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Stabilities of 1,2-dimethyl-3-hydroxy-4-pyridinone chelates of divalent and trivalent metal ions

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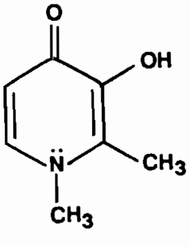
Abstract

The stepwise stability constants of the 1:1, 2:1 and 3:1 complexes of bidentate 1,2-dimethyl-3-hydroxy-4-pyridinone (DMHP) with divalent and trivalent metal ions have been determined in KCl supporting electrolyte (0.100 M) at 25.0 °C. The overall log stability constant (log $\beta_{ML_3}=[ML_3]/[M^{3+}][L^-]^3$) for the Fe(III) and Ga(III) complexes are high, 35.88 and 35.76, respectively. The log β_{ML_3} values for the Al(III) and In(III) complexes with DMHP are 32.62 and 31.71, respectively, while that for the weak complex with Gd(III) is 17.33. The divalent metal ions of Cu(II), Ni(II), Co(II) and Zn(II) form stable 1:1 and 2:1 complexes with DMHP.

Introduction

The bidentate hydroxypyridinone ligand, 1,2-dimethyl-3-hydroxy-4-pyridinone (DMHP), is of interest in medicinal chemistry as a therapeutic agent [1–3] which forms stable hexacoordinate 3:1 ligand to metal complexes with Fe(III) for treatment of iron overload conditions [4–8]. It is also of neurological interest as it forms similar complexes with Al(III) [2, 3, 9] as well as Ga(III) [3, 9] and In(III) [10], which are used for the radioisotopic imaging of tumors [4, 5, 7, 9]. These observations have motivated determinations of the aqueous stability constants for the 1:1, 2:1 and 3:1 chelates with Fe(III), Ga(III), Al(III) and In(III).



DMHP

Spectrometric determinations of the Fe(III) stabilities with unsubstituted hydroxypyridinones have been reported by Scarrow *et al.* [11] while conditional stability constants for Fe(III) complexes with DMHP and the alkyl derivatives of 1-hydroxy-2-pyridinones have been estimated by Kontoghiorges [1]. Recently, accurate stability constants have been determined by spectrophotometric and potentiometric methods for the 1:1, 2:1 and 3:1 Fe(III)–DMHP chelates [12]. Other determinations of stability constants for complexes of DMHP with Al(III), Ga(III) and In(III) have been reported by Orvig and co-workers [13, 14], as well as determinations of similar metal complexes with the phenyl and methyl substituted hydroxypyridinone analogs of DMHP [15]. The purpose of the present paper is to determine divalent and trivalent metal ion stabilities with DMHP in a single paper, and to include a determination for Gd(III), since Gd(III) chelates have been used as paramagnetic ^{1}H NMR contrast agents [16–18] for the imaging of tissues.

Experimental

Characterization of ligand

A sample of DMHP (800 mg) was supplied by M. M. Jones of Vanderbilt University. The sample was tritrated and found to be pure with a formula weight of 137 Daltons (theoretical, 139). DMHP is the neutral form, HL.

Potentiometric determinations

Equilibrium potentiometric determinations of the ligand protonation constants and its metal binding constants for complexes in ligand to metal ratios of 1:1, 2:1 and 3:1 were carried out by the glass electrode

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method at 25.0 °C, 0.100 M (KCl), and with the use of the program BEST [19]. Details of the potentiometric determinations are found in ref. 20.

The potentiometric apparatus consists of a glass jacketed titration cell, a temperature bath (Haake, 25.0 °C) glass, reference electrodes, and a 10 ml capacity Metrohm piston buret, for which the buret tip was sealed in the cap of the titration cell with a clamp and O-rings. The electrodes were calibrated in a thermostated cell 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 metal chelates of DMHP were prepared as 3:1 complexes at 2×10^{-3} M concentration in metal ion and with three molar equivalents of ligand. Most of the metal binding constants were calculated from direct potentiometry, but the first binding constants ($K_{ML} = [ML^{2+}]/[M^{3+}][L^-]$ of the 1:1 complexes with the Fe(III) and Ga(III) chelates were determined at 10^{-4} M in separate experiments by spectroscopic methods at low p[H] since their complexes were formed completely over the range of potentiometric titration, as described below. On the other hand, the 1:1 binding constants for the Al(III) and In(III) complexes were determined directly by potentiometric methods in additional experiments.

