parameters of each path; furthermore, the experimental Arrhenius plot for OD + DCOOD can be reproduced by applying kinetic isotope effects of about 2 and 9 at 298 K to the C–H abstraction and addition paths, respectively. These kinetic isotope effects are reasonable, as discussed below.

The positive Arrhenius activation energy and lower values of k_M (relative to OH + HCOOH) for the OD + DCOOD reaction can be interpreted in terms of the relative difference in isotope effects for the addition path (i.e., the equilibrium constant k_{6a}/k_{6-a} and the rate constant k_{6b}) and the direct abstraction path involving the formyl group. The equilibrium constant for adduct formation, k_{6a}/k_{6-a}, would be expected to be smaller for the deuteriated formic acid by analogy with the equilibrium constants for the dissociation of hydrogen bonded dimers of the acids in Table I. Also, because the acidic O–H bond is broken in the adduct to form H_2O, k_{6b} is expected to have a kinetic isotope effect. The multiplicative effect of the two steps would therefore likely result in the addition path having a greater kinetic isotope effect than the C–H abstraction path. As a result, direct abstraction of hydrogen from the formyl group would be relatively more important for the OD + DCOOD reaction than for the OH + HCOOH reaction, thus accounting for the positive activation energy for OD + DCOOD. This mechanism would predict that k_D/k_M would be greater for DCOOD than for HCOOH. Although our room-temperature results appear consistent with this prediction, the errors in the k_D values are too large to allow a definite conclusion. Also, tunneling effects could contribute to the observed difference in the temperature dependence of the rate constants for HCOOH and DCOOD if tunneling were more important in reaction 6b than in the abstraction from the formyl group.

In the discussion of isotope effects, we assume that the rate constants for the direct abstraction reactions of OH and OD with formic acid would be essentially the same. This is a reasonable assumption because it has been shown in previous work that OH and OD radicals do not have a significant isotope effect in the direct abstraction reactions with alkanes.[26] However, an isotope effect for OH and OD radicals would be expected for the proposed reaction path involving a hydrogen-bonded adduct. It will be difficult to determine experimentally such an isotope effect because of the ease of isotopic scrambling between the source of the hydroxyl radical and the acidic hydrogen of formic acid.

Fluorine atoms, which are isoelectronic with OH, also react with HCOOH by two paths. Macdonald and Sloan[31] found that, under their conditions, abstraction by F of the acidic hydrogen is favored by a 2:1 margin over the formyl hydrogen. Furthermore, the distribution of energy in the HF product indicated that the reaction at the acidic site involves a long-lived complex, whereas direct abstraction occurs at the formyl group.

Further experiments with other acids with varying strengths of C–H and O–H bonds may help to clarify the mechanism further. More important however would be theoretical calculations of the structures of the adducts and the potential energies of the reaction channels.

Acknowledgment. We thank Dr. J. L. Hencher for providing calculated values of vibrational frequencies and rotational constants for the deuteriated formic acids, Dr. S. K. Brownstein for the NMR analyses, and Dr. M. J. Kurylo for a preprint of ref 25.

Supplementary Material Available: Table S1 of vibrational frequencies and rotational constants used to calculate the dimerization equilibrium constants of formic acid and its deuteriated analogues and Table S2 of measured first-order decay rates at each temperature for the reaction of OH with formic acid and OD with formic-d_1 acid-d_1 (6 pages). Ordering information is given on any current masthead page.

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Divalent Metal Ion Catalysis in the Hydrolysis of Phosphomonoesters. Hydrolysis of 2-(1,10-Phenanthrolyl) Phosphate

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Abstract: Rate constants have been determined for hydrolysis of 2-(1,10-phenanthrolyl) phosphate in water at 85 °C and $\mu = 0.1$ M with KCl. The plot of k_{obsd} vs pH is bell-shaped, which shows that the monoanion and the neutral species are the maximally reactive species. Divalent metal ions (Cu^{2+}, Ni^{2+}, Co^{2+}, and Zn^{2+}) exert a pronounced catalytic effect on the hydrolysis reaction of the phosphate dianion species (a dianion reaction cannot be observed in the absence of metal ion). The Cu(II) complex of the 2-(1,10-phenanthrolyl) phosphate dianion hydrolyzes at 40 °C more than 10^8-fold faster than the phenyl phosphate dianion and 60 000-fold faster than *p*-nitrophenyl phosphate dianion. Binding of the metal ions produces an absorbance change near 270 nm, as is the case with 1,10-phenanthroline, and the measured rate constants for metal ion binding are also similar to those of 1,10-phenanthroline. Thus, the metal ions are chelating the phenanthroline nitrogens. Binding of the metal ions is very strong; saturation effects occur at low metal ion concentration (<0.005 M). The plots of k_{obsd} vs pH in the hydrolytic reactions are then pH independent at pH >6. The value of ΔS^* for the pH-independent reaction at pH >6 in the presence of a saturating concentration of Cu^{2+} is −46.8 eu, but ΔH^* is only 8 kcal/mol. The reaction very likely involves nucleophilic attack of H_2O on phosphorus or a kinetic equivalent. There is an accelerating effect of pyridine and imidazole in the reaction of the Ni(II) complex of the 2-(1,10-phenanthrolyl) phosphate dianion. This reaction is highly dependent on the presence of the metal ion; catalysis could not be detected in the absence of metal ion. A metal ion will not favorably chelate the leaving-group oxygen of 2-(1,10-phenanthrolyl) phosphate in a 1:1 complex because of the steric situation; complexation of the other phosphate oxygens will retard the metaphosphate elimination but will enhance nucleophilic attack at phosphorus. Thus, a strongly bound metal ion will produce large rate enhancements in the hydrolysis reactions of such phosphomonoesters and can lead to catalytic processes that proceed most likely by nucleophilic pathways.

Phosphate esters are among the most important of biologically active compounds.[2] There has been considerable effort made to understand the chemistry of their hydrolytic reactions.[3] Phosphomonoesters, e.g., methyl phosphate, exhibit bell-shaped plots

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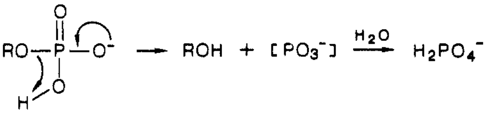
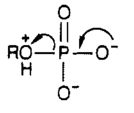
of k_{obsd} vs pH, which indicate that the monoanionic species is maximally reactive.[4] The most likely mechanism for the monoanion reaction was considered to be a unimolecular decomposition to a hypothetical metaphosphate intermediate[4] (eq 1), which



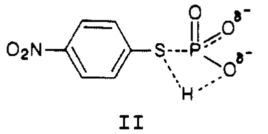
$$\mathrm{RO{-}P(O)(O^-){-}OH} \longrightarrow \mathrm{ROH} + [\mathrm{PO_3^-}] \xrightarrow{H_2O} \mathrm{H_2PO_4^-} \qquad (1)$$

could be assisted by internal proton transfer to the leaving group. Kirby and Varvoglis[5] suggested that phosphomonoester monoanions with aliphatic alcohol leaving groups break down via the kinetically equivalent zwitterion (I). It was further considered



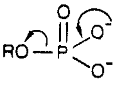
I

that with very good leaving groups, e.g., dinitrophenol, proton transfer would occur in the transition state. Proton transfer to sulfur in the transition state for decomposition of *S*-phenyl phosphorothioate ester monoanions (II) was indicated by the magnitude of the D_2O solvent isotope effect.[6] Phosphomonoester



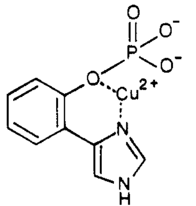
II

dianions hydrolyze much more slowly than the corresponding monoanions[3-6] (except in cases where the leaving group is very good),[5,6] and the dianion reactions are highly dependent upon the basicity of the leaving group ($\beta_{lg} = -1.2$).[5] This should be the case if the dianion reactions also involve elimination to metaphosphate (III). However, there is no evidence that free metaphosphate is formed in aqueous solution.[7-9] Metaphosphate would be expected to be a very unstable species, and therefore, the hydrolysis reaction might be facilitated by attack of H_2O or other nucleophiles on phosphorus if such attack were catalyzed by general acids or metal ions.

