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Macrocyclic Dilactams with Pendant Acidic Functions as Discriminating Agents for Lanthanide Ions

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Abstract: N,N'-bis(carboxymethyl) macrocyclic dilactams were synthesized in good to high yields from diamines and dianhydrides. Their ligand protonation and lanthanide complex stability constants were measured by a potentiometric method in aqueous solution. The lanthanide discriminating power of 12- and 18-membered macrocyclic dilactams derived from EDTA and EGTA measured by their stability constants were compared with other macrocyclic compounds like diaminocrown-ethers and dilactones. In the dilactam series the Eu^{3+} complex was found to be the most stable for the ligand derived from o-phenylene diamine and EGTA dianhydride.

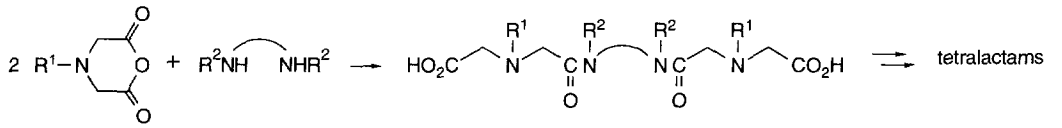
INTRODUCTION

A great deal of interest has been devoted to metal complexes with macrocycles functionalized with pendant groups such as amine, hydroxy, amide and carboxylates.[1-3] Such molecules combine the characteristics of both open-chain and macrocyclic ligands. The cavity of the macrocycles can lead to a size-based selectivity for different cations while the pendant groups can complete the coordination sphere to enhance the stability of the complexes.

On the other hand, lanthanides form supermolecules with synthetic macrocyclic ionophores in which the metal is partly or totally protected from further interactions with both solvent molecules and anions.[4] These complexes present various properties[5] including their use as analytical probes.

The separations of individual lanthanides from each other is difficult[6] due to the slight difference in properties such as cation size. For linear multidentate ligands such as ethylenediamine tetracetic acid[7] lanthanide complex stability constants increase from lanthanum to lutetium with the increase of charge density of the metal ions and then no discrimination was observed. In order to develop lanthanide ion selective ligands several authors have examined the discrimination power of macrocyclic compounds: crown-ethers,[4] N,N'-diacetic acid armed-macrocyclic ethers[8] or dilactones.[9] We extend these studies to the corresponding dilactams.

In the course of our investigations about new selective ionophores[10] we have developed the synthesis of macrocyclic tetralactams[11] by a stepwise procedure involving a first step of condensation of a diamine with a cyclic anhydride (molar ratio 1/2) leading quantitatively to an intermediate diamide diacid.



In this paper we report the extension of this synthesis using stoichiometric amounts of a diamine and a dianhydride derived from ethylenediaminetetracetic acid (EDTA) or ethylene bis(oxyethylenenitrilo) tetracetic acid (EGTA). Four diaza dilactams **1-4** with acetate pendant groups were thus obtained very selectively in good yields and the stability constants with Ca^{2+} and five lanthanide ions were determined by the potentiometric method. They are compared to the cyclic ethers **8, 9** or the dilactones **5-7** derived from EDTA or EGTA structures (Figure 1):