In order to provide potential eight-coordination to the Gd(III) metal ion, a solution of Gd(III)–DMHP was prepared to contain 2×10^{-3} M Gd(III) ion and four equivalents of ligand. Potentiometric titration of the divalent metal ion complexes with Cu(II), Ni(II), Co(II) and Zn(II) were carried out in 3:1 solutions to allow for the possible formation of ML_3 species.

Once the value of K_{ML} was determined for each trivalent metal ion complex, the values of the binding constants for ML_2 and ML_3 species were calculated by BEST from direct titration of the 3:1 solutions while holding the value of K_{ML} constant. Then, an adjustment was made in K_{ML} subsequently for the presence of ML_2 and ML_3 species in all calculations of 1:1 solutions.

Spectrophotometric evaluation of stability constants

Spectral determinations were made for the Fe(III) and Ga(III) chelates of DMHP with a Perkin-Elmer 553 fast scan UV–Vis spectrophotometer equipped with 1.000±0.001 cm matched quartz cells at 25.0 °C (I = 0.100 M KCl). The spectra of the 3:1 Fe(III)–DMHP complex (not shown) are distributed into three well defined zones corresponding to the 3:1, 2:1 and 1:1 species. For Fe(III)–DMHP (1:1), log K_{ML} was determined by spectrophotometric evaluation of the dissociation of the Fe(III) complex at 568 nm (ϵ(FeL) = 1630 M^{-1} cm^{-1}). Fe(III) was induced to dissociate from the Fe(III) complex by lowering the p[H] of a series of bottles containing 10^{-4} M Fe(III) and three equivalents of ligand with added increments of 1.2 M HCl down to p[H] 0.70. For purposes of calculation of the Fe(III) stability constant, the absorbances at 568 nm were used in the range of p[H] 0.10 to 1.4, for which the ionic strength was adjusted to 0.100 M in HCl + KCl. The concentrations of the appropriate metal, ligand and complex species were calculated from mass balance equations and with the use of a BASIC program written especially for this purpose.

Similarly, a series of solutions containing 10^{-4} M Ga(III)–DMHP (as a 1:1 complex) was analyzed spectrophotometrically over the p[H] range from p[H] 0.690 to 3.343, for which the most useful p[H] points were selected between p[H] 2.005 and 1.400. Ga(III)–DMHP absorbs at 295 nm while the free ligand absorbs at 285 nm as HL and at 246 nm as H_2L^+ ($\epsilon(H_2L^+) = 3855$ M^{-1} cm^{-1}). Since the family of curves at 246 nm is distinct from the others, log K_{ML} (25.0 °C, 0.100 M KCl) for Ga(III)–DMHP was calculated from mass balance equations and the following equilibria:

$$H_2L^+ + Ga(III) \rightleftharpoons GaL^{2+} + 2H^+ \qquad (1)$$

$$L^- + 2H^+ \rightleftharpoons H_2L^+ \qquad (2)$$

An exchange constant was calculated from eqn. (1) as $\log K = [GaL][H]^2/[H_2L^+][Ga^{3+}] = -0.28$, and the stability constant (log K_{GaL}) was subsequently calculated from log K relative to the overall protonation constant

TABLE 1. Stability constants for chelates of DMHP with Fe(III), Ga(III), Al(III) and In(III)[a]

Quotient	Clevette *et al.* [13, 14] I=0.15 M NaCl, t=25.0 °C	Present work I=0.10 M KCl, t=25.0 °C
[HL]/[L][H]	9.86(3)	9.77(1)
$[H_2L]/[HL][H]$	3.70(1)	3.68(2)
[FeL]/[Fe][L]	15.14[b]	15.10(1)
$[FeL_2]/[FeL][L]$	11.54[b]	11.51(3)
$[FeL_3]/[FeL_2][L]$	9.24[b]	9.27(5)
$[FeL_3]/[Fe][L]^3$	35.92[b]	35.88(5)
[GaL]/[Ga][L]	17.07(7)	13.17(2)
$[GaL_2]/[GaL][L]$	12.19(9)	12.26(2)
$[GaL_3]/[GaL_2][L]$	9.16(10)	10.33(3)
$[GaL_3]/[Ga][L]^3$	38.42(10)	35.76(3)
[AlL]/[Al][L]	11.91(2)	12.20(3)
$[AlL_2]/[AlL][L]$	10.92(2)	11.05(2)
$[AlL_3]/[AlL_2][L]$	9.42(5)	9.37(4)
$[AlL_3]/[Al][L]^3$	32.2(5)	32.62(4)
[InL]/[In][L]	13.60(2)	11.85(2)
$[InL_2]/[InL][L]$	10.33(3)	10.63(2)
$[InL_3]/[InL_2][L]$	9.00(4)	9.23(4)
$[InL_3]/[In][L]^3$	32.93(4)	31.71(4)

