1-Methyl-3-hydroxy-2-pyridinone and 1,4-dihydroxy-2-pyridinone complexes of the trivalent metal ions of Fe(III), Ga(III), Al(III), In(III) and Gd(III): potentiometric and spectrophotometric determination of stabilities

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Abstract

The trivalent metal ion stability constants for tris bidentate chelates of 1-methyl-3-hydroxy-2-pyridinone (MH2P) and 1,4-dihydroxy-2-pyridinone (DH2P) were determined by potentiometric and spectroscopic methods at 25.0 °C, 0.100 M KCl. The overall log stability constants for Fe(III) complexes (log $\beta FeL_3 = [FeL_3]/[Fe][L]^3$) are 29.99 and 28.18, respectively, and are lower than that of 1,2-dimethyl-3-hydroxy-4-pyridinone (DMHP), published previously (35.88). The placement of the bidentate hydroxy oxygen donors relative to the pyridyl nitrogen atom of the ligand influences the 3:1 stabilities for each of the trivalent metal ions studied (i.e. Fe(III), Ga(III), Al(III), In(III) and Gd(III)), as the relative order of stability is DMHP > MH2P > DH2P. Among these ligands, the relative order of magnitude of metal ion stability is Fe(III) > Ga(III) > Al(III) > In(III) > Gd(III). Influences of structural and inductive effects (resulting from hydroxyl and methyl substitution of hydroxypyridinone ligands) are evaluated.

Introduction

The investigation of oral iron chelating agents [1–3] for mobilization of Fe(III) ion from serum proteins, e.g. transferrin, lactoferrin and ferritin, and for the treatment of iron overload conditions [4–7] have prompted physicochemical characterization of three broad classes of hydroxypyridinone ligands [8–13] represented by the parent ligands: 1-hydroxy-2-pyridinone (**1**), 3-hydroxy-2-pyridinone (**2**), and 3-hydroxy-4-pyridinone (**3**). These are bidentate ligands coordinated through a hydroxy oxygen and an adjacent keto oxygen atom; their structural and electronic properties are related to hydroxamic acids, and **1** is actually a cyclic hydroxamic acid. They have been compared to catechol [8] but differ from it in one important respect: they have less than a formal charge of −2 on the bidentate oxygens of the dissociated (deprotonated) ligands, but more than a charge of −1, as explained by Martell *et al.* [9, 10]. The affinities of these ligands for hard metal ions would be expected to range from a little higher than those of the aliphatic hydroxamates to higher values, but considerably lower than those of the catecholates, which contain bidentate oxygen donors having a charge of −2. Alkyl derivatives of 3-hydroxy-4-pyridinone tend to be more efficient as Fe(III) chelating agents than 3-hydroxy-2-pyridinone and 1-hydroxy-2-pyridinone in clinical trials [2, 4, 5, 7]. Hydroxypyridinone ligands and their derivatives are also of interest as chelants of Al(III), Ga(III) [11, 14], In(III) [12, 15], Gd(III) [9] and the actinides [16].

The bivalent and trivalent metal ion stability constants of 1,2-dimethyl-3-hydroxy-4-pyridinone (DMHP, **4**), which is an effective chelating agent for Fe(III) [4–7], have been previously reported by Clarke and Martell [13] and by Motekaitis and Martell [9]; others have reported its trivalent metal ion stabilities [11, 12]. 1-Methyl-3-hydroxy-2-pyridinone (MH2P, **5**) and 1,4-dihydroxy-2-pyridinone (DH2P, **6**) have some effectiveness as oral iron chelating agents [1, 5]. Neutral tris complexes of DMHP with Fe(III) ion [17], Al(III) and Ga(III) ions [14], and In(III) ion [15] have been prepared and the X-ray crystal structures have been characterized, along with those of the tris Fe(III) chelates of 1-hydroxy-2-pyridinone and 3-hydroxy-2-pyridinone [8]. In addition, multidentate ligands containing three 1-hydroxy-2-pyridinone groups (and its thio carboxylic acid analog) have been prepared and characterized with a nitrogen cap [6], or capped with benzene [16], to provide hexadentate coordination to Fe(III) ion.

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However, trivalent metal ion complexes of unsubstituted 1-hydroxy-2-pyridinone (and 3-hydroxy-2-pyridinone) are insoluble in water [1, 8], thereby rendering the determination of their aqueous stability constants difficult [8]. Kontoghiorghes [1] has estimated the Fe(III) affinities of MH2P and DH2P with Job's plots, but these measurements have neglected the contributions from lower (2:1 and 1:1) species in determination of the overall (β_3) stability constant.

The objectives of the present paper are to determine the stability constants of MH2P and DH2P trivalent metal ion complexes of Fe(III), Ga(III), Al(III), In(III) and Gd(III) by equilibrium potentiometric and spectrophotometric methods, and to compare their stabilities to those of DMHP. The stabilities will be evaluated in terms of variation in structural and electronic properties of the hydroxypyridinone ligands as coordinating oxygen atoms are placed in different positions of the pyridyl ring structure.

Experimental

Ligands

Samples of 1-methyl-3-hydroxy-2-pyridinone (MH2P), or 'L2', and 1,4-dihydroxy-2-pyridinone, or 'L3', were kindly supplied by G. J. Kontoghiorghes for evaluation of their trivalent metal ion stabilities. MH2P has a formula weight of 125.6 Daltons (125, theoretical), from titration, and represents a purity of 99.5%, while DH2P was found to have a formula weight of 130 Daltons (127, theoretical), with 97.7% purity. As MH2P contains a hydroxyl group (in addition to having a keto oxygen at the 2-position), it has the neutral form, HL; whereas DH2P (Y), which contains hydroxy groups in the 4- and N-pyridyl positions, is in the neutral, H_2Y form.

