NEW MULTIDENTATE LIGANDS. XXVI. *N,N'*-BIS(2-HYDROXYBENZYL)ETHYLENEDIAMINE-*N,N'*-BIS(METHYLENEPHOSPHONIC ACID MONOMETHYL ESTER), AND *N,N'*-BIS(2-HYDROXYBENZYL) ETHYLENEDIAMINE-*N,N'*-BIS (METHYLENEPHOSPHONIC ACID MONOETHYL ESTER): NEW CHELATING LIGANDS FOR TRIVALENT METAL IONS

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NEW MULTIDENTATE LIGANDS. XXVI[†].
N,N'-BIS(2-HYDROXYBENZYL)ETHYLENEDIAMINE-N,N'-BIS(METHYLENEPHOSPHONIC ACID MONOMETHYL ESTER), AND N,N'-BIS(2-HYDROXYBENZYL) ETHYLENEDIAMINE-N,N'-BIS (METHYLENEPHOSPHONIC ACID MONOETHYL ESTER): NEW CHELATING LIGANDS FOR TRIVALENT METAL IONS

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The synthesis and equilibrium study of a new type of sexadentate ligand, N,N'-bis(2-hydroxybenzyl)ethylene-diamine-N,N'-bis(methylenephosphonic acid monomethyl ester) (HBEDPOMe) and of the corresponding ethyl ester, are described. Their proton and metal ion affinities are found to be nearly identical. The ligands have two phenolate donors which impart specificity for trivalent metal ions such as Fe(III), In(III) and Ga(III). Potentiometric and spectrophotometric studies of the protonation constants of the ligands and stability constants of their Cu(II), Ni(II), Co(II), Zn(II), Fe(III), In(III) and Ga(III) chelates are compared with those of analogous ligands. The binding of the ligand donor groups to the metal ions occurs in several cases in a stepwise fashion, with the more basic phenolate groups requiring higher pH for activation. The order in which each phenolate group becomes coordinated to metal ions, and the structures of the intermediate complexes, are deduced by correlating the electronic absorption spectra with potentiometric data.

INTRODUCTION

Presently, the only available treatment of iron overload resulting from Cooley's anemia is drug therapy utilizing chelating agents. L'Eplattenier, Murase and Martell[1] and Taliaferro *et al.*,[2] have reported the high stability of the Fe(III), Ga(III) and In(III) chelates of N,N'-bis(2-hydroxybenzyl)-ethylenediamine-N,N'-diacetic acid (HBED), 1, ($K_{ML} = 10^{39.68}$) to be due to the high affinity of Fe(III) for the two phenolate groups present in the ionized ligand and to the favorable orientation of these groups so as to permit their participation in chelate ring formation.

Motekaitis, Murase and Martell[3,4] found that the stability constants, upon substituting phosphonate for the carboxylate groups in ethylenediamine-N,N'-diacetic acid (EDDA), 2, to obtain ethylenediamine-N,N'-bis(methylene-phosphonic) acid (EDDPO), 3, are slightly higher for Cu(II) and slightly lower for Ni(II) and Co(II), compared to the parent ligand EDDA. The same authors concluded that phenolate and phosphonate groups could be effective donors in multidentate ligands having suitable molecular geometry.

MacMillan, Murase and Martell[5] reported the synthesis and study of a new sexadentate ligand having a sterically favorable arrangement of phosphonate and phenolate donor groups' N,N'-bis(2-hydroxybenzyl)ethylenediamine-N,N'-bis (methylenephosphonic) acid (HBEDPO), 4. The authors found that the overall basicity

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of HBEDPO (Σ log K^H = 50.88) is higher than that of HBED (Σ og^H = 41.03) and the stability constants are slightly higher for Cu(II) and lower for Ni(II) and Co(II). Since the Zn(II) and Fe(III) chelates were both insoluble in the pH range of the buffer region in which they are formed, stability constants could not be calculated for these metal ions. However, the Fe(III) chelate of HBEDPO did not hydrolyze even at extremely high pH and the fact that at low pH there was a marked depression of the pH titration curve gives qualitative evidence of the high stability of the complex.
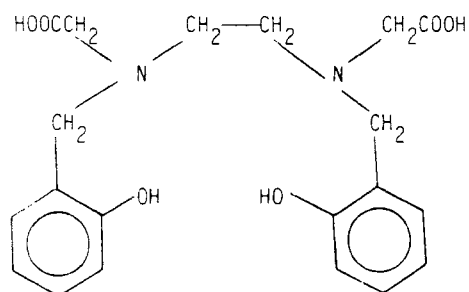
1   HBED
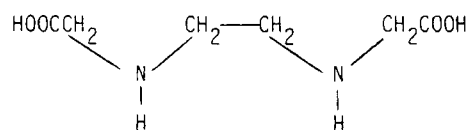
2   EDDA
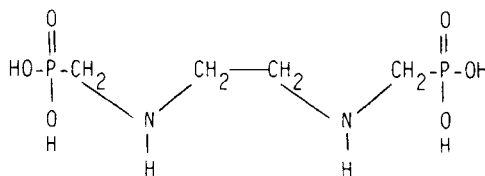
3   EDDPO
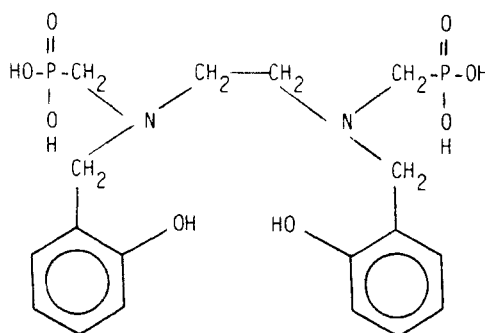
4   HBEDPO

In the search for a more effective chelating agent to be used in the treatment of Cooley's anemia, HBEDPO was converted to its dimethyl and diethyl ester to render it more compatible with lipids and thus increase its assimilation *via* oral administration. The ester derivatives of HBED have proved to be effective in test animals for the removal of iron overload.[6]