[a]The numbers in parentheses represent the errors of the last significant figures. [b]Ref. 12: 0.10 M (KCl), t = 25.0 °C.

of DMHP ($\log \beta_2^H = [H_2L^+]/[L^-][H]^2 = 13.45$), from eqn. (2):

$$\log K_{GaL} = \log K + \log \beta_2^H = [GaL^{2+}]/[Ga^{3+}][L^-] = 13.17$$

Results

Protonation constants of DMHP

DMHP was obtained as the neutral form, HL, with the proton ($\log K_1^H = [HL]/[L^-][H] = 9.77$) going to the hydroxy group. A second proton (supplied by excess mineral acid) is assigned to the pyridyl nitrogen atom ($\log K_2^H = [H_2L^+]/[HL][H] = 3.68$). Potentiometric p[H] measurements are illustrated in Fig. 1. The stepwise protonation constants, presented in Table 1, show good agreement with the literature values [13, 14].

Trivalent stability constants

The shapes of the potentiometric p[H] curves in Fig. 1 show a break for the trivalent metal ion complexes at $m = 3$ (m = mole of base per mole of metal ion). The Fe(III) and Ga(III) titration curves are strong acid curves, indicative of complete formation of the 1:1 metal complex. Spectrophotometric evaluation of the dissociation of the 1:1 Fe(III)-DMHP complex at low p[H] gave a $\log K_{ML} = 15.10$ (Table 1) in agreement with Motekaitis and Martell [19]. Fe(III)-DMHP forms colored complexes in the red (Fig. 2); and FeL and FeL_2 complexes are distinctly discerned at 568 and 510 nm, respectively. An isosbestic point at 620 nm indicates that the FeL and FeL_2 (and possibly FeL_3) complexes were present and these were interconverted into each other as a function of hydrogen ion concentration. Values for the second and third stepwise binding constants as well as the overall binding constants ($\beta_{ML_3} = [ML_3]/[M^{3+}][L^-]^3$) are presented in Table 1 for all of the trivalent metal ions.

By comparison, the Ga(III)-DMHP 1:1 complex is colorless (Fig. 3) and the dissociation of the Ga(III) complex was followed by measuring the absorbance of the free H_2L^+ species released at low p[H] (see 'Experimental'). The result of this spectrophotometric determination for 1:1 Ga(III)-DMHP was $\log K_{ML} = 13.17$. The log values of the overall binding constants for the