Potentiometric titrations

The protonation constants of the ligands and their metal binding constants for complexes in the ligand-to-metal ratios of 1:1, 2:1 and 3:1 were determined by equilibrium potentiometric methods with glass electrodes at 25.0 °C, 0.100 M KCl. The formation constants of the 2:1 and 3:1 metal complexes of DH2P were determined by direct titration while holding the 1:1 metal formation constants at fixed values. The potentiometric data were converted to stability constants with the use of the program BEST [18]. Detailed descriptions of potentiometric determinations are found in ref. 19.

The potentiometric apparatus used to determine the protonation constants of the free ligands and their metal complexes consists of a glass jacketed titration cell, glass electrodes, and a 10-ml capacity Metrohm piston buret which delivers standard KOH titrant solution directly to the sealed cell through a buret tip which is secured to the cell cap with a clamp and O-rings. The electrodes and cell contents were thermostated by connection of the cell to a Haake temperature bath (25.0 °C) and were calibrated with standard acid and base to read p[H] directly (p[H] $= -\log[H^+]$). The ionic strength was adjusted to 0.100 M with KCl. Atmospheric CO_2 was excluded from the titration cell with a purging stream of purified argon gas.

The binding constants for the 2:1 and 3:1 ligand-to-metal complexes of the ligands (and the protonation constants of the metal complexes in the case of DH2P) were determined by potentiometry for solutions containing 2×10^{-3} M concentration in metal ion and with two or three molar equivalents of ligand. The 1:1 binding constants of MH2P (HL) metal complexes ($K_{ML}=[ML^{2+}]/[M^{3+}][L^-]$) with In(III), Al(III) and Gd(III) metal ions as well as the constants for the 1:1 DH2P (H_2Y) complexes ($K_{MHY}=[MHY^{2+}]/[M^{3+}][H^+][Y^{2-}]$) with In(III) and Gd(III) ions were determined by direct potentiometric titration of the 1:1 complex solutions (or the 4:1 solutions of the weak Gd(III) complexes). The 1:1 complexes of Fe(III) and Ga(III) with MH2P and DH2P, together with the Al(III)–DH2P complex, were determined at 10^{-4} M concentration in metal ion and ligand in separate experiments by spectroscopic methods at low p[H], because their complexes were fully formed below the lower limiting p[H] of potentiometric titrations (*c.* p[H] 2).

Once the value of the 1:1 formation constant (log K_{ML} or log K_{MHY}) was determined for each trivalent metal ion complex, the values of the binding constants for 2:1 and 3:1 complexes were calculated with BEST while holding the value of the 1:1 binding constant at a fixed value. Subsequently, adjustments were made in 1:1 formation constants for contributions of 2:1 and 3:1 species in all calculations of 1:1 solutions.

Spectroscopic determination of the 1:1 stability constants

Spectral determinations were made for the red colored Fe(III) chelates of MH2P and DH2P with a Perkin-Elmer 553 Fast Scan UV–Vis spectrophotometer equipped with 1.000 ± 0.001 cm matched quartz cells at 25.0 °C ($\mu=0.100$ M KCl). The spectra of Fe(III)–MH2P (1:1 complex) consist of a single family of curves at 580 nm and coincidentally as a second family of curves (without isosbestic point) at 400 nm (spectra not shown). Log K_{FeL} for Fe(III)–MH2P was determined by evaluation of the dissociation of the 1:1 complex at 580 nm ($\epsilon_{FeL}=1820$ M^{-1} cm^{-1}) over the p[H] range 2.207–1.100 ($\mu=0.100$ M KCl + HCl). The p[H] of the 1:1 solutions containing 10^{-4} M Fe(III) ion and ligand was lowered with added increments of 1.200 M HCl. The concentrations of the metal, ligand

and complex species were calculated from mass balance equations and with the use of a BASIC program written for this purpose.

Similarly, the 1:1 Fe(III) complex of DH2P (as the MHY^{2+} species) absorbs at 500 nm ($\epsilon_{MHY} = 1525$ M^{-1} cm^{-1}) at p[H] 2.5 and below, while the 2:1 Fe(III) complex (as $FeH_2Y_2^+$) absorbs at 400 nm. Log K_{FeHY} was calculated as the Fe(III) ion was induced to dissociate from the DH2P complex over the p[H] range 1.90–1.00. A correction was made for the presence of the $FeH_2Y_2^+$ species as it was determined by potentiometric titration of the 2:1 solution complex.

The absorbance spectra of the Ga(III) complex of MH2P and DH2P at 10^{-4} M concentration in the UV are coincident with the spectra of the free ligands at 300 and 285 nm, respectively. Ga(III)–MH2P (as ML^{2+}) and free MH2P (as HL) absorb also at 243 and 235 nm, respectively, with a broad isosbestic point at 240 nm. The extinction of the HL species at 235 nm is 3285 M^{-1} cm^{-1}, and corrected for ML^{2+} ($\epsilon_{ML(235)} = 860$ M^{-1} cm^{-1}), and was measured over the p[H] range 1.83 to 1.18 in order to calculate the Ga(III)–MH2P binding constant from mass balance equations and the following equilibria

$$HL + Ga(III) \rightleftharpoons GaL^{2+} + H^+ \quad (1)$$

$$L^- + H^+ \rightleftharpoons HL \quad (2)$$

An equilibrium proton displacement constant was calculated from eqn. (1) as log $K = [GaL^{2+}][H^+]/[HL][Ga^{3+}] = 2.33$, and the log protonation constant of MH2P in eqn. (2) was found to have the value 8.89. The formation constant (log K_{GaL}) was calculated as the log sum of the displacement constant and the protonation constant of MH2P to give log $K_{GaL} = 11.22 \pm 0.02$.

