J. Sunamoto, H. Sadamori, H. Kondo, and M. Takagi, This Bulletin, **43**, 2518 (1970).

viously.[1c,2,3] In the case of the thorium-ion-catalyzed reactions, the procedure for kinetic measurements had to be slightly modified because of its extreme rate enhancement relative to the spontaneous hydrolysis. Two different aqueous solutions were initially prepared, the one containing the substrate and the other the catalyst species. A 50-m*l* solution which contained the phosphate ester, an inorganic salt for maintaining the ionic strength constant, and an appropriate amount of acid or base for adjusting the initial pH of an experimental solution was placed in a thermostated reaction cell. Another 50-m*l* solution containing a specified amount of the thorium ion and perchloric acid for minimizing a partial hydrolysis of the metal ion was placed in a thermostated bath controlled at a desired temperature. After both solutions attained an equilibrated temperature, the catalyst solution was quickly transferred into the reaction cell. The resulting solution was so controlled that the initial concentration of the substrate and the ionic strength were maintained at 2×10^{-3}M and 0.10, respectively. The subsequent procedure for kinetic measurements was essentially the same as those described previously.[2,3]

Potentiometric Measurements. A jacketed glass cell of approximately 100-m*l* capacity, which was equipped with a magnetic stirrer, nitrogen inlet and outlet tubes, a microburet delivery tube and electrodes, was adopted. A set of a Beckman glass electrode No. 39099 and a Beckman reference electrode No. 39170 was used in combination with a Horiba-Hitachi Model P pH meter for measurements at 25.0±0.1°C and the ionic strength of 0.10 (KNO_3). The initial concentration of the phosphate was maintained at 2.0×10^{-3}M, while those of the metal ions were varied in a range 1.0—2.0×10^{-3}M. Each titration was carried out under a nitrogen atomosphere and checked by duplicate or triplicate runs. The method of establishing $-\log[H^+]$ values at the constant ionic stength was the same as those employed in a series of our previous studies.

Mathematical Treatment of Equilibrium Data

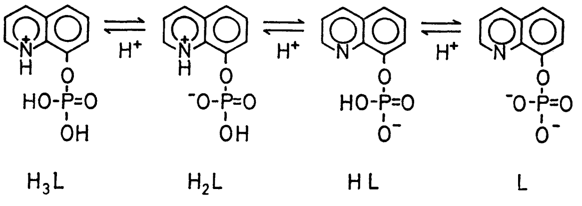
Since 8-quinolyl phosphate and 3-pyridyl phosphate are tribasic acids, the acid dissociation constants are defined as follows:

$$K_{H_3L}=\frac{[H_2L][H^+]}{[H_3L^+]} \tag{1}$$

$$K_{H_2L}=\frac{[HL^-][H^+]}{[H_2L]} \tag{2}$$

$$K_{HL}=\frac{[L^{2-}][H^+]}{[HL^-]} \tag{3}$$

where H_3L^+, H_2L, HL^-, and L^{2-} refer to monocation, neutral zwitterion, monoanion, and dianion, respectively. As an example, the acid diassociation processes for 8-quinolyl phosphate are shown in Scheme 1.



Scheme 1

These phosphate molecules have two coordination sites, an aromatic nitrogen and a phosphate group. On the basis of the results and discussion for the complex-forming interaction of 2-pyridylmethyl phosphate with various bivalent metal ions,[6] we consider that the following reaction scheme may suffice to cover the probable solution equilibria responsible for the present experimental conditions:

$$M^{2+}+L^{2-}\rightleftharpoons ML$$

$$K_1=\frac{[ML]}{[M^{2+}][L^{2-}]} \tag{4}$$

$$M^{2+}+H^++L^{2-}\rightleftharpoons M(HL)^+$$

$$K_\alpha=\frac{[M(HL)^+]}{[M^{2+}][H^+][L^{2-}]} \tag{5}$$

If these two solution equilibria take place to a significant extent, the following relationships are derived under the consideration of ionic neutrality and mass balance for ligand and metal:

$$T_M=[M^{2+}]+[ML]+[M(HL)^+] \tag{6}$$

$$T_L=[L^{2+}]+[HL^-]+[H_2L]+[H_3L^+]+[ML]+[M(HL)^+] \tag{7}$$

$$T_{OH}+[H^+]+[H_3L^+]+2[M^{2+}]+[M(HL)^+]=[OH^-]+2[L^{2-}]+[HL^-]+2T_M+T_H \tag{8}$$

Then, the following two equations are derived from Eqs. (6), (7), and (8) in conjunction with Eqs. (1), (2), and (3) for the acid dissociation constants:

$$RS[L^{2-}]^2+(T_MS+R-T_LS)[L^{2-}]-T_L=0 \tag{9}$$

$$QS[L^{2-}]^2+(PS+Q-T_MJ)[L^{2-}]+P=0 \tag{10}$$

where

$$R=\frac{[H^+]^3}{K_{H_3L}K_{H_2L}K_{HL}}+\frac{[H^+]^2}{K_{H_2L}K_{HL}}+\frac{[H^+]}{K_{HL}}+1$$

$$Q=\frac{[H^+]}{K_{HL}}\left(\frac{[H^+]^2}{K_{H_3L}K_{H_2L}}-1\right)-2$$

$$S=K_1+K_\alpha[H^+]$$

$$J=2K_1+K_\alpha[H^+]$$

$$P=T_{OH}+[H^+]-[OH^-]-T_H$$

T_L, T_M, T_{OH}, and T_H refer to the total concentrations of ligand, metal ion, base, and acid added to the system, respectively. Since the concentration of the ligand dianion $[L^{2-}]$ can not become zero, the following relation is obtained through division of Eq. (10) by Eq. (9):

