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### STABILITIES OF SOME TRIVALENT AND DIVALENT METAL ION COMPLEXES OF N,N'-BIS(2-MERCAPTOETHYL)ETHYLENEDIAMINE-N,N'-DIACETIC ACID, AN EFFECTIVE LIGAND FOR INDIUM(III)

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# STABILITIES OF SOME TRIVALENT AND DIVALENT METAL ION COMPLEXES OF N,N'-BIS(2-MERCAPTOETHYL)ETHYLENEDIAMINE-N,N'-DIACETIC ACID, AN EFFECTIVE LIGAND FOR INDIUM(III)

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Potentiometric methods have been used to determine the equilibrium constants of indium(III), gallium(III), zinc(II), cadmium(II) and lead(II) with the ligand N,N'-bis(2-mercaptoethyl)ethylenediamine-N,N'-diacetic acid. The results reveal that this ligand has unusually high affinity for both In(III) and Ga(III). The formation constant ( $K_{ML} = [ML]/[M][L]$  in 0.100 M KCl at 25.0° for In(III) is  $10^{37.0}$  and its pM at physiological pH (7.4 with 100% excess of the ligand) is 30.4, which are higher than those of any other previously reported ligand for In(III).

**KEYWORDS:** stability constants, mercaptoethyl donor groups, protonation constants, potentiometry, titration curves, indium(III) complexes

## INTRODUCTION

Complex formation of In(III) with various ligands is important for the development of new radiopharmaceuticals.<sup>1</sup> However, many multidentate ligands with hydroxybenzyl or hydroxypyridyl donor groups do not coordinate In(III) as effectively as they do other (smaller) trivalent metal ions (Table 1). HBED and TACN-HP (see Glossary) have very high affinity for Ga(III) ( $\log K_{ML} = 38.51^6$  and  $45.6^3$ ) and Fe(III) ( $\log K_M = 39.01^6$  and  $49.98^3$ ); however their stability constants for In(III) are many orders of magnitude lower. On the other hand In(III) complexes of ligands with many acetate groups such as EDTA and DTPA have higher stability constants than those of the smaller trivalent metal ions such as Ga(III). This is at least partially due to the fact that the acetate donors form five membered chelate rings, and the preference of larger metal ions for the smaller five membered ring has been generally established, as well as the preference of the smaller metal ions for six membered chelate rings, such as those formed by hydroxybenzyl donor groups.<sup>10,11</sup>

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**Table 1** Formation constants ( $\log K_{ML}$ ) and  $pM^a$  of In(III) with some multidentate ligands (see glossary for definitions of ligand names).

	$\log K_{ML}$	$pM$	Reference
EDTA	24.9	22.1	2
DTPA	29.0	24.5	2
PLED	26.5	20.2	2
EDDA-HP	28.0	19.7	3
DTTA-HP	25.7	17.4	3
TACN-HP	28.03	17.4	3
TACN-TX	34.0	14.8	4
N <sub>3</sub> O-HP	26.07	15.4	5
HBED	27.9	17.9	6
SHBED	29.37	20.6	7
DOTA	23.9	17.8	8
TRITA	23.0	16.8	8
TETA	21.9	16.2	8
NOTA	26.2	21.6	9

<sup>a</sup>100% excess ligand at pH 7.4.

It is noted that In(III) complexes of the octadentate ligands DOTA, TRITA, and TETA are also more stable than those of the smaller Ga(III) ion. This may be due, in part, to the ability of the larger In(III) ion to expand its coordination number beyond six.

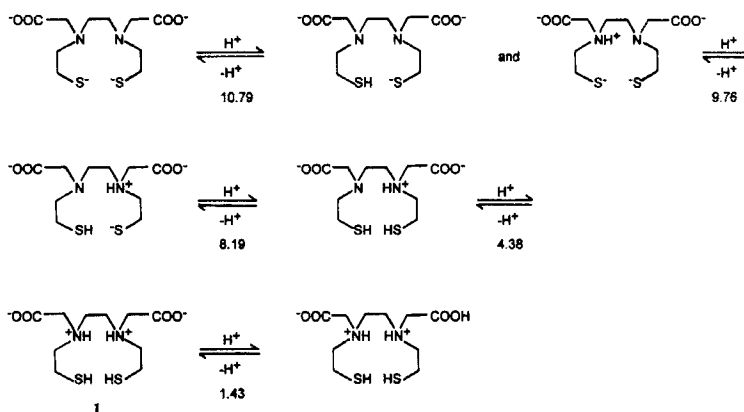
The mercapto or thiol group is weakly acidic (with a  $pK$  of about 9 or 10) and its anion binds to many metal ions with considerable complexing strength, especially with softer metal ions such as Ag(I) and Hg(II).<sup>10</sup> The stability data for 2-mercaptoethanol with trivalent metal ions, on the basis of the meager evidence available, are indicated in Table 2. It seems that the mercaptoethyl group probably has a high affinity for In(III) relative to Ga(III) and Fe(III).

The above experimental data led to our synthesis of N,N'-bis(2-mercaptoethyl) ethylenediamine-N,N'-diacetic acid (EDDASS) and the determination of its stability constants with In(III) and Ga(III). To explore the potential of this ligand for complexing other metal ions and for the possible treatment of metal intoxication, the stability constants of complexes formed with three divalent metal ions, Zn(II), Cd(II) and Pb(II), were also determined.

