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Potentiometric and spectrophotometric determination of stabilities of the 1-hydroxy-2-pyridinone complexes of trivalent and divalent metal ions

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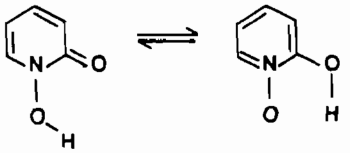
Abstract

The stability constants of complexes formed by 1-hydroxy-2-pyridinone (1H2P) with the divalent metal ions, Cu^{2+}, Ni^{2+}, Zn^{2+} and Co^{2+}, and with the trivalent metal ions, Fe^{3+}, Ga^{3+}, Al^{3+} and In^{3+}, are reported. The relative orders of stabilities of divalent and trivalent metal complexes are Cu(II) > Ni(II) ≥ Zn(II) > Co(II), and Fe(III) > Ga(III) > Al(III) > In(III). The complexes formed, and their stabilities, are compared with the properties of complexes formed by related ligands, such as acetohydroxamic acid (AHA), 1,4-dihydroxy-2-pyridinone (DH2P), 1-methyl-3-hydroxy-2-pyridinone (MH2P) and 1,2-dimethyl-3-hydroxy-4-pyridinone (DMHP). 1H2P and AHA exhibit similar complexation behavior toward metal ions, reflected by a linear relationship between $\log K_{M\text{-}1H2P}$ and $\log K_{M\text{-}AHA}$. The relative effectiveness of these ligands for metal ion binding is discussed, indicating that 1-hydroxy-2-pyridinone is probably the most effective bidentate chelating agent of this class of ligands because of its relatively strong acidity. If structurally similar ligands (1H2P and DH2P) are compared, DH2P has higher basicity and lower stability.

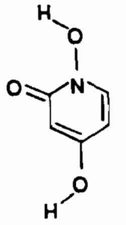
Introduction

Hydroxypyridinone ligands and their derivatives are of interest as chelating agents for Fe(III) [1–4], Ga(III), Al(III) [4, 5] and In(III) [6, 7]. Metal complexes of some bidentate hydroxypyridinone ligands have been investigated for possible use as therapeutic agents [2, 3, 8]. The studies on the 2-hydroxypyridine-*N*-oxide (actually 1-hydroxy-2-pyridinone) derivatives have shown that these chelators could be used as probes for studying iron metabolism and in the treatment of iron overload and other diseases of iron imbalance [9].

The present study involves the determination of the stability constants for metal complexes of unsubstituted 1-hydroxy-2-pyridinone (**1**) (1H2P) with the trivalent metal ions of Fe(III), Ga(III), In(III) and Al(III), and the divalent metal ions of Cu(II), Ni(II), Zn(II) and Co(II). This ligand is particularly interesting since stabilities of divalent and trivalent metal ion complexes with 1,4-dihydroxy-2-pyridinone (**2**) (DH2P) [10], 1-methyl-3-hydroxy-2-pyridinone (**3**) (MH2P) [10] and 1,2-dimethyl-3-hydroxy-4-pyridinone (**4**) (DMHP) [11, 12] have been studied. A partial determination of stability constants of complexes formed by some divalent metal ions with 1-hydroxy-2-pyridinone was reported some time ago [13]. The stability constants of the Fe(III) complexes of 1-hydroxy-2-pyridinone and 3-hydroxy-2-pyridinone were also reported recently [14].



1a **1b**



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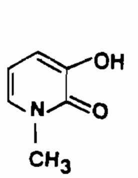

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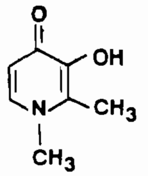

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Experimental

Materials

2-Hydroxypyridine-*N*-oxide (1-hydroxy-2-pyridinone, 1H2P) was purchased in pure form from Aldrich Chem-

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*Author to whom correspondence should be addressed ical Company and was used without further purification. The ^1H NMR spectrum of this sample was recorded with a Varian XL-200 spectrometer and showed that there was no organic impurity. Its purity was also affirmed by potentiometric titration.

All of the metal chloride stock solutions were made up with deionized distilled water. A small excess of HCl was added to the stock solutions of the trivalent metal ions. The metal salts were standardized complexometrically either by EDTA titration with an appropriate indicator [15] or by passage through Dowex 50W-X8 cation-exchange resin. In the latter case, the eluted acid was titrated with standard KOH solution, which was prepared from CO_2-free commercial concentrate (Baker 'Dilut-it' ampules).

Potentiometric determinations

Potentiometric measurements were carried out with the procedures described in detail elsewhere [16].

The potentiometric apparatus consists of a pH meter, a water-jacketed titration cell and a 10 ml capacity Metrohm piston buret which delivers standard KOH titration solution directly to the sealed cell through a buret tip which is secured to the cell cap with a clamp and O-rings. A stream of purified argon was used as the inert atmosphere in the titration cell and to degass all solutions before titrations. Oxygen and carbon dioxide were excluded from the reaction mixture by maintaining a slight positive pressure of purified argon in the titration cell. The last traces of oxygen were removed from the argon by passing it through an alkaline pyrogallol solution. The Corning Research 130 pH meter used in this experiment was fitted with glass (Sargent Welch) and calomel reference electrodes and calibrated to read p[H] directly prior to each experiment with a freshly prepared solution of standard acid (HCl). Thus the term p[H] in this paper is defined as $-\log[H^+]$. The direct pH meter readings were used in the calculations of the equilibrium constants. The value of $K_w([H^+][OH])$ used in the computations was $10^{-13.78}$. The temperature was maintained at 25.0 ± 0.1 °C with a thermostated cell and the ionic strength was adjusted to 0.10 M by the addition of KCl as supporting electrolyte.

