Stabilities of trivalent metal ion complexes of the tetraacetate derivatives of 12-, 13- and 14-membered tetraazamacrocycles

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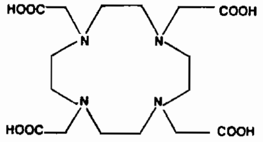
Abstract

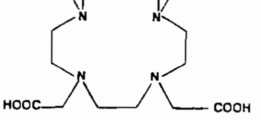
The stabilities of metal complexes of the trivalent metal ions La(III), Gd(III), Fe(III), Ga(III) and In(III) with the tetraazamacrocyclic tetraacetates, 1,4,7,10-tetraazacyclododecane-*N,N′,N″,N‴*-tetraacetic acid (DOTA), 1,4,7,10-tetraazacyclotridecane-*N,N′,N″,N‴*-tetraacetic acid (TRITA) and 1,4,8,11-tetraazacyclotetradecane-*N,N′,N″,N‴*-tetraacetic acid (TETA), have been determined in KCl electrolyte ($I=0.100$ M, 25.0 °C) by potentiometric p[H] methods and by spectrophotometric determination of exchange with a competing ligand. All of the trivalent metal ion complexes of DOTA, TRITA and TETA form precipitates at neutral and higher p[H] but are soluble in acidic solutions. The log stability constants ($\log K_{ML}=[ML^-]/[L^{4-}][M^{3+}]$) of the La(III), Gd(III), Ga(III) and In(III) complexes of DOTA (L) ($\log K_{LaL}=21.7$; $\log K_{GdL}=24.0$; $\log K_{GaL}=21.33$; $\log K_{InL}=23.9$) are low in comparison to that of Fe(III)–DOTA ($\log K_{FeL}=29.4$). The stabilities of the trivalent metal complexes with TRITA and TETA are lower than those of the DOTA complexes. In(III) has slightly higher affinities for these ligands than does Ga(III), while the affinity of Gd(III) is considerably higher than that of La(III).

Introduction

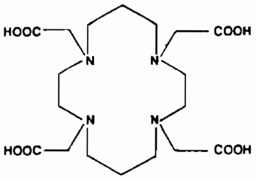
The stabilities of the metal complexes of the tetraazamacrocyclic tetraacetates, 1,4,7,10-tetraazacyclododecane-*N,N′,N″,N‴*-tetraacetic acid (DOTA, **1**), 1,4,7,10-tetraazacyclotridecane-*N,N′,N″,N‴*-tetraacetic acid (TRITA, **2**) and 1,4,8,11-tetraazacyclotetradecane-*N,N′,N″,N‴*-tetraacetic acid (TETA, **3**), with the alkaline earth and bivalent transition metal ions were determined and reported by Clarke and Martell in a previous paper [1].



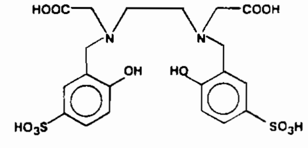
1 DOTA, H_4L



2 TRITA, H_4L



3 TETA, H_4L



4 SHBED, H_6L

Batch methods and ligand exchange methods were used to measure the stability constants for the metal complexes of the macrocyclic ligands which reach equilibrium very slowly. In the present work, the scope of these stability studies is expanded to include the trivalent metal ions La(III), Gd(III), Fe(III), Ga(III) and In(III). The gadolinium complexes have applications in the field of medicine as proton NMR relaxation agents for the imaging of tissues [2, 3]. The ^{67,68}Ga and ^{111}In complexes of the macrocyclic ligands are used as radiopharmaceutical agents for the purpose of enhancing diagnostic images [4] through gamma ray detection. Chelating agents for Fe(III) are of interest as possible drugs for the removal of iron from the body in cases of iron overload [5].

A number of questionable stability constants of the lanthanide complexes of DOTA have accumulated in the literature. Cacheris *et al.* [6] attempted to decrease the time required to reach equilibrium for solutions of lanthanide complexes by heating the solutions and then cooling them to standard conditions just prior to measurement. Loncin *et al.* [7] exchanged lanthanide complexes with oxalate salts and recovered the insoluble oxalate chelates for gravimetric determination of the quantity of lanthanide ion that was exchanged from the macrocyclic

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complex. This method, usually referred to as a gravimetric method, suffers from the possibility of equilibrium shift during the separation process. Desreux [8] reported a stability constant for the Gd(III)–DOTA complex on the basis of a rapid potentiometric titration, which probably did not allow sufficient time to reach equilibrium. Recently, reliable potentiometric determinations for yttrium(III) complexes of DOTA, TRITA and TETA have been reported [9]. Stability constants for the Ga(III), In(III) and Fe(III) complexes of the three tetraazamacrocyclic tetraacetates studied in this investigation have not been determined previously.

Experimental

Synthesis of ligands

The tetraacetate derivatives of the tetraazamacrocyclic ligands used in this study (DOTA, TRITA and TETA) were prepared and characterized in the manner previously described [1].

Spectral determinations

Absorbance measurements were made at 25.0 ± 0.1 °C with a Perkin-Elmer model 553 fast scan UV–Vis spectrophotometer equipped with 1.000 ± 0.001 cm matched quartz cells.