This paper describes the synthesis and quantitative study of the methyl and ethyl ester derivatives of HBEDPO, *N,N'*-bis(2-hydroxybenzyl)ethylene diamine-*N,N'*-bis (methylenephosphonic acid monomethyl ester) (HBEDPOMe), 5, and *N,N'*-bis (2-hydroxybenzyl)ethylenediamine-*N,N'*-bis(methylenephosphonic acid monoethyl ester) (HBEDPOEt), 6.
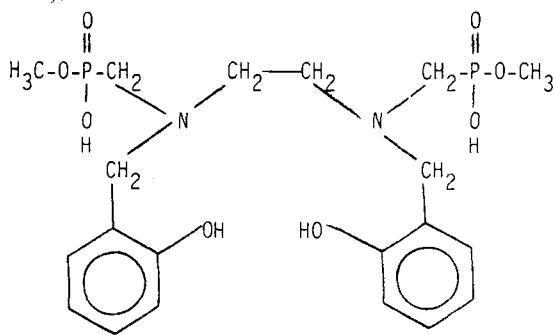
5   HBEDPOMe
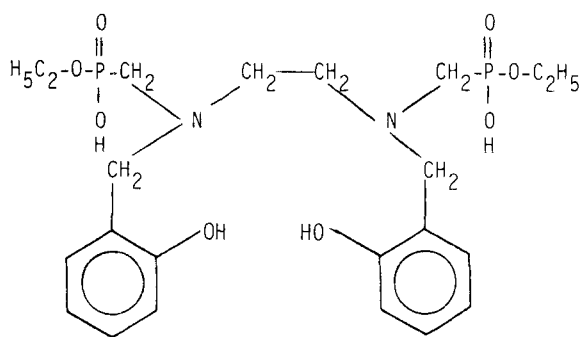
6   HBEDPOEt

EXPERIMENTAL

N,N'-bis(2-hydroxybenzyl)ethylenediamine-N,N'-bis(methylenephosphonic   acid   mono-methylester)   (HBEDPOMe)   and   N,N'-bis(2-hydroxybenzyl)ethylenediamine-N,N'-bis (methylenephosphonic acid monoethyl ester) (HBEDPOEt)

The synthesis of these compounds was carried out by R. Stoldt in this laboratory. A detailed procedure will be published separately.[7]

Potentiometric Equilibrium Measurements

Potentiometric measurements of HBEDPOMe and HBEDPOEt in the absence and presence of metal ions were carried out with a Corning Digital pH meter equipped with glass and calomel reference electrodes calibrated with standard aqueous HCl and

KOH solutions to read $-\log[H^+]$ directly. The temperature was maintained at $25.00 \pm 0.05°$, and the ionic strength was adjusted to 0.100 M by the addition of KCl. The concentrations of the experimental solutions were 2.000×10^{-3} M in metal ions and ligands. Potentiometric measurements were carried out on systems containing molar equivalents of an appropriate metal salt and the ligand. Four equivalents of standard base (0.100 M) were added to the solution in order to dissolve the ligand, and the potentiometric titration curve was obtained from back-titration with standard HCl solution. Small increments of standard acid were added at a concentration equivalent to the ionic strength of the solution (in this work 0.100 M) to minimize changes in ionic strength during the course of the experiments. The reacting species were studied at concentrations low enough $(2 \times 10^{-3}$ M) that they did not significantly contribute to the ionic strength of the medium. For successful determination of the stability constant of the initial complex, it is essential that it be appreciably dissociated to the free metal ion (about 50%) at the lowest pH measured. Further, in order to maintain the linearity of the EMF-hydrogen ion concentration calibration, it is essential that the free $[H^+]$ and $[OH^-]$ concentrations be limited to a very small fraction of that of the supporting electrolyte. This limitation restricts the $-\log[H^+]$ measurements to the range 2-12.

Contrary to the case of HBED, the Fe(III) Ga(III) and In(III) chelates of HBEDPOMe and HBEDPOEt are not completely formed at pH 2. Although the chelates of these metals ions are only 10% formed at pH 2, their formation curves (% species vs pH) rise rapidly to 100% at pH 4. Therefore, convenient buffer regions are not present for the calculation of their formation constants. Thus, in addition to measuring the 1:1 metal-ligand system shown in Figure 1, ligand-ligand competition

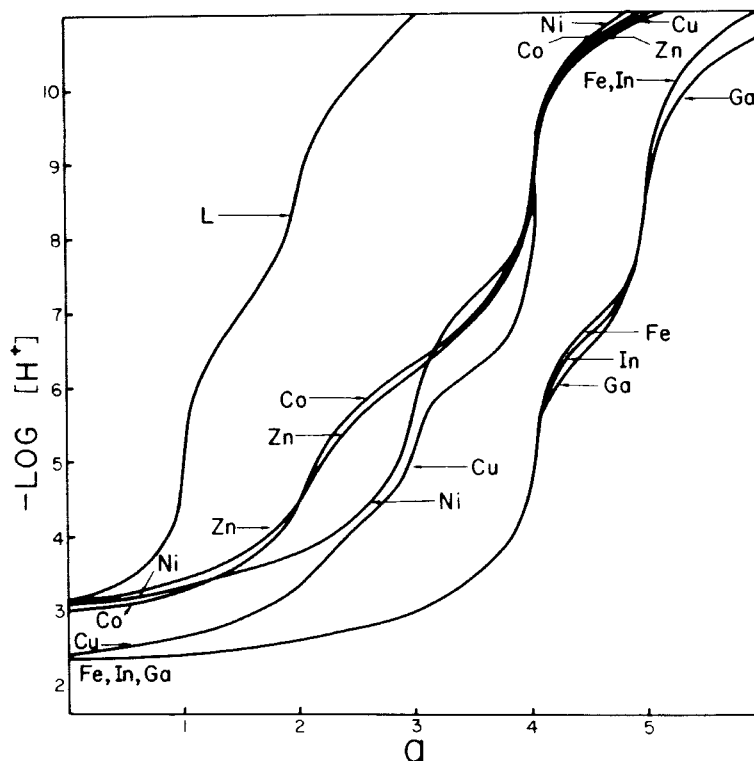FIGURE 1   Potentiometric equilibrium curves of HBEDPOMe in the absence and presence of 1:1 molar ratios of metal ion to ligand: a = moles of base added per mole of ligand present; μ = 0.100 (KCl); t = 25.00°; concentrations of ligand and metal ions 2.00×10^{-3} M. Divalent metal ions: Cu^{2+}, Ni^{2+}, Co^{2+}, and Zn^{2+}. Trivalent metal ions: Fe^{3+}, In^{3+} and Ga^{3+}.

studies[8] were also performed with a 1:1:1 molar ratio of the metal ion, HBEDPOMe or HBEDPOEt and EDTA, which was found to be a suitable reference ligand for these systems.