Equilibrium p[H] values were determined at every incremental addition of standard KOH to the experimental solutions. The experimental p[H] values were plotted as a function of a or m values to obtained p[H] profiles for each system (Figs. 1 and 2). An a value is the ratio of moles of base added to moles of ligand; and m is the ratio of moles of base added to moles of metal ion.

The binding constants of 1H2P complexes with the trivalent metal ions, Al^{3+}, Ga^{3+} and In^{3+} and the divalent metal ions, Cu^{2+}, Ni^{2+}, Zn^{2+} and Co^{2+} were determined by direct potentiometric titration of the complex solutions. The solubilities of trivalent metal ion complexes with Al(III), In(III), Ga(III) and Fe(III) are lower than those of divalent metal complexes. For Al(III) and In(III) complexes, the metal ion concentrations used in potentiometric determination were as low as 5.0×10^{-4} M. However, the stability constant for the 1:3 complex of Ga(III) was not obtained because its solubility in water is too low to determine the stability constant potentiometrically. Also, the metal hydroxide precipitated before 1:2 or 1:3 complexes were fully formed. Therefore it was not possible to determine extinction coefficients for the 1:2 and 1:3 Ga(III) complexes, and thus spectrophotometric determination of the corresponding stability constants was not possible. Direct potentiometric measurement of the equilibrium between Fe(III) and 1H2P was attempted, but was not possible because of low solubility. The spectrophotometric method was employed successfully at lower concentration. The concentration of Fe(III) must be less than 1.8×10^{-5} M; otherwise, Fe(III) complexes would precipitate from solution.

Spectrophotometric measurements

The visible absorbance spectra of Fe(III) complex species were measured with a Perkin-Elmer model 553 fast scan spectrophotometer interfaced with a Perkin-Elmer R-1000 recorder. A matched pair of quartz cells with 1.000 cm path length was used for the routine measurements. The temperature of the sample cell holder was maintained by the circulation of water at 25.0 °C. Ionic strength was maintained at 0.10 M with KCl. The p[H] value of each solution was adjusted by adding increments of relatively concentrated HCl and measured with a Corning 130 digital pH meter. Successive spectra were obtained by addition of aqueous hydrochloric acid to a solution of Fe(III) and 1H2P originally at pH 4–6. All test solutions were blanketed with argon and kept sealed prior to spectral measurements. The series of curves shown in Fig. 3 were obtained on solutions containing 1.65×10^{-5} M Fe(III) and four equivalents of ligand, but which had different p[H] values. The extinction coefficients for the 1:1 and 1:2 Fe(III)–1H2P complexes (1:1, $\epsilon = 1390$ M^{-1} cm^{-1} at 468 nm; 1:2, $\epsilon = 2800$ M^{-1} cm^{-1} at 445 nm) were determined from the absorbance spectra of corresponding solutions. The extinction coefficient ($\epsilon = 4020$ M^{-1} cm^{-1}) for the 1:3 Fe(III)–1H2P complex was obtained from the spectrum of a solution containing a 1:5 (Fe/1H2P) molar ratio of metal ion to ligand, for which FeL_3 is formed completely above pH 6. For the 1:3 solution FeL_3 could be not fully formed, even at higher p[H]. The two cases are clearly indicated by the distribution curves in Figs. 4 and 6.

Calculations

Ligand protonation constants and metal ion stability constants were calculated with the FORTRAN program BEST [16]. The program refines stability constants by iterative non-linear least-squares fit of potentiometric equilibrium curves through a set of simultaneous mass balance equations for all the components expressed in terms of known and unknown equilibrium constants. Stability constants of 1:1, 1:2 and 1:3 metal-to-ligand complexes were evaluated from the p[H] profiles for the solutions containing 1:1, 1:2 and 1:3 molar stoichiometry of metal ion to ligand. Once the value of K_{ML} was determined, the values of the binding constants for ML_2 and ML_3 species were calculated from direct titrations of the 1:2 and 1:3 solutions, respectively, while holding the value of K_{ML} constant, and then all three constants were refined at all three ratios. The species considered present in the experimental solutions were those that one would expect to form according to established principles of coordination chemistry. Stability constants for Fe(III) complexes were calculated from the absorbance data under equilibrium conditions, as described by Clarke and Martell [10].

Species distribution curves were calculated with the FORTRAN program SPE [16] and plotted with the program SPEPLOT [16]. In some cases the formation constants were not high enough to prevent the precipitation of the metal hydroxide. In such cases the species distribution curve for the insoluble hydroxide was also included. Such curves of course do not represent concentrations in solution but do represent the per cent of metal precipitated at equilibrium. Frequently the separation of the solid phase takes some time and a temporary metastable equilibrium of the solution species persists for a while. The K_{sp} at 25.0 °C of the metal hydroxides employed [19] are for $Fe(OH)_3$, $10^{-38\,8}$; $In(OH)_3$, $10^{-36\,9}$; $Cu(OH)_2$, $10^{-19\,32}$; $Co(OH)_2$, $10^{-14\,9}$. Metal hydrolysis constants [19] have also been considered in the calculations.