$$[L^{2-}]=\frac{T_M(T_LS+T_LK_1-PS)-(PR+T_LQ)}{(PR+T_LQ)S} \tag{11}$$

Equations (9) and (10) are nonlinear with respect to equilibrium constants K_1 and K_α. In order to obtain the unknown equilibrium constants cited above, Rubin's method[7] was applied to our present system. An iterative calculation was performed to minimize the residual sum of squares (U)

$$U=\sum_{i=1}^{N}\{T_L(\mathrm{obs})_i-T_L(\mathrm{calc})_i\}^2 \tag{12}$$

until

$$\max_j\left|\frac{A_j^{(1)}-A_j^{(0)}}{A_j^{(0)}}\right|<\varepsilon$$

---

[6] Y. Murakami and M. Takagi, *J. Phys. Chem.*, **72**, 116 (1968).

[7] D. I. Rubin, *Chem. Eng. Progr. Symp. Ser.*, **59**, 90 (1963).

holds, where N is the number of observations and the subscript i is the observation-number index; $\Lambda_j^{(0)}$ and $\Lambda_j^{(1)}$ refer, respectively, to the approximation at one stage and to the next approximation to the jth parameter to be determined in the course of iterative calculation. The ε-value is a convergence criterion preassigned and was set at 1×10^{-4} in the present calculation.

All the calculation processes were programmed by means of the Fortran language for use with a FACOM 230-60 electronic computer of the Computation Center of Kyushu University.[8]

Results

Effects of Copper(II) and Nickel(II) Ions. The hydrolysis reactions of 8-quinolyl and 3-pyridyl phosphates were investigated in the presence of the copper(II) ion and the nickel(II) ion under various conditions. The reaction followed apparent first-order kinetics with respect to the total concentration of unreacted phosphate in homogeneous phase over the whole pH region and the metal concentration range studied. However, the nickel ion did not show any significant effect on the hydrolysis of both phosphates as can be seen in Table 1. On the other hand, the copper ion showed a positive catalytic effect only on the hydrolysis of 8-quinolyl phosphate. Such catalytic efficiency was subjected to a significant pH-dependency as shown in Table 2. The reaction rate increased markedly with the rise of pH-value of the solution. As for the concentration effect on the catalytic efficiency of the copper ion, the observed overall reaction rate was found to be consistent with Eq. (13).

$$k_{obs} = k_{H_2L}X_{H_2L} + k_{H^+}[H^+]X_{H_2L} + k_{Cu}[Cu^{2+}] \quad (13)$$

where k_{obs} is the observed overall rate constant and X_{H_2L} is the mole fraction of the zwitterion species: k_{H_2L}, k_{H^+}, and k_{Cu} refer to the specific rate constants for the hydrolysis of zwitterion, acid catalysis, and copper-ion catalysis, respectively. The validity of this equation was checked by varying the T_M/T_E value from 0.2 to 2.0 at a particular pH-value ($-\log[H^+]=2.01\pm0.02$) as listed in Table 2. The k_{Cu} value for the hydrolysis of 8-quinolyl phosphate was estimated at 80°C and at this pH: $k_{Cu}=5.55\times10^{-2}\text{M}^{-1}\ \text{sec}^{-1}$. Figure 1 illustrates the Arrhenius plots for the spontaneous and copper(II)-ion catalyzed reactions measured at 60°, 70°, and 80°C with the T_M/T_E value of 1.0, the $-\log[H^+]$ value being maintained at 2.01 ± 0.02. The temperature-dependence of the catalytic reaction rate has a close resemblance to that of the spontaneous one. Thus, the activation energy for the true catalytic reaction, which corresponds to the third term on the right hand side of Eq. (13), is almost negligible relative to that for the spontaneous reaction.

The presence of the copper(II) ion did not result in

TABLE 1. METAL-ION-CATALYZED HYDROLYSIS OF 8-QUINOLYL AND 3-PYRIDYL PHOSPHATES AT $\mu=0.1(KNO_3)$[a)]

$-\log[H^+]$	Temp. °C	Metal ion	$k_c\times10^5$ sec^{-1}	$k_o\times10^5$ sec^{-1}	k_c/k_o
		8-Quinolyl phosphate			
2.03	80	Cu^{2+}	18.6	7.69	2.42
2.02	80	Ni^{2+}	7.75	7.69	1.01
1.88	25	Th^{4+}	12.0[b)]	0.0089[c)]	1×10^3
		3-Pyridyl phosphate			
2.03	70	Cu^{2+}	7.23	7.51	0.96
2.02	70	Ni^{2+}	7.45	7.49	0.99
1.88	25	Th^{4+}	36.8[b)]	0.014[c)]	3×10^3

a) $T_M=T_E=2.0\times10^{-3}$M, where T_M and T_E stand for the total concentrations of the metal ion and of the substrate, respectively; k_c and k_o refer to overall rate constants for the hydrolysis in the presence of metal ion and for the spontaneous reaction, respectively.

b) Deviated from the first-order plot; estimated from the initial stage of reaction.

c) Estimated using the activation energy.