Spectrophotometric Measurements

The visible and ultraviolet absorption spectra of the ligand and metal chelate solutions were determined with a Perkin-Elmer Model 553 Fast Scan UV/VIS spectrophotometer adapted to a Perkin-Elmer R100 Recorder. The quartz absorption cells were placed in a constant temperature ($25.00 \pm 0.05°$) compartment in the spectrophotometer.

RESULTS

The results of the equilibrium determinations on HBEDPOMe and HBEDPOEt are presented in Table I, along with comparable data for the analogous phenolic ligands, HBEDPO and HBED. Data for the well-known parent chelating agent, EDTA, are included for comparison. Because the equilibrium constants obtained for HBEDPOMe and HBEDPOEt are nearly identical, the Results and Discussion will be given in terms of HBEDPOMe only, but will apply equally to both ligands.

TABLE I

Protonation Constants and Metal Chelate Stability Constants of HBEDPOMe, HBEDPOEt and Related Ligands at $T = 25.00°$ and $\mu = 0.100$ M(KCl).

Equilibrium Quotient	Log K				
	HBEDPOMe*	HBEDPOEt*	HBED¹	HBEDPO⁵	EDTA⁹
$[HL]/[L][H]$	12.23	12.17	12.60**	13.57	10.17
$[H_2L]/[HL][H]$	11.64	11.61	11.00**	11.48	6.11
$[H_3L]/[H_2L][H]$	7.04	6.98	8.44**	9.67	2.68
$[H_4L]/[H_3L][H]$	3.33	3.28	4.72**	7.24	1.95
$[H_5L]/[H_4L][H]$	< 2		2.53**	5.31	1.5
$[H_6L]/[H_5L][H]$	< 2		1.74**	3.61	
$[CuL]/[Cu][L]$	23.04	23.01	23.69**	24.0	18.70
$[CuHL]/[CuL][H]$	6.60	6.65	8.49**	9.39	3.0
$[CuH_2L]/[CuHL][H]$	3.74	3.79	5.04**	7.75	
$[CuH_2L]/[Cu][H_2L]$	9.51	9.67			
$[NiL]/[Ni][L]$	18.51	18.47	19.31	17.9	18.52
$[NiHL]/[NiL][H]$	7.04	7.09	8.51	10.02	3.2
$[NiH_2L]/[NiHL][H]$	3.98	4.04	6.45	7.95	
$[NiH_2L]/[Ni][H_2L]$	5.66	5.82			
$[CoL]/[Co][L]$	19.11	19.05	19.89	18.0	16.26
$[CoHL]/[CoL][H]$	6.92	6.97	7.77	9.88	3.0
$[CoH_2L]/[CoHL][H]$	5.93	5.98	5.56	6.70	
$[CoH_2L]/[Co][H_2L]$	8.09	8.22			
$[ZnL]/[Zn][L]$	17.61	17.56	18.37		16.44
$[ZnHL]/[ZnL][H]$	6.63	6.68	8.27	10.27	3.0
$[ZnH_2L]/[ZnHL][H]$	5.43	5.47	5.99		
$[ZnH_2L]/[Zn][H_2L]$	5.80	5.93			
$[FeL]/[Fe][L]$	28.21	28.19	39.68		25.0
$[FeL]/[FeOHL][H]$	6.72	6.70			7.37*
$[InL]/[In][L]$	28.12	28.05	39.66***		24.9
$[InL]/[InOHL][H]$	6.63	6.61			8.49*
$[GaL]/[Ga][L]$	28.03	27.98	39.57⁸		21.70
$[GaL]/[GaOHL][H]$	6.51	6.46			5.63*

*Present work. **Ref. 10. ***Ref. 2.

Protonation Constants

The first protonation reactions of the most basic form of the ligand. L^{4-}, occur above pH 11, where potentiometric measurements become inaccurate. Therefore, they were investigated spectrophotometrically, since they involve the protonation of the two phenolic groups and are therefore accompanied by an extensive change in the UV absorption spectrum. Figure 2 illustrates the measured absorbances at 292 nm, the wavelength at the maximum of the phenolate absorption band (Fig. 3), as a function of pH. The sharp increase in absorptivity between pH 11 and 13 may be considered a measure of the degree of dissociation of the two phenolic groups.

The ultraviolet absorption spectra of HBEDPOMe as a function of pH are shown in Figure 3. The equilibrium involves a phenol-phenolate system, with the two species having absorption maxima at 276 and 292 nm, respectively. The measured absorbance is the sum of the products of the molar extinction coefficient ϵ_{H_pL} (p = 0, 1, 2, 3, and 4) and the concentrations of the corresponding species, H_pL. A and ϵ_{H_pL} must correspond to the same wavelength. The total ligand concentration is also known.

$$A = \sum_{0}^{4} \epsilon_{H_pL} [H_pL] \tag{1}$$

$$L_t = \sum_{0}^{4} [H_pL] = \sum_{0}^{4} K_p^H [H^+] [H_{p-1} L] \tag{2}$$
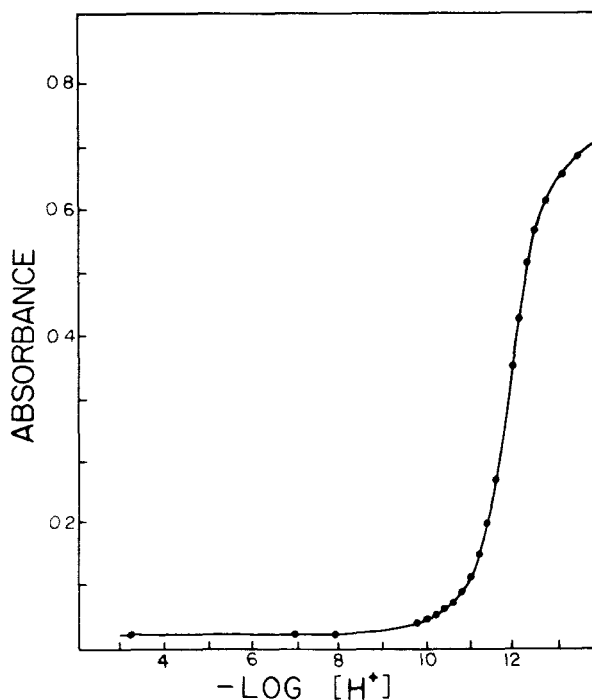