For calculation of the 1:1 binding constant of Ga(III)–DH2P (as log K_{GaHY}) it was necessary to evaluate the change in the absorbance spectra of the free ligand as it was displaced as H_3Y^+ at 265 nm over the p[H] range 0.24–0.09. The family of curves at 265 nm is unique to the H_3Y^+ species of DH2P, and no correction was necessary when using the extinction ($\epsilon_{H_3Y} = 2790$ M^{-1} cm^{-1}) to calculate the equilibrium constant for Ga(III)–DH2P (log $K = [GaHY^{2+}][H^+]^2/[H_3Y^+][Ga^{3+}] = 3.16$). The third protonation constant for DH2P, log $K_3^H = 0.12$, is assigned to the pyridyl nitrogen atom, as it was determined in a separate spectral experiment by analysis of the change in absorbance at 265 nm upon addition of 1.2 M HCl down to p[H] zero. The Ga(III) formation constant (log $K_{GaHY} = 17.7 \pm 0.1$) was subsequently calculated from log K relative to the overall protonation constant for DH2P (log $\beta_3^H = [H_3Y^+]/[Y^{2-}][H^+]^3 = 14.54$). In a similar manner, the binding constant for Al(III)–DH2P was computed as log $K_{AlHY} = 16.5 \pm 0.1$ from the reaction with H_3Y^+ at 265 nm over the p[H] range 0.28–0.05.

Results

Protonation constants of the ligands

For MH2P a single protonation constant (log $K_1^H = 8.89 \pm 0.01$) was obtained with BEST (25.0 °C, 0.100 M KCl) from the equilibrium titration profile (Fig. 1, Table 1). The potentiometric determinations of the 3:1 ligand-to-metal complexes in Fig. 1 are plotted relative to the m value, where m is the ratio of mol base to mol metal ion (a values, mole of base per mole of ligand, are 1/3 of the m values). For three molar equivalents of ligand (0.3 mmol), the neutral form of MH2P is placed at $m = 0$, while the break in the titration falls at $m = 3$. The single buffer region between $m = 0$ and $m = 3$ is therefore assigned to the 3-hydroxy group of MH2P. There is no potentiometric (or spectral) evidence of a second protonation constant for MH2P in the p[H] profile below $m = 0$, since all of the acidity below p[H] 5.7 is explained by the presence of excess mineral acid.

Two protonation constants were determined for DH2P by direct potentiometric titration (Fig. 2, Table 1) with breaks falling at $m = 3$ and $m = 6$: log $K_1^H = 8.28 \pm 0.01$ and log $K_2^H = 6.14 \pm 0.01$ are assigned to the 4-hydroxyl and N-hydroxyl positions, respectively. For reference, log K_1^H for 1-hydroxy-2-pyridinone (**1**) is 5.76 ± 0.01 (25.0 °C, 0.100 M KCl). A third protonation constant for DH2P (log $K_3^H = 0.12 \pm 0.03$) was determined by spectral titration at very low p[H] and is assigned to the pyridyl nitrogen atom (see 'Experimental').

Stability constants

The equilibrium potentiometric profiles of the tris bidentate complexes with Fe(III), Ga(III), Al(III) and In(III) ions that are formed with MH2P and DH2P are shown in Figs. 1 and 2, respectively. For MH2P, the trivalent metal ion complex titration curves are quite normal with a strong inflection showing complete 3:1 complex formation at $m = 3$, as expected. The trivalent metal ion complexes of DH2P are formed at $m = 6$, owing to the acidity of the second hydroxyl group at the remote 4-position. The 3:1 complexes are unstable at p[H] values near 8–9 where the metal ions are initially hydrolyzed to form the trihydroxo metal precipitates of Fe(III), Al(III), and In(III). The Ga(III) complexes dissociate Ga(III) metal ion within this p[H] range to form the soluble gallate anion, $Ga(OH)_4^-$. The profiles of Gd(III) complexes are not included in Figs. 1 and 2 since the Gd(III) determinations were made in 4:1 solutions. The 1:1, 2:1 and 3:1 formation

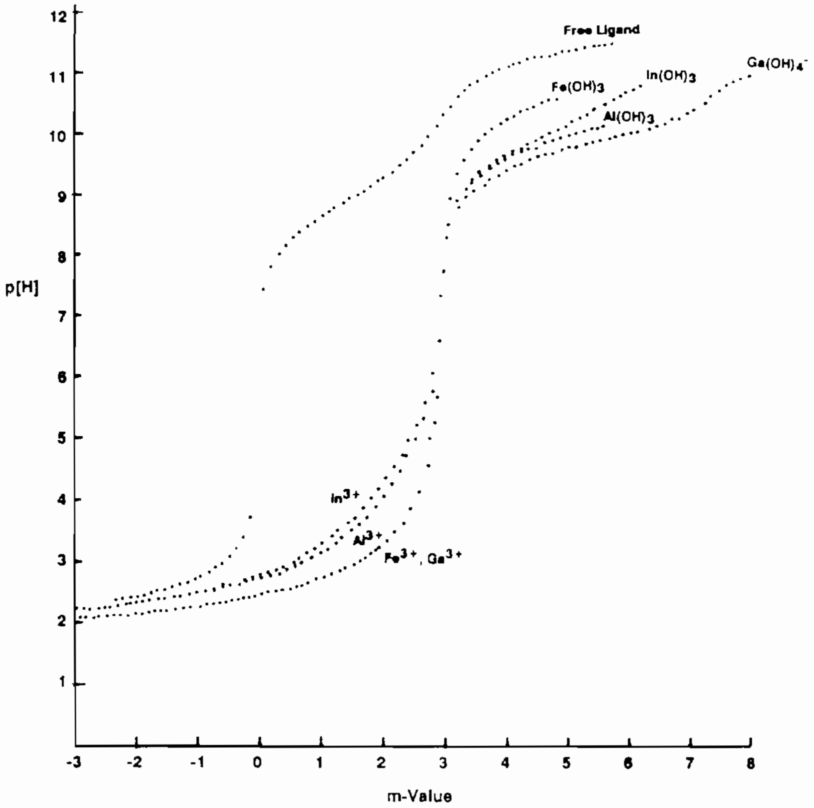

Fig. 1. Titration profile of MH2P (0.3 mmol) and its 3:1 complexes with metal ions. Excess mineral acid was added. *m* Value = ratio mole base per mole metal ion.