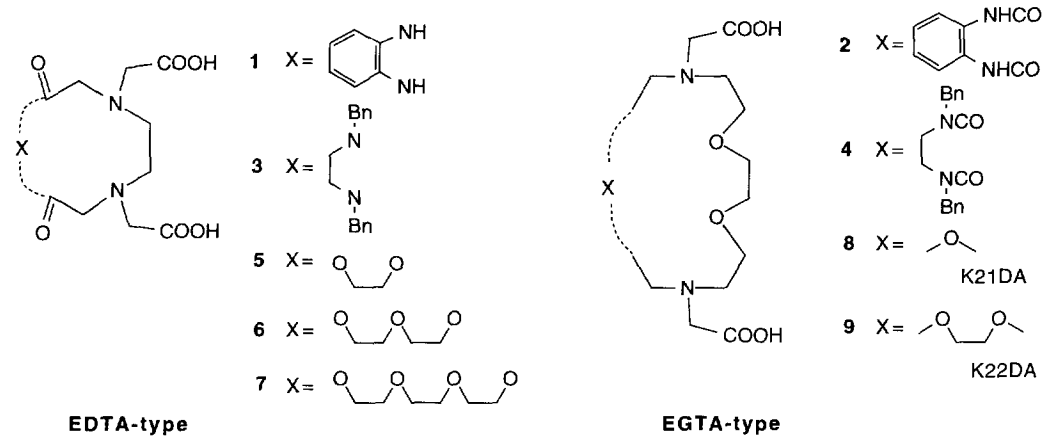


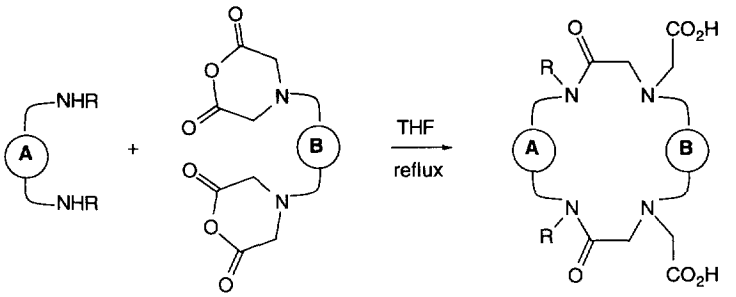
Figure 1: Formulas of N,N'-Bis(carboxymethyl) Macrocyclic Compounds of EDTA and EGTA-types.

RESULTS AND DISCUSSION

Ligand synthesis

Some examples of this class of macrocyclic diaza diamides have been synthesized[9, 12-15] unselectively or in modest to medium yields by direct condensation of a diamine and a dianhydride. Using a modified procedure, and a very simple purification process, we obtained in good to high yields the desired macrocycles (Scheme).

The EDTA dianhydride is commercially available while EGTA dianhydride was prepared by acetic anhydride dehydration of the parent tetracid in pyridine.[16] The cyclization was realized without high dilution conditions [10^{-2}M] (nor using simultaneous addition methods). The yields ranging from 95% to 45% are dependent on the degree of flexibility of both reagents. All the compounds were purified using C_{18} reverse phase chromatography with a H_2O/MeOH eluent, and no trace of 24- or-36-membered dimeric compounds was observed.



					yield
A =	R = H	B =	-$(CH_2)_2$-	**1**	95
-	-	=	-$(CH_2)_2$-O$(CH_2)_2$-O$(CH_2)_2$-	**2**	77
A = -$(CH_2)_2$-	R = Bn	B =	-$(CH_2)_2$-	**3**	60
-	-	=	-$(CH_2)_2$-O$(CH_2)_2$-O$(CH_2)_2$-	**4**	45

Scheme: Synthesis of N,N'-Bis(carboxymethyl) Macrocyclic Dilactams

The structures of the products were assigned using mass spectrometry and NMR data. In ^1H decoupled ^{13}C NMR spectra compounds **1** and **2** display only one signal for each carbon in contrast to compounds **3** and **4** which present more complex features. Owing to the restricted rotations around the carbon-nitrogen bond in the amide groups[17] these data suggest that compounds **3** and **4** exist in several conformations at room temperature while compounds **1** and **2** are present either as an unique form, or as a more complex equilibrium if the conformational exchange rates are fast with respect to the NMR time scale.

Ligand protonation constants

The protonation constants for the two basic nitrogen atoms for ligands **1-4** and related compounds are reported in Table 1.

Table 1 - Protonation Constants for Ligands **1-4** and Related Compounds [a]

	1	**2**	**3**	**4**	EDTA ref 7	EGTA ref 7	**5** ref 9	**6** ref 9	**7** ref 9	**8** ref 18	**9** ref 8
$\log\frac{[HL]}{[H][L]} = pKa_1$	6.20	6.39	7.55	7.78	10.17	9.40	6.44	6.82	6.97	9.02	8.45
$\log\frac{[H_2L]}{[H][HL]} = pKa_2$	3.33	5.14	3.95	6.98	6.11	8.78	3.49	3.84	3.75	8.79	7.80
$\sum$pKa	9.53	11.53	11.50	14.76	16.28	18.18	9.93	10.66	10.72	17.81	16.25

a) The ionic strength was fixed to 0.1 (Me_4NCl) and the temperature was 25.0 ± 0.1°C. Standard deviations were all within ± 0.1 log K units.

The two protonation constants of the more acidic carboxylic groups have lower values and could not be determined.