FIGURE 2   The ultraviolet absorbance of HBEDPOMe(L) as a function of pH at 292 nm: |L| = 1.178 × 10⁻⁴ M: μ = 0.100 M(KCl + KOH); 1.00 cm cell; T = 25.00°

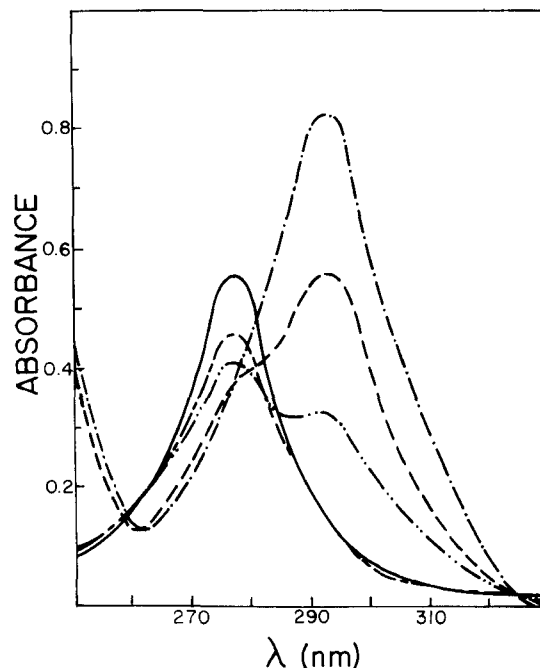FIGURE 3   Ultraviolet absorption spectra of HBEDPOMe (L) as a function of pH: ——————————,
pH = 3.285; — — —, pH = 6.985; - · · -, pH = 11.640; - - -, pH 12.200; - · - · , pH = 14.003. L = 1.178 × 10⁻⁴ M;
μ = 0.100 M (KCl + KOH); 1.00 cm cell; T = 25.00°

With the aid of the relationships (1) and (2), the first two proton association constants may be determined, as described below.

Because of inevitable experimental errors, there will always be some difference between the measured A and the sum calculated with (1). The unknown parameters are chosen so that this difference is minimized. The calculation is divided into two steps:

(a) Independent determination of K_3^H and K_4^H from the potentiometric titration curve, with the FORTRAN computer program BEST,[11] which will be described briefly in the next section. K_5^H and K_6^H could not be determined potentiometrically in the experimental pH range (pH 2-12); both pK_a values are probably much lower than 2.

(b) Determination of K_1^H and K_2^H using spectrophotometric measurements between pH 10.0 and 12.8. In this pH range,

$$A = \varepsilon_{H_2L}[H_2L^{2-}] + \varepsilon_{HL}[HL^{3-}] + \varepsilon_L[L^{4-}] \qquad (3)$$

$$L_t = [H_2L^{2-}] + [HL^{3-}] + [L^{4-}] \qquad (4)$$

$$= K_2^H[H^+]^2[L^{4-}] + K_1^H[H^+][L^{4-}] + [L^{4-}]$$

(Dividing (3) by (4) and eliminating [L⁴⁻], one gets)

$$A = L_t \; \frac{\varepsilon_{H_2L} K_2^H [H^+]^2 + \varepsilon_{HL} K_1^H [H^+] + \varepsilon_L}{K_2^H [H^+]^2 + K_1^H [H^+] + 1} \qquad (5)$$

K_1^H and K_2^H are determined so as to give constant values for ε_{H_2L}, ε_{HL} and ε_L and $\lambda = 292$ nm at a series of pH values, (3)–(5).

The values of the protonation constants thus obtained for $\mu = 0.100$ M (KCl + KOH), at $25.00 \pm 0.05°$, are log $K_1^H = 12.23 \pm 0.02$ and log $K_2^H = 11.64 \pm 0.02$.

Potentiometric Determination of Stability Constants

Equilibrium constants for the formation of the normal metal chelates, the protonated metal chelates and the hydrolyzed metal chelates were determined by using the FORTRAN computer program BEST.[11] The input for BEST consists of the components and their concentrations, the initial estimates of the equilibrium constant for each species considered to be present in terms of these solution components, and finally the potentiometric equilibrium data determined experimentally. With this program simultaneous mass-balance equations are set up for all the components present at each increment of base added and, with initial assumptions for the equilibrium constants, the concentration of each species present and the pH at each data point are calculated. Equilbrium constants are varied in order to effect a minimization in the difference between the calculated and observed values of $-\log[H^+]$, thus giving ultimately a close approximation of the original potentiometric equilibrium curve, the concentrations of the individual species present at each data point, and the corresponding equilibrium constants for metal chelate formation, protonation, and deprotonation.

Determination of Species Distribution Curves

The species distribution curves (% species vs pH) were generated with the FORTRAN computer program SPE written in this laboratory. This program basically uses the algorithm of the BEST program to calculate the percentage concentration of the individual solution species at each pH value. The plot shown in Figure 4 was obtained with a Printronix Plotter Subroutine.

DISCUSSION

Protonation Constants

The first two protonation constants of HBEDPOMe (which correspond to the phenolic groups) involve overlapping equilibria; this is not the case for HBEDPO and HBED. The reason for the difference is undoubtedly due to the methyl ester groups, which reduce basicities of the phosphonate oxygens and related phenomena, such as possible hydrogen bonding with the phenolic groups and protonated amino groups. The sums of the logarithms of the first two protonation constants of HBED (23.60) and HBEDPOMe (23.87) are similar. For HBEDPO the sum is much higher (25.05) due to the much higher negative charges of the two binegative phosphonate groups.