TABLE 2. COPPER(II)-CATALYZED HYDROLYSIS OF 8-QUINOLYL PHOSPHATE AT $\mu=0.1$ (KNO_3)[a)]

$-\log[H^+]$	Temp. °C	T_M/T_E	$k_c\times10^5$ sec^{-1}	$k_o\times10^5$[b)] sec^{-1}	k_c/k_o
2.03	80	2.0	30.2	7.69	3.93
2.03	80	1.0	18.6	7.69	2.42
2.01	80	0.5	13.1	7.80	1.68
2.00	80	0.2	9.95	7.80	1.28
2.00	70	1.0	6.02	2.11	2.85
2.00	60	1.0	1.75	0.717	2.44
2.76	60	1.0	29.7	0.747	3.96×10
2.26	40	1.0	0.136	0.0592	2.29
2.92	40	1.0	3.78	0.0614	6.16×10
3.21	40	1.0	13.9	0.0561	2.48×10^2
3.56	40	1.0	43.1	0.0514	8.37×10^2
3.85	30	1.0	17.4	0.107	1.62×10^3

a) $T_E=2.0\times10^{-3}$M.

b) At lower temperature, k_os were estimated using the activation energy.

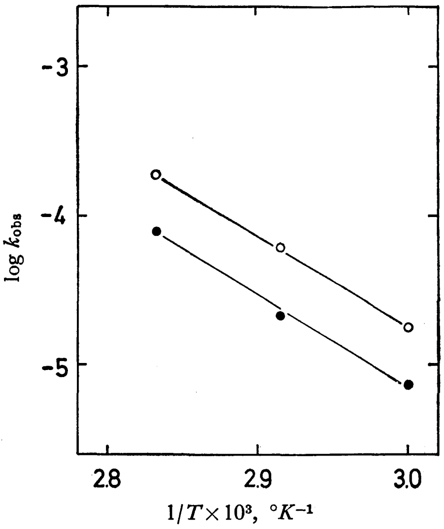


Fig. 1. Arrhenius plots of the first-order reaction rates for the hydrolysis of 8-quinolyl phosphate: ○, copper(II)-catalyzed reaction; ●, spontaneous reaction; rate constant (k_{obs}) in sec^{-1}.

---

8) For the detailed computational procedure: J. Sunamoto and Y. Murakami, *Kyushu Daigaku Kogaku Shuho* (Tech. Reports Kyushu Univ.), **44**, 199 (1971).

TABLE 3. COPPER(II)-CATALYZED HYDROLYSIS OF 3-PYRIDYL PHOSPHATE AT 70°C AND μ=0.1 (KNO_3)[a)]

$-\log[H^+]$	T_M/T_E	$k_c\times10^5$ sec^{-1}	$k_o\times10^5$ sec^{-1}	k_c/k_o
2.00	0.5	7.03	7.70	0.91
2.02	2.0	7.67	7.70	1.00
2.03	1.0	7.22	7.68	0.94
3.45	1.0	6.03	6.10	0.99
3.82	1.0	5.33	4.80	1.11
4.07	1.0	5.00	4.13	1.21

a) $T_E=2.0\times10^{-3}$M.

any enhancement of the reaction rate in the hydrolysis of 3-pyridyl phosphate, as seen in Table 3.

Effect of Thorium(IV) Ion. The presence of the thorium(IV) ion resulted in a profound acceleration of the hydrolysis of both phosphates, although the reaction rate did not follow the simple kinetic law. During the course of reaction, formation of any insoluble materials was not detected and a good homogeneous system was maintained. Figure 2 shows the rate plots for the hydrolysis of 3-pyridyl and 8-quinolyl phosphates in terms of the first-order kinetic law under the identical experimental conditions, where the corresponding spontaneous reactions did not proceed to any appreciable extent. The extent of catalytic efficiency in both reactions is nearly the same, and thus the apparent difference in reaction rates in Fig. 2, for example, can be ascribed to the nature of the leaving alcohol groups. For both phosphates, the catalyzed reactions appear to be largely controlled by concentrations of the hydrogen ion and the thorium ion as well as the reaction temperature as illustrated in Figs. 3 and 4. The increase of these controlling factors, *i.e.*, pH, metal-concentration, and temperature, caused a significant rate enhancement. In these thorium-ion catalysis, the slow but appreciable liberation of proton was always observed before the hydrolysis proceeded to any detectable extent: this became more apparent in lower concentration of the thorium ion at lower temperature. The sluggish formation of some thorium complexes with the substrates appears to be responsible for this phenomenon. The reaction rate in the presence of the thorium ion deviated downward significantly from the first-order plot; this deviation increased as the reaction proceeded further. In order to examine whether the rate deceleration effect is due to the removal of the thorium ion from the reaction system through the complex-formation with the yielded alcohol, 3-pyridinol and 8-quinolinol were added in a half of the equimolar amount of the corresponding substrates into the corresponding reaction systems at the begining of the reaction. However, the addition of such alcohols did not result in any significant change in reaction rate.

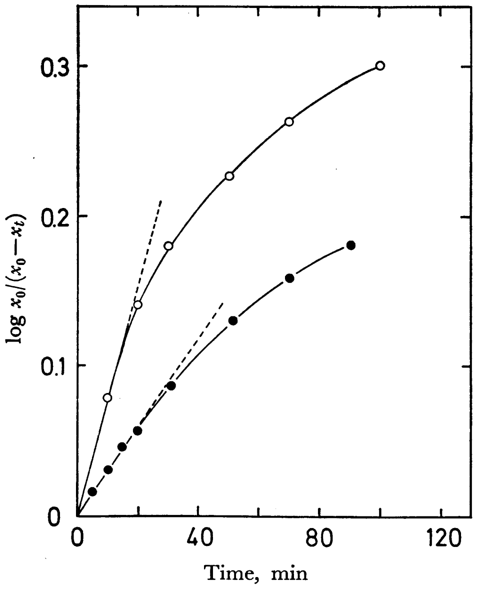


Fig. 2. Rate plots in terms of first-order kinetics for the thorium(IV)-catalyzed hydrolysis of 8-quinolyl phosphate (●) and 3-pyridyl phosphate (○) at 25°C, $-\log[H^+]=1.88$, $T_M/T_E=1.0$, and $\mu=0.10$ ($NaClO_4$). Broken lines stand for the first-order rate relation extrapolated from the initial reaction rate.