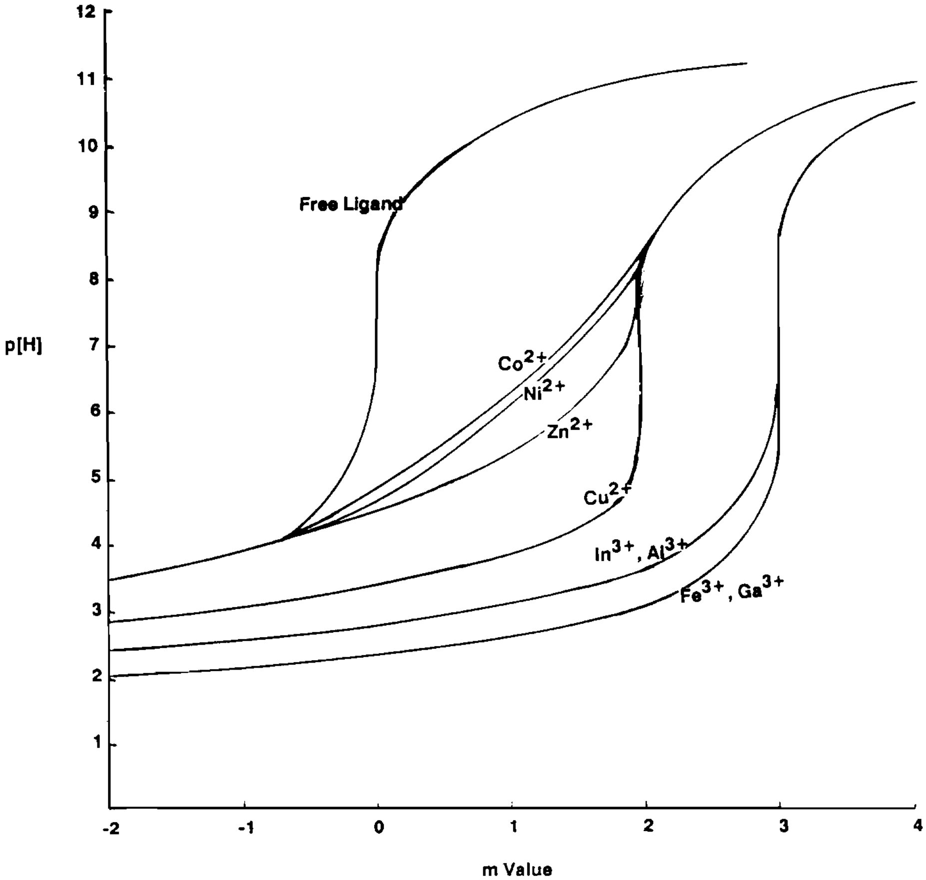

Fig. 1. Titration profile of DMHP and its 3:1 complexes with metal ions. Excess mineral acid (0.2006 mmol) was added in each case. The concentration of ligand is 6×10^{-3} M. Stability constants ($t = 25.0$ °C, 0.100 M KCl) appear in Tables 1 and 2.

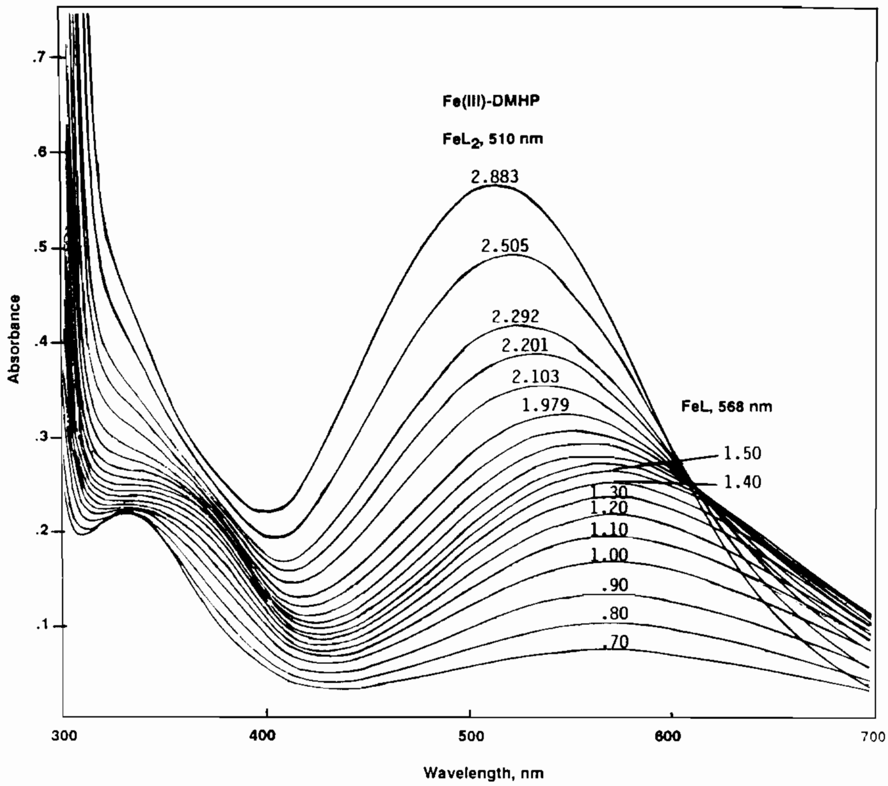

Fig. 2. Absorbance of 1:1 and 2:1 Fe(III) complexes with DMHP at indicated p[H] values. $T_M = 1.773 \times 10^{-4}$ M, $T_L = 5.384 \times 10^{-4}$ M ($t = 25.0$ °C, 0.100 M, KCl+HCl). The extinction of the 1:1 Fe(III) complex at 568 nm is 1630 M^{-1} cm^{-1}.

