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Preliminary Communication

N,N'-Bis(2-mercaptoethyl)ethylenediamine-N,N'-diacetic acid; an effective ligand for indium(III)

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Abstract

The formation constant of the In(III) complex of the sexadentate ligand N,N'-bis(2-mercaptoethyl)ethylenediamine-N,N'-diacetic acid has been determined by potentiometric measurement of its competition with EDTA. Its stability constant, $10^{37.0}$, is higher than that of Ga(III) ($10^{35.6}$) and is higher than that of any In(III) complex thus far reported. Its pM value of 30.4 under physiological conditions (pH 7.4, 100% excess ligand) indicates that the ^{111}In complex of this ligand would be a very effective radiopharmaceutical for diagnostic purposes.

Keywords: Indium complexes; Mercaptoethyl donor groups; Stability constants; Radiopharmaceuticals; Sulfur donor ligand complexes

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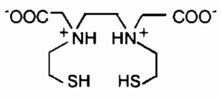
The study of complex formation of In(III) with various ligands is important for the development of new radiopharmaceuticals [1]. Many multidentate ligands that have been studied do not coordinate In(III) as effectively as they do smaller trivalent metal ions. N,N'-Bis(2-hydroxybenzyl)ethylenediamine-N,N'-diacetic acid (HBED) and N,N',N''-tris(3-hydroxy-6-methyl-2-pyridylmethyl)-1,4,7-triazacyclononane (TACN-HP) have very high affinities for Ga(III), however the stability constants for In(III) are many orders of magnitude lower (see Table 1). This implies that the nature of the phenolate and *o*-hydroxypyridyl groups, and the six-membered chelate rings that are formed, favor complex formation with small metal ions.

The mercapto group is weakly acidic and its anion binds to many metal ions with considerable complexing strength, especially with large heavy metal ions such as those of Hg(II) and Bi(III) [7]. The ligand EDDASS (**1**) (N,N'-bis(2-mercaptoethyl)ethylenediamine-N,N'-diacetic acid, H_4L) was designed by substituting two acetate groups of EDTA with two mercaptoethyl groups. The ligand is a good candidate for exploring the tendency of the relatively large mercapto donor group for complexing the In(III) ion, which is significantly larger than the Ga(III) and Fe(III) but smaller than the Hg(II) and Bi(III) ions. The ligand was first described by Bracco [8] in a British patent. Chiotellis et al. [9] reported its NMR titration and the biological distribution of its ^{99m}Tc-labeled complex in experimental animals, but did not report any equilibrium studies. Thus far no other work related to the stability constants of its metal complexes has been published. Reported here are the protonation constants and the In(III) and Ga(III) formation constants for this ligand.



1 EDDASS

EDDASS was synthesized by Bracco's procedure, and was characterized by ^{13}C and ^{1}H NMR, FAB-MS, and elemental analysis. *Anal.* Calc. for $C_{10}H_{20}N_2S_2O_4 \cdot 2H_2O$: 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%.

Details of the protonation constants and metal binding constants for EDDASS with In(III), Ga(III) and some divalent metal ions will be reported elsewhere [10]. The protonation constants of EDDASS were determined by direct potentiometric p[H] (where p[H] is defined as -log [H$^+$]) measurements (Fig. 1 and Table 2). The

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Table 1
Formation constants (log K_{ML}) and pM [a] of In(III) with some multidentate ligands (where known Ga(III) and Fe(III) constants are also indicated for comparison)

Ligand	Log K_{InL} (p[In^{3+}])	Log K_{GaL}	Log $K_{Fe(III)}$	Ref.
EDTA	24.9 (22.1)	20.1	25.1	[2]
DTPA	29.0 (24.5)	24.3	28.0	[2]
HBED	27.9 (17.9)	38.51	39.0	[3]
TACN-HP	28.03 (17.4)	45.6	49.98	[4]
NOTA [b]	26.2 (21.6)	30.98	28.3	[5]
Transferrin	18.30 [c] 16.44 [d] (18.3)	19.75 [c] 18.80 [d]	21.44 [c] 20.34 [d]	[6]
EDDASS	37.0 (30.4)	35.6		this work

[a] 100% excess ligand at pH 7.4.
[b] 1,4,7-Triazacyclononane-N,N'',N'''-triacetic acid.
[c] Conditional constant for K_{ML} at p[H] 7.4.
[d] Conditional constant for K_{M2L} at p[H] 7.4.