Potentiometric Titration. In order to obtain a

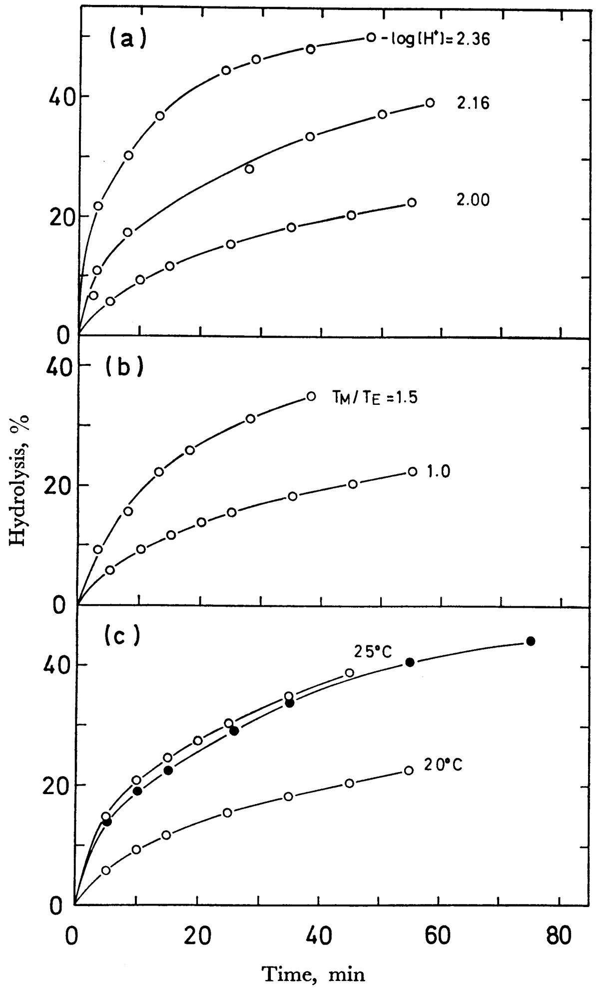


Fig. 3. Hydrolysis of 8-quinolyl phosphate in the presence of thorium(IV) ion: $T_E=2.00\times10^{-3}$M, $\mu=0.10$ (KNO_3 or $NaClO_4$); (a) 20.0°C, $T_M/T_E=1.0$; (b) 20.0°C, $-\log[H^+]=2.00$; (c) $-\log[H^+]=2.00$, $T_M/T_E=1.0$. Solid circles in (c) refer to the rate data for the presence of 8-quinolinol (1.00×10^{-3}M).

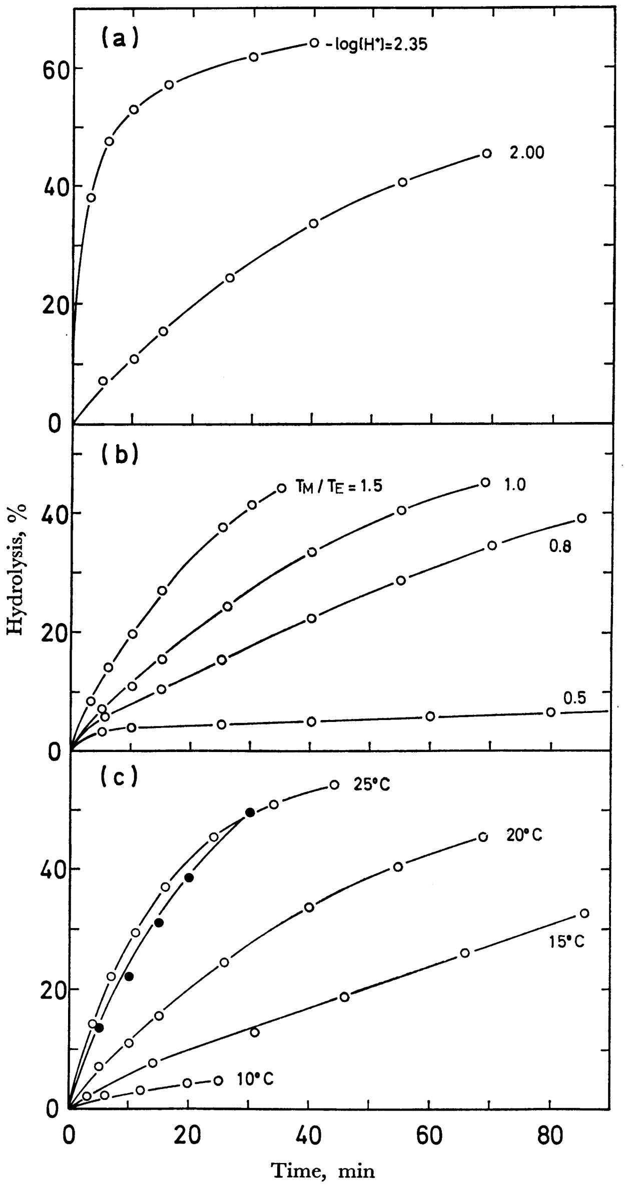


Fig. 4. Hydrolysis of 3-pyridyl phosphate in the presence of thorium(IV) ion: $T_E=2.00\times10^{-3}$M, $\mu=0.10$ (KNO_3 or $NaClO_4$); (a) 20.0°C, $T_M/T_E=1.0$; (b) 20.0°C, $-\log[H^+]=2.00$; (c) $-\log[H^+]=2.00$, $T_M/T_E=1.0$. Solid circles in (c) refer to the rate data for the presence of 3-pyridinol (1.0×10^{-3}M).