Results

Protonation constants of 1H2P

The formula of the mono-protonated neutral compound of 1H2P can be designated as HL, with one hydroxy group on the nitrogen of the pyridine ring. The curve for potentiometric titration of 1H2P with KOH, shown in Fig. 1, shows two inflection points at $a=0$ and 1. The break in the titration curve for free 1H2P occurs at $a=0$ (moles of base titrated per mole of ligand) corresponding to the monoprotonated neutral form of the ligand. The buffer region between $a=0$ and $a=1$ involves the equilibrium for conversion of the neutral ligand (as HL) to its unprotonated form L^-. The protonation constant for the equilibrium between HL and L^- has a log value of 5.86 (at 25.0 °C, ionic strength 0.10 M KCl). There is also potentiometric evidence of a second protonation constant ($\log K_2^H = [H_2L^+/]/[H^+][HL] = 1.2$) for 1H2P in the p[H] profile below $a=0$. The second proton is supplied by excess mineral acid.

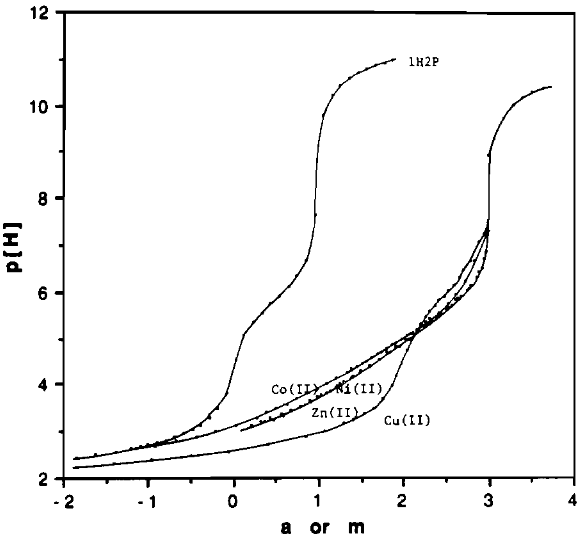


Fig. 1 Potentiometric equilibrium curves of 1-hydroxy-2-pyridinone and the 1·3 metal ion–1H2P systems; $t=25.0$ °C, $\mu=0.10$ M (KCl); 1H2P, Co(II), Zn(II), Ni(II), Cu(II).

Stability constants

The experimental data from potentiometric titrations may be described by considering equilibria (1)–(5) (charges omitted), provided the evaluation of the data is not carried into the pH range where hydroxo complexes may form. The initial computations were obtained in the form of overall stability constants (β_n; eqn. (6)). Differences between the various $\log \beta$ values give the stepwise formation constants defined by eqns. (3)–(5).

$$H + L \rightleftharpoons HL \qquad K_{HL} = [HL]/[H][L] \qquad (1)$$

$$H + HL \rightleftharpoons H_2L \qquad K_{H_2L} = [H_2L]/[H][HL] \qquad (2)$$

$$M + L \rightleftharpoons ML \qquad K_{ML} = [ML]/[M][L] \qquad (3)$$

$$ML + L \rightleftharpoons ML_2 \qquad K_{ML_2} = [ML_2]/[ML][L] \qquad (4)$$

$$ML_2 + L \rightleftharpoons ML_3 \qquad K_{ML_3} = [ML_3]/[ML_2][L] \qquad (5)$$

$$M + nL \rightleftharpoons ML_n \qquad \beta_n = [ML_n]/[M][L]^n \qquad (6)$$

The titration curves for the divalent metal complexes in Fig. 1 show an inflection at $m=3$ (three equivalent of base) for Ni(II), Zn(II) and Co(II), and at $m=2$ for Cu(II). The breaks in the titration curves for In(III) and Al(III) complexes fall at $m=3$ (Fig. 2). The trivalent metal ions form stable complexes in the acidic p[H] range but dissociate to form metal hydroxide precipitates

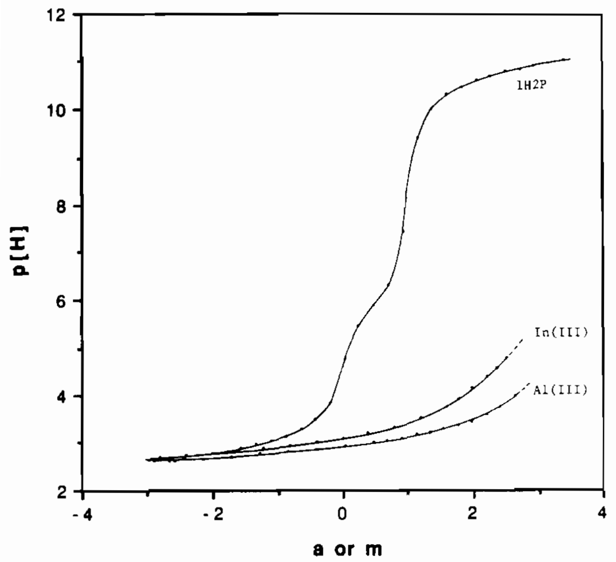


Fig 2. Potentiometric equilibrium curves of 1-hydroxy-2-pyridinone and the 1:3 metal ion–1H2P systems; $t=25.0$ °C, $\mu=0.10$ M (KCl), 1H2P, In(III), Al(III)

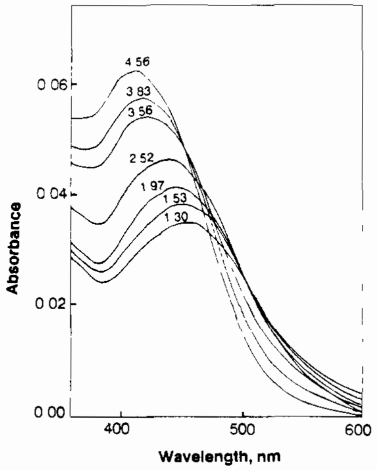


Fig. 3 Spectrophotometric absorbance curves of Fe(III)–1H2P complexes at various p[H] values $[\mathrm{Fe(III)}]_T=1.65\times10^{-5}$ M, $[\mathrm{1H2P}]_T=6.55\times10^{-5}$ M.

at or above neutral p[H]. The solution of the 1:3 Ga(III) complex at 5×10^{-4} M could not be made up because of low solubility. Therefore only stability constants of 1:1 and 1:2 Ga(III) complexes were obtained. The low solubility and high stability of Fe(III) complexes precluded any potentiometric analysis. All of the stability constants of Fe(III) complexes were obtained from spectrophotometric determinations.