The pKa values in Table 1 indicate that the cyclic ligands **1-4**, possess lower proton affinities than those of the parent EDTA and EGTA compounds or diaza crown-ethers **8** and **9**. The electron withdrawing effect of the amide moiety decreases strongly the basicity of the amino group as noticed for dipeptides.[7] A similar behaviour is observed for compounds **5-7** [9] in relation with the presence of lactone moieties. On the other hand for **1** and **2** the presence of a hydrogen bond involving the hydrogen atom of the secondary amide group and the amino nitrogen electronic pair may be invoked to explain an increase of about 1.4 pKa units for the first protonation constant with respect of compounds **3** or **4**.

The difference between the first and second protonation pKa values is more important for the products derived from EDTA (**1**, **3**, **5-7**) than for those derived from EGTA (**2**, **4**, **8**, **9**). As for the parent tetracids, the proximity of the two amino sites in EDTA results in a decrease of the second protonation constant which is more pronounced than for the EGTA derivatives.

Stabilities of metal chelates

The stability constants of Ca^{2+} and some lanthanide ions complexes were determined from potentiometric measurements as illustrated in Figure 2 for ligand **2**. The logarithms of the stability constants for the various complexes are listed in Table 2 along with some reference compounds and plotted against atomic radius in Figure 3.

Table 2: Stability Constants of Metal Complexes of Ligands **1-4** and Related Compounds

	atomic radius Å [b]	log K_{ML}^{M} [a]								
		1	**2**	**3**	**4**	**5** [c]	**6** [c]	**7** [c]	**8** [d]	**9** [e]
ring size		*12*	*18*	*12*	*18*	*12*	*15*	*18*	*15*	*18*
Σ pKa		9.53	11.53	11.50	14.76	9.93	10.66	10.72	17.81	16.25
Ca^{2+}	1.120	3.76	2.78	3.51	5.54	-	-	-	8.74	8.39
Ce^{3+}	1.143	6.84	5.60	6.73	9.70	5.55	7.40	8.44	10.89	12.23
Sm^{3+}	1.079	6.94	7.20	7.05	9.82	6.13	8.58	9.37	11.72	12.12
Eu^{3+}	1.066	6.86	7.23	7.11	9.59	6.06	8.80	10.03	11.85	12.02
Gd^{3+}	1.053	6.86	6.88	7.19	9.22	5.63	8.61	9.59	11.66	11.93
Yb^{3+}	0.985	6.96	5.95	7.43	8.40	6.64	7.92	8.52	10.76	10.90

a) $\log K_{ML}^{M} = [ML]/[M][L]$; ionic strength 0.1 M, 25°C ± 0.1°C; standard deviations are all within ± 0.1 log K unit; b) eight-coordinated ion radius from ref. 19; c) from ref. 9; d) from ref. 18; e) from ref. 8

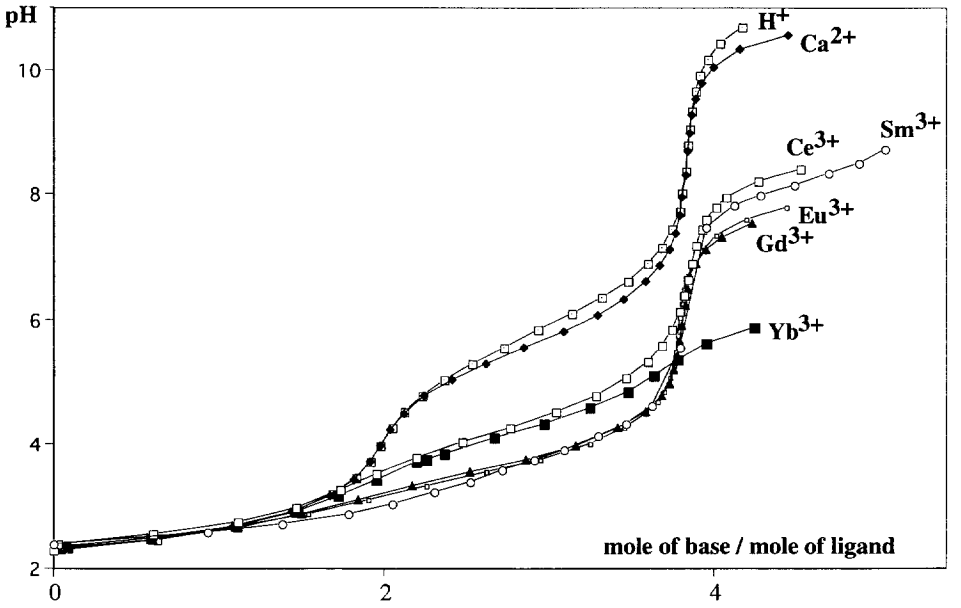


Figure 2. Potentiometric equilibrium curves of ligand **2** and 1:1 ratio of ligand **2** with Ca^{2+} and several lanthanide ions. [Ln] = [**2**] = 0.25 x 10^{-3} M; 25 ± 0.1°C; μ = 0.10. $(CH_3)_4NCl$