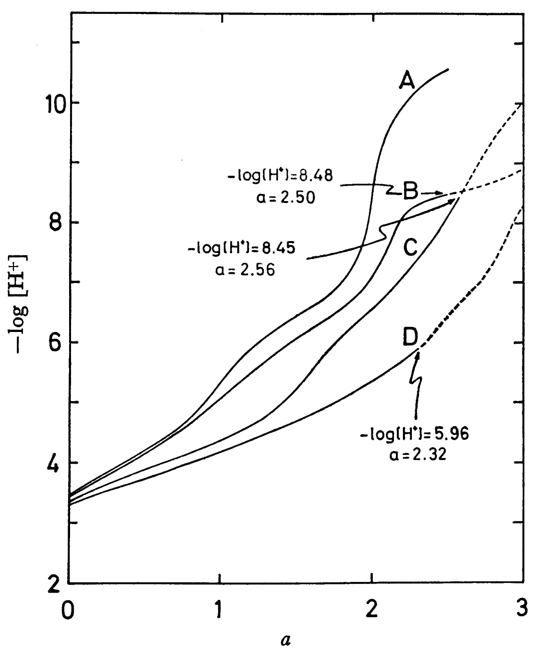


Fig. 5. Titration curves for 8-quinolyl phosphate—bivalent metal systems at 25.0°C and $\mu=0.10$ (KNO_3): A, ligand alone; B, Ni(II) system with $T_M/T_L=1.0$; C, Cu(II) system with $T_M/T_L=0.5$; D, Cu(II) system with $T_M/T_L=1.0$; initial concentration of ligand (T_L), 2.00×10^{-3}M; a=moles of base added per mole of ligand. Arrows indicate the region where pH-reading starts to become unstable on standing.

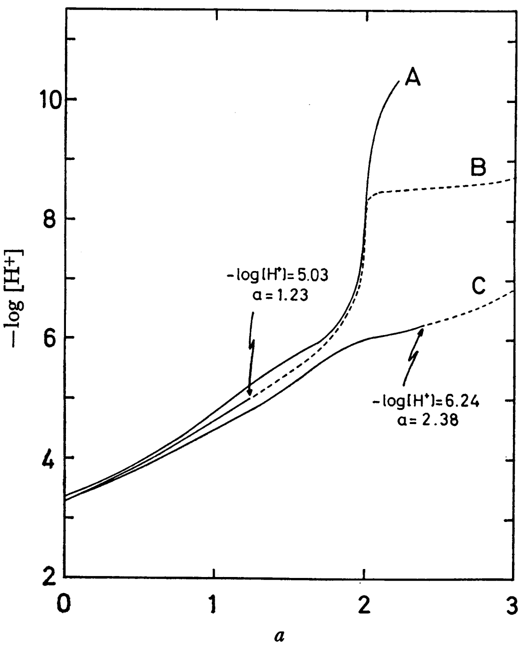


Fig. 6. Titration curves for 3-pyridyl phosphate—bivalent metal systems at 25.0°C, $\mu=0.10$ (KNO_3), and $T_M/T_L=1.0$: A, ligand alone; B, Ni(II) system; C, Cu(II) system; initial concentration of ligand (T_L), 2.00×10^{-3}M, a=moles of base added per mole of ligand. Arrows indicate the region where pH-reading starts to become unstable on standing.

clue to understanding the catalytic mechanism in the hydrolysis of organic phosphates and to examine a correlation between the catalytic efficiency and the complex-forming tendency of metal ions with the phosphates, we have carried out potentiometric measurements of these chelate systems, in which copper(II), nickel(II), and thorium(IV) ions were included, in aqueous media at 25°C and $\mu=0.1$ (KNO_3). An attempt was made to carry out some quantitative measurements and analysis for the thorium chelate system. This was not successful, however, due to the markedly rapid hydrolysis even in a temperature range as low as 10°C. The titration curves for 8-quinolyl phosphate with copper(II) and nickel(II) are shown in Fig. 5, and for 3-pyridyl phosphate with the same metal ions in Fig. 6. Solution equilibria were attained shortly after addition of base in a relatively low a-region (a being the degree of neutralization of the ligand). Beyond a certain a-value for each titration of the chelate systems, pH-reading became unsteady on standing probably because of the hydrolytic tendencies of the metal ions. These non-equilibrated regions are shown in Figs. 5 and 6 by broken lines. The nickel ion obviously exhibited lower complex-forming ability toward the phosphates than the copper ion. The difference is apparent for the 8-quinolyl phosphate systems in particular. The formation of the copper complex is already appreciable in a region below $a=1.0$ while that of the nickel complex is not significant. Stability constants for metal complexes of a 1:1 ratio of ligand to metal and for the corresponding protonated complexes were calculated by means of the computational method described in the preceding section: the results are summarized in Table 4.