EDDASS (1 in Scheme I) was first prepared in 1958.<sup>12</sup> In 1982, Chiotellis, *et al.*<sup>13</sup> reported its NMR titration and the biological distribution of its <sup>99m</sup>Tc-labeled complex in experimental animals. Thus far, no other work related to the stability constants of metal complexes with EDDASS has been published, except for a brief communication by the present authors.<sup>14</sup>

**Table 2** The estimated  $\log K_{ML}$  of HOC<sub>2</sub>H<sub>4</sub>SH (HL) with some trivalent metal ions.

Metal ion	$\log K_{ML}$
Bi <sup>3+</sup>	13
In <sup>3+</sup>	10
Ga <sup>3+</sup>	~8
Fe <sup>3+</sup>	~7
Gd <sup>3+</sup>	very small



Scheme 1 Protonation of EDDA-SS.

## EXPERIMENTAL

### *Ligand Synthesis and Characterization*

#### *Materials and methods*

2-Mercaptoethylamine hydrochloride, benzyl chloride, 1,2-dibromoethane, bromoacetic acid, and mercuric chloride were obtained from Aldrich Chemical Co. and were used as supplied. Amberlite-IRA-400 anion exchange resins (OH-form) was purchased from Sigma Chemical Co. The proton and carbon-13 NMR spectra were recorded on a Varian XL-200 spectrometer operating at 200 MHz, and the chemical shifts are reported in ppm relative to tetramethylsilane. The mass spectra were obtained by Dr. Lloyd W. Sumner with the Department VG analytical 70S high resolution double focusing magnetic sector spectrometer with an attached VG analytical 11/250J data system. The C, H, N and S analyses were performed by Galbraith Laboratories, Inc., Knoxville, TN.

#### *Synthetic procedure*

EDDASS was synthesized by Bracco and the synthetic procedures are described in a British patent.<sup>12</sup> Modifications of Bracco's procedure for each step, and more complete characterization, were made as follows:

#### *(2-Aminoethyl)-benzyl sulfide*

2-Aminoethanethiol hydrochloride, 11.4 g (0.1 m), was dissolved in 60 mL of absolute ethanol. This solution was mixed with 50 mL of 2 M sodium hydroxide solution. To the turbid solution, 14 g (0.11 m) of benzyl chloride was added dropwise, and the reaction mixture was stirred at room temperature for 1.5 h. The ethanol was removed by evaporation. About 30 mL of water was added to dissolve the white precipitate which had separated. The clear aqueous solution was extracted with three 50 mL portions of methylene chloride. The aqueous phase was then made alkaline and the product was extracted twice with 60 mL of methylene chloride, which was

then dried with anhydrous  $\text{MgSO}_4$  for 16 h. After the  $\text{MgSO}_4 \cdot \text{H}_2\text{O}$  was removed and the solvent was evaporated, a pale yellow oil (17 g) was obtained, in a nearly quantitative yield.  $^1\text{H}$  NMR (in  $\text{CDCl}_3$ ): 7.34–7.2 (m, 5H, aromatic); 3.72 (s, 2H,  $-\text{CH}_2-$  of benzyl); 2.83 (t, 2H,  $\text{NH}_2\text{CH}_2$ ); 2.53 (t, 2H,  $\text{CH}_2\text{S}$ ); 1.5 (s, 2H,  $\text{NH}_2$ ).

*N,N'*-Bis(*S*-benzylmercaptoethyl)ethylenediamine dihydrochloride

A solution of 17 g (0.1 m) 2-aminoethyl benzyl sulfide in 25 mL of dry toluene was mixed with 4.5 g (0.024 m) of 1,2-dibromoethane. The colorless solution was heated to reflux for 3 h. After cooling, the reaction solution was poured into a solution of 3 g (0.075 m) of NaOH in 20 mL water. Two 50 mL batches of chloroform were used to extract the product. The chloroform-toluene solutions were combined and dried with anhydrous  $\text{MgSO}_4$  for 16 h. After filtering off the drying agent and removing the solvents by evaporation, 18.8 g of pale yellow oil was obtained. The unreacted 2-aminoethyl benzyl sulfide was removed by vacuum distillation at 95–100°C/0.1 mm Hg; and 7.3 g of colorless oil was obtained. This crude product was dissolved in 30 mL of ethanol, and 8.3 mL of 6 M HCl (0.05 m) was added. A large amount of pale yellow precipitate separated out. It was collected by filtration, washed with ethanol and ether and vacuum dried over  $\text{P}_2\text{O}_5$  at room temperature for 16 h; 6 g of product (as dihydrochloride) was obtained; yield 58%.  $^1\text{H}$  NMR of the free base (in  $\text{CDCl}_3$ ): 7.34–7.20 (m, 10H, aromatic); 3.71 (s, 4H,  $-\text{CH}_2-$  of benzyl); 2.77 (t, 4H,  $-\text{CH}_2-\text{NH}$ ); 2.63 (t, 4H,  $-\text{CH}_2-\text{S}$ ); 2.67 (s, 4H, ethylene); 1.7 (s, 2H,  $-\text{NH}$ ).  $^{13}\text{C}$  NMR (in  $\text{CDCl}_3$ ): 138.6 (1-C of benzyl); 129.0 and 128.7 (2 and 3-C of benzyl); 127.2 (4-C of benzyl); 49.1 and 48.4 ( $-\text{CH}_2-\text{S}-\text{CH}_2-$ ); 36.3 and 31.9 ( $-\text{CH}_2-\text{NH}-\text{CH}_2-$ ).