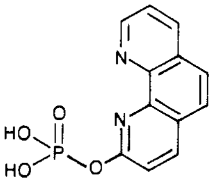


III

Many of the enzymes that catalyze the hydrolysis of phosphomonoesters or phosphoryl group transfer reactions are metalloenzymes or metal ion activated enzymes.[10-12] For example, alkaline phosphatase requires the presence of a Zn^{2+} ion,[11] and kinase enzymes usually require Mg^{2+} or Mn^{2+}.[12] The role of the metal ion in these reactions is not well understood, although various suggestions have been put forth.[10-13] There have been surprisingly few studies of divalent metal ion catalysis in the reactions of phosphomonoesters.[14-19] The catalysis by metal ions in these reactions has been ascribed to screening of the negative charges and a template effect[16] or assistance of leaving group departure.[10] In the hydrolysis of salicyl phosphate[14] the presence of the neighboring carboxyl group gives rise to several kinetically equivalent species, but the metal ion should be in an excellent position to bind to the leaving group. Likewise, in the hydrolysis of 8-quinolyl phosphate metal ion coordination of the leaving-group oxygen could be an important factor.[18] Benkovic and Dunikoski[15] have suggested that Cu^{2+} catalyzes the hydrolysis of (*o*-imidazol-4-ylphenyl) phosphate dianion (IV) by binding to the leaving-group oxygen, i.e., the metal ion functions in the same manner as a proton in the monoanion reaction. Binding of the metal ion to the leaving-group oxygen will enhance metaphosphate elimination, whereas coordination of the other phosphate oxygens should inhibit the dissociative process and enhance associative mechanisms, e.g., nucleophilic attack at phosphorus by water or other nucleophiles. However, there have been no previous detailed studies of systems in which metal ion binding is strong due to a chelating functional group in the molecule but where coordination of the leaving-group oxygen would be unfavorable. To gain insight into the chemistry of metal ion catalyzed hydrolysis reactions of phosphomonoesters we have in the present work studied the hydrolysis of 2-(1,10-phenanthrolyl) phosphate (V). With this ester a metal ion is very strongly chelated to the phenanthroline nitrogens, and binding to the leaving oxygen group in a 1:1 complex is sterically quite difficult because a four-membered chelate ring would be required. We have found that divalent metal ions exert a pronounced catalysis in the hydrolysis of the dianionic species of V, very likely through promotion of a water reaction.



IV



V

Experimental Section

Materials. 2-(1,10-Phenanthrolyl) phosphate was prepared from 1,10-phenanthroline in a six-step synthesis:

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(1) 1,10-Phenanthroline methiodide was prepared by the method reported by Halcrow and Kermack.[20] The compound was twice recrystallized from ethanol and melted at 212 °C (lit.[20] mp 210–213 °C).

(2) 1-Methyl-2-*o*-phenanthrolone was prepared by a modification of the published method of Halcrow and Kermack.[20] The reaction was carried out at 0–5 °C (in an ice bath). 1,10-Phenanthroline methiodide (7 g) was suspended in a three-necked flask in 100 mL of water and was continuously stirred. Potassium ferricyanide (4.5 g) and 2 g of NaOH were dissolved separately in water and were cooled to 0 °C. Both of the concentrated solutions were added to the methiodide solution slowly so that all of the NaOH solution was introduced before half of the potassium ferricyanide solution was added. The rest of the potassium ferricyanide solution was added very slowly, and the mixture was stirred overnight at room temperature. The water was removed by rotary evaporation at reduced pressure, and the residue was then refluxed in dry benzene. The desired compound was obtained after rotary evaporation of the benzene. The brown solid thus obtained was recrystallized from benzene and then from ethanol/water. The compound had a mp 122 °C (lit.[20] mp 123–124 °C).

(3) 2-Chloro-1,10-phenanthroline was prepared from the 1-methyl-2-*o*-phenanthrolone by the method of Halcrow and Kermack.[20] The product was recrystallized three times from hot water as colorless needles, mp 130 °C (lit.[20] mp 129–130 °C).

(4) A mixture of 2-chloro-1,10-phenanthroline (1.5 g), phenol (2.2 g), and 0.8 g of NaOH was heated at 100 °C for 2 days. (Note: Heating the mixture above 110 °C led to decomposition.) Then 18 mL of 20% NaOH was added, and the solution was again refluxed for at least 2 h. The mixture was cooled to room temperature. The crystallized 2-phenoxy-1,10-phenanthroline was obtained by filtration and was twice recrystallized from ethanol/ether. The compound melted sharply at 160 °C (lit.[21] mp 160–161 °C).

(5) A solution of 1.5 g of 2-phenoxy-1,10-phenanthroline in 30 mL of 50% hydroiodic acid was refluxed overnight. The solution was cooled and then neutralized with 20% NaOH to pH 7. 2-Hydroxy-1,10-phenanthroline precipitated and was recrystallized from benzene/ethanol. The compound melted at 159–160 °C (lit.[22] mp 159–160 °C).

(6) Freshly prepared 2-hydroxy-1,10-phenanthroline (1 g, 0.005 mol) was dissolved in 10 mL of $POCl_3$ in the presence of 0.5 g of calcium carbonate. The mixture was refluxed for 4 h and was then quickly filtered while hot. The excess $POCl_3$ was removed by vacuum distillation. The thick brown oil thus obtained was extracted with 100 mL of dry acetone, and 100 mL of benzene was added. The solution was cooled in an ice/salt bath at 0 °C, and 5 mL of water was very slowly added dropwise with stirring over a period of 1 h. The solution was neutralized with NaOH, 100 mL of additional benzene was added, and the solution was allowed to stand overnight at room temperature in the dark. The precipitate thus obtained was dried in vacuo. The material was recrystallized from a solution containing 10 mL of acetone, 1 mL of water, and 50 mL of benzene. Small needles were obtained with mp 166 °C. Anal. Calcd for $C_{12}H_9N_2O_4P$: C, 52.19; H, 3.28; N, 10.14. Found: C, 52.43; H, 3.19; N, 10.01.