Potentiometric determinations

The potentiometric determinations of metal complex stability constants used in this research are described in a handbook by Martell and Motekaitis [10]. The Corning model 130 pH meter employed was equipped with a thermostated (25.0 °C) 100 ml glass-jacketed titration cell fitted with a Schott Blue Stem glass electrode, a reference calomel electrode, inert gas inlet and outlet fittings, and a 10 ml capacity Metrohm piston buret with a capillary delivery tip placed just below the surface of the solution. The pH meter–electrode system was calibrated with standard acid and standard base at an ionic strength adjusted to 0.100 M with KCl. All pH values were directly expressed as $-\log [H^+]$, designated as p[H]. The calibration was performed over the p[H] range of 2.2 to 11.3, for which the electrodes gave a reliable Nernstian response, with a value of $-\log K_w = 13.78$ ($K_w = [H^+][OH^-]$).

Standard KOH solution was prepared with the exclusion of atmospheric CO_2 gas by dilution of an ampoule of carbonate-free DILUT-IT® analytical concentrate with boiled doubly-distilled water under a stream of purified N_2 gas. Atmospheric CO_2 was excluded from the titration cell during the course of the titration by passing purified N_2 at slightly higher than atmospheric pressure across the top of the experimental solution in the reaction cell, which was sealed from the atmosphere. Metal ion standard solutions were prepared at ~0.02 M from the nitrate and chloride salts of the metals and were standardized against EDTA by the methods of Schwarzenbach *et al.* [11].

Experimental solutions of 1:1 molar ratios of metal ion to ligand were prepared in the titration cell by weighing out about 0.100 mmol of ligand and adding an equivalent amount of standard metal ion stock solution. The volume was made up to 50.00 ml with doubly-distilled water and 5.00 ml of 1.00 M KCl to bring the solution up to 0.100 M ionic strength. The contributions of the metal ion and the ligand to ionic strength were ignored since the concentrations of the supporting electrolyte and the metal complex were maintained at a ratio of 50:1. Stepwise protonation constants ($K_n{}^H = [H_nL]/[H_{(n-1)}L][H]$) were calculated by fitting the calculated to the experimental potentiometric p[H] data with program BEST [12]. With the exception of the Fe(III) chelates, and the In(III)–DOTA and TRITA complexes, described below, metal chelate stability constants ($K_{ML} = [ML^-]/[L^{4-}][M^{3+}]$) and protonation constants of the metal chelates ($K_{MLH} = [MHL]/[ML^-][H]$) were also calculated from potentiometric data by the use of program BEST. Most of the equilibrium periods were sufficiently long to require the use of batch solutions, described below.

The batch method

Solutions of macrocyclic complexes with La(III), Gd(III) and Ga(III) were prepared at ~10^{-3} M in separate sealed containers with equivalent amounts of metal ion and ligand but differing in the amount of titrant. The proton stoichiometry or *a*- value was set with incremental additions of acid or base to fall within a region of partial complex formation. The p[H] of each series of batch solutions was determined until values had become constant. The electrodes and titration cell were rinsed with distilled water and blotted dry between measurements. Equilibrium was approached from two directions by adding standard acid to the batch solutions (after they had stabilized in one direction resulting from added base). The time to reach equilibrium varied from 10 to 16 days depending on the slow proton equilibrium between the ML and MHL species for each of the trivalent metal ion complexes. Stability constants were calculated from both the ascending and descending set of p[H] values, and reported as averages.

Potentiometric determination of Fe(III) stability constants by competition with EDTA or NTA

Ligand exchange methods were used for the determination of the Fe(III) complexes with the tetraazamacrocyclic tetraacetates in competition with equivalent amounts of ethylenediaminetetraacetic acid (EDTA) or nitrilotriacetic acid (NTA). In the titration cell, equilibrium of the ternary solutions was sufficiently rapid so that several potentiometric p[H] points were taken per *a* value. A good match of equilibrium p[H] values approached from two directions was obtained.

Fe(III) ion was displaced from Fe(III)–DOTA (ML) by EDTA (Y) according to the following equilibrium:

$$ML + H_mY \rightleftharpoons MY + H_nL + (m-n)H^+$$

Both DOTA and EDTA contain four dissociable protons. The Fe(III)–EDTA complex is formed to the extent of 92% of the Fe(III) present at p[H] 3, while Fe(III)–DOTA is completely formed in the alkaline region. Fe(III)–EDTA and Fe(III)–DOTA are both ~50% present at p[H] 5.9, well below neutral p[H] at which a precipitate (presumably ferric hydroxide) is formed. The acidity (T_H) was adequately explained at and below p[H] 7.5 by the following mass balance equations (where T_{LY} is the sum of the total ligand concentrations: L is DOTA, Y is EDTA):

$$\begin{aligned} T_H - aT_{LY} = {} & \sum_{n=0}^{4}[H_nL] + [MHL] + 2[MH_2L] \\ & + \sum_{m=0}^{4}[H_mY] + [MHY] + 2[MH_2Y] \\ & + [H^+] - [OH^-] \end{aligned}$$

However, problems of precipitate formation at neutral p[H] interfered with the determination of the TRITA and TETA complex stabilities because Fe(III)–TRITA and Fe(III)–TETA were only minor species at neutral p[H], compared to the Fe(III)–EDTA complex. To circumvent this problem, a weaker competing ligand, NTA, was used.

The 1:1:1 molar ratios of Fe(III)–TRITA–NTA (and TETA) were slowly titrated from p[H] 2.0 to about 4.5, beyond which a light precipitate was observed. For these ternary solutions, Fe(III) crosses over from NTA to TRITA or TETA at about p[H] 2. The protonation constants and stability constants for EDTA and NTA were taken from the Critical Stability Constants [13, 14].