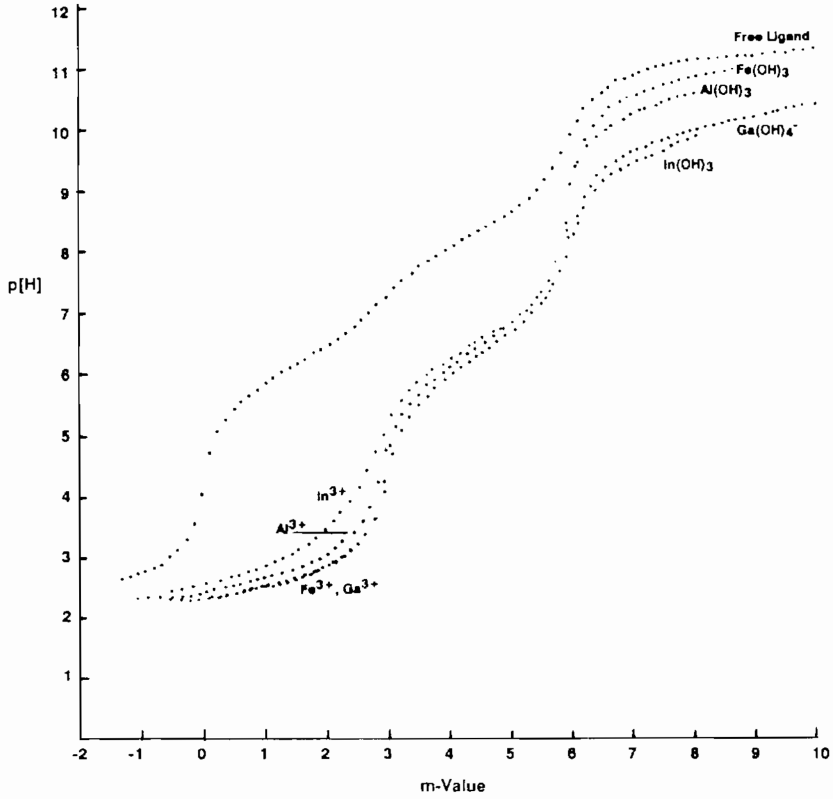

Fig. 2. Titration profile of DH2P (0.3 mmol) and its 3:1 complexes with metal ions. Excess mineral acid was added. *m* Value = ratio mole base per mole metal ion.

TABLE 1. Stability constants for chelates of 1,4-dihydroxy-2-pyridinone (DH2P)[a], 1-methyl-3-hydroxy-2-pyridinone (MH2P)[b] and 1,2-dimethyl-3-hydroxy-4-pyridinone (DMHP)[c], in complexes with Fe(III), Ga(III), In(III), Al(III) and Gd(III). Log K (25.0 °C, μ = 0.100 M KCl)

Quotient/Metal Ion	Ligand		
	DH2P[d]	MH2P	DMHP[e]
$[ML]/[M][L]$			
Fe(III)		11.8(1)	15.1(1)
Ga(III)		11.2(1)	13.17(2)
In(III)		9.35(3)	11.85(2)
Al(III)		9.41(1)	12.20(3)
Gd(III)		6.36(2)	7.82(2)
$[MHL]/[M][H][L]$			
Fe(III)	18.5(1)		
Ga(III)	17.7(1)		
In(III)	15.26(2)		
Al(III)	16.5(1)		
Gd(III)	14.41(2)		
$[ML_2]/[M][L]^2$			
Fe(III)	21.31(3)	21.63(3)	26.61(3)
Ga(III)	22.48(3)	21.10(2)	25.43(2)
In(III)	17.22(4)	17.35(1)	22.48(2)
Al(III)	21.20(2)	17.79(2)	23.25(2)
Gd(III)		11.64(2)	13.86(2)
$[MHL_2]/[M][L]^2[H]$			
Fe(III)	25.62(2)		
Ga(III)	29.00(2)		
In(III)	24.45(3)		
Al(III)	27.22(5)		
Gd(III)			
$[MH_2L_2]/[M][L]^2[H]^2$			
Fe(III)	34.26(1)		
Ga(III)	34.25(1)		
In(III)	29.89(1)		
Al(III)	32.64(2)		
Gd(III)			
$[ML_3]/[M][L]^3$			
Fe(III)	28.18(3)	29.99(3)	35.88(3)
Ga(III)	25.96(2)	29.66(3)	35.76(3)
In(III)	22.29(2)	24.44(1)	31.71(4)
Al(III)	25.16(1)	25.10(3)	32.62(4)
Gd(III)		15.68(4)	17.33(3)
$[MHL_3]/[M][L]^3[H]$			
Fe(III)	35.02(4)		
Ga(III)	29.53(4)		
In(III)	29.20(3)		
Al(III)			
Gd(III)			
$[MH_2L_3]/[M][L]^3[H]^2$			
Fe(III)	41.35(3)		
Ga(III)			
In(III)			
Al(III)			
Gd(III)			

[a] Log protonation constants for DH2P (25.0 °C, 0.100 M KCl): log $K_1^H = 8.28(1)$, log $K_2^H = 6.14(1)$ and log $K_3^H = 0.12(3)$. [b] Protonation constant for MH2P (25.0 °C, 0.100 M KCl): log $K_1^H = 8.89(1)$. [c] Protonation constants for DMHP were originally published in ref. 13: log $K_1^H = 9.77(1)$ and log $K_2^H = 3.68(2)$. [d] DH2P (H_2Y) does not form an MY^+ complex species because the 4-OH group of the ligand remains associated in MHY^{2+} species at low p[H]. At higher p[H], the 4-hydroxyl proton may be dissociated in 2:1 and 3:1 complexes with the trivalent metal ions. [e] Ref. 13.

constants for Gd(III)-MH2P (Table 1) were calculated from titrations up to p[H] 8, but the formation of a heavy hydrolytic precipitate in the Gd(III)-DH2P solutions at and above p[H] 4.7 precluded stability determinations except for the 1:1 ($GdHY^+$) complex. Stability constants for the 1:1, 2:1 and 3:1 formation constants of MH2P and DH2P are summarized in Table 1, and are compared to the literature constants for DMHP [11] for purposes of discussion.