The phosphonate groups in HBEDPO increase the basicities of the nitrogen atoms, as compared to HBED, because of their higher negative charges. This effect can also be observed by comparing the results for the analogous ligands, EDDA and EDDPO, in Table II. However, the phosphonic ester groups in HBEDPOMe decrease the basicities of the nitrogen atoms (third and fourth protonation constants), as compared to HBED because the oxygen donors of the phosphonate monoesters are more electronegative (i.e, less basic) than those of carboxylate groups.

### Stability Constants of the Metal Complexes

A comparison of the stability constants of the completely deprotonated complexes of
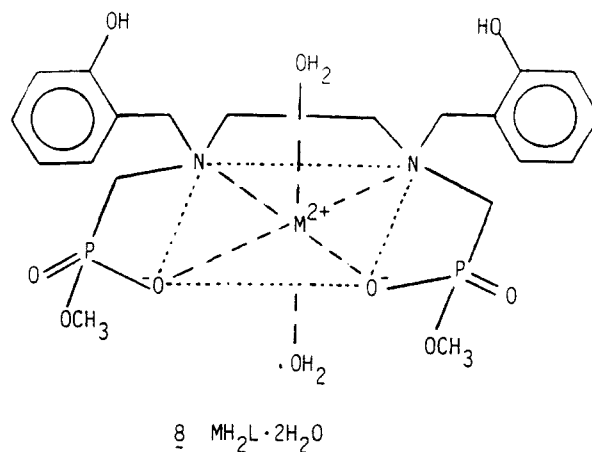
TABLE II

Protonation Constants and Metal Chelate Stability Constants of EDDA. HBED. EDDPO. HBEDPO and HBEDPOMe at t = 25.00° and μ = 0.100 M (KCl).

	EDDA³	HBED¹	EDDPO³	HBEDPO⁵	HBEDPOMe*
Log K_n^H	$K_1^H = 9.60$	$K_3^H = 8.44$	$K_1^H = 10.60$	$K_3^H = 9.67$	$K_3^H = 7.04$
	$K_2^H = 6.53$	$K_4^H = 4.72$	$K_2^H = 7.72$	$K_4^H = 7.24$	$K_4^H = 3.33$
	$K_3^H = 2.36$	$K_5^H = 2.53$	$K_3^H = 5.74$	$K_5^H = 5.31$	$K_5^H < 2$
	$K_4^H = 1.3$	$K_6^H = 1.74$	$K_4^H = 4.58$	K_6^H 3.61	$K_6^H < 2$
	Log K_{ML}	Log $K^M_{MH_2L}$*	Log K_{ML}	Log $K^M_{MH_2L}$	Log $K^M_{MH_2L}$
Cu^{2+}	16.2	13.62	17.52	16.09	9.51
Ni^{2+}	13.5	10.67	11.70	10.83	5.66
Co^{2+}	11.2	9.62	10.23	9.58	8.09
Zn^{2+}	11.1	9.03			5.80

*Present work

the divalent metal ions (Table I) shows that HBEDPOMe forms chelates that are less stable than those of HBED. This observation is consistent with the fact that the overall basicity of HBEDPOMe (Σ log $K^H \cong 36$) is lower than for HBED (Σ log $K^H \cong 41$). The overall basicity of HBEDPO is much higher (Σ log $K^H \cong 52$) than for HBED and HBEDPOMe. However, the stability constants for Ni(II) and Co(II) are lower when compared to the analogous ligands, probably because of the large mutual charge repulsions between the binegative phosphonate groups when more than one such group is coordinated to the same metal ion. The Cu(II) chelate has a slightly higher stability because the phosphonate groups are probably coordinated in the axial positions (formula 7) and interact less with the metal ion and with each other in the tetragonal coordination sphere of Cu(II), as compared to the other divalent metal ions, which have more nearly octahedral arrangements of donor groups.

7 $ML^{+(n-4)}$

$\underline{8}$ $MH_2L \cdot 2H_2O$
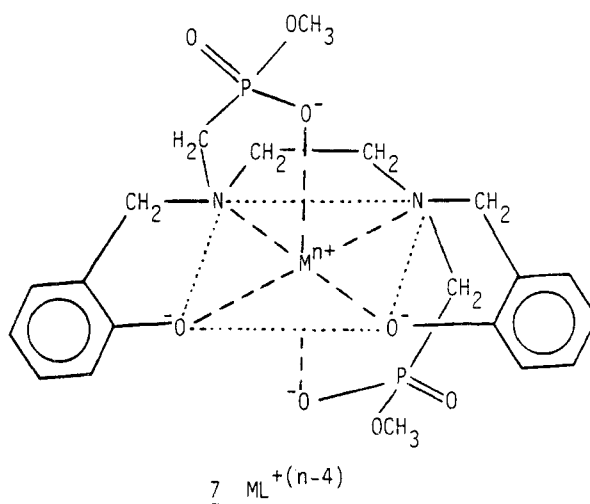
Comparison of the diprotonated chelates of HBED. HBEDPO and HBEDPOMe with divalent metal ions (Table II) shows that the stability constants are highest for HBEDPO. Since the protons are considered to be combined with the phenolic groups, coordination of the metal ion by these ligands involves tetradentate functional groups analogous to those in EDDA and EDDPO. The protonation constants indicate that the amino and phosphonate functions of HBDEPOMe are much less basic than the analogous ligands in Table II. The exceptionally large drop in basicity of the half-esterified phosphonate groups in HBEDPOMe is especially interesting. because it has no parallel in the protonated forms of the ligands. even for the diprotonated species in Table II. It is important to note here that HBEDPO actually has eight protonation constants. Log K_7^H and log K_8^H are probably lower than 2 and therefore could not be determined potentiometrically in the accurately measurable experimental pH range (2–12). Most of the coordinating tendency of the phosphonate groups is lost through half esterification. because the basicities of the remaining unesterified phosphonate oxygens are extremely low. corresponding to the 7th and 8th protonation.