Kinetic Methods. The rates of hydrolysis of 2-(1,10-phenanthrolyl) phosphate were measured spectrophotometrically with a Pye-Unicam SP8-100 recording spectrophotometer by following the absorbance increase at 320 nm due to the appearance of the product (2-hydroxy-1,10-phenanthroline or its metal ion complex). There was a sharp isosbestic point when repetitive scans were taken at various times during the hydrolytic reaction. For example, in the presence of a saturating concentration of Cu^{2+} at 30 °C (pH 5.0) there is an isosbestic point at 274 nm. Stock solutions were 4×10^{-3} M in ethanol. To initiate a kinetic run, 20 μL of the stock solution was injected into 3 mL of the reaction solution maintained at the desired temperature. The reactions followed good pseudo-first-order kinetics for at least 4 half-lives. The values of k_{obsd}, the pseudo-first-order rate constant, were calculated with a least-squares computer program. Reaction mixture pH values were measured with a Beckman Model 3500 pH meter.

The ionic strength was 0.1 M, maintained with KCl, and the solutions used for the studies in the absence of metal ion contained 2×10^{-5} M EDTA as a precaution against trace metal ion in the buffer or salt. No corrections were made for buffer-metal ion complexation. In the pH range 1–3, HCl solutions were employed. The buffers employed in kinetic studies were formate (pH 3.2–4.5), acetate (pH 4.2–5.3), pyridine (pH 4.0–5.5), cacodylate (pH 5.5–6.5), 2,6-lutidine (pH 5.2–6.5), *N*-ethylmorpholine (pH 6.6–8.4), and morpholine (pH 8.0–8.6). The buffer concentration was always 0.02 M. Such low concentrations of buffer do not have an experimentally significant catalytic effect on the observed reactions (except with acetate).

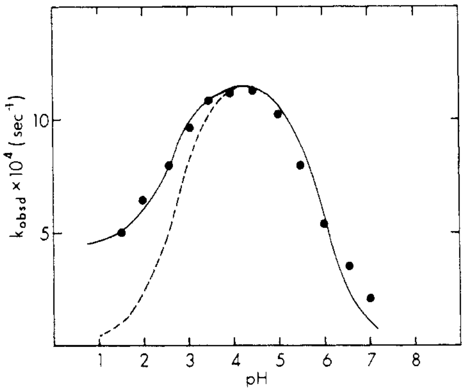


Figure 1. Plot of k_{obsd} vs pH for hydrolysis of 2-(1,10-phenanthrolyl) phosphate in H_2O at 85 °C, μ = 0.1 M with KCl.

Complexation reactions of the metal ions with V were followed with a Durrum D110 stopped-flow spectrophotometer. The absorbance changes at 270 nm after the rapid mixing of the substrate in 0.1 M KCl solution with the buffer (μ = 0.1 M) containing the appropriate metal ion were recorded on a Hewlett Packard storage oscilloscope (Model 1207B).

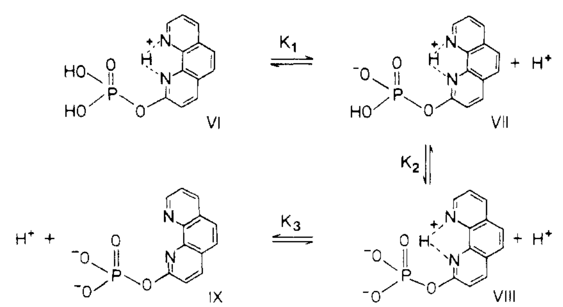
Titration of 2-(1,10-Phenanthrolyl) Phosphate. A solution (25 mL) of 3.30×10^{-3} M 2-(1,10-phenanthrolyl) phosphate was titrated with 3.51×10^{-2} M NaOH solution at 30 °C. Both of the solutions were 0.1 M in KCl. The solution containing the phosphate ester was first adjusted to pH 2.2 with HCl. A blank titration vs HCl was also carried out. The titrations were conducted with a Beckman 3500 pH meter and a combination glass electrode. Nitrogen was continuously passed through the solution containing the phosphate ester. Two distinct pK_a's were found in the pH range 2–11. The value of p$K_{a,1}$ is 2.9 while that of p$K_{a,2}$ is 6.0. A spectrophotometric titration at 30 °C and 275 nm indicated a pK_a of 5.9.

Results

In Figure 1 is shown a plot of k_{obsd} vs pH for hydrolysis of 2-(1,10-phenanthrolyl) phosphate at 85 °C and μ = 0.1 M with KCl. The plot is bell-shaped with a maximum at pH ~4.5. The dashed line in Figure 1 shows the pH dependence of k_{obsd} if only the monoanionic species were reactive ($k_M = 1.2 \times 10^{-3}$ s^{-1}), whereas the solid line is that for reaction of both the monoanion and the neutral species ($k_N = 4.5 \times 10^{-4}$ s^{-1}). The theoretical plot was constructed from eq 2 employing the above rate constants

$$k_{obsd} = \frac{k_N K_1 a_H^2 + k_M K_1 K_2 a_H}{a_H^3 + K_1 a_H^2 + K_1 K_2 a_H + K_1 K_2 K_3} \tag{2}$$

for the two species and the appropriate pK_a values. The equilibria involved are shown in eq 3. There are two kinetically equivalent



(3)

neutral species (presented in eq 4) and also two kinetically equivalent monoanions (VIII and X; eq 5) plus other less stable species in which there is a proton on the leaving-group oxygen. Titration of the ester at 30 °C with NaOH in the pH range 2–11 showed two well-defined pK_a values of 2.9 and 6.0. These values are very likely the pK_a's of the neutral (zwitterionic) and the monoanion species, respectively. The first pK_a (for the protonated species) must be less than 2. This is reasonable considering that a positive charge in the molecule will have a large acid-strengthening effect. The experimental values of k_{obsd} give a good

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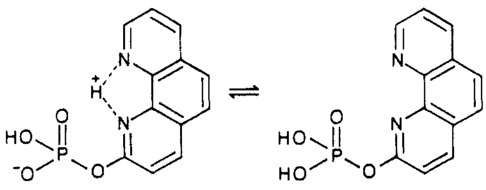
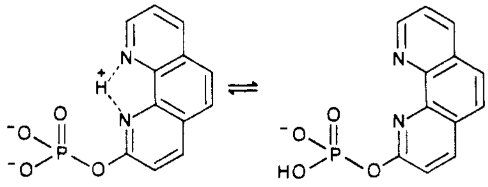


(4)

VII



(5)

VIII X

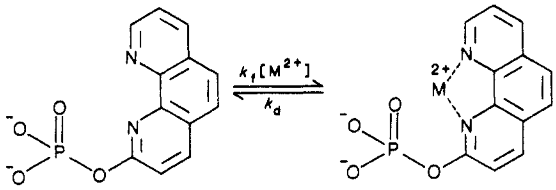
fit to eq 6, which follows from eq 2 assuming that $K_1 > a_H$. The

$$k_{\mathrm{obsd}} = \frac{k_N a_H^2 + k_M K_2 a_H}{a_H^2 + K_2 a_H + K_2 K_3} \qquad (6)$$

decrease in k_{obsd} for the hydrolysis of 2-(1,10-phenanthrolyl) phosphate at pH >6 shows that the dianionic species (IX) is relatively unreactive. In fact, a hydrolytic reaction at pH 8 (85 °C) was too slow to measure accurately.