*N,N'*-Bis(3-benzylthioethyl)ethylenediamine-*N,N'*-diacetic acid

*N,N'*-Bis(*S*-benzylmercaptoethyl)ethylenediamine (2.2 g, 6.1 mmole) was dissolved in 45 mL of ethanol. An ice-cold solution of 1.87 g (13.4 mmole) of bromoacetic acid neutralized with 0.54 g of NaOH in 8 mL of water was then added. The reaction solution was heated to 40°C and the pH was maintained at 11.8–12.0 (by the addition of a 2.5 M NaOH solution) for 6 h. After cooling the ethanol was removed by evaporation. More water was added to make an aqueous solution of about 30 mL. This basic solution was extracted with ethyl ether; the ether solution was discarded. The pH of the aqueous phase was adjusted to 4.7 with a 6 M HCl solution. An oily product separated; to this mixture 40 mL of  $\text{CHCl}_3$  was added. After stirring and scratching, a white solid was obtained. It was filtered off and washed with  $\text{CHCl}_3$  and water. After vacuum drying over  $\text{P}_2\text{O}_5$  at room temperature for 2 days, 4.34 g of product was obtained, yield 50%.  $^1\text{H}$  NMR ( $\text{D}_2\text{O}-\text{NaOD}$ , pD = 13.2): 7.3 (m, 10H, aromatic); 3.68 (s, 4H,  $-\text{CH}_2-$  of benzyl); 3.10 (s, 4H,  $-\text{CH}_2-$  of acetate); 2.59 and 2.50 (m, 8H  $-\text{NCH}_2\text{CH}_2\text{S}$ ); 2.41 (s, 4H, ethylene).

*N,N'*-Bis(2-mercaptoethyl)ethylene diamine-*N,N'*-diacetic acid

In a three-necked flask, 130–150 mL of liquid ammonia was collected. While covered with dry argon, 0.6 g of thin pieces of sodium metal were added. After stirring at -60 to 70°C for 20 min 2.1 g (4.4 mmole) of *N,N'*-bis(3-benzylthioethyl)ethylenediamine-*N,N'*-diacetic acid was added portionwise. The reaction mixture was kept at this

temperature for 3 h; then the reaction was quenched by the addition of  $\text{NH}_4\text{Cl}$ . The excess  $\text{NH}_3$  was removed by evaporation at room temperature. To the white residue 25 mL of 1M HCl was added and the resulting solution was treated with charcoal and filtered. The filtrate and washings were combined (about 45 mL) and poured into a solution of 3.5 g  $\text{HgCl}_2$  (12.9 mmole) in 40 mL of water at 50–60°C. A large amount of white precipitate separated out. The bath temperature was increased to 105°C for 15 min, then the reaction mixture was allowed to stand at room temperature for 16 h. The white precipitate was collected by filtration and was washed thoroughly with water and methanol. The white precipitate was suspended in 60 mL of water and  $\text{H}_2\text{S}$  gas was passed into it for 7 hr. The  $\text{HgS}$  was removed by filtration, and the colorless filtrate was concentrated to about 20 mL. Amberlite-IRA-400 ( $\text{OH}^-$  form) was added until the pH of the solution became about 3.0. The anion exchange resin was removed by filtration and the aqueous solution was further concentrated to about 10–15 mL. It was allowed to stand in the refrigerator for two days and then filtered and the solid washed with cold water. After it was vacuum dried over  $\text{P}_2\text{O}_5$  at room temperature for two days, 0.78 g of product was obtained; yield 50%.  $^1\text{H}$  NMR (in  $\text{D}_2\text{O}$ -DCl,  $t\text{-BuOH} = 1.29$  ppm) 4.39 (s, 4H- $\text{CH}_2\text{COOH}$ ); 4.00 (s, 4H, ethylene); 3.69 (t, 4H,  $\text{HSCH}_2\text{-CH}_2\text{-N}$ ); 3.04 (t, 4H,  $\text{HSCH}_2\text{CH}_2\text{-}$ ).  $^{13}\text{C}$  NMR (in  $\text{D}_2\text{O}$ -DCl): 169.7 ( $-\text{COOH}$ ); 59.48 ( $-\text{CH}_2\text{COOH}$ ); 55.88 ( $-\text{N-CH}_2\text{CH}_2\text{-N-}$ ); 50.77 ( $-\text{N-CH}_2\text{-CH}_2\text{-SH}$ ); 19.59 ( $-\text{CH}_2\text{SH}$ ). FAB M.S.: ( $\text{M} + \text{H}$ ) = 297. *Anal.* Calcd. for  $\text{C}_{10}\text{H}_{20}\text{N}_2\text{S}_2\text{O}_4 \cdot 2\text{H}_2\text{O}$  (%) C, 36.14; H, 7.23; N, 8.43; S, 19.28. Found: C, 36.10; H, 7.49; N, 8.38; S, 19.96.