Fe(III) and Ga(III) complexes are nearly the same, i.e. log $\beta_{ML_3} = 35.88$ and 35.76, respectively (Table 1). However, the distributions of the stepwise binding constants for these complexes are different, as illustrated by their species distribution curves in Figs. 4 and 5.

The present determination of log $K_{GaL} = 13.17$ is nearly four log units less than the literature value of 17.07 reported by Clevette *et al.* [14] (Table 1). A possible reason for this discrepancy is that Clevette measured the dissociation of Ga(III) ion at a p[H] as low as 1.5 by potentiometric methods, but a species distribution plot can be constructed using the reported stability constants (Table 1) to show that there was no uncomplexed metal ion available at or above this p[H] (work not shown). Therefore, the literature value of log $K_{GaL} = 17.07$ is in doubt.

The first stepwise binding constant (log K_{ML}) for the Al(III) and In(III) chelates of DMHP were readily determined by equilibrium potentiometric titration methods for 1:1 solutions, and are log $K_{ML} = 12.20$ and 11.85, respectively (Table 1). The Al(III) and In(III) 1:1 complexes were stable in acidic solution up to p[H] 4.2 to 4.4, corresponding to the inflection that falls at $m = 1$ (work not shown). The agreement with the literature determination for the first stepwise binding constant of the Al(III) complex is good (log $K_{ML} = 11.91$) [13], but the present determination for log K_{InL} is less than the literature value of 13.60 [14] (Table 1), which was determined in a 3:1 solution. The most likely reason for the discrepancy is the same as that given for the Ga(III) determinations above. Better agreement is observed among the second and third stepwise binding constants for the Al(III) and In(III) complexes in Table 1.

By contrast, Gd(III) forms weak 1:1, 2:1 and 3:1 complexes with DMHP in a 4:1 solution (Table 2). There was no evidence for an ML_4 species of Gd(III)–DMPH even when sufficient excess ligand was provided. Log β_{ML_3} for Gd(III) = 17.33, and is considerably lower than for the other trivalent metal ions of interest. Excess ligand prevents the dissociation of the metal complex at alkaline p[H] (work not shown).

Bivalent stability constants

The titration profiles for the bivalent complexes (Fig. 1) show an inflection at $m = 2$ for Cu(II), Ni(II), Co(II) and Zn(II). The values of the stepwise binding constants were computed by BEST and are presented in Table 2. 1:1 and 2:1 metal complexes with DMHP are formed with these bivalent metal ions. In addition, Ni(II) was found to form a 3:1 complex (log $K_{ML_3} = [ML_3^-]/[ML_2][L^-] = 2.54$) as determined by the BEST fit of the potentiometric p[H] data. Sexacoordinate Ni(II)