The divalent metal ions Cu^{2+}, Ni^{2+}, Co^{2+}, and Zn^{2+} exert a significant catalytic effect in the hydrolysis of 2-(1,10-phenanthrolyl) phosphate. The binding of the metal ions is very strong. Plots of k_{obsd} for hydrolysis of V vs the concentration of Cu^{2+} at 30 °C showed that k_{obsd} is independent of metal ion concentration at concentrations greater than 0.001 M. Thus, saturation is achieved at very low metal ion concentration. From the plot of k_{obsd} vs $[Cu^{2+}]$ at 30 °C and pH 3.02 (HCl solution), the metal ion binding constant K_M was calculated to be 3.4×10^5 M^{-1} at that pH, and k_M, the limiting rate constant, is 7×10^{-4} s^{-1}. The K_M is the experimental value and is uncorrected for protonation of the phenanthroline nitrogens. Similar plots were obtained at 85 °C with Ni^{2+}, Co^{2+}, and Zn^{2+} at values greater than pH 5.

Binding of the metal ions to V gives rise to an enhancement in absorbance near 270 nm as previously found with 1,10-phenanthroline.[23,24] The UV–vis spectra of V with and without a saturating concentration of Ni^{2+} are shown in Figure 2. Rate constants for metal ion binding in the process of eq 7 were obtained



(7)

with stopped-flow measurements and are given in Table I. These constants are similar to those obtained for binding to 1,10-phenanthroline.[24] Figure 3 is a plot of k_{obsd} for binding of Co^{2+} to V vs the concentration of Co^{2+}. The intercept represents the rate constant for dissociation of the metal ion complex k_d, and from the slope the rate constant for association k_f can be obtained by means of eq 8, where K_N is the acid dissociation constant of

$$k_{\mathrm{obsd}} = k_d\left(1 + \frac{K_N[M^{2+}]}{K_D[H^+]}\right) \qquad (8)$$

the phenanthroline nitrogen conjugate acid and K_D is the ratio k_d/k_f. Note that the ratio k_f/k_d is the association constant K_M for the metal ion binding. These values are also given in Table I and are uncorrected for preferential binding to a particular species.

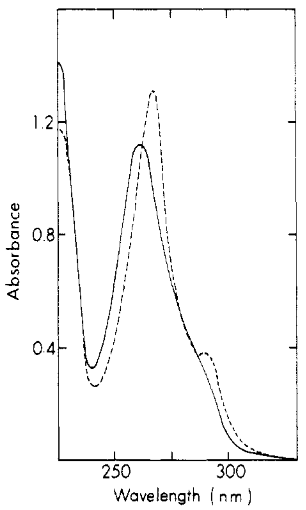


Figure 2. UV spectra of 5×10^{-5} M 2-(1,10-phenanthrolyl) phosphate in H_2O at pH 5.23 and 30 °C (—) and in the presence of 2×10^{-3} M Ni^{2+} (- - -) at 30 °C.

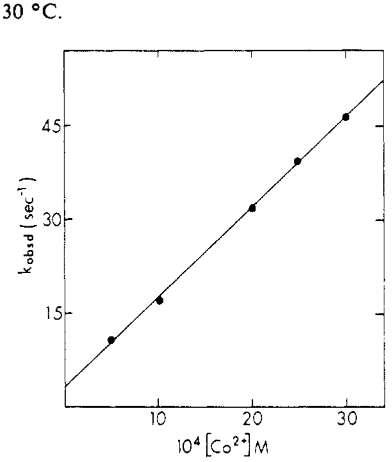


Figure 3. Plot of k_{obsd} vs Co^{2+} concentration for binding of the metal ion to 2-(1,10-phenanthrolyl) phosphate at pH 5.21 and 30 °C, $\mu = 0.1$ M with KCl.

Table I. Rate Constants for Complexation of Metal Ions with 2-(1,10-Phenanthrolyl) Phosphate at 30 °C and $\mu = 0.1$ M (KCl)

pH	metal ion	$10^4[M^{2+}]$, M	k_{obsd}, s^{-1}	k_f, $M^{-1}\ s^{-1}$	k_d, s^{-1}	K_M, M^{-1}
5.21	Ni^{2+}	5	0.27	2500	0.07	3.5×10^4
		10	0.46			
		20	0.87			
		25	1.06			
		30	1.25			
5.21	Co^{2+}	5	10.88	8.9×10^4	3.1	2.9×10^4
		10	17.03			
		20	31.82			
		25	39.26			
		30	46.61			
2.72	Zn^{2+}	5	2.42	7.0×10^6	0.7	1.0×10^7
		10	4.07			
		15	5.91			
		20	7.16			
		30	10.61			

The plot of k_{obsd} for hydrolysis of V at 30 °C vs pH in the presence of a saturating concentration of Cu^{2+} (2×10^{-3} M) is presented in Figure 4. The plot is again bell-shaped as in the absence of metal ions, but in addition there is a pH-independent region at pH >6.5 with $k_{Cu} = 6.5 \times 10^{-4}\ s^{-1}$. Similar pH-independent reactions were observed at pH >4 with Ni^{2+}, Co^{2+}, and Zn^{2+} at 85 °C (Figure 5) with $k_{Ni} = 9.8 \times 10^{-4}\ s^{-1}$, $k_{Co} = 8.5 \times 10^{-4}\ s^{-1}$, and $k_{Zn} = 6.8 \times 10^{-4}\ s^{-1}$. In the plots of Figure 5 Ni^{2+} and Co^{2+} are at saturating concentration only at values greater than pH 4. Acetate buffer (0.02 M) has a small specific enhancing effect on k_{obsd} in comparison with other buffers in reactions of

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(23) Bell, R. S.; Sutin, N. *Inorg. Chem.* **1962**, *1*, 359.

(24) Holyer, R. H.; Hubbard, C. D.; Kettle, S. F. A.; Wilkins, R. G. *Inorg. Chem.* **1965**, *4*, 929.

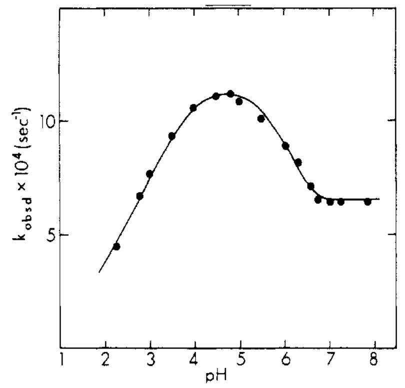


Figure 4. Plot of k_{obsd} vs pH for the hydrolysis of 2-(1,10-phenanthrolyl) phosphate at 30 °C (μ = 0.1 M with KCl) in the presence of 2×10^{-3} M Cu^{2+}. The ester concentration was 2.6×10^{-5} M.