Most of the 1:1 formation constants were determined by direct potentiometric methods as described in 'Experimental'. The determinations of the Fe(III) and Ga(III) 1:1 stability constants required the use of spectral titration methods since these complexes were fully formed at the initiation of the potentiometric titration. The Fe(III) stabilities of MH2P (HL) and DH2P (H_2Y) were computed by spectrophotometric evaluation of the dissociation of their red colored complexes at 580 and 500 nm, respectively (spectra not shown): $\log K_{FeL} = 11.8 \pm 0.1$ and $\log K_{FeHY} = 18.5 \pm 0.1$ (Table 1). The 1:1 formation constants for DH2P are reported as $\log K_{MHY} = [MHY^{2+}]/[M^{3+}][H^+][Y^{2-}]$ because the equilibrium $MHY^{2+} \rightleftharpoons MY^+ + H^+$ was not observed where the 1:1 complex species remained protonated at the 4-hydroxyl position. Therefore the stabilities of the metal ion complexes of DH2P, MH2P and DMHP are reported as β values in Table 1 for purposes of direct comparison.

The Ga(III) stabilities of MH2P and DH2P were calculated from spectral measurements of the displacement of the free ligands from their colorless metal complexes in the UV. In Fig. 3, free MH2P, which absorbs at 235 nm, is displaced as HL from the ML^{2+} complex. The extinction of HL at 235 nm ($\epsilon = 3285$ M^{-1} cm^{-1}) was used with correction for baseline contribution to calculate the Ga(III)-MH2P formation constant as $\log K_{GaL} = 11.2 \pm 0.1$ (Table 1). The family of curves at 300 nm in Fig. 3 was not used for calculation since this absorbance is a composite of HL, ML^{2+} and ML_2^+ species. A second composite absorbance (with an isosbestic point at 218 nm) lies at 205 nm.

In Fig. 4, the displacement of DH2P as the H_3Y^+ species is shown at 265 nm, while the absorbance at 285 nm is attributed to a mixture of H_2Y and MHY^{2+}

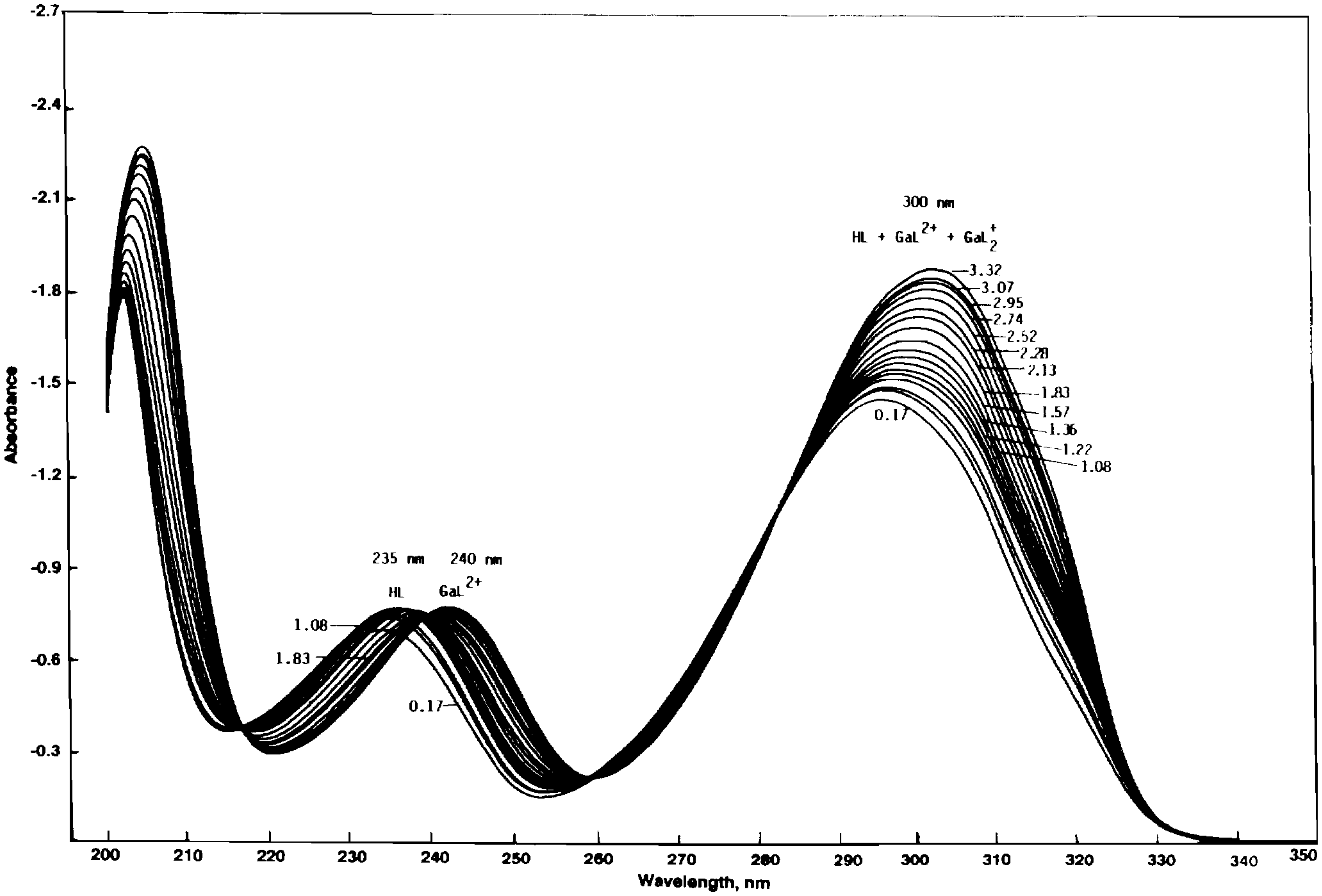

Fig. 3. Absorbance of 1:1 Ga(III)-MH2P at indicated p[H] values. $T_M = 1.796 \times 10^{-4}$ M, $T_L = 1.815 \times 10^{-4}$ M ($t = 25.0$ °C, $\mu = 0.100$ M KCl+HCl). The extinction of the HL species at 235 nm is 3285 M^{-1} cm^{-1}.