Spectrophotometric determination of In(III) binding constants

For In(III)–DOTA and In(III)–TRITA, spectral determinations of ligand displacement were made in the presence of the competing ligand, *N,N'*-bis(2-hydroxy-5-sulfobenzyl)ethylenediamine-*N,N'*-diacetic acid (SHBED) (H_6Y, **4**) which forms a complex with In(III) ion [15], which is stable over the p[H] range 2 to 12. The stability constants (K_{ML}) of In(III)–DOTA (ML) and In(III)–TRITA (ML) were calculated from the changes in absorbance of In(III)–SHBED (MY) by the use of the appropriate mass balance equations and equilibrium constant expressions. The major species present are: ML^-, MHL, H_2L^{2-}, H_3L^-, H_4L, MY^{3-}, MHY^{2-}, H_3Y^{3-}, H_4Y^{2-} and H_5Y^-.

For the ternary solutions (at about 10^{-4} M) containing equivalent amounts of In(III), DOTA or TRITA and SHBED, the distribution of In(III) ion between the ligand (L) and SHBED (Y) was measured spectrophotometrically ($I = 0.100$ M KCl, 25.0 °C) over the p[H] range from 2.2 to 4.7 according to the following equilibrium.

$$\begin{aligned} & InY^{3-} + InHY^{2-} + H_3L^- + H_4L \rightleftharpoons \\ & \quad InL^- + InHL + H_2L^{2-} + H_3Y^{3-} + H_4Y^{2-} + H_5Y^- \end{aligned}$$

The phenolic groups of free SHBED absorb at 235 nm while the phenolate groups of the In(III)–SHBED complex absorb at 255 nm. The molar absorbance of In(III)–SHBED at this wavelength is 19 630 M^{-1} cm^{-1} at p[H] 3. The In(III) complexes of DOTA and TRITA do not absorb appreciably in the UV wavelength range measured. Ternary solutions of In(III):DOTA:SHBED and In(III):TRITA:SHBED were prepared in a series of 10.0 ml volumetric flasks. The p[H] of each flask was adjusted with 0.100 M KOH to fall in the p[H] range from 2.2 to 4.7 with increments of about 0.3. The ionic strength was adjusted to 0.100 M with KCl. For the In(III)–DOTA–SHBED competition system, the p[H] and absorbance at 255 nm were monitored for up to 4 weeks until the solutions became unstable with respect to the formation of a precipitate. The In(III)–TRITA–SHBED system developed a precipitate after 9 days.

The concentration of In(III)–SHBED (MY^{3-}) was calculated directly from the molar absorbance, while the concentration of In(III)–DOTA (or In(III)–TRITA) as ML^- was taken by difference. The concentrations of free SHBED (Y^{6-}) and free DOTA or TRITA (L^{4-}) were calculated from the mass balance equations and the protonation constants of SHBED [15, 16], and the appropriate macrocyclic ligand. A correction for the absorbance of free SHBED at 255 nm was necessary since the SHBED absorbance reaches a limit (~0.132 absorbance units) over the p[H] range employed. An exchange constant for the quotient of the In(III) stability constants for DOTA (K_{ML}) and SHBED (K_{MY}) was calculated in the following equation.

$$K_{ex} = K_{ML}/K_{MY} = [ML^-][Y^{6-}]/[MY^{3-}][L^{4-}]$$

The exchange constant was reliable when the exchange ratio (i.e. ratio of [InSHBED] to [InDOTA] or [InTRITA]) was about 1.0 to 2.0, as calculated from the p[H] and absorbance data previously described. The stability constants (log K_{ML}) for In(III)–DOTA and In(III)–TRITA were computed from K_{ex} and the known stability constant for In(III)–SHBED (log $K_{MY} = [MY^{3-}]/[Y^{6-}][M^{3+}] = 29.37$) [14].

Results

Potentiometric data

The equilibrium p[H] profiles of the free ligands DOTA, TRITA and TETA appear with 1:1 molar ratios to La(III), Gd(III), Fe(III), Ga(III) and In(III) in Figs. 1–3, respectively. The breaks in the titration curve for the free ligands fall at $a = 2$ in each case, while the breaks for metal complexes fall at $a = 4$. The macrocyclic ligands have the form of H_4L ligands and contain four dissociable protons. The La(III) and Gd(III) complexes of DOTA, TRITA and TETA form stable complexes in the acid p[H] range but dissociate to form metal hydroxide precipitates at neutral and higher p[H]. Only the ML^- and MLH

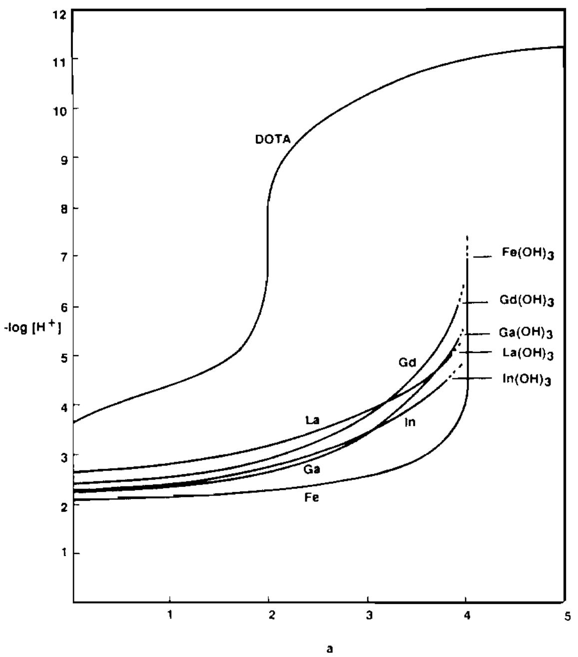

Fig. 2. Potentiometric equilibrium pH profiles for TRITA and for 1:1 molar ratios of TRITA to Fe(III), Ga(III), In(III), La(III) and Gd(III) at ~2.0×10^{-3} M. $\mu = 0.100$ M (KCl), $t = 25.0$ °C.