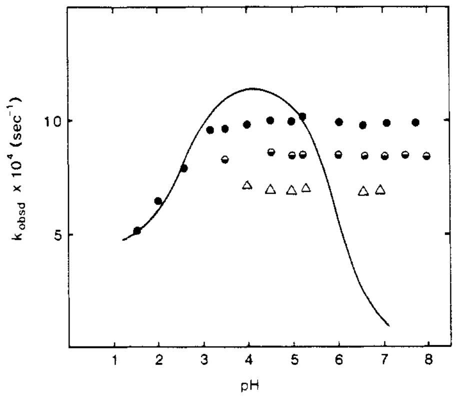


Figure 5. Plots of k_{obsd} for the hydrolysis of 2-(1,10-phenanthrolyl) phosphate at 85 °C (μ = 0.1 M with KCl) in the presence of 4×10^{-3} M Ni^{2+} (●), Co^{2+} (⊖), and Zn^{2+} (△). The solid line (—) is the plot for hydrolysis in the absence of metal ions. The ester concentration was 2.6 $\times 10^{-5}$ M.

the Ni^{II}, Co^{II}, and Zn^{II} complexes. For example, at pH 5.0 the value of k_{obsd} determined in acetate buffer for hydrolysis of the Ni^{II} complex at 85 °C is 1.26×10^{-3} s^{-1}, whereas that determined by extrapolation to zero pyridine buffer at pH 5.0 is 1.07×10^{-3} s^{-1}. A similar difference was also found with acetate and 2,6-lutidine buffers. Therefore, points determined in acetate buffer have not been included in Figure 5. In contrast, in the reactions of the Cu^{II} complex at 30 °C the values of k_{obsd} determined in acetate and pyridine buffer at zero buffer concentration were in excellent agreement. Likewise, rate constants for hydrolysis of the Cu^{II} complex measured in 2,6-lutidine buffer were the same as those measured in cacodylate buffers at the same pH. Rate constants could not be determined at pH >8 because of precipitation of the metal ion. In the presence of Cu^{2+} at pH >7 the solutions remained clear during the time course of the hydrolytic reaction but became cloudy if allowed to stand for longer periods. One cannot normally work at such high pH values with Cu^{2+} because of precipitation of the metal ion, but in view of the extremely large binding constant of V with Cu^{2+} it is possible to maintain saturation with little or no excess metal ion in solution, i.e., $[Cu^{2+}]/[\text{ligand}] \cong 1.0$. In fact, rate constants were the same at pH >7 when measured under these conditions and with the metal ion in excess. Complete k_{obsd} vs pH profiles were also obtained in the presence of a saturating concentration of Cu^{2+} at 40, 50, and 60 °C. The value of ΔH^* in the metal ion catalyzed phosphate dianion reaction is 7.8 ± 1 kcal/mol, and the value of ΔS^* at 30 °C is −46.8 ± 3 eu. Likewise at the top of the bell-shaped curve (pH 5.0) ΔH^* is 8.7 kcal/mol and ΔS^* is −43.4 eu.

There is no significant catalysis by buffer bases in the hydrolysis of V in the absence of metal ions as shown in Figure 6 for an imidazole buffer at pH 7.05. However, the reactions of the metal ion complexes (at saturating metal ion concentration) are markedly promoted by amine buffers. In Figure 6 plots of k_{obsd} vs total imidazole concentration are shown for the reaction of the Ni(II) complex at two constant pH values. The slope increases as the pH is increased, which indicates that it is the base species of the buffer that is kinetically active. The value of k_{Im}, the second-order rate constant for imidazole reaction, is 5×10^{-3} M^{-1} s^{-1} at 85 °C. Pyridine is also an excellent catalyst at pH 5.0, $k_{py} = 5.8 \times 10^{-3}$ M^{-1} s^{-1}. The catalysis of the hydrolysis of the Cu(II) complex by acetate buffer was not large. For example, a 0.5 M concentration of acetate buffer at pH 5 enhanced the hydrolysis of the Cu(II) complex of V (30 °C) by 43% in comparison with 0.02 M buffer ($k_{AC} = 1.4 \times 10^{-3}$ M^{-1} s^{-1}). Cacodylate buffer in the same concentration range (0.02–0.5 M) at pH 5.54 showed only 10% catalysis. Pyridine, however, is a good catalyst in hydrolysis of the Cu(II) complex at 30 °C, $k_{py} = 1.12 \times 10^{-2}$ M^{-1} s^{-1}. The concentration of metal ion was sufficiently large in these reactions to maintain saturation at high buffer concentration.

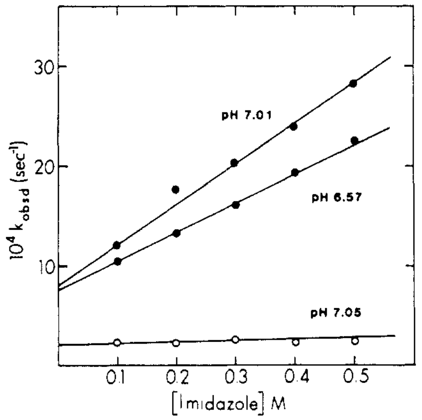
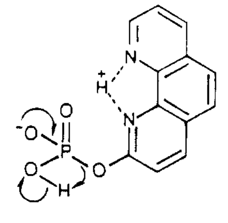


Figure 6. Plots of k_{obsd} for the reaction of 2-(1,10-phenanthrolyl) phosphate vs the total concentration of imidazole buffer (Im + ImH^+) in the presence of a saturating concentration of Ni^{2+} (●; 4×10^{-2} M) and in the absence of Ni^{2+} (○) at 85 °C and μ = 0.5 M with KCl.

Discussion

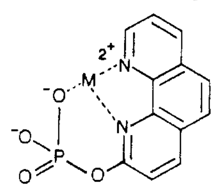
The bell-shaped plot of Figure 1 for the hydrolysis of 2-(1,10-phenanthrolyl) phosphate at 85 °C is similar in shape to profiles for the hydrolysis of phosphomonoesters that have been obtained previously, e.g., methyl phosphate[4] and phenyl phosphate.[5] With these esters the monoanion is the most reactive species, and it is likely that the mechanism involves elimination of metaphosphate as in eq 1.[3-5] Thus, it is important for one of the phosphate oxygens to be ionized to provide driving force for P–O bond breaking, and it is necessary that a proton be available to protonate the leaving group. The same type of mechanism possibly occurs in the hydrolysis of V, but it should be noted that there are now two species with which the above structural requirements are met. In addition to VIII the formally neutral species VII should also be highly reactive since the zwitterion species (protonated phenanthroline nitrogens) would have a leaving group of low pK_a. 2-(1,10-Phenanthrolyl) phosphate in fact hydrolyzes considerably faster than phenyl phosphate ($k_{monoanion}$ = 9.55×10^{-8} s^{-1} at 39 °C).[5] Thus, the 2-(1,10-phenanthrolyl) phosphate monoanion hydrolyzes 10^4-fold faster than the phenyl phosphate monoanion with only a 46 °C difference in temperature. The dianionic species of V appears to be completely unreactive in the absence of metal ions.



The enhanced absorbance at 270 nm due to metal ion binding to 2-(1,10-phenanthrolyl) phosphate and the magnitude of the rate constants for such binding show conclusively that the metal ions are complexed to the phenanthroline nitrogens.[23,24] The values of k_f and k_d for the metal ion binding (eq 7) can be calculated from the plots of k_{obsd} vs metal ion concentration by employing eq 8.[23] In order to calculate k_f from eq 8 one must know the acid dissociation constant of the phenanthroline nitrogen conjugate acid. Only the high titrimetrically determined pK_a value of V (pK_a = 6) leads to a reasonable value of k_f. The magnitude of k_f in formation of the Ni(II) complex (2500 M^{-1} s^{-1}) is then in excellent accord with the literature values for binding of Ni^{2+} to 1,10-phenanthroline and other ligands; the value of k_f for binding of Ni^{2+} to neutral ligands is invariably near 4×10^3 M^{-1} s^{-1}.[25] On the other hand, if pK_N is assumed to be the low pK_a (2.9), then k_f is calculated to be only 1.9 M^{-1} s^{-1}, an unreasonably low value. Therefore, the phenanthroline nitrogen conjugate acid must have a pK_a of 6, and consequently, the monoanion is VIII. The fast rate of hydrolysis of this species in comparison with the monoanion of phenyl phosphate must be due to the excellent leaving group provided by protonation of the phenanthroline nitrogens. Likewise, the rapidly hydrolyzing neutral species of V must be VII in which one of the phosphate oxygens is in the anionic form. Note that VII is less reactive than VIII. When the leaving group of a phosphate[5] or *S*-phenyl thiolphosphate[6] ester has a sufficiently low pK_a, then the dianionic species becomes more reactive than the corresponding monoanion.