#### *Other reagents and standard solutions*

Metal ion solutions of In(III), Ga(III), Zn(II), Cd(II) and Pb(II) were prepared at about 0.02 M from analytical grade chloride or nitrate salts with demineralized water and were standardized by titration with EDTA<sup>15</sup> and by acidometric determination of concentration by cation exchange<sup>16</sup> (Dowex 50W  $\times$  8 cation exchange resin 20–50 mesh, hydrogen form). Disodium ethylenediaminetetraacetate (EDTA) and potassium hydrogen phthalate, an acidometric standard, were purchased from Fisher Scientific Co.; HBED was supplied by Dr. I. Murase of Dojindo Laboratories, Kumamoto, Japan. *Anal.* Calcd. for  $\text{C}_{20}\text{H}_{24}\text{N}_2\text{O}_6 \cdot \text{HCl} \cdot 2\text{H}_2\text{O}$ : C, 52.11; H, 6.35; N, 6.08. Found: C, 52.13; H, 6.34; N, 6.01.

A carbonate-free solution of the titrant, KOH, was prepared by dilution of analytical concentrate "Dilut-It" (J.T. Baker Chemical Co.) with demineralized water under a stream of purified argon gas. The solution was standardized against potassium acid phthalate, and the extent of the carbonate accumulation was checked periodically by titration with a standard hydrochloric acid solution.<sup>17</sup>

#### *Potentiometric equipment and measurements*

A Corning pH/ion analyzer 250 pH Meter was used together with a Model S-30056–10C Sargent Welch glass electrode and a Fisher 13-639-52 calomel reference electrode. A completely sealed 75 mL glass-jacketed titration cell was used, and the temperature ( $25.0^\circ\text{C} \pm 0.1^\circ\text{C}$ ) was controlled with a Fisher Model 90 refrigerated constant temperature bath. Atmospheric  $\text{CO}_2$  was excluded from the cell during the titration by passing purified argon through the experimental solution in

the reaction cell. The standard base was delivered through a capillary tip just under the surface of the solution by means of a 10 mL capacity Metrohm piston-type burette.<sup>17</sup>

Prior to each potentiometric equilibrium study, calibration of the pH meter and electrode system was made using standard dilute HCl solution at ionic strength 0.100 M adjusted with KCl or KNO<sub>3</sub> in the thermostated cell at 25.0°C, so as to read hydrogen ion concentration directly. The value of  $K_w = ([H^+][OH^-])$  used in the computations was  $10^{-13.78}$ .<sup>17</sup> The potentiometric equilibrium measurements were made on 40–50 mL of ligand solutions (initially  $5.30 \times 10^{-3}$  M) first in the absence of metal ions and then in the presence of each metal ion with ligand to metal ion ratio about 1.04:1. The pH values were measured after addition of 0.100 mL increments of standard KOH solution.

The equilibrium constants of zinc(II) and cadmium(II) complexes were determined by direct potentiometric titration. The degree of formation of the In(III) and Ga(III) complexes, even at low pH, was too high for determination of stability constants by use of direct potentiometry; therefore the ligand-ligand competition potentiometric titration method was used. The In(III) complex was determined by EDTA-EDDASS competition and Ga(III) by HBED-EDDASS competition. Because of the slow equilibrium for both systems a batch method was used.<sup>18</sup> In this procedure, sets of solutions were prepared in individual vials containing equimolar amounts of metal and ligands, sufficient potassium chloride for a 0.100 M solution, water to the appropriate volume and the amount of base required to achieve a specific pH value, each solution corresponding to a single point in a normal titration. Lead(II) forms an insoluble material with this ligand at low pH (~2.5–3.9) (at  $C_{Pb^{2+}} = C_{EDDASS} = 0.002$  M,  $\mu = 0.100$  M KNO<sub>3</sub>, 25.0°C). Its stability constants were determined by EDTA-EDDASS competition titration. The slowest equilibrium point for this system takes about 20 min. The protonation constants of the ligand and the stability constants of Zn(II), Cd(II), Pb(II), In(III) and Ga(III) were obtained from the experimental data with the aid of the program BEST.<sup>16</sup> The distribution curves were calculated and plotted with programs SPE and SPEPLOT.<sup>16</sup>

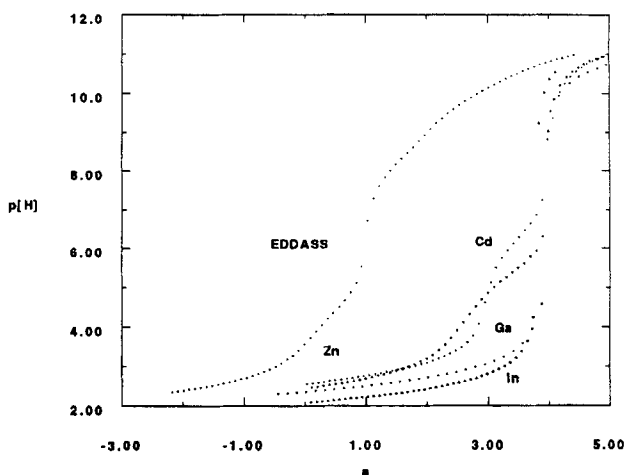
The number of data points recorded in a direct potentiometric measurement are shown in Figures 1 and 2. For the competition experiments ten data points were used for the In-EDDASS-EDTA or Ga-EDDASS-HBED system with the batch method; and 73 data points were used for the Pb-EDDASS-EDTA system by direct titration. The protonation constants of the pure ligands and the log  $K_{In-EDDASS}$  and log  $K_{Ga-EDDASS}$  were measured twice. The  $\Sigma_{fit}$  of each system is shown in the footnotes with the stability constants in Tables 4 and 5.