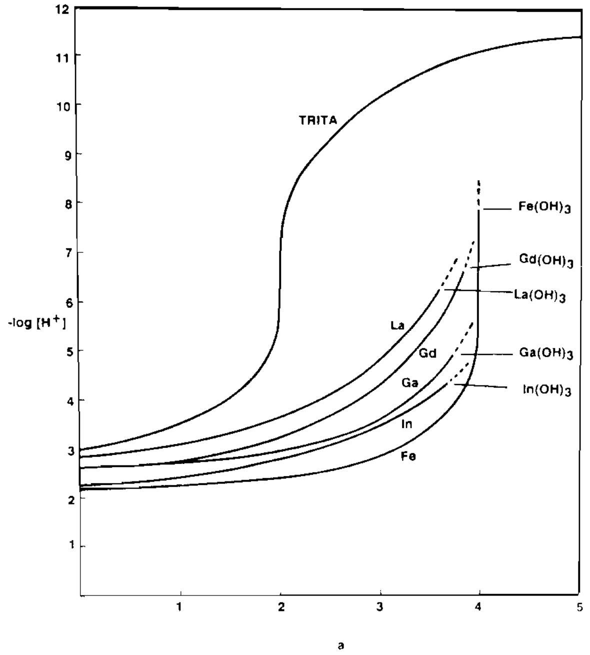

Fig. 1. Potentiometric equilibrium pH profiles for DOTA and for 1:1 molar ratios of DOTA to Fe(III), Ga(III), In(III), La(III) and Gd(III) at ~2.0×10^{-3} M. $\mu = 0.100$ M (KCl), $t = 25.0$ °C.

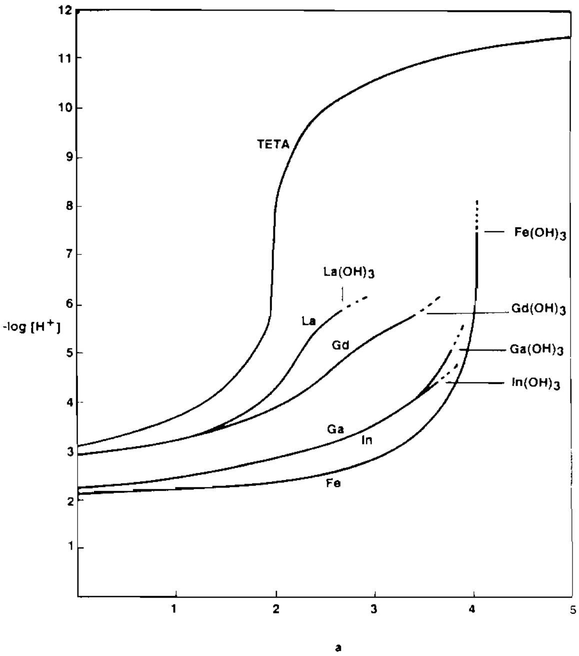

Fig. 3. Potentiometric equilibrium pH profiles for TETA and for 1:1 molar ratios of TETA to Fe(III), Ga(III), In(III), La(III) and Gd(III) at ~2.0×10^{-3} M. $\mu = 0.100$ M KCl, $t = 25.0$ °C.

species were found to be present in solution. In the strongly acid p[H] region, from 2 to 3, nearly four protons per ligand are displaced by formation of trivalent metal complexes. At $a=0$, the initial p[H] values of the Ga(III) and In(III) complexes are lower than those of the La(III) and Gd(III) complexes indicating the relative extents to which protons are displaced from complexes with DOTA, TRITA and TETA by these metal ions and indicate the relative stabilities of the complexes formed. The complex formation curves for Fe(III) with DOTA, TRITA and TETA lie at still lower p[H] as a consequence of the relatively higher affinity of these ligands for the Fe(III) cation. The p[H] levels of the acid buffer regions are a general indication of metal ion affinity, but the higher curves do not necessarily mean partial dissociation of the ML^- complex, but could be due to formation of protonated complexes, MHL. The p[H] levels of precipitation indicated do not follow linearly with the stabilities of the complexes, because they are also dependent on the magnitudes of the solubility products.

Stability constants

The protonation constants (K_n^H) for DOTA, TRITA and TETA were determined previously [1] and appear in Table 1. The log stability constants (log K_{ML}) and log protonation constants of the metal complexes (log K_{MHL}) listed in Table 1 were determined by various methods, described in 'Experimental'. Those of the TETA complexes with La(III), Gd(III) and In(III) were determined by potentiometric titration, whereas the remaining stability constants were calculated by batch titration and exchange with a competing ligand.