The Uv–Vis spectra as a function of p[H] of the 1:1 Fe(III) complex indicate that the 1:1 Fe(III)–1H2P complex is not dissociated at p[H] values as low as 1.0, which is far below the limit of p[H] 2.0 at which accurate potentiometric p[H] measurements can be made. Figure 3 shows the UV–Vis absorbance spectra of 1:4 Fe–1H2P solutions at the p[H] values indicated on the curves. Two isosbestic points were found at 452 and 505 nm which correspond the conversions of the 1:3 complex to the 1:2 and then to the 1:1 complex.

Qualitatively, solubilities of the divalent metal complexes are higher than those of the trivalent ones. Solubilities of the trivalent metal complexes are in the sequence of Fe(III), Ga(III) < In(III), Al(III).

All equilibrium constants obtained are listed in Table 1.

Discussion

Although there is a tautometric equilibrium for 2-hydroxypyridine-*N*-oxide, as indicated by formulas **1a** and **1b**, UV and IR evidence show that 2-hydroxypyridine-*N*-oxide exists in solution as strongly hydrogen-bonded 1-hydroxypyridine-2-one [17]. More recently, the molecular structure of 2-hydroxypyridine-*N*-oxide was determined by X-ray diffraction; as in solution, 1H2P exists in the crystal state as the 1-hydroxypyridine-2-one tautomer [18]. Therefore the pK_a $(-\log K_1^H)$ value of the ligand represents the loss of the proton of the hydroxyl group bound to the pyridine nitrogen. The protonation of the pyridine nitrogen is very weak $(\log K_2^H=1.2)$. The pK of -0.8 in ref. 13 seems too low but the conditions used in its determination were not given.

Sun *et al.* [13] reported the spectrophotometric determination of the stability constants for the 1:1 divalent metal complexes of 1-hydroxy-2-pyridinone at ionic strength 0.10 M in water. Their results are similar to the present results measured potentiometrically under the same experimental conditions (Table 2). Comparable data for 1:2 and 1:3 complexes were not reported. The same paper also reported stepwise constants of 1:1 and 1:2 complexes determined potentiometrically at ionic strength 0.005 M, but stability constants of 1:3 complexes were not reported. The present investigations were all carried out on 1:1, 1:2 and 1:3 solutions, respectively, the latter of which allowed for the possible formation of ML_3 species. Ni(II), Zn(II), and Co(II) form ML_3 species with three bidentate 1H2P ligands. No 1:3 species was found for Cu(II)–1H2P which probably prefers a four-coordinate planar geometry in complexes with two 1H2P ligands. 1H2P coordinates to metal ions as a negatively charged (-1) ligand and forms 1:1, 1:2 and 1:3 complexes with the metal ions, Fe^{3+}, Al^{3+}, In^{3+}, Ni^{2+}, Zn^{2+}, Co^{2+} and possibly Ga^{3+}. The crystal structure [14] of the Fe(III) tris complex of 1-hydroxy-2-pyridinonate shows that the bidentate coordination for the binding to metal ion by 1H2P occurs through the two oxygen atoms. The complex is formed with a pseudo-octahedral arrangement of the three 1H2Ps with

TABLE 1. Logarithms of stepwise stability constants for the complexes of 1H2P with divalent metal ions of Cu(II), Ni(II), Zn(II) and Co(II) and trivalent metal ions of Fe(III), Ga(III) and In(III), and of protonation constants for 1H2P measured potentiometrically in water at $t=25.0$ °C±0.1 and ionic strength 0.10 M (KCl)

Metal ion (M)	Present work			Previous work[a]		
	K_{ML}	K_{ML_2}	K_{ML_3}	K_{ML}	K_{ML_2}	K_{ML_3}
H	5.86(1) (K_1^H)	1.2(1) (K_2^H)		5.81 (K_1^H)	-0.8[b] (K_2^H)	
Cu^{2+}	7.29(2)	5.77(3)		7.3		
Ni^{2+}	5.16(3)	4.16(4)	2.80(3)	5.1		
Zn^{2+}	5.09(2)	4.16(4)	2.78(4)	5.1		
Co^{2+}	4.85(2)	3.98(2)	2.74(3)	4.9		
Fe^{3+}[c]	10.6(1)	9.5(1)	7.1(1)	10.3	9.0	7.55
Ga^{3+}	9.12(5)	7.6(1)	[d]			
Al^{3+}	8.16(6)	7.38(8)	6.05(6)			
In^{3+}	8.09(3)	5.88(5)	4.53(8)			

[a] Refs. 13 and 14. [b] Questionable value. [c] Measured spectrophotometrically. [d] Data for 1:3 Ga(III) complex is not available.