The four successive proton dissociation constants for Ga(III) used in the calculation are  $10^{-2.91}$ ,  $10^{-3.70}$ ,  $10^{-4.40}$  and  $10^{-5.77}$ .<sup>19</sup> The protonation constants and formation constants used in the ligand-ligand competition experiment are listed in Table 3.

## RESULTS AND DISCUSSION

### *Protonation of EDDASS*

EDDASS protonation constants are shown in Table 4. They were calculated from direct potentiometric pH measurements illustrated in Figure 1 since protonation



**Figure 1** Potentiometric pH profiles of EDDASS and its 1:1 metal complexes with In(III), Ga(III), Zn(II) and Cd(II) at  $\mu = 0.100$  M KCl,  $t = 25.0^\circ\text{C}$ .  $a =$  moles of base added per mole of ligand present.  $C_{\text{In}} = 1.91 \times 10^{-3}$  M;  $C_{\text{EDDASS}} = 2.19 \times 10^{-3}$  M;  $C_{\text{GaCl}_3} = 1.27 \times 10^{-3}$  M;  $C_{\text{EDDASS}} = 1.32 \times 10^{-3}$  M;  $C_{\text{ZnCl}_2} = 2.10 \times 10^{-3}$  M;  $C_{\text{EDDASS}} = 2.17 \times 10^{-3}$  M;  $C_{\text{Cd(NO}_3)_2} = 2.00 \times 10^{-3}$  M;  $C_{\text{EDDASS}} = 2.04 \times 10^{-3}$  M.

reactions were observed to take place within the potentiometrically measurable pH range. The logarithms of the successive protonation constants were found to be 10.78, 9.76, 8.19, 4.38 and 1.4. In considering the nature of the donor groups involved in successive protonation reactions, it is helpful to compare them with the protonation constants of cysteine (10.29, 8.16 and 1.91) and cystine (8.80 and 8.03). The two higher values of the protonation constants correspond to the protonation of the mercapto groups. Scheme I illustrates the probable protonation sequence of EDDASS, in which only the protonated forms considered to be the major species for each step are shown. This scheme shows that between the third and fourth  $\text{pK}_a$ 's (*i.e.*, at pH about 6) the main species should be the ligand with total change of -1; and the neutral compound, which is the tetraprotonated zwitterionic form with total charge of zero, should predominate at and below pH about 3. This result is consistent with the NMR titration result of Chiotellis.<sup>13</sup>

**Table 3** Protonation constants and formation constants used in the ligand-ligand competition experiments

EDTA		HBED	
Equilibrium	Log K	Equilibrium	Log K <sup>a</sup>
HL/H·L	9.93 <sup>b</sup>	HL/H·L	12.64
H <sub>2</sub> L/HL·H	6.05 <sup>b</sup>	H <sub>2</sub> L/HL·H	11.03
H <sub>3</sub> L/H <sub>2</sub> L·H	2.68 <sup>b</sup>	H <sub>3</sub> L/H <sub>2</sub> L·H	8.34
H <sub>4</sub> L/H <sub>3</sub> L·H	2.07 <sup>b</sup>	H <sub>4</sub> L/H <sub>3</sub> L·H	4.40
InL/In·L	24.90 <sup>c</sup>	H <sub>5</sub> L/ H <sub>4</sub> L·L	2.24
InHL/InL·H	1.5 <sup>c</sup>	GaL/Ga·L	38.51
PbL/Pb·L	18.0 <sup>c</sup>	GaHL/GaL·H	3.49
PbHL/PbL·H	2.8 <sup>c</sup>		

<sup>a</sup>Ref. 6. <sup>b</sup>Determined in this work;  $\mu = 0.100$  M KCl,  $t = 25.0^\circ\text{C}$ . <sup>c</sup>Ref. 2 Vol. VI.



**Table 4** Protonation constants of EDDASS and its metal ion affinities with In(III) and Ga(III) ( $\mu = 0.100$  M KCl,  $t = 25.0^\circ\text{C}$ ).