The probable arrangement of ligand donor groups and coordinate bonds of the completely deprotonated metal chelates of HBEDPOMe is given by formula 7. The initial displacement of two protons from the ligand H_4L in acid solution to form the diprotonated metal chelates MH_2L. 8. involves the loss of a proton from each of the less basic tertiary amino groups. Divalent metal ions are thus able to form complexes having three chelate rings with the tetradentate diprotonated ligand. With increasing pH. the metal ion begins to compete successfully with protons for the phenolate groups and appreciable amounts of complexes MHL and ML form in solution. For CuL^{2-}. as with HBED. there is probably strong coordination of the metal ion with the amino nitrogens and phenolate oxygens in approximately co-planar positions. and weaker coordination with the phosphonate or carboxylate oxygens in the fifth and sixth positions above and below the plane. The conversion $CuH_2L \rightarrow CuL^{2-}$ is accompanied by a strong color change in the solution (Fig. 5). Below pH 3.0 the Cu(II) chelate solution is blue. characterized by a broad absorption band with a maximum at about 670 nm (655 nm for HBED). The CuH_2L^{2-} complex is probably a distorted octahedron with weakly bonded water molecules in the fifth and sixth positions (formula 8). As the pH is increased above 3.0. a new. much stronger band appears at 396 nm (385 for HBED). the intensity of which increases with increasing pH and remains constant above pH 11. where the formation of CuL^{4-} is complete. This new band can be associated with the formation of metal-phenolate linkages and is probably a $L \rightarrow M$ charge transfer band. A shift in color of the complex from blue to green is observed as the pH is increased from pH 3 to 10.

The potentiometric curves in Figure 1 show that the protonation equilibria for Co(II) and Zn(II) are closely parallel, and change relative positions. Also, these curves differ from those of Cu(II) and Ni(II) in that they do not show a break in the conversion of MH_2L to ML. This behavior is in accord with the possible interpretation that successive removal of phenolate protons may involve a change in geometry, from octahedral (8) to tetrahedral (9) in the formation of the fully deprotonated complex. This is supported by a color change from pink to deep violet, observed during the potentiometric equilibrium determination of the interaction of Co(II) with HBEDPOMe.
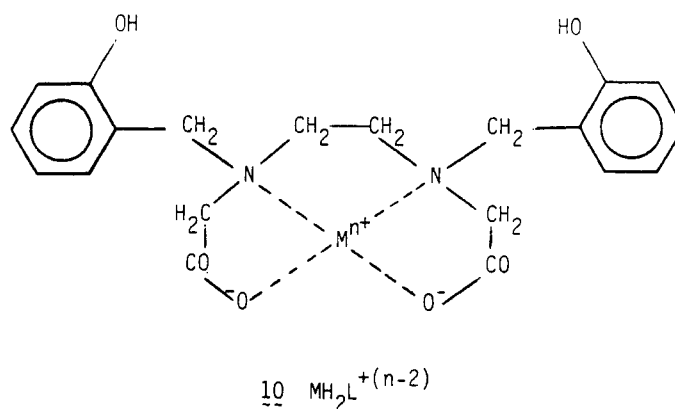

$$\underline{9} \quad ML^{-2}$$

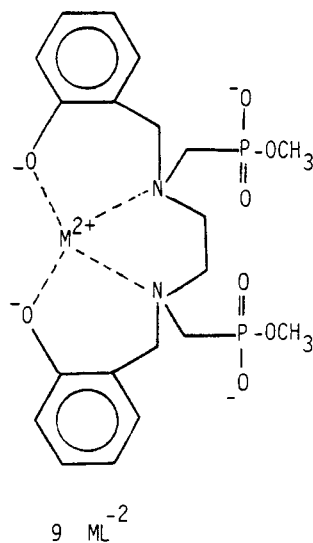
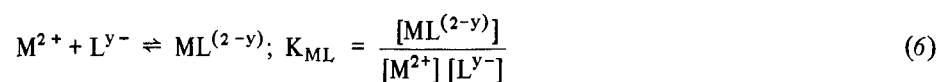$$\underline{10} \quad MH_2L^{+(n-2)}$$

Table II presents a comparison of the stabilities of the diprotonated complexes of HBED, HBEDPO and HBEDPOMe with those of the analogous chelates of EDDA and EDDPO. Values of log K_{ML} are shown for EDDA and EDDPO, representing the equilibrium (6).

$$M^{2+} + L^{y-} \rightleftharpoons ML^{(2-y)}; \quad K_{ML} = \frac{[ML^{(2-y)}]}{[M^{2+}][L^{y-}]} \tag{6}$$

Values of log $K^M_{MH_2L}$ are shown for the remaining ligands, representing the analogous equilibrium (7).

$$M^{2+} + H_2L^{y-} \rightleftharpoons MH_2L^{(2-y)} \quad K^M_{MH_2L} = \frac{[MH_2L^{(2-y)}]}{[M^{2+}][H_2L^{y-}]} \tag{7}$$
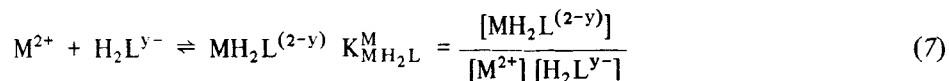
If the diprotonated complexes of HBED, MH_2L, (10), are compared with the analogous chelates of EDDA, a decrease of the stability constants is observed. This change in stability correlates well with the lower basicities of the amino groups (K^H_3 and K^H_4) compared to the values of K^H_1 and K^H_2 of EDDA. The lower affinities of the donor groups of HBED are due to the fact that coordination of the metal ion with the ethylenediamine diacetate group is accompanied by the breaking of hydrogen bonds of the type shown in 11 and 12, a condition which does not apply to the coordination of a metal ion by the dianion of EDDA. The same reasoning can be applied to the comparison of the stabilities of the diprotonated chelates of HBEDPO with the completely deprotonated chelates of EDDPO. The diprotonated chelates of HBEDPOMe are even less stable than the analogous chelates of HBED, due to the much lower basicites of the amino and phosphonate ester groups.