TABLE 4. STABILITY CONSTANTS OF METAL COMPLEXES OF SOME HETERO-AROMATIC PHOSPHATES AT 25±0.1°C AND $\mu=0.1$ (KNO_3)[a)]

Metal ion	Log K_1[b)]	Log K_{MHL}[c)]	U[d)]
2-Pyridylmethyl phosphate[e)]			
	$pK_{H_3L}=1.8$	$pK_{H_2L}=4.42$	$pK_{HL}=6.30$
Cu(II)	4.44	2.23	0.1537×10^{-7}
Ni(II)	2.85	1.06	—
3-Pyridyl phosphate			
	$pK_{H_3L}=1.0$	$pK_{H_2L}=3.86$	$pK_{HL}=5.64$
Cu(II)	3.27	2.00	0.1042×10^{-4}
Ni(II)	1.93	1.99	0.2687×10^{-3}
8-Quinolyl phosphate			
	$pK_{H_3L}=1.0$	$pK_{H_2L}=4.17$	$pK_{HL}=6.42$
Cu(II)	5.29	2.43	0.7951×10^{-5}

a) Calculated from the titration data of a 1:1 molar ratio of ligand-metal.

b) $K_1=[ML]/[M^{2+}][L^{2-}]$.

c) $K_{MHL}=[MHL^+]/[M^{2+}][HL^-]$.

d) A residual sum of squares in the computational procedure; see text.

e) Previously reported.[6)]

Discussion

Bivalent Metal Catalysis. In earlier papers, the effects of various metal ions on the hydrolysis of pyridylmethyl phosphates[2,3)] and of salicyl phosphate[9,10)] have been reported. Catalytic mechanism and efficiency for these hydrolysis reactions have been discussed from the viewpoint of complex-forming ability of metal ions at various stages of the reaction process.[2–4)] 8-Quinolyl phosphate has a structural similarity to 2-pyridylmethyl phosphate although the former has a more rigid structure due to the presence of fused rings. Therefore, a comparison of the catalytic efficiency of metal ions in these phosphate hydrolyses is particularly interesting.

For the hydrolysis of 2-pyridylmethyl phosphate, only the copper ion was significantly effective among various bivalent metal ions.[2)] The hydrolysis of 8-quinolyl phosphate was promoted appreciably with copper(II), but not at all with nickel(II), as shown in Tables 1 and 2. On the other hand, both metal ions were almost ineffective in the hydrolysis of 3-pyridyl phosphate as can be seen in Tables 1 and 3. Stability order among the copper complexes formed with the above three phosphates is in the following sequence (log K_1) with respect to the ligands: 8-quinolyl phosphate>2-pyridylmethyl phosphate>3-pyridyl phosphate. The former two phosphates appear to form a chelate ring for which the hetero-aromatic nitrogen and the terminal phosphate-oxygen act as donor atoms, judging from the magnitude of stability constants for 1:1 complexes.[6)] The catalytic efficiency of copper(II) in terms of k_c/k_o, where k_c and k_o refer, respectively, to the overall rate constant for metal-ion-catalyzed hydrolysis and that for the spontaneous reaction, follows the sequence with respect to the phosphates: 8-quinolyl phosphate ($k_c/k_o=8.4\times10^2$; 40°C $-\log[H^+]=3.56$)>2-pyridylmethyl phosphate (1.65; 90°C, 3.67)> 3-pyridylmethyl phosphate (0.96; 90°C, 3.49)~4-pyridylmethyl phosphate (1.07; 90°C, 3.59)~3-pyridyl phosphate (1.11; 70°C, 3.82). The latter three phosphates can not form a chelate ring with a metal ion but rather act as unidentate ligands, due to their structural nature. In order to clarify the correlation between the catalytic efficiency and the initial formation of metal chelate species with the substrate, the concentrations of metal species involved in the copper chelate systems, the free metal ion (M^{2+}), the 1:1 complex (ML), and its protonated complex ($M(HL)^+$), were

TABLE 5. CORRELATION BETWEEN CATALYTIC EFFICIENCY AND COMPLEX-FORMATION[a)]

$-\log[H^+]$	$[M^{2+}]$, M	[ML], M	$[M(HL)^+]$, M	k_c/k_o (Temp., °C)
8-Quinolyl phosphate-Cu(II) (1:1)				
2.03	0.1982×10^{-2}	0.2051×10^{-6}	0.1734×10^{-4}	2.42 (80)
2.92	0.1934×10^{-2}	0.1213×10^{-4}	0.5337×10^{-4}	6.16×10 (40)
3.85	0.1456×10^{-2}	0.3587×10^{-3}	0.1856×10^{-3}	1.62×10^3 (30)
2-Pyridylmethyl phosphate-Cu(II) (1:1)				
3.76	0.1849×10^{-2}	0.4844×10^{-4}	0.1025×10^{-3}	1.65 (90)
4.36	0.1497×10^{-2}	0.3287×10^{-3}	0.1746×10^{-3}	1.1×10 (90)
3-Pyridyl phosphate-Cu(II) (1:1)				
2.03	0.1995×10^{-2}	0.2435×10^{-7}	0.5289×10^{-5}	0.94 (70)
3.45	0.1889×10^{-2}	0.1200×10^{-4}	0.9913×10^{-4}	0.99 (70)
4.07	0.1728×10^{-2}	0.9132×10^{-4}	0.1809×10^{-3}	1.21 (70)

a) Calculated from the acid dissociation constants of ligands and the stability constants given in Table 4; $T_M=T_L=2.0\times10^{-3}$M.

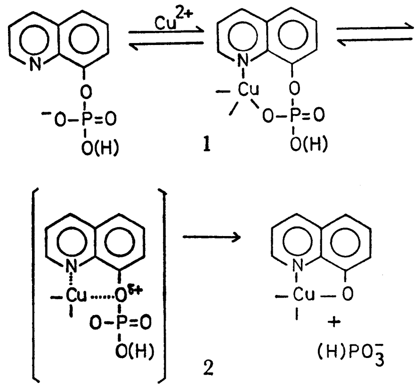
---

9) R. Hofstetter, Y. Murakami, G. Mont, and A. E. Martell, *J. Amer. Chem. Soc.*, **84**, 3041 (1962).