The rate-determining step in the formation of the complexes of Ni^{2+} may be the replacement of water in the aquo complex.[25,26] Therefore, it would be expected that k_f values would be similar for various ligands. As a consequence, the k_f determined for binding of Ni^{2+} to 2-(1,10-phenanthrolyl) phosphate gives no information on whether the phosphate oxygens are chelated in the 1:1 complex in addition to the phenanthroline nitrogens. However, the values of k_f for the formation of the Co^{II} and Zn^{II} complexes are also similar to those for 1,10-phenanthroline.[24] Thus, if chelation of the phosphate oxygens occurs it must be after the rate-determining step. The k_d values for Ni^{2+} and Co^{2+} are larger than those constants in the chelation of 1,10-phenanthroline. The k_d for decomposition of the Zn^{II} complex of V is, however, 5-fold less than that for decomposition of the complex of 1,10-phenanthroline. Therefore, the binding of Ni^{2+} and Co^{2+} to V is not as favorable as to 1,10-phenanthroline, although binding is somewhat stronger with Zn^{2+} (K_M is 20-fold larger for binding to V).

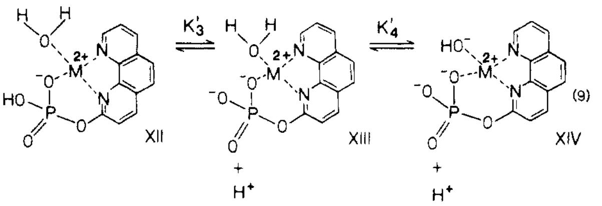
2-(1,10-Phenanthrolyl) phosphate is the first phosphomonoester studied in detail with which a divalent metal ion can chelate strongly to the ester but in which metal ion binding to the leaving-group oxygen would not be favorable in a 1:1 complex (in this case a four-membered ring would be required). The presence of the chelated metal ion has a large effect on the rate of hydrolysis of the ester. In the presence of a saturating concentration of Cu^{2+} rate constants for hydrolysis can be easily determined at 30 °C, whereas in the absence of the metal ion the reactions are too slow to allow accurate measurement of the rate constants. Thus, Cu^{2+} is enhancing the rate of hydrolysis at all pH values studied. The values of k_{obsd} for the hydrolytic reaction at 30 °C in the presence of Cu^{2+} are at least 75-fold larger than those in the absence of the metal ion in the pH range 3–5.5. In contrast, the plots of Figure 5 show that even high concentrations of Ni^{2+}, Co^{2+}, and Zn^{2+} do not appreciably enhance the hydrolysis of V at 85 °C in the pH range 2–5. Increasing the concentration of Ni^{2+} to 0.1 M in that pH range increased k_{obsd} by only ~10%. Therefore, when these metal ions are bound to the phenanthroline nitrogens at 85 °C the catalytic effect is nearly the same as that produced by a proton. The rate enhancements produced by these metal ions at 85 °C are, however, large at pH values greater than 6, where the reactions are pH independent.



XI

Extrapolation to 85 °C of the plots of log k_{obsd} for hydrolysis of the Cu(II) complex of V vs $1/T$ shows that the value of k_{obsd} at pH 5 (the pH–rate maximum) is 1.19×10^{-2} s^{-1}, which is 12-fold greater than in the absence of the metal ion. At higher pH the rate enhancements become very large; at pH 7 and 85 °C the Cu^{2+}-catalyzed reaction is 30-fold faster than spontaneous hydrolysis. Since the metal ion catalyzed reaction is then pH independent, the rate enhancement increases to a factor of 300 at pH 8 and would increase by a factor of 10 for each increase in pH of 1 unit if such measurements were experimentally possible. The rate enhancements due to Cu^{2+} are much larger at lower temperature because of the small activation energy for hydrolysis of the Cu^{II} complex; the ΔH^* for hydrolysis of phosphomonoester monoanions is normally 24–30 kcal/mol[5] and that for the hydrolysis of the *p*-nitrophenyl phosphate dianion is 30.6 kcal/mol (ΔS^* = +3.5 eu).[27]

The equilibria in the presence of a saturating concentration of Cu^{2+} are shown in eq 9.[28] A metal ion and a proton complexed to the phenanthroline nitrogens need not have the same effect on the phosphate group pK_a values; the metal ion is divalent and will be bound differently. However, the plot of Figure 4 indicates that the apparent value of pK_3' of the Cu(II) complex is 2.8. The profiles of Figures 4 and 5 indicate that XIII and possibly XIV are the major reactive species. The neutral species XIII (metal ion complex of the phosphate dianion) would give a bell-shaped k_{obsd} vs pH profile, and the profile of Figure 4 at pH >5 shows a decline in k_{obsd} with increasing pH until the reaction becomes pH independent at pH >6.5. At pH >5 the ionization of Cu(II)-complexed water may be influencing k_{obsd} (the pK_a of the aquo complex of Cu^{2+} is 6.8).[29] The experimental points in the profile of Figure 4 give a good fit to eq 10 with $k_1 = 1.2 \times 10^{-3}$ s^{-1}, $k_2 = 6.5 \times 10^{-4}$ s^{-1}, $pK_3' = 2.8$, and $pK_4' = 5.9$.



$$k_{obsd} = \frac{k_1K_3'a_H + k_2K_3'K_4'}{a_H^2 + K_3'a_H + K_3'K_4'} \quad (10)$$

Ionization of metal ion bound water would not be expected to influence the reactions of the Co^{II}, Ni^{II}, and Zn^{II} complexes because of the probable high pK_a values. The pK_a values of the aquo complexes are as follows (25 °C): Co^{2+}, 8.9; Zn^{2+}, 8.8; Ni^{2+}, 10.6.[29] A large heat of ionization[30] would reduce these values at 85 °C, but the reactions are still pH independent at pH ~8.

The metal ion catalysis in the hydrolysis of V cannot be ascribed to an enhancement of metaphosphate elimination, since the leaving-group oxygen cannot be easily bound to the metal ion and since binding to the other phosphate oxygens, which would be

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(25) Wilkens, R. G. *Acc. Chem. Res.* **1970**, *3*, 408.

(26) Replacement of a ligand water molecule in aquo complexes of Ni^{2+} is characterized by a rate constant of 2×10^4 s^{-1}, whereas with Cu^{2+}, Zn^{2+}, and Co^{2+} this rate constant is much larger (5×10^8, 3×10^7, and 4×10^5 s^{-1}, respectively): Cotton, F. A.; Wilkinson, G. *Advanced Inorganic Chemistry*, 3rd ed.; Wiley-Interscience: New York, 1972; p 656.