$$11 \quad H_2L^{2-}$$

$$\updownarrow \quad K^H_3$$

$$12 \quad H_3L^-$$
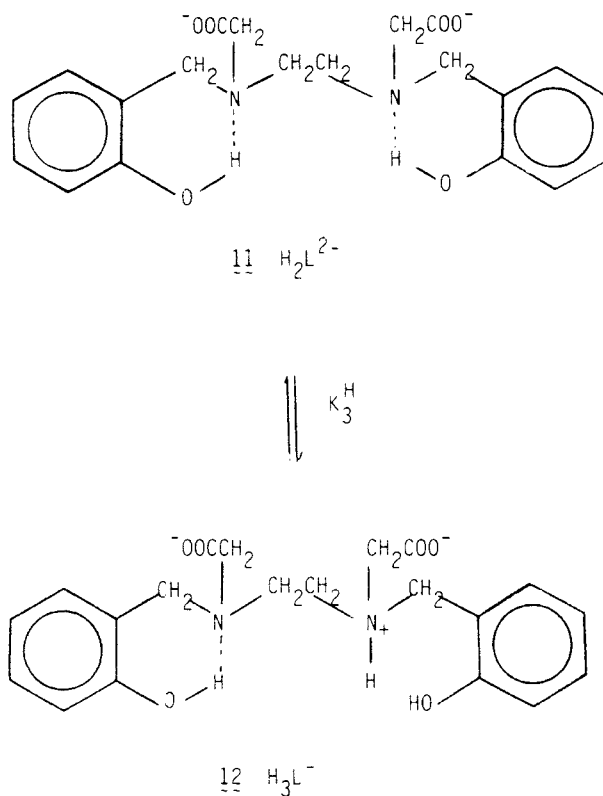
The large decrease in $K^M_{MH_2L}$ from Cu(II) to Ni(II) is not surprising. The absolute value of this decrease (3.85 log units) falls between the corresponding difference for HBED (2.95 log units) and HBEDPO (5.26 log units), and is closer to the decrease observed in HBED. However, the large increase in $K^M_{MH_2L}$ from Ni(II) to Co(II) seems

unusual in that it indicates the diprotonated chelate of Co(II) to be much more stable than the analogous chelate of Ni(II). This can also be seen from the values listed in Table I for the protonation constants of these chelates. Log K^H_{MHL} for Co(II) (6.92) is just slightly lower than for Ni(II) (7.04) but log $K^H_{MH_2L}$ for Co(II) (5.93) is much higher than for Ni(II) (3.98). These values show that as the pH is increased, the MH_2L chelate of Co(II) starts deprotonating at a pH value about 2 log units higher than is the case for the corresponding Ni(II) chelate. Once this first step is overcome, the deprotonation of the second phenolic group occurs at approximately the same pH value. It seems that the MH_2L chelate of Co(II) undergoes a change in geometry in the course of its conversion to the deprotonated chelate. This is in accord with the fact that for Co(II), a d^7 ion, ligand field stabilization energies disfavor the tetrahedral configuration relative to the octahedral one to a smaller extent than for any other d^n ($1 \le n \le 9$) configuration, although it should be noted that this argument is valid only in comparing the behavior of one metal ion to another, for a specific ligand, and not for assessing the absolute stabilities of the configurations for any particular ion.

The same type of behavior is also observed for the Zn(II) ion, but to a much lower extent. The values of log $K^M_{MH_2L}$ and log K^H_{MHL} for Zn(II) fall between the values for Co(II) and Ni(II). Since the chelate protonation constants of Zn(II) also overlap it seems that Zn(II) also undergoes a change in geometry in order to form the deprotanated chelate. This is in accord with the fact that there is no ligand field stabilization effect for the Zn(II) ion because its d shell is full. Therefore, the stereochemistry of the Zn(II) ion is determined solely by consideration of electrostatic and bonding forces, and steric effects.

Molecular models show that the six donor groups in HBED (two phenolic oxygens, two amino nitrogens and two carboxylate oxygens) can be optimally arranged in the six octahedral positions around the metal ion. However, in HBEDPOMe, the larger size of the phosphorus atom, as compared to the carbon atom, is responsible for a small displacement of the methylphosphonate oxygens from the most favorable octahedral positions around the metal ion. This fact, in addition to the lower basicities of the methylphosphonate oxygens and the tendency of Co(II) and Zn(II) to form tetrahedral complexes, provides a logical rationale for the observation that the diprotonated chelates of Co(II) and Zn(II) are relatively stable (high log $K^M_{MH_2L}$ value). Molecular models show that the four donor groups (two amino nitrogens and two methyl-phosphonate oxygens) in the diprotonated chelate of HBEDPOMe are optimally arranged in the four tetrahedral positions around the metal ion. Therefore, the weakly coordinating phosphonate oxygens are in a more favorable position for coordination in the tetrahedral geometry, as compared to the octahedral one.

The potentiometric equilibrium curves in Figure 1 show that Fe(III), In(III), and Ga(III) displace four protons from the ligand in one step. In contrast to the analogous HBED chelates, these metal ions form hydroxo-complexes with HBEDPOMe between pH 5.5 and 8.0. At pH 8.5 the complete breakdown of the Ga(III) chelate is observed, with the formation of the gallate anion $[Ga(OH)_4]^-$ and free ligand in its diprotonated, monoprotonated and deprotonated forms. The breakdown of the hydroxo-chelate at higher pH to gallate is a consequence of the extremely high stability of the gallate anion; the effective stability of this complex increases with the fourth power of the hydroxide concentration as the pH increases[12].