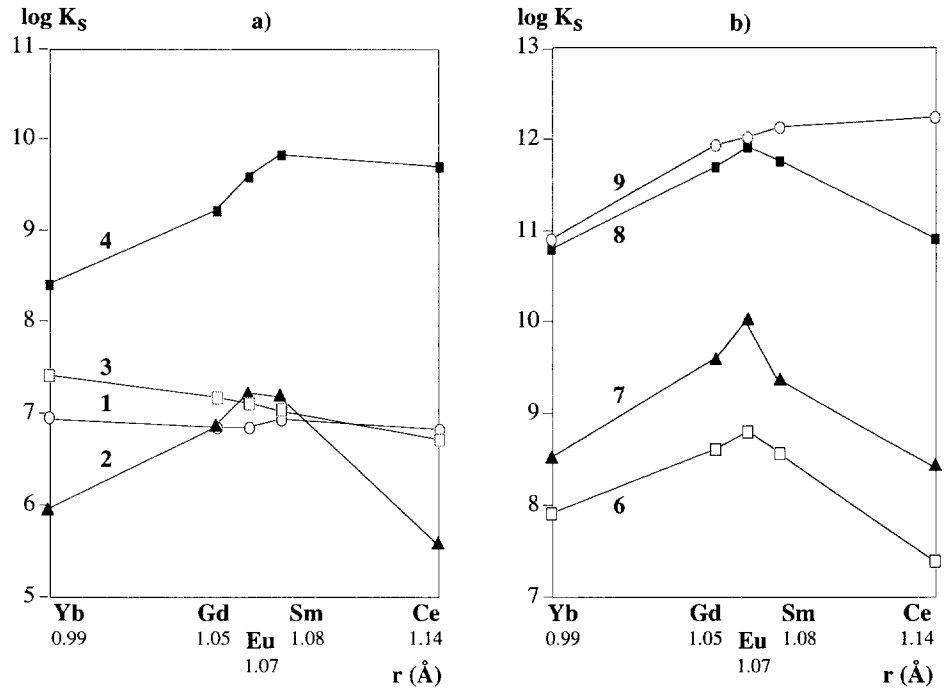


Figure 3. Variation of the stability constants (K_{ML}) of the complexes with ligands **1-4** (a) or **6-9** (b) as a function of the ionic radius of the trivalent metal ions.

The examination of these values leads to the following comments:

Charge is a preeminent stabilizing factor as indicated by the difference in stability constants for Ca^{2+} and Eu^{3+} ions (nearly twice for Eu^{3+}) despite the fact that all the ligands can furnish only two anionic counterparts.

The ligands **1** and **3** containing an EDTA moiety display a similar behaviour without a marked size selectivity. The "size of the cavity" of these 12-membered rings is too small to involve such a selectivity and the stability of the complexes is governed mainly by charge density. Whatever the lanthanide ion, 1,2-phenylenediamine and N,N'-dibenzylethylenediamine moieties lead nearly to the same log Ks values ca. 7 for the 12-membered dilactams **1** and **3**. The 12-membered dilactone **5** displays a similar pattern[9] but with smaller stability constants (log Ks ~ 6). Like crown-ethers,[4] 12-membered dilactones[9] or dilactams diacetic acids (**1**, **3**, **5**) form lanthanide complexes less stable than 18-membered rings (**4**, **7**, **9**). The compound **2** is an exception.

In the EDTA series a regular increase of the stability constants occurs from 12- to 15- and 18-membered lactones (compounds **5**-**7**). This trend is related, of course, to the size complementarity of the ion and the ring, but also to other factors such as the presence of additional carboxylate side chains offering a three-dimensional complexation ability.