TABLE 2 Stability constants of the 1:1 divalent metal complexes and of the Fe(III) complexes formed with 1-hydroxy-2-pyridinone and acetohydroxamic acid

Quotient[c]	Log K_{ML}	
	1H2P[a] present work	AHA[b] ref 19
[HL]/[H][L]	5.86	9.36
[CuL]/[Cu][L]	7.29	7.9
[NiL]/[Ni][L]	5.16	5.3
[ZnL]/[Zn][L]	5.09	5.4[d]
[CoL]/[Co][L]	4.85	5.1
[FeL]/[Fe][L]	10.6	11.42
$[FeL_2]/[FeL][L]$	9.52	9.68
$[FeL_3]/[FeL_2][L]$	7.12	7.2

[a] $t=25.0$ °C; $\mu=0.10$ M (KCl) [b] $t=20.0$ °C, $\mu=0.10$ M (KCl). [c] Charges omitted [d] Same value at 25.0 °C; $\mu=0.10$ M

iron in the center. Spectrophotometric determinations of the Fe(III) stabilities with 1H2P have been reported by Scarrow *et al.* [14]. Table 2 presents the stability constants of 1H2P complexes and those of aliphatic hydroxamic acid. It is seen that the stabilities of the metal complexes of the hydroxamates are uniformly a little higher than those of 1H2P, as one would expect from the fact that the ligand is more basic. However, the difference in p*K* values is much greater than the small difference in stability constants would lead one to expect.

In Table 1, the relative order of trivalent metal ion stability constants appears to be Fe(III) > Ga(III) > Al(III) > In(III), which sequence is also found in related systems involving complexes of trivalent metal ions with hydroxypyridinone ligands. The order of stabilities of divalent metal ions, Cu(II) ≫ Ni(II) ≥ Zn(II) > Co(II).

Species distributions of complexes formed at different concentrations of metal ion and ligand will be different because of the dilution effect that is well known for bidentate ligands. Figures 4 and 5 present an example of Fe(III) complexes in 1:3 Fe(III)–1H2P solution and show the strong effect of dilution on the species distributions at 1.8×10^{-5} M Fe(III) ion and 5.4×10^{-5} M 1H2P, compared with 1.8×10^{-7} M Fe(III) and 5.4×10^{-7} M 1H2P, respectively. At p[H] 2 and 1.8×10^{-5} M, all Fe^{3+} ion exists in the form of metal complexes and nearly 90% of the 1:2 complex is already formed. At p[H] 2 and 1.8×10^{-7} M, there is about 25% free Fe^{3+} and only about 10% of 1:2 complex is formed. At 1.8×10^{-5} M, the percentage of the 1:3 complex reaches 90% above pH 5.7, but at 1.8×10^{-7}, the maximum percentage of that species is only 25%. For both cases, Fe(III) hydroxides precipitate after pH 5.2 and 4.3, respectively. The maximum concentration attainable of Fe(III) for the preparation of the 1:3

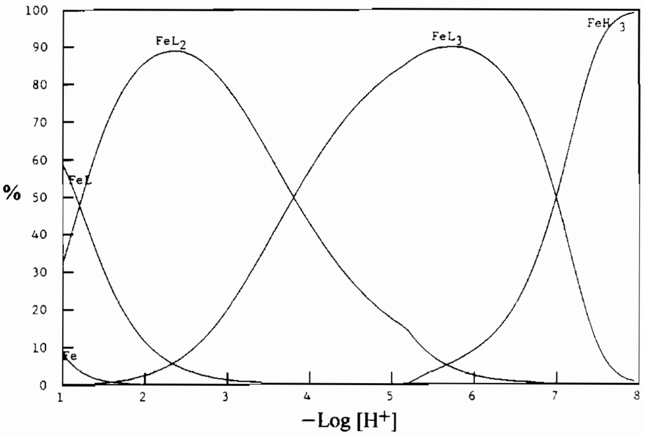


Fig. 4. Metal ion species distribution curves for the 1:3 Fe(III)–1H2P system, 1.8×10^{-5} M Fe(III) and 5.4×10^{-5} M 1H2P, L = 1H2P.

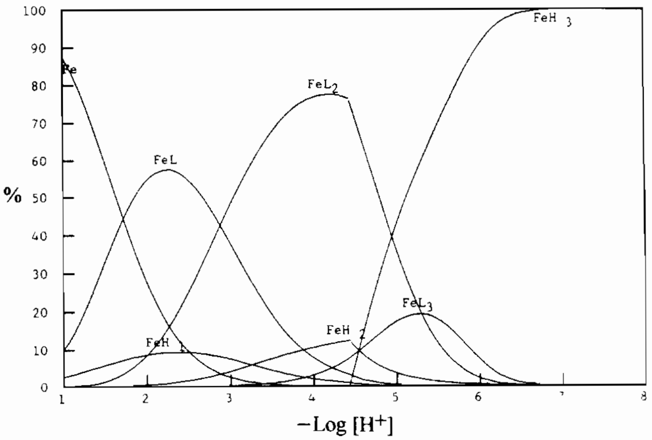


Fig. 5. Metal ion species distribution curves for the 1:3 Fe(III)–1H2P system, 1.8×10^{-7} M Fe(III) and 5.4×10^{-7} M 1H2P; L = 1H2P.