Batch determinations of stability constants

Batch determinations of the stability constants of the macrocyclic complexes of La(III), Gd(III) and Ga(III) (Table 1) were performed over periods extending up to 16 days. Log protonation constants (log K_{MHL}) for these metal complexes were determined simultaneously with the batch p[H] measurements. The relative order of stability constants for the macrocyclic complexes with La(III), Gd(III) and Ga(III) is DOTA > TRITA > TETA. DOTA has a preferential selectivity for the large size metal ions, La(III) and Gd(III), over TRITA and TETA. The log stability constants for the La(III) complexes with DOTA, TRITA and TETA (log $K_{ML}=21.7$, 17.02 and 11.60, respectively) and the Gd(III) complexes (log $K_{ML}=24.0$, 19.17 and 13.77, respectively) tend to fall off faster with size of the macrocyclic ring than those of the In(III), Ga(III) and Fe(III) complexes (log K_{ML} for Ga(III) = 21.33, 19.91 and 19.74, respectively).

Stability constants for the Fe(III) macrocyclic complexes

The stability constant (log K_{ML}) for the Fe(III)–DOTA complex determined by competition with EDTA was found to have the log value of 29.4 ± 0.1 (Table 1). The species distribution curves for the ternary Fe(III)–DOTA–EDTA solution (Fig. 4) show that Fe(III)–EDTA (as MY) accounts for 92% of the total Fe(III) at p[H] 3 while Fe(III)–DOTA (ML) is formed in increasing amounts between p[H] 3.5 and 7.5. A precipitate of $Fe(OH)_3$ is formed near p[H] 7.5 (Fig. 4). The log stability constants of Fe(III)–TRITA and Fe(III)–TETA were determined by competition with NTA (see 'Experimental') as 27.46 ± 0.02 and 26.53 ± 0.01, respectively (Table 1). Fe(III) forms stable complexes with DOTA, TRITA and TETA in acidic media, but Fe(III) is released from these complexes as ferric hydroxide at neutral and higher p[H]. The log protonation constants (log K_{MHL}) for the Fe(III) complexes were determined in separate potentiometric titrations in the absence of EDTA. The protonation constants and metal ion stability constants for EDTA and NTA used in these determinations are listed in Table 2.

Stability constants of the In(III) complexes of DOTA and TRITA

Figure 5 shows the changes in absorbance of SHBED in the presence of equimolar concentrations of In(III) and TRITA at 255 nm, attributed to the phenolate groups of In(III)–SHBED over the p[H] range from 2.17 to 4.30, as In(III) ion is partitioned between TRITA and SHBED. These spectrophotometric data were used to calculate the exchange constant data (see 'Experimental') as -6.37 ± 0.02. From this value, and the value of 29.37 as the log K_{ML} of In(III)–SHBED [15], the value of log K_{ML} of In(III)–TRITA was calculated as 23.00 ± 0.02. The internal agreement in the exchange constant for TRITA showed that equilibrium was attained or nearly attained before the onset of a precipitate in the ternary In(III)–TRITA–SHBED solution. Similar spectrophotometric data taken for the ternary In(III)–DOTA–SHBED solution (not shown) gave the exchange constant as -5.6 ± 0.1, from which log $K_{ML}=23.9\pm0.1$. As indicated in the species distribution curves for the In(III)–TRITA–SHBED system, In(III)–TRITA (ML^-) is a minor species which forms a maximum of 27% of the total In(III) present at p[H] 3.7 (Fig. 6), while In(III)–SHBED is protonated as MHY^{2-} below p[H] 5 but is formed completely as MY^{3-}, which is the only complex present at p[H] 8.0 and above. The hydroxo In(III)–SHBED complex is present at higher p[H]

TABLE 1. Protonation constants of DOTA, TRITA and TETA, and stability constants of their 1:1 trivalent metal ion complexes (μ = 0.100 M (KCl), t = 25.0 °C). Values in parentheses are taken from the literature

Quotient	Log *K*		
	DOTA	TRITA	TETA
$[HL]/[L][H]$[a]	11.14	11.79	10.28
$[H_2L]/[HL][H]$	9.69	9.20	10.10
$[H_3L]/[H_2L][H]$	4.84	4.00	4.15
$[H_4L]/[H_3L][H]$	3.95	2.57	3.21
$[LaL]/[L][La]$	21.7 ± 0.1	17.02 ± 0.03	11.60 ± 0.01[b]
	(23.0)[c]		
$[LaHL]/[LaL][H]$	2.5 ± 0.2	3.8 ± 0.1	6.05 ± 0.01[b]
$[GdL]/[L][Gd]$	24.0 ± 0.1	19.17 ± 0.06	13.77 ± 0.02
	(24.6)[c]		(15.75 ± 0.04)[d]
	(28.0)[e] (24.9)[f]	(19.6 ± 0.3)[f]	(16.1 ± 0.2)[f]
$[GdHL]/[GdL][H]$	2.3 ± 0.2	3.2 ± 0.2	4.52 ± 0.05[b]
	(1.35 ± 0.02)[e]		(3.75 ± 0.13)[d]
$[GaL]/[L][Ga]$	21.33 ± 0.05	19.91 ± 0.03	19.74 ± 0.01
$[GaHL]/[GaL][H]$	4.00 ± 0.04	3.66 ± 0.01	3.65 ± 0.01
$[FeL]/[L][H]$	29.4 ± 0.1[g]	27.46 ± 0.02[h]	26.53 ± 0.01[h]
$[FeHL]/[FeL][H]$[b]	3.23 ± 0.02	2.64 ± 0.01	3.53 ± 0.03
$[InL]/[L][In]$	23.9 ± 0.1[i]	23.00 ± 0.02[i]	21.89 ± 0.01[b]
$[InHL]/[InL][H]$[b]	3.44 ± 0.02	3.33 ± 0.02	2.71 ± 0.02

[a] Protonation constants for DOTA, TRITA and TETA were originally reported in ref. 1. [b] Determined by continuous potentiometric titration. [c] Ref. 6: 0.1 M NaCl, 25.0 °C. [d] Ref. 7: 0.1 M NaCl, 20.0 °C. [e] Ref. 8: 0.1 M NaCl, 25.0 °C. [f] Stability constants for yttrium(III) complexes of DOTA, TRITA and TETA determined by ref. 9, 0.1 M Me_4NO_3, 25.0 °C. [g] Determined potentiometrically in competition with EDTA. [h] Determined potentiometrically in competition with NTA. [i] Determined spectrophotometrically in competition with SHBED.