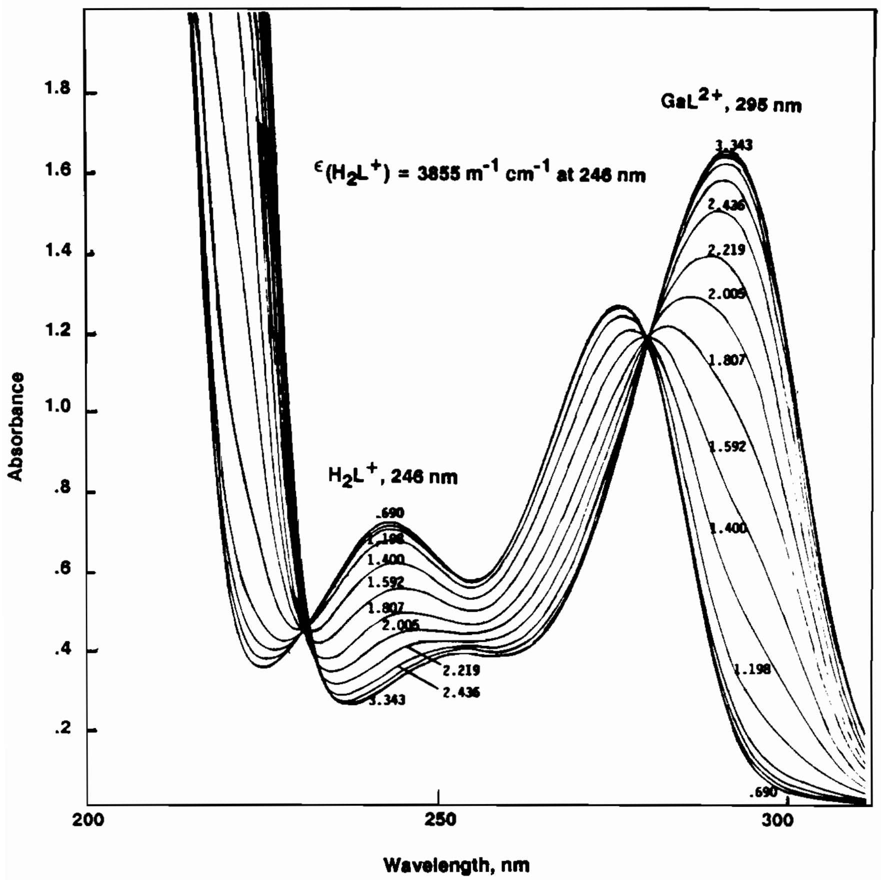

Fig. 3. Absorbance of 1:1 Ga(III)–DMHP complex at indicated p[H] points. $T_M = 1.588\times10^{-4}$ M, $T_L = 1.612\times10^{-4}$ M ($t = 25.0$ °C, 0.100 M KCl). the extinction of H_2L^+ species at 246 nm is 3855 M^{-1} cm^{-1}.

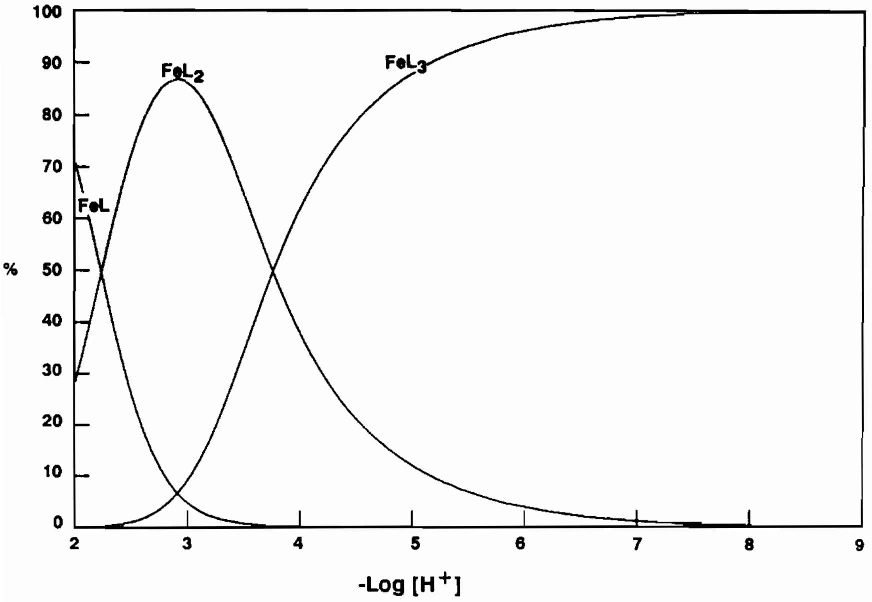

Fig. 4. Distribution of Fe(III) in 1:1, 2:1 and 3:1 complexes with DMHP ($t = 25.0$ °C, 0.100 M KCl) for 2×10^{-3} M Fe(III). The distribution curves were calculated from the stability constants that appear in Table 1.