10) Y. Murakami and A. E. Martell, *J. Phys. Chem.*, **67**, 582 (1963).

calculated for the systems of 8-quinolyl, 2-pyridylmethyl, and 3-pyridyl phosphates from the data given in Table. 4. The results for the limited pH range of present interest are listed in Table 5. It is apparent that the catalytic efficiency is sensitively affected by the formation of chelate species, ML and $M(HL)^+$. With the increase of concentrations of these chelate species, a significant rate enhancement was observed accordingly for the hydrolyses of 8-quinolyl and 2-pyridylmethyl phosphates. On the other hand, 3-pyridyl phosphate does not secure a catalytic efficiency of similar trend in its hydrolysis due to the lack of chelate-ring formation. The hydrolysis of salicyl phosphate was accelerated by the presence of copper(II) as investigated previously.[10] Since this phosphate was found to form a 1:1 chelate with copper(II) (log $K_1=3.64$ at 10.0°C and $\mu=0.10$), the catalytic mechanism was considered to start with the initial formation of such a complex followed by the intramolecular rearrangement to form a chelate ring with the ester oxygen and the carboxylate group as donor groups in the transition state.[4] On the other hand, the potentiometric study on the interaction of nickel(II) with the present phosphates indicated that this metal ion does not form complexes to any detectable extent in a relatively low pH region. The difference between copper(II) and nickel(II) in such interaction is more apparent with 8-quinolyl phosphate. This is quite consistent with the inert character of nickel(II) for the hydrolysis of the phosphates.

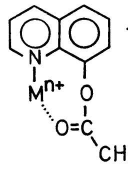
Judging from the results obtained for the bivalent metal catalysis, the following interaction is required at the initial stage of reaction to secure an effective catalytic action of metal ions in the hydrolysis. An organic phosphate must demonstrate a significant chelate-forming tendency toward a metal ion at the initial stage. In order to make this interaction possible, a phosphate molecule must possess at least one more functional group besides the phosphate moiety, which shows a satisfactory donating affinity for a metal ion. In the present case, a hetero-aromatic nitrogen atom is considered to be such an extra donor goup. Both the phosphate group and another functional group must be situated in a molecule, so that a chelate formation becomes favored. The nitrogen atom in 3-pyridyl phosphate is not suitably oriented for chelation with a metal ion in conjunction with the phosphate moiety, while that in 8-quinolyl phosphate is placed in a desired manner. Meanwhile, in the course of such a chelate-forming interaction the copper ion demonstrated enough coordination affinity for the nitrogen atom to secure an effective catalytic action. The nickel ion, however, does not seem to have a satisfactory affinity for the nitrogen atom as the stability data indicate. We thus invoke to postulate the reaction mechanism shown in Scheme 2 for an elucidation of significant catalytic effect of copper(II) on the hydrolysis of 8-quinolyl phosphate. This mechanism has a close similarity to that for the hydrolysis of 2-pyridylmethyl phosphate,[2] although the copper ion appears to be less active in the latter reaction.



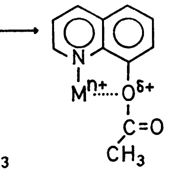
Scheme 2

The mechanism is also understood as an analogy to the intramolecular proton transfer mechanism in the corresponding spontaneous hydrolysis,[1c,2] since an effective metal ion for this type of reaction in general tends to act as a pseudo-proton. Chelate formation would consequently require participation of the nitrogen atom in a manner as shown by **1** and **2** (Scheme 2). If the role of a metal ion is only to neutralize the charge of the substrate as postulated for the magnesium-catalyzed hydrolysis of acyl phosphate,[11] the nitrogen atom would not necessarily be required to participate in coordination with a metal ion. As to the ground state in the copper-catalyzed hydrolysis of 8-quinolyl phosphate, the formation of the initial intermediate **1** is of no doubt judging from the relatively large stability constants listed in Table 4. Although the activation energy for the copper-catalyzed hydrolysis of 8-quinolyl phosphate is negligibly small relative to that for the spontaneous reaction as can be seen in Fig. 1, we can not eliminate the initial process of complex formation prior to the transition state for hydrolysis. Furthermore, a large negative value of apparent activation entropy ($\Delta S^{\ddagger}_{\mathrm{Cu}}=-67$ e.u. at 80°C and $-\log[H^+]=2.01 \pm 0.02$) was obtained for the copper-catalyzed reaction of 8-quinolyl phosphate. This suggests that the activated complex formed in the transition state becomes considerably rigid due to the presence of the metal ion.

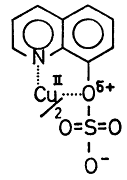
A similar mechanistic elucidation has been proposed to account for the copper-catalyzed hydrolysis of 8-actoxyquinoline;[12] the formation of an activated complex, either **3** or **4**, was suggested. With reference to our studies on the phosphate hydrolysis, we rather suggest that the weak interaction forming complex **3** at the initial stage is followed by the formation of complex **4** in the transition state. Hay and Edmonds[13]



3



4



5

---

[11] C. H. Oestreich and M. M. Jones, *Biochem.*, **6**, 1515 (1967).

[12] R. H. Barca and H. Freiser, *J. Amer. Chem. Soc.*, **88**, 3744 (1966).

[13] R. W. Hay and J. A. G. Edmonds, *J. Chem. Soc., D*, **1967**, 969.

reported that the hydrolysis of 8-hydroxyquinoline sulfate was accelerated by copper(II). They suggested the formation of complex **5** as an activated intermediate.