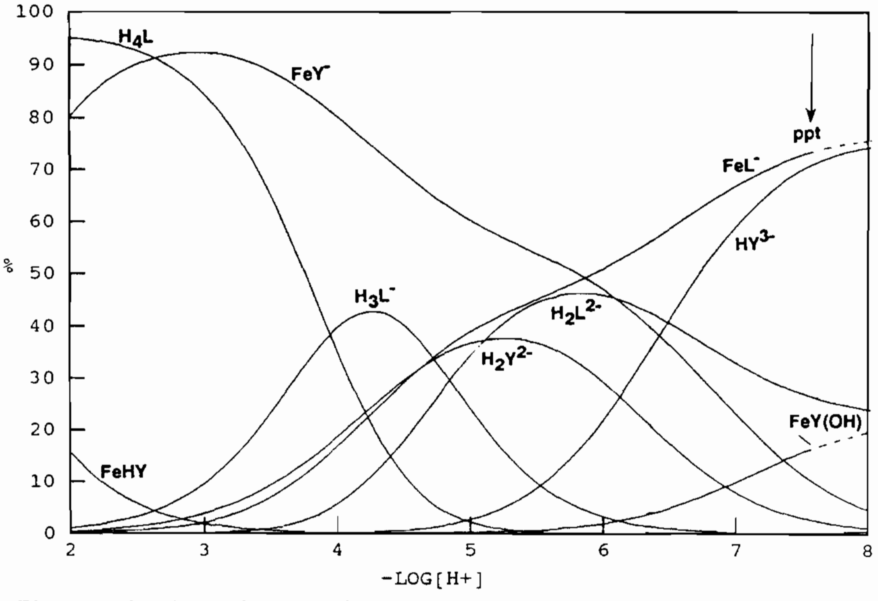

Fig. 4. Species distribution curves for a solution containing DOTA (L), EDTA (Y) and Fe(III). $[Fe]_T = [L]_T = [Y]_T = 2.00 \times 10^{-3}$ M; μ = 0.100 M (KCl), t = 25.0 °C. The protonation constants and stability constants employed appear in Tables 1 and 2.

(not shown) [15]. At low p[H], the TRITA complexes predominate with the formation of the protonated complex, MHL, in increasing concentration as the p[H] is lowered below p[H] 4. Although the distribution curves of the In(III)–DOTA–SHBED system are not shown, it is apparent from the magnitudes of the In(III)–DOTA stability constants in Table 1 that they would be very similar to those of TRITA,

TABLE 2. Protonation constants and stability constants for EDTA, NTA and SHBED with Fe(III) and In(III) ($\mu = 0.100$ M (KCl), $t = 25.0$ °C)

Quotient	Log *K*		
	EDTA [12]	NTA [12, 13]	SHBED [14, 15]
$[HL]/[L][H]$	10.19	9.67	12.27
$[H_2L]/[HL][H]$	6.13	2.52	10.65
$[H_3L]/[H_2L][H]$	2.69	(1.9)	7.89
$[H_4L]/[H_3L][H]$	2.00		4.25
$[H_5L]/[H_4L][H]$			1.96
$[H_6L]/[H_5L][H]$			1.2
$[FeL]/[L][Fe]$	25.1	15.9 [13]	
$[FeHL]/[FeL][H]$	1.3		
$[FeL(OH)][H]/[FeL]$	−7.37	−4.1 [13]	
$[InL]/[L][In]$			29.37 [14]
$[InHL]/[InL][H]$			2.82
$[InL(OH)][H]/[InL]$			−10.82 [14]

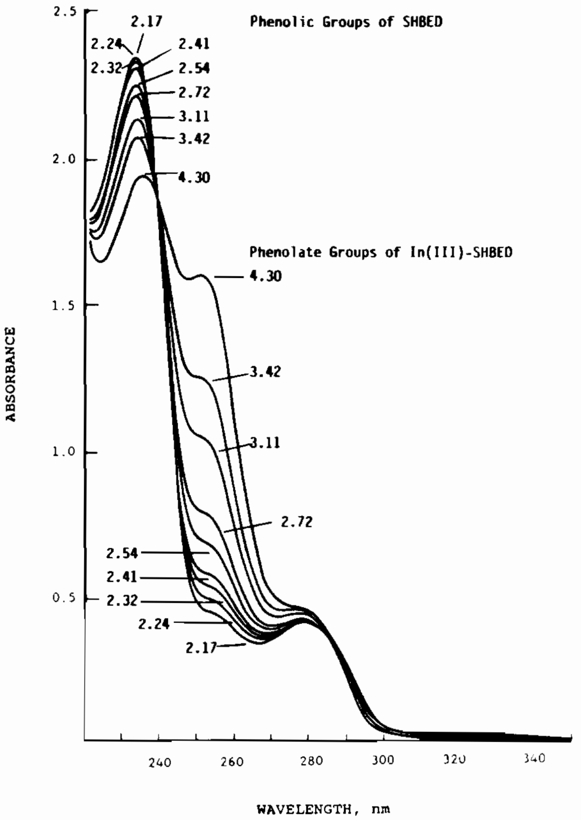

Fig. 5. Absorbance of the 1:1:1 In(III)–TRITA–SHBED solutions at the p[H] values indicated. Total analytical concentration of In(III) is 1.00×10^{-4} M; $\mu = 0.100$ M (KCl), $t = 25.0$ °C.