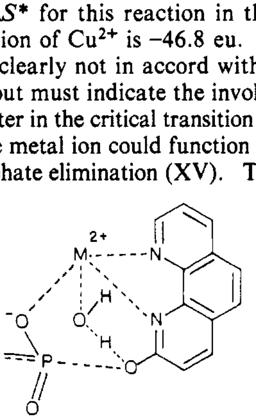
(27) Kirby, A. J.; Jencks, W. P. *J. Am. Chem. Soc.* **1965**, *87*, 3209.

(28) With 1,10-phenanthroline as the ligand (1:1) the $Cu_2(OH)_2L_2^{2+}$ species is formed in appreciable concentrations in the neutral-pH range: Perrin, D. D.; Sharma, V. S. *J. Inorg. Nucl. Chem.* **1966**, *28*, 1271. The negatively charged phosphate group in the 2-position of V would, of course, greatly reduce the likelihood of such a dimer complex.

(29) At 25 °C: Basolo, F.; Pearson, R. G. *Mechanisms of Inorganic Reactions*, 2nd ed.; Wiley: New York, 1967; p 32.

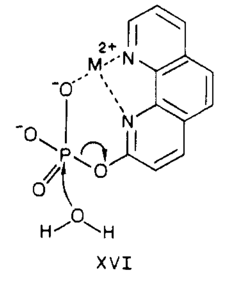
(30) A ΔH_i of 6.0–8.3 kcal/mol has been found for ionization of Zn^{II}-bound water in macrocyclic complexes: Woolley, P. *Nature (London)* **1975**, *258*, 677.

sterically favorable (six-membered ring), would retard the elimination process. The pH-independent reaction at pH >6 of the plot of k_{obsd} vs pH in the presence of cupric ion is occurring in a pH region in which the phosphate dianion species (XIV) is predominant. The ΔS^* for this reaction in the presence of a saturating concentration of Cu^{2+} is −46.8 eu. A negative ΔS^* of that magnitude is clearly not in accord with a unimolecular elimination reaction but must indicate the involvement of water or metal ion bound water in the critical transition state.[31] A water molecule bound to the metal ion could function as a general acid in assisting metaphosphate elimination (XV). The acid strengths of the metal ion coordinated water will differ considerably depending upon the identity of the metal ion.[29] Thus, Cu^{2+}-bound water will be the strongest acid in the series, and Cu^{2+} is the best catalyst. However, Ni^{2+}-bound water would be expected to be a much poorer general acid than with Co^{2+} and Zn^{2+}, but the three metal ions are of nearly equal effectiveness as catalysts. Furthermore, since water would be coordinated to the metal ion in the reactant it is unlikely that the mechanism XV could account for the highly negative value of ΔS^* found in the reactions of the Cu^{II} complex. The value of k_{obsd} for a reaction proceeding by mechanism XV will, of course, decline with increasing pH at pH values greater than the pK_a.

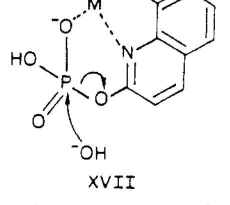


XV

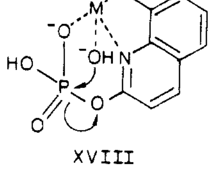
The pH independence of the metal ion catalyzed reactions at pH >6 and the highly negative ΔS^* is most simply explained in terms of nucleophilic attack upon phosphorus by an external water molecule (XVI). A kinetic equivalent process would involve attack of hydroxide ion on a protonated species (XII or a kinetic equivalent) as in XVII. Mechanism XVII would require a second-order rate constant k_{OH} of 7 × 10^7 M^{-1} s^{-1} at 30 °C with the Cu^{II} complex. Such a mechanism is unlikely considering that the reactions of other anionic nucleophiles (acetate and cacodylate) with the Cu^{II} complex are not highly favorable. A reaction involving attack of metal ion bound hydroxide ion (XVIII) would be pH independent at pH values below the pK_a of the metal ion bound water molecule, but the rate of hydrolysis would decline with increasing pH at pH values greater than the pK_a. With Cu^{2+} the highest experimental pH values are very likely above the pK_a. The values of k_{obsd} at pH >6.5 are pH independent and show no influence of the ionization state of the metal ion bound water molecule. Therefore, the most likely mechanism is XVI. Proton transfer from water to the leaving-group oxygen could also occur in the transition state to facilitate leaving group departure. Nevertheless, the principal catalytic role of the metal ion must be to enhance the ease of nucleophilic attack at phosphorus and thereby to markedly lower the ΔH^* for the hydrolytic reaction. This rate-enhancing effect is then only partially compensated by the negative ΔS^* due to restriction of the water molecule in the transition state, and the rate enhancements at low temperatures will be quite large. Bromilow and Kirby[32] have calculated that the rate constant for hydrolysis of the phenyl phosphate dianion at 39 °C is 4.2 × 10^{-12} s^{-1}, whereas that for the Cu(II) complex of the 2-(1,10-phenanthrolyl) phosphate dianion (XIV) at 40 °C is 1.02 × 10^{-3} s^{-1}, approximately 2.5 × 10^8-fold larger. The Cu(II) complex (XIV) hydrolyzes ~60 000-fold faster than the p-nitrophenyl phosphate dianion.[27]



XVI



XVII



XVIII

The lack of evidence for a nucleophilic reaction of metal ion bound OH^- is of considerable interest, since the attack of metal ion bound OH^- on phosphorus apparently takes place in reactions of the substitution-inert ethylenediamine–Co(III) complex of p-nitrophenyl phosphate.[33] A similar type of mechanism has been suggested as a possibility in the alkaline phosphatase dephosphorylation step in hydrolysis of phosphomonoesters.[13] Metal ion promoted OH^- catalyzed reactions of carboxylate esters,[34-39] amides,[40,41] and anhydrides[42,43] are very favorable and give rise to rate enhancements as large as 10^9 (ref 41) in these systems where attack of OH^- is at a carbonyl group. The absence of such a reaction in the hydrolysis of V is consistent with the lack of large catalytic effects by anionic nucleophiles, i.e., it is difficult for such nucleophiles to attack the phosphorus of phosphomonoesters.

Amine bases are excellent catalysts for reactions of the Ni(II) and Cu(II) complexes of the phosphate dianion species of V. This process is almost totally dependent on the presence of the metal ion; as seen in Figure 6, catalysis by imidazole in the absence of metal ion is not significant. It should be noted that the second-order rate constants for imidazole and pyridine are quite similar even though the pK_a values differ by nearly 2 pK_a units. Kirby and Jencks[27,44] found nucleophilic displacements by amines at 39 °C in the reactions of p-nitrophenyl phosphate dianion (but not phenyl phosphate),[32] and again the rate constants for a series of amines were similar. If the amines are acting as nucleophiles toward phosphorus, the lack of sensitivity of the rate constants to the pK_a of the amine must mean that there is little N–P bond formation in the transition state. The small catalytic effect of the negatively charged bases acetate and cacodylate would be expected if the reactions were nucleophilic. The second-order rate constant for pyridine catalysis of the hydrolysis of the Cu(II) complex of V at 30 °C is 4.5 × 10^4-fold larger than that for hydrolysis of p-nitrophenyl phosphate at 39 °C,[27] while the sec-

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(31) (a) Schaleger, L. L.; Long, F. A. *Adv. Phys. Org. Chem.* **1963**, *1*, 1. (b) Long, F. A.; Pritchard, J. G.; Stafford, F. E. *J. Am. Chem. Soc.* **1957**, *79*, 2362.