In case of the catalytic hydrolysis of 2-pyridylmethyl phosphate, the alcohol product (2-pyridylmethanol) forms the stable complexes only with copper(II), among various bivalent ions, upon liberation of the alcohol-proton at 1:1 and 2:1 molar ratios of ligand to metal ion;[14] thus, the copper ion has a profound affinity for the alcohol-oxygen of 2-pyridylmethanol. In the present work, 8-quinolinol, the hydrolysis product of 8-quinolyl phosphate, yields quite stable complexes with copper(II) and nickel(II): log K_1=13.49 for the copper complex and log K_1=11.44 for the nickel complex at 25°C in 50% aqueous dioxane.[15] Therefore, an affinity of these metal ions for the leaving alcohol group does not primarily control the catalytic efficiency in this instance. Rather, interaction of these metal ions with the substrate at the initial stage through pre-equilibrated complex-formation appears to be the necessary cause of the catalysis.

Thorium(IV) Catalysis. Since the extent of catalytic efficiency does not show large structural dependency, as was the case in the hydrolysis of pyridylmethyl phosphates,[3] the catalytic action must involve primarily the interaction between the thorium ion and the phosphate moiety of the substrate. The hydrolysis rate tends to level off after a while as shown in Figs. 3 and 4. Since addition of the alcohols did not result in any significant change in hydrolysis rate as mentioned in the preceding section, the rate retardation does not appear to be due to the produced alcohol but to the liberated inorganic phosphate. Judging from the relatively large stability constants for the thorium complexes formed with inorganic phosphate,[16] the potent interaction of thorium(IV) with the phosphate moiety at the initial stage of reaction and with the liberated inorganic phosphate in hydrolysis is to be expected. We observed the slow but appreciable liberation of proton at the initial stage. This finding definitely indicates the formation of certain thorium complexes in the early stage of reaction.

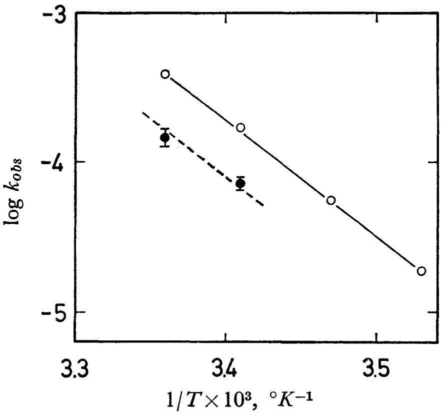


Fig. 7. Arrhenius plots of the apparent first-order reaction rates evaluated at the initial stage for the thorium(IV)-catalyzed hydrolysis of 3-pyridyl phosphate (○) and 8-quinolyl phosphate (●); rate constant (k_{obs}) in sec^{-1}.

Figure 7 shows the temperature dependence of an overall rate constant for the hydrolysis of 3-pyridyl phosphate in the presence of thorium(IV) at $-\log[H^+]=2.0$.[17] An apparent activation energy graphically estimated was 40 cal mol^{-1}. The hydrolysis reaction appears to be almost entirely due to the thorium-ion catalysis, since the spontaneous hydrolysis does not proceed to any detectable extent under these experimental conditions. This activation energy is almost in the same order of magnitude as that for the copper-catalyzed reaction described above. Therefore, a similar mechanistic elucidation may be applied to both cases: the hydrolysis reaction needs to pass through potential energy maxima forming two kinds of reaction intermediates as shown in Fig. 8.

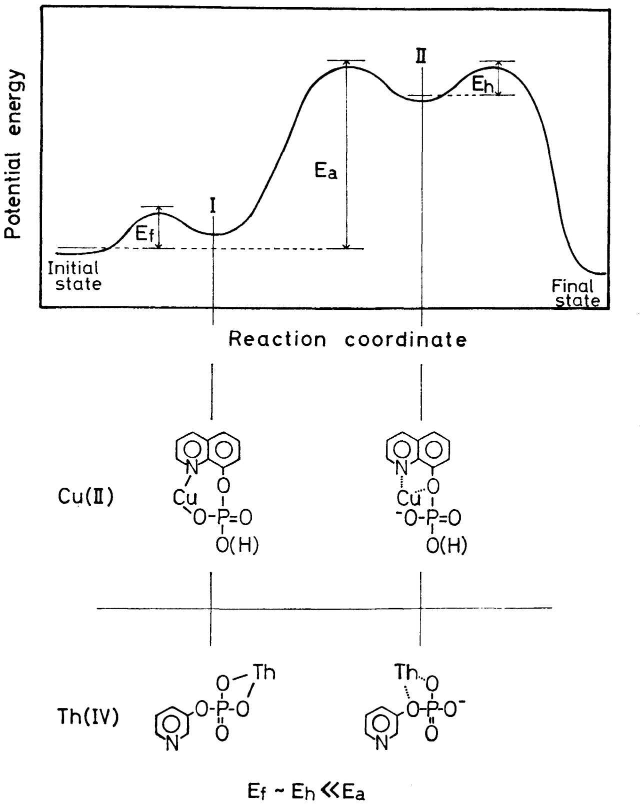


Fig. 8. Schematic representation of reaction mechanisms in terms of potential energy *vs.* reaction coordinate correlation.

In conclusion, the chelate-forming ability is the most important factor for the catalytic efficiency of bivalent metal ions, but this is not necessarily required for the thorium ion. Judging from the relatively large stability constants for the thorium(IV) complexes formed with inorganic phosphate, complex formation with the phosphate moiety is most likely the necessary cause for the catalysis. This interaction would provide effective charge neutralization for the substrate.

---

[14] Y. Murakami and M. Takagi, This Bulletin, **38**, 828 (1965).

[15] W. D. Johnston and H. Freiser, *J. Amer. Chem. Soc.*, **74**, 5239 (1952).

[16] L. G. Sillén and A. E. Martell, "Stability Constants of Metal-Ion Complexes," Special Publication No. 17, The Chemical Society, London (1964).

[17] When the deviation from the first-order plot was observed, the apparent first-order rate constant was evaluated from the initial part of reaction.