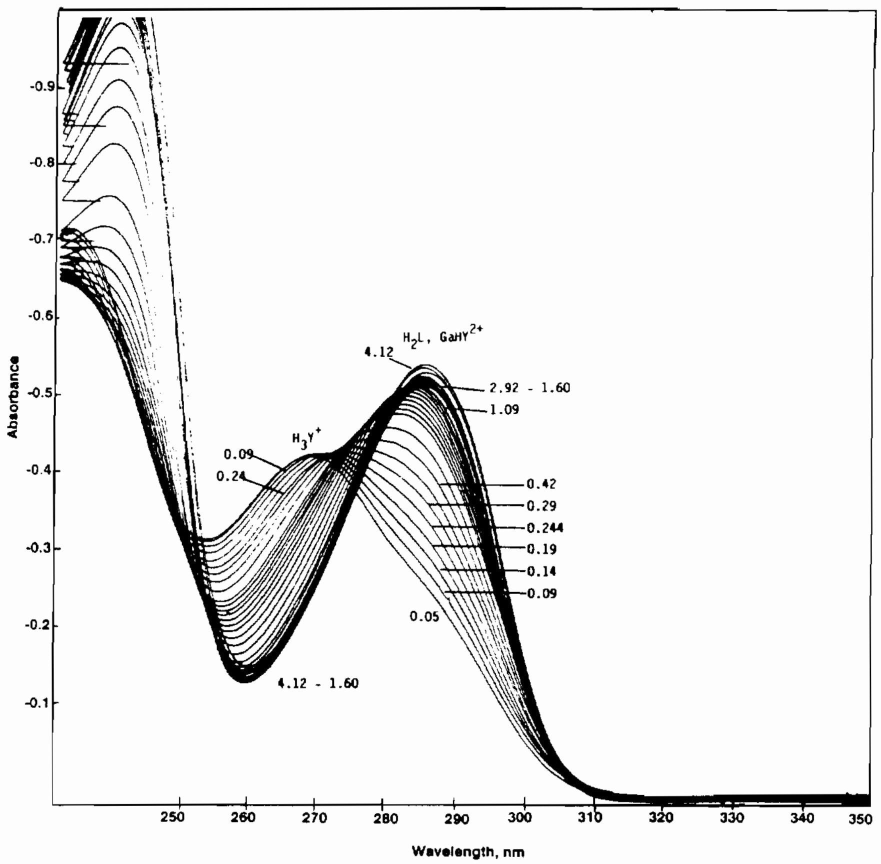

Fig. 4. Absorbance of 1:1 Ga(III)-DH2P (GaY) at indicated p[H] values. $T_M = 1.535 \times 10^{-4}$ M, $T_Y = 1.529 \times 10^{-4}$ M ($t = 25.0$ °C, $\mu = 0.100$ M KCl+HCl). The extinction of the H_3Y^+ species at 265 nm is 2790 M^{-1} cm^{-1}.

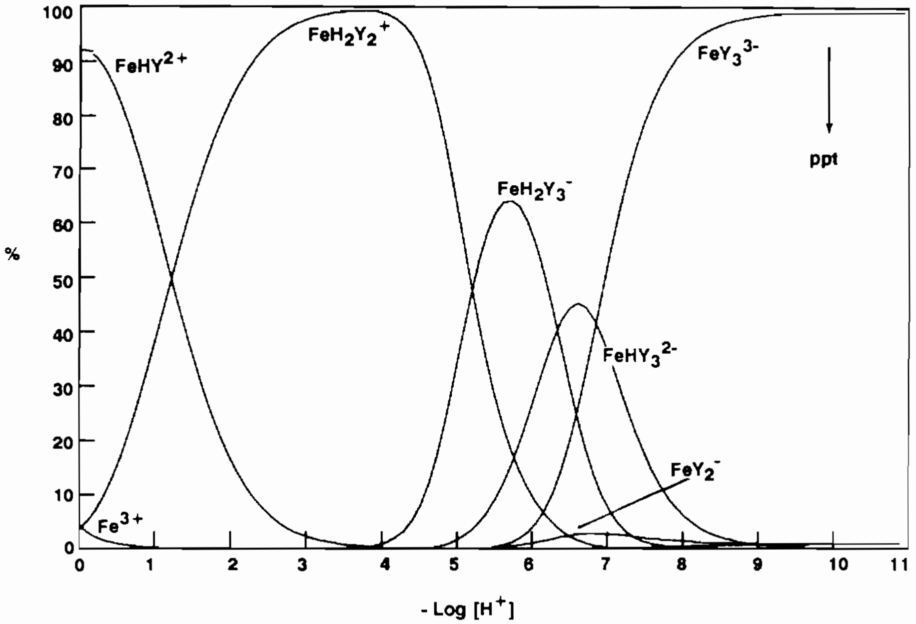

Fig. 5. Distribution of Fe(III) in 1:1, 2:1 and 3:1 complexes with DH2P (Y) ($t = 25.0$ °C, $\mu = 0.100$ M KCl) for 2×10^{-3} M Fe(III). The distribution curves were calculated from the stability constants that appear in Table 1.

species. A composite absorption occurs at 240 nm. The extinction of H_3Y^+ at 235 nm ($\epsilon = 2790$ M^{-1} cm^{-1}) was used to calculate the Ga(III)–DH2P 1:1 binding constant ($\log K_{GaHY}$) as 17.7±0.1. A similar spectral titration of Al(III)–DH2P gave $\log K_{AlHY} = 16.5$ (Table 1).