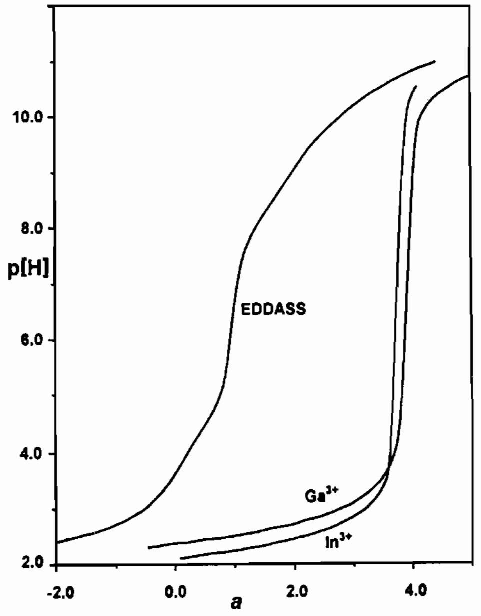

Fig. 1. Potentiometric p[H] profiles of EDDASS and its 1:1 metal complexes with In(III) and Ga(III); μ=0.100 M KCl, t=25.0 °C. a=moles of base added per mole of ligand present. For the In^{3+} curve, $C_{In}=1.91\times10^{-3}$ M; $C_{EDDASS}=2.19\times10^{-3}$ M; for the Ga^{3+} curve, $C_{GaCl_3}=1.27\times10^{-3}$ M; $C_{EDDASS}=1.32\times10^{-3}$ M. Each curve represents more than 10 data points per equivalent of hydrogen ion or acid group neutralized.

potentiometric equilibrium profile of the 1:1 In(III)–EDDASS system (Fig. 1) shows that the In(III) complex of EDDASS forms completely below p[H] 2.1. Also, the titration curve shows that protonated and hydroxo forms of the In(III) chelate are not formed. The formation constant of the In(III)–EDDASS complex was determined by competition with EDTA and was found to be $10^{37.0}$. The species distribution curves for the 1:1:1 In(III):EDDASS:EDTA system (Fig. 2, plotted by program SPEPLOT [11]) show that at p[H] 2.0 about 58% of the In(III) ion is coordinated with EDTA. When the p[H] is increased to 4, In(III)–EDDASS becomes the major species.

Table 2
Log protonation constants of EDDASS and its metal ion affinities with In(III) and Ga(III) (μ=0.100 M KCl, t=25.0 °C) [a]

Protonation constants		Log stability constants [b]		
		Equilibrium quotient	In(III)	Ga(III)
Log K_{HL}	10.79(3)	ML/M·L	37.0	35.6
Log K_{H2L}	9.76(2)	MHL/ML·H		2.4
Log K_{H3L}	8.19(2)	MOHL·H/ML		−11.1
Log K_{H4L}	4.38(1)			
Log K_{H5L}	1.4(1)			
		pM [c]	30.4	29.0

[a] All units are M^{-1} where M=moles/liter, except the chelate hydrolysis constant, where the unit is M.
[b] Estimated errors for the stability constants reported here are one digit or less in the last decimal number shown.
[c] 100% excess ligand at p[H] 7.4.

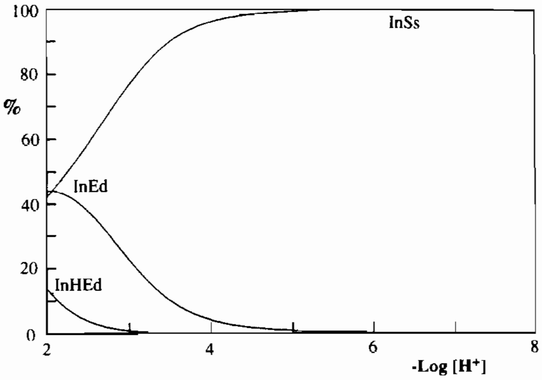

Fig. 2. Species distribution curves of the In(III)–EDDASS–EDTA system. $C_{EDDASS}=C_{EDTA}=C_{InCl_3}=1.00\times10^{-3}$ M; μ=0.100 M KCl, t=25.0 °C. The labels Ed and Ss represent EDTA and EDDASS, respectively.

The formation constant of the In(III)–EDDASS complex is higher than the stability constant of any previously reported In(III) complex. With 100% excess of ligand at physiological p[H] (7.4) the In(III) ion concentration is 4.46×10^{-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 lower than that of the In(III) complex of any other previously reported ligand. Thus the mercaptoethyl donor group is considered important in the design of new In(III) radiopharmaceuticals since the high affinity for In(III) imparted to ligands containing this donor group will make the resulting complexes resistant to metal ion exchange with natural chelating ligands in biological systems.

For comparison, the stability constants of Ga(III)–EDDASS complexes were also studied. The log $K_{Ga(III)-EDDASS}$ value was determined by a 1:1:1 Ga(III)–EDDASS–HBED system; the values of log K_{GaHL} and log K_{GaOHL} were obtained from direct titration (Fig. 1). These results, Table 2, show that the Ga(III) complex is somewhat less stable than that of In(III) and undergoes protonation and hydroxo complex formation.

Attempts to obtain crystals of In(III)–EDDASS$^-$ for structure determination have thus far not been successful, but the nature of the p[H] profile in Fig. 1 indicates that all the strongly basic donor groups of the ligand are coordinated to the In(III) ions. In aqueous solution the coordination number of In(III)–EDDASS is six, or seven if a water molecule is also coordinated.

Based on the above results a new series of In(III) complexors with mercaptoethyl and dithiadiaza containing donor groups, but having greater lipophilicity and high thermodynamic stability, and which are expected to form stable neutral complexes with In(III) at physiological pH, have been designed and synthetic work is now in progress.

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