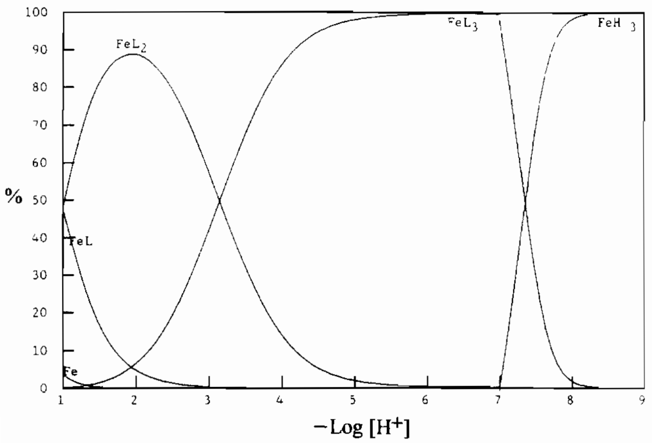


Fig. 6. Metal ion species distribution curves for the 1:5 Fe(III)–1H2P system, 1.65×10^{-5} M Fe(III) and 8.26×10^{-5} M 1H2P; L = 1H2P.

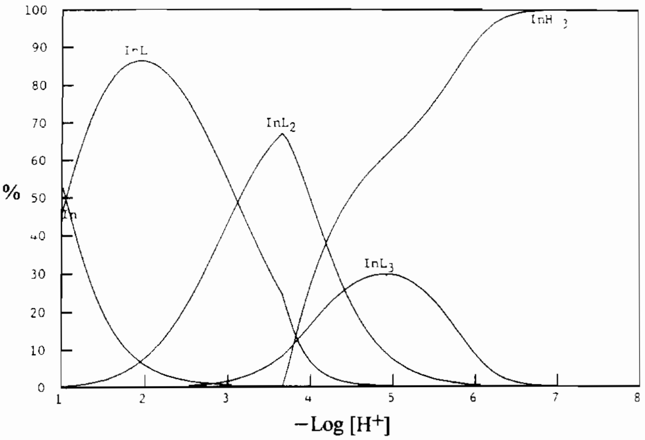


Fig. 7. Distribution curves for the 1:3 In(III)–1H2P system, 5.0×10^{-4} M In(III) and 1.5×10^{-3} M 1H2P

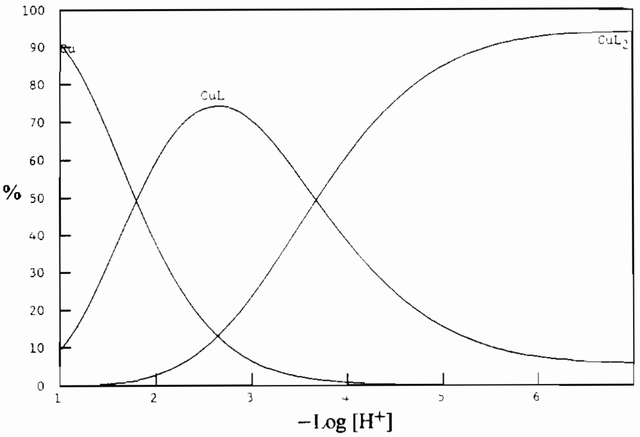


Fig 8. Distribution curves for the 1:2 Cu(II)–1H2P system, 5.0×10^{-4} M Cu(II) and 1.0×10^{-3} M 1H2P

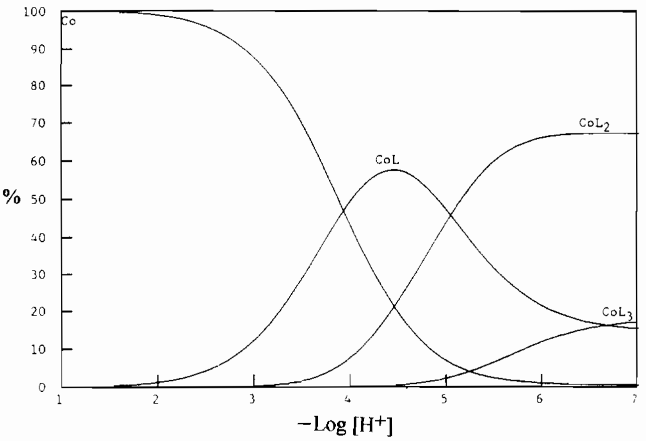
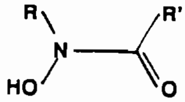


Fig 9. Distribution curves for the 1:3 Co(II)–1H2P system, 5.0×10^{-4} M Co(II) and 1.5×10^{-3} M 1H2P

complex is 1.8×10^{-5} M because of low solubility in aqueous solution. Therefore, the 1:3 Fe(III)–1H2P complex could not be fully formed in 1:3 Fe(III) to 1H2P solution, even at very high pH values. A higher ratio of ligand to metal ion is needed in order to obtain the complete formation of the 1:3 complex. Figure 6 is a species distribution diagram illustrating the complete formation of the 1:3 Fe(III)–1H2P complex between pH 6 and 7 in a 1:5 Fe(III)–1H2P solution. This use of excess ligand may be helpful in spectrophotometric determinations to obtain the extinction coefficient of 1:3 Fe(III)–1H2P complex in the visible range. Figures 7, 8 and 9 show the species distributions of the complexes with In(III), Cu(II) and Co(II), respectively. These Figures are helpful in showing the degrees of formation of the 1:1, 1:2, and 1:3 complexes in a way that cannot be seen in the titration curves themselves. It is interesting to see that only a small percentage of the 1:3 indium(III) complex is formed and the indium(III) complexes are not stable enough to prevent the precipitation of $In(OH)_3$. Also a comparison of the Cu(II) and Co(II) distribution diagrams shows that the Cu(II) complexes are more completely formed.