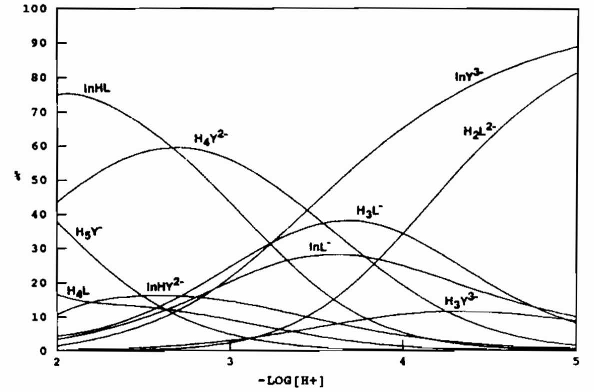

Fig. 6. Species distribution curves for a solution containing 1:1:1 molar ratios of TRITA (L) to SHBED (Y) and In(III). $[In]_T = [L]_T = [Y]_T = 2.00 \times 10^{-4}$ M; $\mu = 0.100$ M (KCl), $t = 25.0$ °C. Protonation constants and stability constants employed appear in Tables 1 and 2.

with the exception of higher concentrations of ML^- and MHL species in acid solution. The stability constants for SHBED used in the determination are given in Table 2. The stability constant for In(III)–TETA (log $K_{ML} = 21.89 \pm 0.01$) was determined by direct potentiometry (Table 1). It is seen that the In(III) complexes of the macrocyclic tetraazatetraacetates all have higher stability constants than the Ga(III) complexes. The decrease in log stability constants with macrocyclic ring size is about the same for In(III) as it is for Ga(III) and Fe(III).

Discussion

As indicated in the 'Introduction', the stability constants of only three of the complexes determined here have been reported previously: the La(III)–DOTA complex by Cacheris *et al.* [6], the Gd(III)–DOTA complex by Cacheris *et al.* [6] and by Desreux [8], and the Gd(III)–TETA complex by Loncin *et al.* [7]. These values, listed in Table 1 in parentheses, differ considerably from the constants reported in the present work. The present determinations of log K_{ML} for La(III)–DOTA and Gd(III)–DOTA are somewhat smaller than those reported by Cacheris *et al.* [6] (log $K_{ML} = 23.0$ and 24.6, respectively) and that for Yb(III)–DOTA (24.9) reported by Broan *et al.* [9]. On the other hand, Desreux [8] reported a log stability constant for Gd(III)–DOTA (28.0) calculated from data obtained from a rapid continuous potentiometric titration, so it seems that the equilibrium p[H] data were fitted to a large stability constant in an insensitive portion of the titration profile. Furthermore, the high log value that they reported was assigned to a strong acid portion of the titration curve so that the constant amounts to a guess. The log K_{ML} of 15.75 for Gd(III)–TETA, reported by Loncin *et al.* [7], is larger than that reported in the present work (13.78), but their result agrees with that for Yb(III)–TETA (16.1) [9].

The literature stability constant determinations (log K_{ML}) for the Yb(III) complexes of DOTA, TRITA and TETA were performed by continuous potentiometric titrations methods as reported by Broan *et al.* [9], and imply that the rates of lanthanide complex formation for these macrocyclic ligands should be sufficiently rapid as to allow accurate measurement by direct potentiometry. The present work indicates that the La(III) and Gd(III) complexes of DOTA and TRITA were formed within 2 days but that the protonated metal complexes, MHL, were formed much more slowly over periods of time extending up to 16 days. These slow proton equilibria necessitated the use of the batch potentiometric method in stability determinations as described in 'Experimental'. The advantage of the batch method is that it approaches equilibrium p[H] from two directions so that equilibrium is more accurately determined. For example, the batch determination for La(III)–DOTA (21.7) is 1.7 log units higher than the estimate taken from a standard potentiometric cell after 48 h (20.0), as has been done by Broan *et al.* [9] for Yb(III)–DOTA. Fast equilibration periods were observed in this work for ML and MHL complex species formation in the cases of La(III)–TETA and Gd(III)–TETA.

The stability constants reported for the lanthanide complexes, and their correspondingly poor resistance to hydrolysis, are somewhat disappointing in view of the octadentate nature of the ligands. Each of the ligands show a preference for Gd(III) over La(III). The moderate differences obtained for the stabilities of the La(III) and Gd(III) complexes of DOTA and TRITA ($\sim 10^{2.3}$) can be explained in part by the effective ionic radii of the metal ions: 1.160 pm for La(III) and 1.053 pm for Gd(III), assuming the metal ions to be eight-coordinate [17]. The relative magnitude of the metal protonation constants increase in the order DOTA < TRITA < TETA as the size of their binding constants (log K_{ML}) are decreasing. It is noted that a similar difference between the La(III) and Gd(III) stability constants of DOTA has been reported by Cacheris *et al.* [6].