Protonation constants <sup>a</sup>		Stability constants		
		Equilibrium quotient	In(III)	Ga(III)
Log $K_{\text{HL}}$	10.79	ML/M·L	37.0 <sup>b</sup>	35.6 <sup>c</sup>
Log $K_{\text{H}_2\text{L}}$	9.76	MHL/ML·H	—	2.4 <sup>d</sup>
Log $K_{\text{H}_3\text{L}}$	8.19	MOHL·H/ML	—	-11.1 <sup>d</sup>
Log $K_{\text{H}_4\text{L}}$	4.3 <sup>R</sup>			
Log $K_{\text{H}_5\text{L}}$	1.4			
		pM <sup>e</sup>	30.4	29.0

<sup>a</sup> $\sigma_{\text{fit}} = 0.002$ . <sup>b</sup> $\sigma_{\text{fit}} = 0.04$ . <sup>c</sup> $\sigma_{\text{fit}} = 0.004$ . <sup>d</sup> $\sigma_{\text{fit}} = 0.002$ . <sup>e</sup>100% excess ligand at pH = 7.4.

### Metal Complexes of EDDASS with Zn(II), Cd(II) and Pb(II)

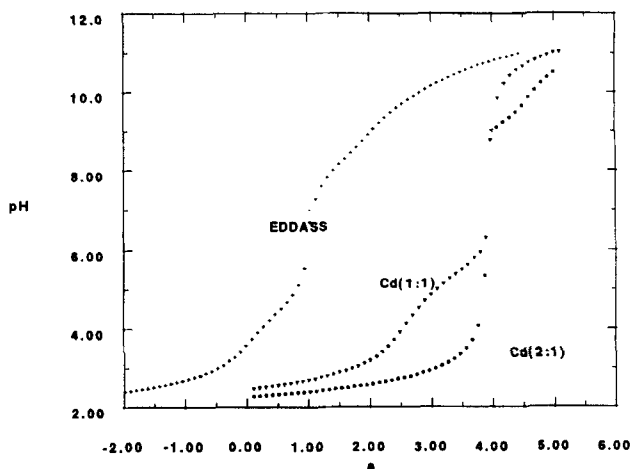
The stability constants for the complexes of Zn(II), Cd(II) and Pb(II) studied in this work are shown in Table 5. For comparison the published values for the same set of metal ions with EDTA are also indicated. The data show that the EDDASS chelates are considerably more stable for all of these metal ions. The titration curve of the Cd(II)-EDDASS system (Figure 1) ( $M_{\text{M}}:M_{\text{L}} = 1:1$ ) shows a shallow inflection at  $a = 2.5$ . This implies the existence of some dinuclear species. Titration of a solution containing a 2:1 molar ratio of metal ion to ligand  $M_{\text{M}}:M_{\text{L}} = 2:1$  showed the species  $K_{\text{M}_2\text{L}}$ ,  $K_{\text{M}_2\text{HL}}$ , and  $K_{\text{M}_2\text{OHL}}$ . Equilibrium constants for these complexes were found to improve the sigma pH fit of the 1:1 system. The shapes of the titration curves for the 2:1 and 1:1 systems are entirely different, due to the greater degree of formation of the 2:1 complex in the 2:1 system. The structure of the 2:1 complex is not known, but the nature of the pH profile in Figure 2 indicates that all strongly basic donor groups of the ligand are coordinated to the metal ions. This means that each Cd(II) ion is coordinated to an amino group and a thiolate group, as well as to a carboxylate group. Also, the 2:1 complex is more easily hydrolyzed than the 1:1 complex as expected.

Zinc(II) and Cd(II), as congeners of Hg(II), have higher affinity for mercapto groups than for acetate.<sup>2</sup> Therefore it is not surprising that they both form much more stable complexes with EDDASS than with EDTA. The EDDASS open chain backbone not only allows the mercaptoethyl and acetate donor groups more flexibility to meet the coordination and geometric requirements of the metal ions, but also help to improve the water solubility of these metal complexes.

**Table 5** Log stability constants of EDDASS with Zn(II), Cd(II) and Pb(II), and those with EDTA<sup>2</sup>;  $\mu = 0.100$  M KCl,  $t = 25.0^\circ\text{C}$ .

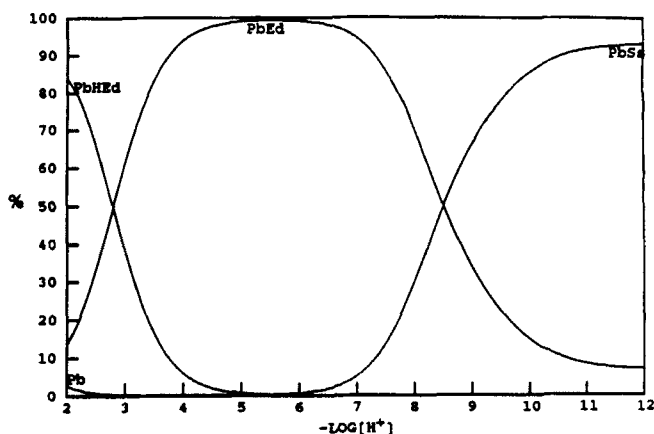
Quotient	EDDASS			EDTA		
	Zn(II) <sup>a</sup>	Cd(II) <sup>b</sup>	Pb(II) <sup>c</sup>	Zn(II)	Cd(II)	Pb(II)
[ML]/[M][L]	22.13	23.34	20.28	16.44	16.36	18.0
[MHL]/[ML][H]	6.12	5.47	5.41	3.0	2.9	2.8
[MH <sub>2</sub> L]/[MHL][H]	2.65	2.5	—			
[M <sub>2</sub> L]/[M] <sup>2</sup> [L]	—	30.74	—			
[M <sub>2</sub> HL]/[M <sub>2</sub> L][H]		2.5				
[M <sub>2</sub> OHL][H]/[M <sub>2</sub> L]		-9.7				
[MOHL][H]/[ML]	-11.41	-11.73	—	-11.6		

<sup>a</sup> $\sigma_{\text{fit}} = 0.008$ , <sup>b</sup> $\sigma_{\text{fit}} = 0.02$ . <sup>c</sup> $\mu = 0.100$  M KNO<sub>3</sub>,  $t = 25.0^\circ\text{C}$ ,  $\sigma_{\text{fit}} = 0.02$ .