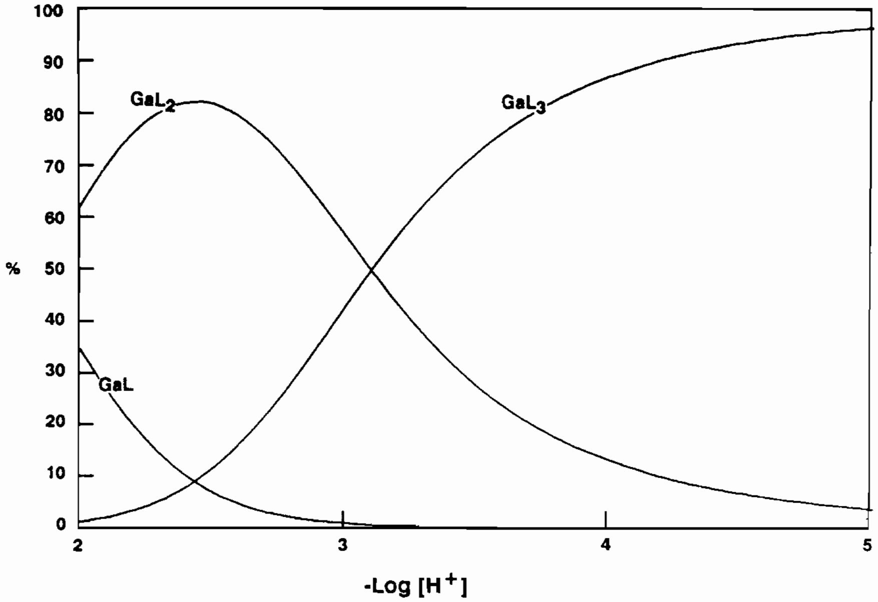

Fig. 5. Distribution of Ga(III) in 1:1, 2:1 and 3:1 complexes with DMHP (t = 25.0 °C, 0.100 M KCl) for 2×10^{-3} M Ga(III). The stability constants are presented in Table 1.

TABLE 2. Stepwise stability constants for chelates of DMHP with Gd(III), and bivalent metal ions of Cu(II), Co(II), Ni(II) and Zn(II)[a]

Quotient	Log K				
	Gd(III)	Cu(II)	Ni(II)	Co(II)	Zn(II)
[ML]/[M][L]	7.82(2)	10.62(2)	6.92(1)	6.60(1)	7.19(2)
[ML$_2$]/[ML][L]	6.04(2)	8.99(2)	5.21(2)	5.13(1)	6.34(2)
[ML$_3$]/[ML$_2$][L]	3.47(3)		2.54(5)		

[a]The numbers in parentheses represent the errors of the last significant figures.

may form a 3:1 species with three bidentate DMHP ligands while Cu(II) and Zn(II) may have preferred four-coordinate geometries in complexes with two molar equivalents of DMHP. No ML$_3$ species was found for Co(II)–DMHP. The observed order of stability for the bivalent DMHP complexes, Cu(II) ≫ Zn(II) > Ni(II) > Co(II), is unusual because most Zn(II) complexes with aminocarboxylate ligands show a lower relative order of stability constants with respect to Ni(II) and Co(II) [21]. However, Zn(II) forms complexes with catechol with a higher stability constant (25 °C, 0.1 M) [21] than those of Ni(II) and Co(II) (i.e. $\log \beta_{ML_2} = [ML_2]/[M^{2+}][L^-]^2 = 17.4$, 14.4 and 15.0, for Zn(II), Ni(II) and Co(II), respectively), but it is lower than Cu(II) (24.9). A similar trend in bivalent stability constants (20 °C, 0.1 M) [22] is observed for 4-nitro-1,2-dihydroxybenzene, $\log\beta_{ML_2} = 14.8$, 13.3, 12.72 and 21.0, for Zn(II), Ni(II), Co(II) and Cu(II), respectively. It is conceivable that the selectivity of four-coordinate Zn(II)–DMHP over Ni(II) and Co(III) may be attributed to its stabilization in a preferred tetrahedral geometry, but X-ray crystal structures are not available to support this contention.

Conclusions

DMHP forms stable 3:1 complexes with the trivalent metal ions of Fe(III), Ga(III), Al(III), In(III) and Gd(III). The order of stability is Fe(III) > Ga(III) > Al(III) > In(III) ≫ Gd(III). Bivalent metal ions of Cu(II), Ni(II), Co(II) and Zn(II) form stable 2:1 complexes with DMHP, with Cu(II) having the greatest selectivity among the bivalent complexes.

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