The species distribution curves for Fe(III)–DH2P (Fig. 5) were calculated from the stability constants reported in Table 1. The 1:1 $FeHY^{2+}$ species is formed to the extent of 92% at p[H] zero and is transformed into the diprotonated 2:1 species, $FeH_2Y_2^+$, at p[H] 3.4. (The protons are assigned to the 4-hydroxyl groups of the ligand.) Between p[H] 5 and 7 the 2:1 complex is converted to the protonated 3:1 complex species, $FeHY_3^{2-}$ and $FeH_2Y_3^-$. At p[H] 7 and above, the tribasic FeY_3^{3-} species becomes the dominant 3:1 com-

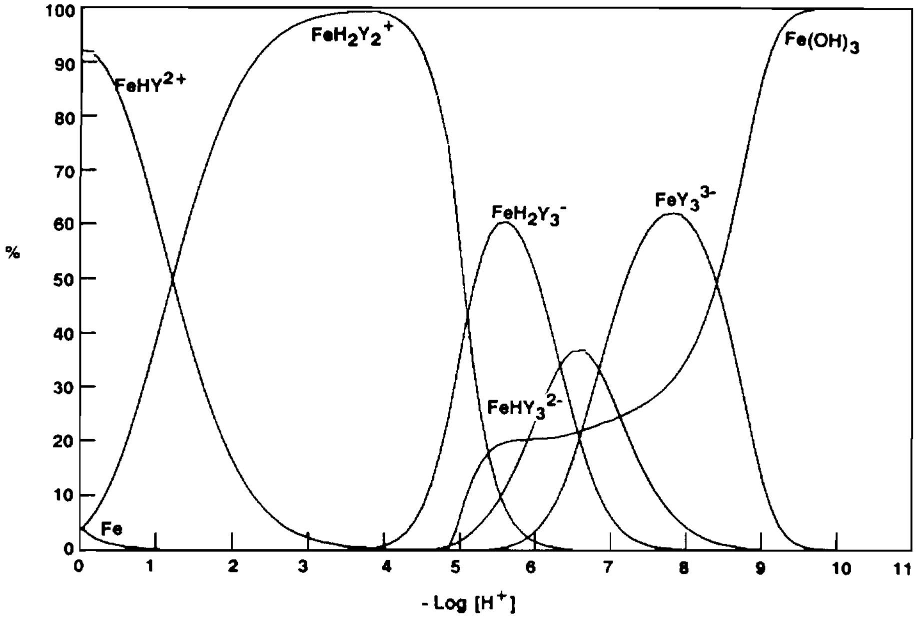

Fig. 6. Distribution of Fe(III)–DH2P (FeY) complexes (1:1, 2:1 and 3:1). Conditions of metal and ligand are the same as in Fig. 5 except that the distribution is calculated in the presence of soluble $Fe(OH)_3$ ($\log K_{sol} = [Fe^{3+}][OH^-]^3 = 36.8$), from ref. 20.

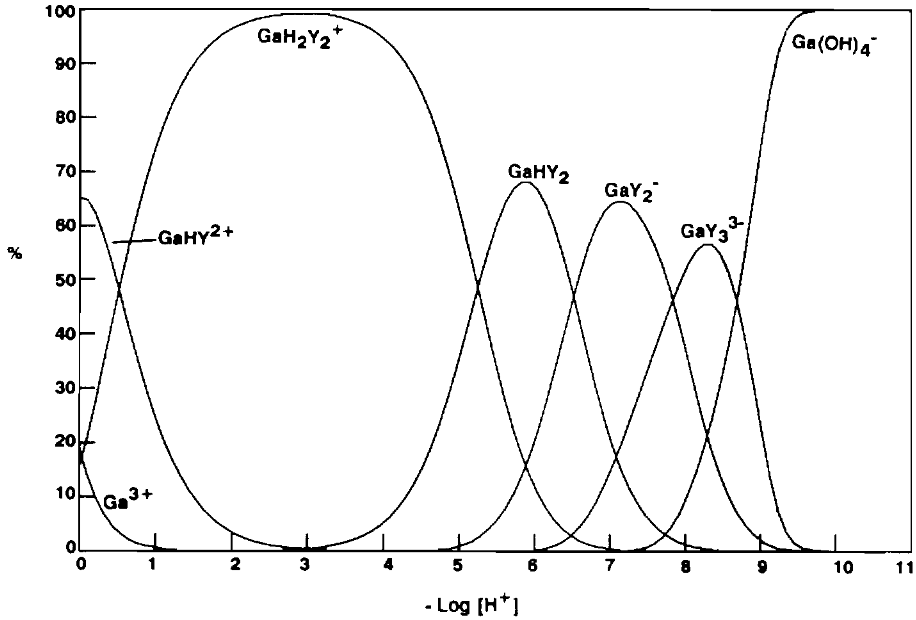

Fig. 7. Distribution of Ga(III) in 1:1, 2:1 and 3:1 complexes of DH2P (Y) ($t = 25.0$ °C, $\mu = 0.100$ M KCl) for 2×10^{-3} M Ga(III). The gallate formation constant, $-\log K_{Ga(OH)_4^-} = 16.81$, is taken from ref. 21. The complex stability constants for Ga(III)–DH2P are presented in Table 1.

plex. The p[H] at which the $Fe(OH)_3$ precipitate eventually appears after 12 h is indicated in Fig. 5. Figure 6 shows how species distribution would be affected by $Fe(OH)_3$ precipitation. For the purposes of calculation of the distribution of solution species in the presence $Fe(OH)_3$, the solubility product of $Fe(OH)_3$ ($K_{sol} = [Fe^{3+}][OH^-]^3$) was taken as $10^{-38.6}$ from ref. 20. The $Fe(OH)_3$ curve shows the amount of $Fe(OH)_3$ precipitated in equilibrium with the complexes in solution. The distribution of $FeHY_3^{2-}$ and FeY_3^{3-} is changed in the presence of $Fe(OH)_3$ to 35% and 65% formation at p[H] 6.8 and 7.9, respectively.