**Figure 2** Potentiometric pH profiles of EDDASS and its  $M_M = M_L = 1:1$  and  $2:1$  complexes with Cd(II) at  $\mu = 0.100$  M KCl,  $t = 25.0^\circ\text{C}$ .  $a =$  moles of base added per mole of ligand present.  $1:1$  system:  $C_{\text{Cd}^{2+}} = 2.00 \times 10^{-3}$  M;  $C_{\text{EDDASS}} = 2.04 \times 10^{-3}$  M.  $2:1$  system:  $C_{\text{Cd}^{2+}} = 4.01 \times 10^{-3}$  M;  $C_{\text{EDDASS}} = 2.00 \times 10^{-3}$  M.

Lead(II) forms insoluble material at ligand and metal ion concentration of  $2 \times 10^{-3}$  below pH 3.5. EDTA competes with this ligand for Pb(II), and for the titration of a  $1:1$  molar ratio of EDTA: EDDASS, a clear solution was obtained from pH 2.5 to 11. The two stability constants  $\log K_{\text{PbL}}$  and  $\log K_{\text{PbHL}}$  (Table 5) were obtained with sufficient accuracy. The species distribution curves for the  $1:1:1$  Pb(II):EDDASS:EDTA system are shown in Figure 3. It is seen that the EDTA complexes of Pb(II) are more stable and predominate up to about pH 8.5, above which the EDDASS chelate predominates. This behaviour is due to the fact that the proton affinity of the ligand is higher than that of EDTA, but as hydrogen ions are



**Figure 3** Species distribution curves of In(III)-EDDASS-EDTA system.  $C_{\text{EDDASS}} = C_{\text{EDTA}} = C_{\text{Pb}(\text{NO}_3)_2} = 2.05 \times 10^{-3}$  M;  $\mu = 0.100$  M  $\text{KNO}_3$ ,  $t = 25.0^\circ\text{C}$ .

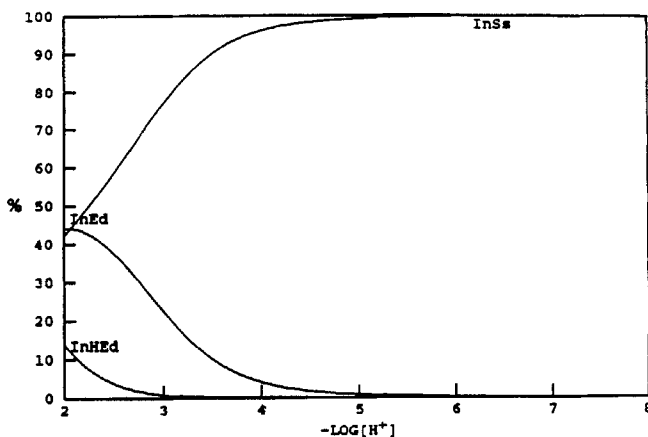
removed from the solution (by raising the pH) the system shows the effect of the higher stability constant for the Pb(II) chelate of EDDASS relative to that of the Pb(II)-EDTA complex.

Although these three divalent metal ions form very stable complexes, EDDASS is not an ideal ligand for treatment of lead or cadmium intoxication because of the high stability of its Zn(II) chelate, an essential trace metal ion that should not be removed from the body.<sup>10</sup>

#### *Metal Complexes of EDDASS with In(III) and Ga(III)*

The In(III) complex of EDDASS was found to form completely in the acid region below pH = 2.1 (Figure 1), excluding the possibility of direct potentiometric determination. Its stability was determined by competition reactions with EDTA (Figure 4). It took about 24 hr to reach equilibrium in the mixture. Equilibrium was confirmed by measuring the pH of each point 3 and 5 days after preparation of the solution and finding the pH values unchanged.

The formation constant of the In(III)-EDDASS complex can be calculated from the titration curve of the solution in competition with EDTA using the protonation constants of the ligand of EDTA, and the stability constants of the In(III)-EDTA complexes. The potentiometric equilibrium profile of the 1:1 In(III)-EDDASS system provides no evidence for protonation or hydrolysis of the In(III)-chelate, and it is therefore concluded that these forms, InHL and In(OH)L<sup>2-</sup>, do not exist, at least in appreciable amounts. Because of this high stability, and the lack of protonated and hydrolyzed forms, a species distribution plot for the In(III) chelate (not shown) would be featureless, showing 100% formation of the complex In(III)L<sup>-</sup> over the range from 2 to 11. With 100% excess ligand at physiological pH (7.4) the In(III) concentration is  $4.46 \times 10^{-31}$  M (pM = 30.4) which is six orders of magnitude lower than that of the In(III)-DTPA complex (pM = 24.5) and is also lower than the value achieved by any other previously reported ligand. This high stability is important in the design of new indium radiopharmaceuticals.