It is seen that the abrupt changes of slope of the species distribution curves in Figures 4, 5, 6, 7, 10 and 11 occur at the initial appearance of the solid metal hydroxide ($In(OH)_3$, indicated as InH_{-3}, for Fig. 7 and $Fe(OH)_3$, indicated as FeH_{-3}, for all the remainder). This is due to the fact that the removal of some of the metal ion from solution by precipitation changes the composition of the solution, and an abrupt change in the concentrations of the species in solution takes place. It is seen from Fig. 11, which illustrates the competition between 1H2P and DMHP for Fe(III), precipitation of $Fe(OH)_3$ is delayed to about pH 7.2 at which the DMHP has begun to be superior to 1H2P in complexing Fe^{3+}. Moreover, from about p[H] 7 to 9 the DMHP successfully competes with $Fe(OH)_3$, precipitation and sequesters over 60% of the Fe^{3+} in that range.



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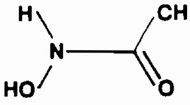

6

Like hydroxamic acids (5), 1-hydroxy-2-pyridinone has an N–OH group adjacent to a carbonyl function and may be viewed as a cyclic hydroxamic acid. However, there is considerable difference in protonation constants between 1H2P ($\log K_{1H} = 5.86$) and an aliphatic hydroxamic acid, such as acetohydroxamic acid (AHA (6), $\log K_{1H} = 9.31$). The dramatic drop in the protonation constant for 1H2P reflects the electron-withdrawing influence of the aromatic ring. All of the substituted hydroxypyridinones studied previously such as, DH2P, MH2P and DMHP, have first protonation constants higher than 8 log units (Table 3). The unsubstituted 1H2P studied in the present work has a first protonation constant less than 6 log units. This difference in the protonation constants apparently gives 1H2P considerable advantage over the other ligands in binding metal ions up to pH ~7 since the competition with hydrogen ions is significantly less. Figures 10 and 11 show the Fe(III)-containing species formed as a function of pH in solutions containing 1:3:3 ratio of Fe(III):1H2P:AHA and Fe(III):1H2P:DMHP, respectively. For the Fe–1H2P–AHA system, AHA has actually no competition with 1H2P over the whole pH range if the precipitation of $Fe(OH)_3$ is considered (Fig. 10). Although the lower pK values of 1H2P favor the formation of its iron(III) chelates over those of DMHP in acid solution, the higher stability constants favor the formation of 1:3 Fe(III)–DMHP complex above pH ~7 (Fig. 11) but the situation is somewhat complicated by precipitation. If structurally similar ligands (coordinated through a hydroxy oxygen on the nitrogen atom in the pyridine ring and an adjacent keto oxygen atom) are compared, DH2P has higher basicity and lower stability, particularly for 1:2 and 1:3 complexes (distribution curves not shown). Undoubtedly, this difference is due to the 4-hydroxy group. As in the case of AHA, the ligand DH2P has almost no significant competition with 1H2P over the whole pH range as well. The effectiveness of these ligands in binding metal ions may be more suitably compared by considering pM ($-\log [M^{n+}]$) as a direct measure of the amount of free metal ion present at equilibrium. pM values are conditional, unlike stability constants, and can be calculated from corresponding complex stability constants and ligand protonation constants. The pM values listed in Table 4 were calculated for pH 4.0 at 10^{-3} M and 10^{-6} M concentrations of the 3:1 metal complex and equivalent excess ligand, respectively, assuming no metal hydrolysis and precipitation takes place. Obviously, 1H2P is much more effective in binding Fe(III) than are the others at pH 4.0. Thus it is seen that 1H2P is the most effective bidentate chelator of this class of ligands in acidic and neutral solution because of its relatively strong acidity. By comparing pM values at different concentrations of metal complexes, it is seen that 1H2P is much less effective at high dilution.

Figure 12 shows the correlation between the stability constants of various divalent metal ion complexes with acetohydroxamic acid and those with 1H2P. There is a good linear relationship ($r = 0.998$) between

TABLE 3 Protonation constants of ligands and stability constants of Fe(III) and In(III) complexes[a]

Ligand	Log K					
	Log K_1^H	Log K_2^H	FeL	FeL_2	FeL_3	InL
1-Hydroxy-2-pyridinone (1H2P)[b]	5.86	1.2	10.7	9.5	7.1	8.09
Acetohydroxamic acid (AHA)[c]	9.31		11.38			
	9.36[d]		11.42[d]	21.10[d]	29.33[d]	
1,4-Dihydroxy-2-pyridinone (DH2P)[e]	8.28	6.14	10.22	7.48	3.96	6.98
1-Methyl-3-hydroxy-2-pyridinone (MH2P)[e]	8.89		11.80	9.83	8.36	9.35
1,2-Dimethyl-3-hydroxy-4-pyridinone (DMHP)[e]	9.76	3.62	15.14	11.54	9.24	11.85

[a] $t = 25.0$ °C; $\mu = 0.100$ M (KCl). [b] This work. [c] Ref. 19. [d] $t = 20.0$ °C, ref. 19. [e] Ref. 10.

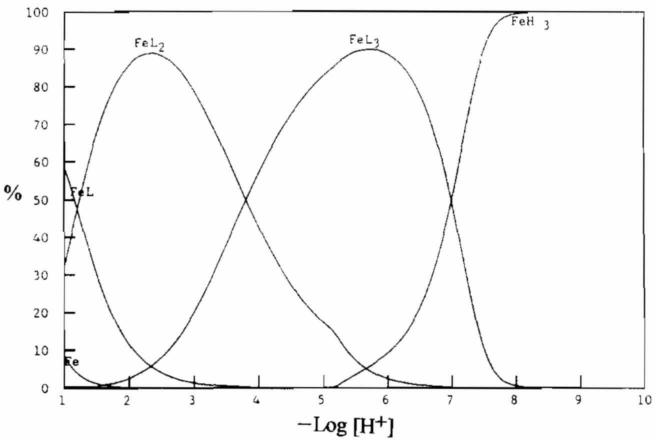

Fig. 10. Fe(III) distribution curves showing competition between 5.4×10^{-5} M 1H2P and 5.4×10^{-5} M AHA for 1.8×10^{-5} M Fe(III); L = 1H2P, L′ = AHA.