Probable coordination numbers of metal complexes of DOTA, TRITA and TETA

Although the stability data reported here do not provide definite information on the structures and coordinate bonding modes of the complexes formed, some inferences may be drawn from the stabilities and from the structures of analogous complexes [18–20]. A total of eight donor groups (four nitrogen and four carboxylate oxygen atoms) are potentially available to coordinate the trivalent metal ions. The X-ray crystal structure of $Na(EuDOTA \cdot H_2O) \cdot 4H_2O$ [18] shows a nine-coordinate Eu(III) cation complexed by octadentate DOTA and one water molecule. The structure of $Na(Tb\text{-}TETA) \cdot 6H_2O$ [18] has an eight-coordinate Tb(III) ion which is coordinated to each of the donor groups of TETA. Thus one can conclude that the La(III) and Gd(III) ions are probably eight-coordinate in solution complexes with the tetraacetato tetraazamacrocyclic ligands with the possibility of an additional aquo site. Fe(III) and Ga(III) are probably six-coordinate in their complexes with DOTA, TRITA and TETA, while In(III) is probably seven-coordinate in its complexes with these macrocyclic ligands. In(III) has been shown to be seven-coordinate with triacetato derivatives of tetraazamacrocyclic ligands such as $[12]AneN_4\text{-}ac_3$ and $[13]AneN_4\text{-}ac_3$, as determined by their crystal structures [20]. In addition, In(III) has recently been shown to form a presumably seven-coordinate hydroxo metal complex with *N,N′,N″*-triazacyclononanetriacetic acid (NOTA) [21] in solution.

The high stabilities of the Fe(III) complexes of DOTA, TRITA and TETA may be rationalized by the small ionic radius and high ionic character of the Fe(III) ions. The Fe(III) complexes are probably six-coordinate, or at the most, seven-coordinate as in Fe(III)–EDTA [22]. Octa- or nona-coordinate La(III) and Gd(III) may prefer octadentate DOTA over TRITA and TETA, but it is possible that the size of these larger cations precludes a good match with the spacing of the nitrogen donors of the tetraazamacrocyclic tetraacetates. The Eu(III) cation [18] is elevated above the plane of nitrogen donors in its complex with DOTA. Septa-coordinate In(III) seems to have a preference over sexa-coordinate

Ga(III) for ligands with potentially eight-coordinate macrocyclic ligands. Because of the similarity of ionic radii it is expected that the stabilities of the Ga(III) chelates would be similar to those of Fe(III), but that does not seem to be the case, and it is In(III) which it seems to resemble more closely.

Trends in stability constants

Trends of stabilities of the tetraacetato derivatives of the tetraazamacrocyclic ligands with La(III), Gd(III), Fe(III), Ga(III) and In(III) (Table 1) do not seem to follow predictable patterns, probably due to a mix of differing constitutional factors such as metal ion electron negativity, effective ionic radii, and steric factors resulting from differences in chelate ring size. Large differences in stability constants within the series DOTA, TRITA and TETA are observed for complexes with large size La(III) and Gd(III) ions, while smaller differences are observed for the smaller size Fe(III), Ga(III) and even In(III), which is of intermediate size.

For the tetraazamacrocyclic ligands, a preferential interaction of La(III) and Gd(III) with DOTA is implied by the trends in the stability data. Hancock and Martell [23] have interpreted the influences of macrocyclic ring size on stability constants in terms of the size of the metal chelate rings formed: five-membered chelate rings can accommodate large size metal ions, while six-membered chelate rings have a preference for smaller metal ions as a consequence of difference in bite size and bite angles in metal ion coordination. Hence one may reason that the higher number of five-membered chelate rings in DOTA (eight) may allow for coordination of the four ring nitrogen atoms to the larger size ions, La(III) and Gd(III), and result in relatively higher stability constants over the lanthanide complexes of TRITA (which contains seven five-membered chelate rings and one six-membered chelate ring) and TETA (which contains six five-membered chelate rings and two six-membered chelate rings). The smaller size trivalent metal ions, Fe(III), Ga(III) and In(III), show small decreases in stability in going from DOTA to TRITA to TETA. The fact that an increase of stability with increasing ring size is not observed is probably due to the fact that not all donor groups of the ligands are coordinated.

It has been noted [24] that Ga(III) chelates with hard oxygen donors such as phenolate are more stable than those of the softer, larger In(III) ion, as one would predict for highly ionic complexes, but that analogous In(III) chelates with softer oxygen donors, such as carboxylate, are more stable than the corresponding chelates of Ga(III). This is true of the aminopolycarboxylate complexes such as those of NTA, EDTA and DTPA. It can be seen from the data in Table 1 that it is also true for the macrocyclic aminopolycarboxylates DOTA, TRITA and TETA.

Molecular mechanics studies of size–fit interactions of the parent tetraazamacrocyclic ligands with a variety of metal ions have been reported by Thom *et al.* [25, 26]. The conformations of the [12]AneN$_4$ and [14]AneN$_4$ ligands were different in that the boat conformation of [12]AneN$_4$ allows greater variation in the size of the complexed metal ion over the more rigid chair conformation of complexes with [14]AneN$_4$. A molecular mechanics study of the interactions of the tetraacetato derivatives of these tetraazamacrocyclic ligands may provide additional insight into the problem of selective fit of metal ions coordinated to macrocyclic ligands with concomitantly higher stability constants.

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