**Figure 4** Species distribution curves of In(III)-EDDASS-EDTA system.  $C_{\text{EDDASS}} = C_{\text{EDTA}} = C_{\text{InCl}_3} = 2.08 \times 10^{-3}$  M;  $\mu = 0.100$  M KCl,  $t = 25.0^\circ\text{C}$ .

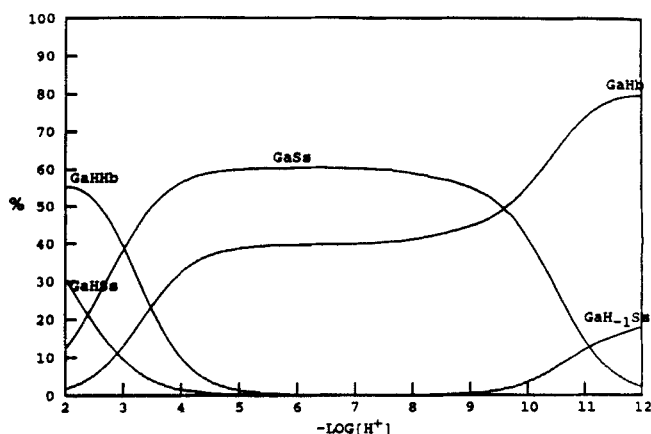


Figure 5 Species distribution curves of Ga(III)-EDDASS-HBED system.  $C_{\text{EDDASS}} = C_{\text{HBED}} = C_{\text{GaCl}_3} = 1.29 \times 10^{-3} \text{ M}$ ;  $\mu = 0.100 \text{ M KCl}$ ,  $t = 25.0^\circ\text{C}$ .

The Ga(III)-EDDASS complexes are also 100% formed at low pH and competition by  $\text{OH}^-$  to form  $\text{Ga}(\text{OH})_4^-$  does not cause significant dissociation. The log stability constant of Ga(III)-EDTA,  $\text{Log } K_{\text{GaEDTA}}$ , is 21.0,<sup>2</sup> which is not high enough to compete with this ligand. The stability constant of Ga(III)-EDDASS ( $\text{log } K_{\text{GaEDDASS}}$ ) was determined by potentiometric titration of a 1:1:1 Ga(III)-EDDASS-HBED system (Figure 5). Since it takes 24 h to reach equilibrium between the complexes formed by the competing ligands, a batch method was used. The pH value of each solution was read 3 and 5 days after preparation of the solution to confirm equilibrium. With the values of  $\text{log } K_{\text{GaHL}}$  and  $\text{log } K_{\text{GaOHL}}$  obtained from direct titration, and known constants of HBED and Ga(III)-HBED,  $\text{log } K_{\text{GaL}}$  of Ga(III)-EDDASS was obtained:  $\text{log } K_{\text{ML}} = 35.6$ ,  $\text{pM} = 29.0$ .

Based on the above results a new series of In(III) complexors with mercaptoethyl and dithiadiazia containing groups having good lipophilicity and high thermodynamic stability have been designed. Synthetic work is in progress to form stable neutral complexes with In(III) at physiological pH.

### Glossary

DOTA	1,4,7,10-tetraazacyclododecane-N,N',N'',N'''-tetraacetic acid
DTPA	diethylenetriaminepentaacetic acid
DTTA-HP	N,N''-bis(3-hydroxy-6-methyl-2-pyridylmethyl)diethylenetriamine-N,N',N'''-triacetic acid
EDDA-HP	N,N'-bis(3-hydroxy-6-methyl-2-pyridylmethyl)ethylenediamine-N,N'-diacetic acid
EDDASS	N,N'-bis(2-mercaptoethyl)ethylenediamine-N,N'-diacetic acid
EDTA	ethylenediaminetetraacetic acid
HBED	N,N'-bis(hydroxybenzyl)ethylenediamine-N,N'-diacetic acid
N <sub>3</sub> O-HP	4,7,10-tris(3-hydroxy-6-methyl-2-pyridylmethyl)-1-oxa-4,7,10-triazacyclododecane

NOTA	1,4,7-triazacyclononane-N,N',N''-triacetic acid
P LED	N,N'-bis(pyridoxyl)ethylenediamine-N,N'-diacetic acid
TACN-HP	N,N',N''-tris(3-hydroxy-6-methyl-2-pyridylmethyl)1,4,7-triazacyclononane
TACN-TX	N,N',N''-tris(3,5-dimethyl-3-hydroxybenzyl)-1,4,7-triazacyclonane
SHBED	N,N'-bis-(2-hydroxy-5-sulfobenzyl)ethylenediamine-N,N'-diacetic acid
TETA	1,4,8,11-tetraazacyclotetradecane-N,N',N'',N'''-tetraacetic acid
TRITA	1,4,7,10-tetraazacyclotridecane-N,N',N'',N'''-tetraacetic acid

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