As opposed to the analogous chelates of HBED, the trivalent metal ion chelates of HBEDPOMe are not 100% formed at pH 2.0. The formation of the chelates is complete at pH 3.60 for In(III), at pH 3.80 for Ga(III) and pH 4.00 for Fe(III). Below these pH values, the ionic (aquo) forms of Fe(III) and In(III) are partially hydrolyzed in solution.[13] However for the Ga(III) system, the solution was slightly turbid at pH less than 3.80, indicating the presence of a small amount of $Ga(OH)_3$ in the solid state. This difference in behavior may be understood on the basis of the considerable differences
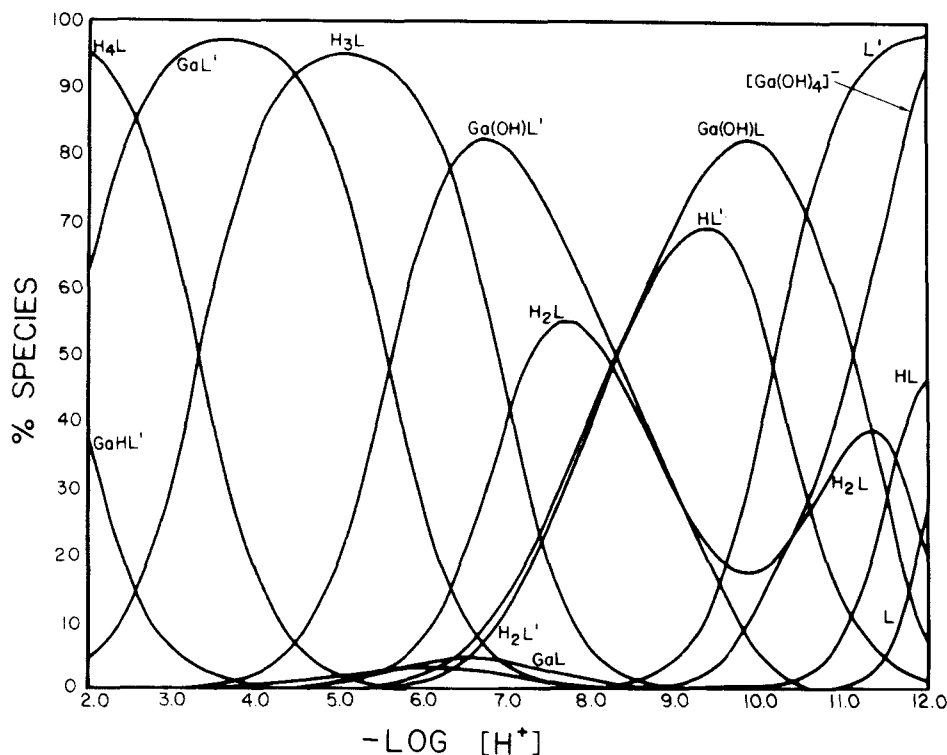
FIGURE 4   Distribution of species as a function of -log[H⁺] in a system containing equimolar concentrations of Ga(III), HBEDPOMe (L) and EDTA (L'): μ = 0.100 M (KCl); T = 25.00°; concentrations of metal ion and ligands = 2.000 × 10⁻³ M.

in the solubility products of these metal ions. For Fe(III), log K_{sp} = -36.0, for In(III), log K_{sp} = -36.1 and for Ga(II), log K_{sp} = -39.1.[13]

The considerably lower stability of the trivalent metal ion chelates of HBEDPOMe as compared to the analogous phenolic ligands and the formation of hydroxo-chelates at intermediate pH may be explained as arising from the lower basicity of the ligand and the weaker coordination by the methylphosphonate oxygens, as compared to the carboxylate oxygens.

Spectra taken of the Fe(III)-HBEDPOMe complex from pH 2 to 11 confirmed the fact that the Fe(III) complex is only 10% formed at pH 2.0, about 50% formed at 2.4 and 100% formed at pH 4.0. The complex has an intense red color. The molar extinction coefficient at λ_{max} of 501 nm, ε_{FeL}, is 4271 M^{-1} cm^{-1}. For HBED, λ_{max} is 485 nm, and ε_{FeL} is 3935 M^{-1} cm^{-1}. The position and intensity of the absorption band did not change with the formation of the hydroxo-complex from pH 4.5 to 11.0.

Figure 4 shows the distribution of species as a function of -log [H⁺] in a system containing equimolar concentrations of Ga(III), HBEDPOMe and EDTA. At pH 2.0, 37% of the Ga(III) ion is present in the form of GaH(EDTA) and 63% in the form of GaEDTA⁻. The formation of the Ga(OH)EDTA²⁻ complex occurs between pH 3.0 and 6.7. At pH 6.7 the breakdown of the Ga(OH)EDTA²⁻ complex starts to occur with the formation of the Ga(OH)HBEDPOMe complex. The latter complex is completely formed at pH 9.9. It is this buffer region, between pH 6.7 and 9.9, that makes it possible to calculate the stability constant of the Ga(III)-HBEDPOMe
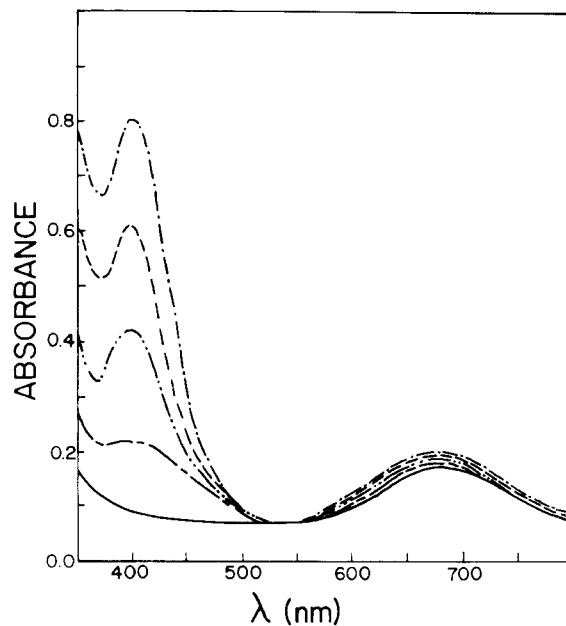
FIGURE 5   Visible absorption spectra of the HBEDPOMe-Cu(II) chelate as a function of
pH:————, pH = 2.70; — — —, pH = 3.724; - · · · - · · , pH 5.312; -----, pH = 6.740; - · - · -, pH 10.975.
$[Cu]_t = [L]_t = 8.48 \times 10^{-4}$; $\mu = 0.100$ M KCl; 1.000 cm cell; t = 25.00°

complex. The hydrolysis constant of the Ga(III) chelate was calculated separately
from the potentiometric titration curve shown in Figure 1. At pH 9.8, the
breakdown of the Ga(III) hydroxocomplex starts to occur, and as indicated in
Figure 4, becomes complete just above pH 12. In a similar manner, the
competition between EDTA and HBEDPOMe was also used to calculate the
stability constants of the Fe(III) and In(III) chelates.

Although the Fe(III) chelates of HBEDPOMe and HBEDPOEt are not nearly as
stable as the analogous chelates of HBED, they are of interest from a therapeutic or
diagnostic point of view since they are soluble (as opposed to the Fe(III)-HBEDPO
chelate) and are 100% formed at physiological pH. These ligands also have an
interesting possible application in the treatment of iron overload since they widen the
range of stability constants (for Fe(III)) of the chelators available for that purpose.

ACKNOWLEDGEMENT

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