The distribution pattern for Ga(III)–DH2P (Fig. 7) is different from the Fe(III) complex in that the 2:1 Ga(III) species is transformed in a stepwise series of dissociations of the 4-hydroxyl groups for the series, $GaH_2Y_2^+$, $GaHY_2$ and GaY_2^-, over the p[H] range 5.5 to 9.0. These 2:1 complexes are formed at the exclusion of protonated 3:1 species. At p[H] 9 and greater, gallate anion is predicted to be the dominant species ($-\log K_{Ga(OH)_4^-} = 16.81$) [21]. The preference of DH2P for Fe(III) ion ($\log \beta_{FeY_3} = 28.18$) over Ga(III) (25.96) may explain the differences in metal complex species distributions. (An alternative explanation could be that Ga(III) prefers to form four-coordinate structures with DH2P). By contrast, Ga(III)–MH2P completely forms as the 3:1 GaL_3 species which is dominant over the p[H] range 3.5–9.5, and as the 2:1 GaL_2^+ and 1:1 GaL^{2+} species, which are formed 70% and 25%, respectively, at p[H] 2.3 (distribution not shown).

For each ligand, the relative order of trivalent metal ion stability constants appears to be Fe(III) > Ga(III) > Al(III) > In(III) ≫ Gd(III) in Table 1. Among the ligands, the metal stabilities of DMHP [13] are greater than those of MH2P, while those of DH2P are lowest in comparison to the other two ligands, with the exception of the stabilities of Al(III) complexes of DH2P and MH2P, which are of near equal value ($\log \beta_{ML_3} = 25.16$). The influence of structure and inductive effects on the stabilities of this series of hydroxypyridinone ligands are the subject of the discussion.

TABLE 2. Evaluation of structural influences on trivalent metal ion complexes of the hydroxypyridinones

Metal ion	Log *K*		
	DH2P (H2Y)	MH2P (HL)	DMHP (HL′)
1:1 Complex	M(HY)	ML	ML′
Fe(III)	10.22	11.8	15.1
Ga(III)	9.42	11.2	13.17
In(III)	6.98	9.35	11.85
Al(III)	8.22	9.41	12.20
2:1 Complex	$M(HY)_2$	ML_2	ML'_2
Fe(III)	17.7	21.63	26.61
Ga(III)	17.69	21.10	25.43
In(III)	13.33	17.35	22.48
Al(III)	16.08	17.79	23.25
3:1 Complex	$M(HY)_3$	ML_3	ML'_3
Fe(III)[a]	21.66	29.99	35.88

[a] Calculated by correlation with 3-hydroxy-2-pyridinone and 3-hydroxy-4-pyridinone, from ref. 8: $\log \beta_{FeH_3Y_3}$ is estimated to be 46.5. (Correlation of this type for the other trivalent metal ions was not possible.)

TABLE 3. Evaluation of inductive influences of hydroxyl and methyl substitution for the stepwise Fe(III) stabilities

Complex	Log *K*					
	Hydroxy substitution		Methyl substitution		Dimethyl substitution	
	DH2P	1H2P[a]	MH2P	3H2P[a]	DMHP	3H4P[a]
1:1	10.22	NB	11.8	11.48	15.1	14.26
2:1	7.48	9.04	9.83	9.77	11.51	11.47
3:1	3.96	7.55	8.36	8.01	9.27	9.18

[a] Abbreviations for the reference ligands [8] are as follows: 1-hydroxy-2-pyridinone (1H2P); 3-hydroxy-2-pyridinone (3H2P); and 3-hydroxy-4-pyridinone (3H4P). The Fe(III) stabilities [8] for these reference compounds were determined at 10^{-5} M concentrations in 10.00 cm cells to adjust for the low solubilities of these complexes in water.

Discussion

The formation constants obtained in this investigation are compared with those of DMHP (1,2-dimethyl-3-hydroxy-4-pyridinone) or L1 in Table 1. In Table 2 the stabilities of DH2P are written in a form such that the proton is still present on the metal chelate, presumably on the remote phenol groups. Therefore the comparison shows the electron-withdrawing effect of the remote phenolic groups in decreasing the stabilities of the various complexes listed. In all cases the stabilities of the DMHP complexes are much higher than those of the ligands studied in this investigation. Also, the presence of the second phenolic group apparently reduces the stabilities of the metal complexes. The evidence for this is in the comparison of the stabilities of the DH2P complexes containing the hydroxyl group in the four position when they are compared with analogous complexes which do not contain the second hydroxy group. For all the complexes listed, the stabilities of the ligand not containing the second hydroxyl group are appreciably higher than those with the electron-withdrawing group present.

An even more effective and convincing comparison is that of the three ligands discussed in Table 2 with the parent unsubstituted compounds, **1**, **2** and **3**. This comparison is made in Table 3. One sees right away the much greater stability of the complexes formed from 3H4P and DMHP. The main effect observed here is the remoteness of the two donor oxygens from the partially positive nitrogen of the pyridine ring. Apparently the 3-hydroxy-4-pyridinone structure gives the most stable iron chelates. The effect of methyl substitution is also obvious from the data in Table 3. One methyl produces a small but definite increase in the stability of the iron complexes as is obvious from the comparison of the stabilities of 3H2P and MH2P. A further effect obtained by adding two methyl groups is seen in the two columns on the right of Table 3 in which DMHP complexes of iron are compared with 3H4P complexes. The considerable electron-withdrawal effect of the second hydroxy group on the stabilities of the Fe(III) complexes is seen in the first two columns of Table 3 in which the complexes formed from DH2P are much less stable than the complexes formed from the parent compound, without the hydroxy group, 1H2P.

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