For the 18-membered ring in the EGTA type series, a regular decrease of about 2.5 log units can be noticed for the sequence **9**, **4**, **2** corresponding to the respective moieties ethylenedioxy, N,N'-dibenzylethylene diamine and 1,2-phenylenediamine. This behaviour can be correlated to the basicity of the donor nitrogen atoms quantified by the sum of the pKa values. Another parameter concerns the reduced flexibility of the macrocycle following the same sequence leading to a bell-shaped variation for the dilactam **2**. A similar result is obtained by reducing the ring size in the diazacrown-ether series (**9** → **8**).

The discriminating power of aminodiacetic acid branched macrocycles versus the lanthanide ions and the stability constants of their complexes depend upon four characteristics: i) the ring size (i.e. 15- or 18-membered ring and not 12-), ii) the number and the arrangement of the heteroatomes (e.g. ethylenedioxy); for all the ligands the optimal coordination number of the lanthanide ion must be satisfied and water molecules can be involved for completion of the coordination sphere, iii) the basicity of the ligand (ΣpKa) and the charge density of the ion, iv) the rigidity of the macrocycle. This latter feature can result from the presence of lactone, lactam or benzo groups.

Another example of size selectivity towards lanthanides was recently reported in biological virus systems (satellite tobacco necrosis virus).[20] A marked size-dependence is revealed, the maximum affinity being exhibited for Sm^{3+}. The selectivity is related to a Ca^{2+} ion channel which presents lanthanide affinities varying by more than one order of magnitude.

EXPERIMENTAL SECTION

Synthesis of the ligands. Melting points were determined on a Kofler apparatus. Infrared spectra were recorded on a Perkin Elmer 883 spectrophotometer with potassium bromide discs or in 0.1M CD_3OD solutions using CaF_2 0.1 mm cells. ^1H magnetic resonance spectra (200.13 MHz in CD_3OD solutions unless otherwise indicated) and ^{13}C magnetic resonance spectra (50.3 MHz in CD_3OD) were recorded on Bruker AC200 spectrometer and are reported in parts per million from internal tetramethylsilane on the δ scale. Data

are reported in the following order: chemical shift. spin multiplicity (s = singlet, m = multiplet), integration and assignment. For compounds **3** and **4** which may present several signals for each carbon (see discussion), the multiplicity is given by the number n. Mass spectra were performed with a NERMAG R10-10C spectrometer using Fast Atom Bombardment (FAB) or desorption-chemical ionization (DCI) techniques.

General Procedure. 2.5 mmol of dianhydride were suspended in 250 ml of THF freshly distilled from sodium. The suspension was heated under argon atmosphere, then 2.5 mmol of diamine were added dropwise during 2 hours. The reaction was kept on reflux during 18 additional hours. The solvent was removed under vacuum and the crude product was purified on C18 silica reverse phase (H_2O/MeOH) chromatography. After the removal of the solvent the residual water was lyophilised and the pure product was obtained as a white solid.

Compound **1**. Purification H_2O/MeOH 1/1 (95% yield); mp = 152 °C; IR (CD_3OD) 1673 (CO amide); 1730, 1715 cm^{-1} (acid); ^1H NMR 2.93 (s, 4H, NCH_2CH_2N), 3.50 (s, 4H, NCH_2CON), 3.61 (s, 4H, NCH_2CO_2H), 7.25-7.30, 7.50-7.55 (mx2, 4H, CH arom); ^{13}C NMR: 55.74 (NCH_2CH_2N), 57.65 ($N\underline{C}H_2CON$), 61.65 ($N\underline{C}H_2CO_2H$), 126.76, 127.77 (CH arom), 132.30 (Cq arom), 172.88 ($\underline{C}ONH$), 174.86 (CO_2H); MS (FAB, Gly/TGly/TCA) m/e = 365 $[MH]^+$ (100%); Anal. Calcd for $C_{16}H_{20}N_4O_6$, $1H_2O$: C, 50.26; H, 5.80; N, 14.62. Found: C, 49.97; H, 5.67; N, 14. 63.