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(33) Jones, D. R.; Lindoy, L. F.; Sargeson, A. M. *J. Am. Chem. Soc.* **1983**, *105*, 7327.

(34) Wells, M. A.; Rogers, G. A.; Bruice, T. C. *J. Am. Chem. Soc.* **1976**, *98*, 4336. Wells, M. A.; Bruice, T. C. *Ibid.* **1977**, *99*, 5341.

(35) Hay, R. W.; Clark, C. R. *J. Chem. Soc., Dalton Trans.* **1977**, 1866, 1993.

(36) Fife, T. H.; Przystas, T. J.; Squillacote, V. L. *J. Am. Chem. Soc.* **1979**, *101*, 3017.

(37) Fife, T. H.; Przystas, T. J. *J. Am. Chem. Soc.* **1982**, *104*, 2251.

(38) Breslow, R.; McAllister, C. *J. Am. Chem. Soc.* **1971**, *93*, 7096.

(39) Fife, T. H.; Przystas, T. J. *J. Am. Chem. Soc.* **1985**, *107*, 1041.

(40) (a) Groves, J. T.; Dias, R. M. *J. Am. Chem. Soc.* **1979**, *101*, 1033. (b) Groves, J. T.; Chambers, R. R., Jr. *J. Am. Chem. Soc.* **1984**, *106*, 630.

(41) Fife, T. H.; Przystas, T. J. *J. Am. Chem. Soc.* **1986**, *108*, 4631.

(42) Fife, T. H.; Pyzystas, T. J. *J. Am. Chem. Soc.* **1983**, *105*, 1638.

(43) Breslow, R.; McClure, D. E.; Brown, R. S.; Eisenach, J. *J. Am. Chem. Soc.* **1975**, *97*, 194.

(44) (a) See also: Kirby, A. J.; Varvoglis, A. G. *J. Chem. Soc. B* **1968**, 135. (b) Rate constants for hydrolysis of phosphorylated pyridine and imidazole are given in ref 8a and 16.

ond-order rate constants for pyridine and imidazole promotion of the reactions of the Ni(II) complex of V at 85 °C are 20 000- and 80 000-fold larger than those for reactions of *p*-nitrophenyl phosphate[27] at 39 °C. Therefore, the effect of the metal ion is profound.

High concentrations of Mg^{2+} or Ca^{2+} (0.33 M) were recently reported[19] to have only a small catalytic effect on the pyridine-catalyzed hydrolysis of *p*-nitrophenyl phosphate. It was concluded that metal ion binding to the phosphate oxygens has little effect on the ability of pyridine to attack phosphorus as a nucleophile. In contrast, pyridine is a good catalyst in the hydrolysis of the Ni^{II} complex of V where binding of the metal ion is strong, even though no reaction can be observed in the absence of the metal ion.

Alkaline Phosphatase. The mechanisms of metalloenzyme-catalyzed phosphate ester hydrolysis or phosphoryl group transfer are not understood.[45] However, most of the proposals that have been put forth involve the metal ion in some manner. For example, it was suggested that the zinc ion in the active site of alkaline phosphatase coordinates the two negative charges of a phosphomonoester dianion and thereby enhances nucleophilic attack of a serine hydroxyl group.[11,46] A phosphorylated serine is an intermediate in the reaction. Others have pointed out that the Zn^{II} may enhance metaphosphate elimination;[10] serine is then phosphorylated by metaphosphate capture. The key question would appear to concern binding of the metal ion to the phosphate ester substrate. If Zn^{II} binds to the leaving-group oxygen, then the mechanism probably involves metaphosphate elimination. If, however, the leaving group is not complexed but the other oxygens are chelated, then the mechanism probably involves a direct nucleophilic attack by the serine hydroxyl on phosphorus. This is, of course, based on the consideration that the metal ion is directly complexed to the phosphomonoester substrate.[47–49] If a metal ion bound water molecule is located between the metal ion and the substrate, then the mechanistic considerations will be unchanged, and the water molecule can then act as a general acid to facilitate either nucleophilic attack by serine or metaphosphate elimination.[50] The present work shows that when the leaving-group oxygen of a phosphomonoester is not significantly chelated in a 1:1 complex, a strongly bound metal ion will nevertheless produce large rate enhancements in the hydrolysis reactions and will lead to catalytic processes involving water and amines that proceed most likely by nucleophilic pathways. The conceptually simplest mechanism in the alkaline phosphatase catalyzed hydrolysis of phosphomonoesters would be that in which the neutral serine hydroxyl attacks at phosphorus.

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Registry No. KCl, 7447-40-7; Ni^{2+}, 14701-22-5; Co^{2+}, 22541-53-3; Zn^{2+}, 23713-49-7; 1,10-phenanthroline methiodide, 112399-14-1; 1-methyl-2-*o*-phenanthrolone, 1-methyl-2-*o*-phenanthrolone; 2-chloro-1,10-phenanthroline, 7089-68-1; 2-phenoxy-1,10-phenanthroline, 22426-17-1; 2-hydroxy-1,10-phenanthroline, 92695-50-6; 2-(1,10-phenanthrolyl)phosphate, 112399-15-2.

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Semifluorinated Hydrocarbons: Primitive Surfactant Molecules

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Abstract: $F(CF_2)_8(CH_2)_{12}H$ and $F(CF_2)_8(CH_2)_{16}H$ form reversed micelles in perfluorotributylamine and perfluorooctane, respectively. Static and dynamic light scattering, NMR, and fluorescence and absorbance probe solubilization demonstrate the presence of micelles. There is also preliminary evidence of normal micelle formation by $F(CF_2)_8(CH_2)_{16}H$ and $F(CF_2)_{10}(CH_2)_{16}H$ in toluene. These are the first examples of micelle formation by nonpolar *low molecular weight* molecules and they demonstrate that semifluorinated hydrocarbons are a new class of surfactant.

Surfactant solutions, particularly those in concentration regimes which result in the formation of association aggregates (micelles, reversed micelles, vesicles, microemulsions), are important in diverse applications. The dispersed pseudophase of complementary "polarity" provided by the aggregates often conveys properties to surfactant solutions that are inaccessible to single or mixed molecular solvent systems. In part, the rational design and selection of surfactants to achieve specified aggregate architectures can be based on simple hard-core geometric-packing arguments.[1,2] However, as with molecular fluids, even though gross structural issues largely devolve to hard-core packing considerations, the thermodynamic properties of the aggregates critically depend on the intermolecular energetics of the amphiphilic molecule. Yet, in contrast to the situation encountered with pure molecular fluids, little effort has been expended in the development and study of functionally primitive surfactant systems. By functionally primitive we mean aprotic species which possess no (or minimal) permanent molecular dipole. Without such benchmark examples available for study, molecular theories of surfactant aggregation must incorporate rather severe approximations to treat experimental data. In this regard, concordance between theory and experiment must be viewed with caution.

The *detailed* structural and energetic requirements for a molecule to display surfactant behavior have yet to be satisfactorily elucidated even though the qualitative guidelines of surfactant

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