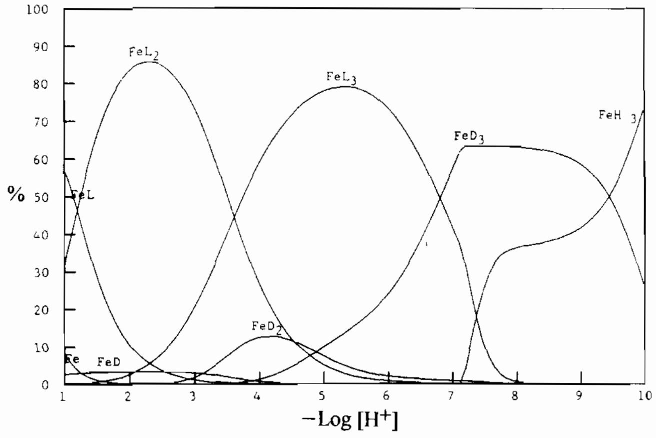

Fig. 11. Fe(III) distribution curves showing competition between 5.4×10^{-5} M 1H2P and 5.4×10^{-5} M DMHP for 1.8×10^{-5} M Fe(III), L = 1H2P, D = DMHP.

TABLE 4 pM Values for Fe(III) complexes[a]

Ligand	10^{-3} M	10^{-6} M
1H2P	17.0	11.7
DM2P	14.6	10.3
MH2P	10.8	9.7
DH2P	11.6	9.0
AHA	8.6	6.9

[a] t = 25.0 °C, μ = 0.100 M. For equivalent concentration of excess free ligand at pH 4.0

$\log K_{M\text{-}AHA}$ and $\log K_{M\text{-}1H2P}$. This correlation indicates that 1H2P and AHA exhibit similar complexation behavior toward these metal ions.

From plot of the stabilities of the Fe(III) or In(III) complexes against the basicities of some hydroxypyridinones (Fig. 13), the largest positive deviation is found for 1H2P. It means that 1H2P exhibits somewhat different coordination behavior compared to that of the other three ligands. There may be some steric hindrance in the coordination of metal ions for the substituted hydroxypyridinone ligands, leading to lower stabilities of the corresponding metal complexes. Steric hindrance may affect the nature and stoichiometry of the coordination complexes formed. The present results indicate that Zn(II) and Co(II) form 1:3 complexes with 1H2P but only 1:2 complexes are formed with DH2P, MH2P and DMHP [10]. The steric effect of the alkyl substituents may prevent the formation of 1:3 Zn(II) and Co(II) chelates with the substituted hydroxypyridinone ligands.

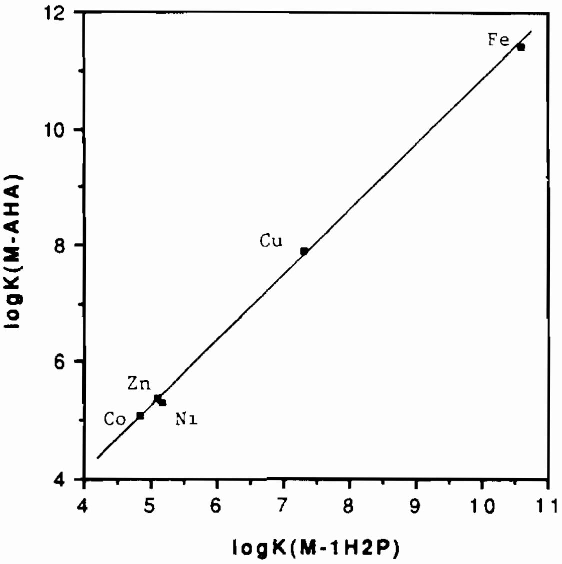

Fig 12 Correlation between the stability constants of various divalent metal ion complexes with acetohydroxamic acid(AHA) and 1-hydroxy-2-pyridinone(1H2P)

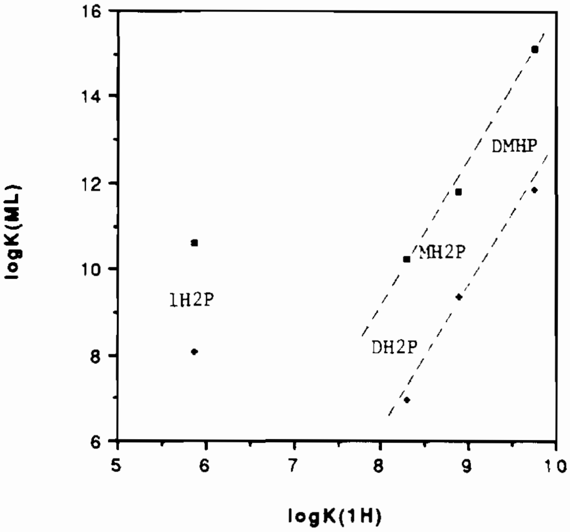

Fig 13. Correlation between the stabilities of Fe(III) and In(III) complexes and the basicities of some hydroxypyridinones.

Acknowledgement

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