Compound **2**. Purification H_2O/MeOH 1/1 (77 % yield); mp = 130 °C; IR (KBr): 3236 (NH), 1636 (CO amide), 1731, 1691 cm^{-1} (acid); ^1H NMR: 3.07-3.11 (m, 4H, $N\underline{C}H_2CH_2O$), 3.54-3.70 (m, 16H, CH_2), 7.16-7.23, 7.72-7.80 (mx2, 4H, CH arom); ^{13}C NMR: 56.5 ($N\underline{C}H_2CH_2O$), 58.01 ($NCO\underline{C}H_2N$), 60.25 ($N\underline{C}H_2CO_2H$), 69.16 ($NCH_2\underline{C}H_2O$), 71.16 (OCH_2CH_2O), 125.52-126.82 (CH arom), 130.98 (Cq arom), 171.84 (CONH), 174.32 (CO_2H); MS (FAB, Gly/T Gly), m/e = 453 $[MH]^+$ (100%); Anal calcd for $C_{20}H_{28}N_4O_8$, 1/2 H_2O: C, 52.11; H, 6.23; N, 12.15; Found: C, 52.28; H, 6.14; N, 12.14.

Compound **3**. Purification H_2O/MeOH 1/1(60% yield); mp = 135 °C; IR (CD_3OD) 1659, 1630 (CO amide), 1728, 1720, 1698 (CO acid); ^1H NMR: 2.6-4.07 (m, 16 H, CH_2), 4.42-4.78 (m, 4H, NCH_2Ph), 7.07-7.42 (m, 10H, CH arom); ^{13}C NMR: 43.0 (n = 1, $CONCH_2CH_2NCO$), 48.0 (n = 1, NCH_2CH_2N), 51.23, 51.61 (n = 2, $\underline{C}H_2Ph$), 55.67-58.84 (n = 4, $N\underline{C}H_2CO_2H$, $N\underline{C}H_2CON$), 127.70-130.15 (n = 9, CH arom), 137.92-138.82 (n = 2, Cq arom), 170.69, 172.07 (n = 2, $N\underline{C}OCH_2$), 173.85.174.27 (n = 2, CO_2H); MS (DCI/NH_3) m/e = 497 $[MH]^+$ (100%); Anal. calcd. for $C_{26}H_{32}N_4O_6$, 1/2 H_2O: C, 61.77; H, 6.58; N, 10.89; Found: C, 61.62; H, 6.52; N, 10.96.

Compound **4**. Purification H_2O/MeOH, 1/1 (45% yield), mp = 152 °C; IR (CD_3OD) 1663, 1634 (CO amide), 1737, 1716 (CO acid); ^1H NMR 3.1-4.05 (m, 20H, CH_2), 4.21-4.39 (m, 4H, OCH_2CH_2O), 4.53-4.62 (m, 4H, NCH_2Ph); ^{13}C NMR 44.6-47.07 (n = 4, NCH_2CH_2N), 52.09, 52.49 ($N\underline{C}H_2Ph$), 55.22-58.54 (n = 10, $N\underline{C}H_2CON$, $N\underline{C}H_2CH_2O$, $N\underline{C}H_2CO_2H$), 65.69-67.41 (n = 4, $O\underline{C}H_2CH_2N$), 70.65-72.08 (n = 3, OCH_2CH_2O), 128.10-130.28 (n = 7, CH arom), 136.65-137.98 (n = 4, Cq arom), 167.64-167.91 (n = 3, $N\underline{C}OCH_2$), 169.51-171.88 (n = 5, CO_2H); MS (FAB/Gly); m/e = 585 $[MH]^+$ (100%); Anal calcd for $C_{30}H_{40}N_4O_8$, 1.5 H_2O: C, 58.91; H, 7.09; N, 9.16; Found: C, 58.85; H, 6.97; N, 9.12

Potentiometric titrations. The potentiometric titrations were performed with an automated titration system. The autotitrating system consists of a TT2 Tacussel titrimeter, a pH electrode and a Tacussel digital autoburette. The pH electrode was calibrated at pH 4.00 and 7.00 ± 0.02 pH unit with SDS buffer capsule set. The data were collected with the aid of a computer, then treated by three programs: the pKa and log Ks values were calculated respectively with the PKA and STABIL programs following the classical mass-balance equations[21]. The iterations between calculated and experimental data were performed using the VA04A algorithm. Stability constants were improved with the aid of the SUPERQUAD program.[22] All calibration and titration constants were carried out at 25°C ± 0.1 and at a constant ionic strength of 0.1 M $(CH_3)_4\ N^+\ Cl^-$. Each experiment was repeated two or three times and reproducible results were obtained. For the preparation of sample solutions, deionized water was degassed under vacuum then saturated with helium. The titration mixtures were prepared by pipeting an exact amount of each stock solutions so that the final concentration was 2.5 10^{-3} M on both the ligand and the metal salt.

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