Lipophilic Ligands Derived from 1,3,5-Triamino-1,3,5-trideoxy-*cis*-inositol (Taci) for Trivalent Lanthanide Complexation in Aqueous and Organic Solutions

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New lipophilic ligands derived from 1,3,5-triamino-1,3,5-trideoxy-*cis*-inositol (taci), namely 1,3,5-trideoxy-1,3,5-tris(ethylamino)-*cis*-inositol (L^1), 1,3,5-tris(butylamino)-1,3,5-trideoxy-*cis*-inositol (L^2), 1,3,5-trideoxy-1,3,5-tris(hexylamino)-*cis*-inositol (L^3) have been synthesized by reductive amination of taci. Their complexing properties towards trivalent lanthanide cations, together with those of 1,3,5-tris(benzylamino)-1,3,5-trideoxy-*cis*-inositol (L^4), have been investigated in solution using mass spectrometry, NMR spectroscopy and potentiometry. It has been shown that each ligand forms trinuclear complexes with the composition $[Ln_3(LH_{-3})_2]^{3+}$. The stability constants (log β_{32-6}) of these complexes have been calculated for Nd^{3+}, Eu^{3+}, and in some cases for Lu^{3+}. The affinity for the lanthanide cations follows the sequence $Lu^{3+} > Eu^{3+} > Nd^{3+}$, for all the ligands. This sequence follows the well-known electrostatic trend. The stability of the complex depends on the conjugate effects of the steric hindrance of the substituents and the basicity of the ligands: $L^1 \approx L^2 <$ taci, in water, and $L^3 < L^2 << L^4$, in water/methanol. Among the ligands studied in this work, L^4 appears to be the most effective complexing agent for the lanthanide cations in water/methanol under slightly acidic conditions.
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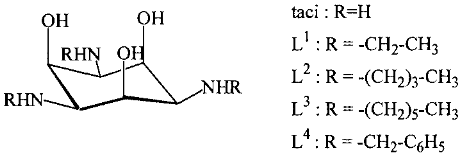
Introduction

The design of selective chelating agents represents one of the basic challenges in the field of coordination chemistry.[1,2] Important medicinal and technological areas such as the treatment of metal intoxication,[3] ligands for magnetic resonance, radiochemical imaging[4,5] or luminescent probes,[6] and selective extractants in industrial processes[7,8] may greatly benefit from such studies.

Separation of trivalent lanthanide and actinide cations, both present in nuclear fuel, is required for nuclear waste management.[9,10] Due to the chemical similarity of these two cation families, their selective extraction by tailored ligands still remains a challenge. For several years, we have been engaged in the studies of polyfunctional ligands based on cyclohexanic platforms for group *f* element selective complexation.[11,12] Among the ligands studied in our laboratory, 1,3,5-triamino-1,3,5-trideoxy-*cis*-inositol (taci) was found to be a model compound of great interest for this purpose. It is a rigid receptor with preorganized N- and O-donor atoms (Scheme 1), which offer different chelating modes for metal binding. Its coordination properties have been widely investigated and described in the literature.[13,14] In particular, it has been shown that taci forms trinuclear species of the type $[M_3(taciH_{-3})_2]^{3+}$, with trivalent lanthanide cations with an original "sandwich-type" structure (Scheme 2).[15,16] In these complexes, each of the three metal cations binds to an amino group and to two alkoxo groups of each of the two deprotonated ligands. The coordination sphere is completed by peripheral ligands such as H_2O or counterions. For the purposes of our research, taci is especially attractive because, although the 4f complexes are isostructural across the lanthanide series, it shows an uncommon selectivity for the elements at the end of the series.[17]



Scheme 1

Despite the rich coordination chemistry of taci,[14] only a few derivatives have been described in the literature. Several *O*-[18] or *N*-substituted derivatives have been elaborated by Hegetschweiler et al. to modulate metal binding properties.

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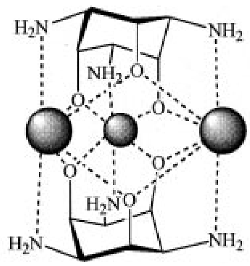


Scheme 2

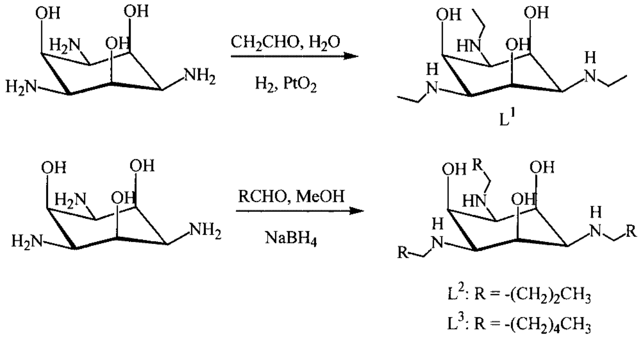
Two types of substituents, with or without additional donor groups, have been introduced at the nitrogen atoms. 1,3,5-trideoxy-1,3,5-tris[(2-hydroxybenzyl)amino]-*cis*-inositol (H_3thci),[19] 1,3,5-trideoxy-1,3-bis[(2-hydroxybenzyl)amino]-*cis*-inositol (H_3bhci) and its bifunctionalized analog, 1,3,5-trideoxy-5-glutaramido-1,3-bis[(2-hydroxybenzyl)amino]-*cis*-inositol (H_3bhci-glu-H)[20] have been prepared as new types of potential hexa- and pentadentate chelators, by hydrogenation of a mixture of taci and salicylaldehyde using Pt as a catalyst. Furthermore, several methylated derivatives have been synthesized to favor one of the binding modes, for steric reasons. For this purpose, 1,3,5-trideoxy-1,3,5-tris(dimethylamino)-*cis*-inositol (tdci)[21] was obtained by catalytic hydrogenation of taci in the presence of formaldehyde with Pt as the catalyst, and 1,3,5-trideoxy-1,3,5-tris(trimethylamino)-*cis*-inositol (ttci)[21] was obtained by complete methylation of the amino groups using an excess of methyliodide. Even if the direct treatment of taci with methylating agents resulted in *N*- rather than *O*-alkylation, the introduction of only one methyl group at each primary amine proved to be difficult. Hence, starting from taci, 1,3,5-trideoxy-1,3,5-tris(methylamino)-*cis*-inositol (tmaci) was obtained by an indirect route using the corresponding Co^{III} complex $[Co(taci)_2]^{3+}$ as an intermediate.[22] Recently, 1,3,5-tris(benzylamino)-1,3,5-trideoxy-*cis*-inositol (tbci or L^4), obtained by reductive alkylation of taci using $NaBH_4$ as the reducing agent, and 1,3,5-tris(benzylmethylamino)-1,3,5-trideoxy-*cis*-inositol (tbmci) have been reported for the preparation, in nonaqueous medium, of a new type of Ba^{2+} complex having a chiral structure.[23]

In order to develop new lipophilic ligands based on the taci framework, we decided to prepare a series of *N*-alkylated derivatives. To retain the specific coordination properties of taci towards lanthanide(III) ions, the alcohol functions, which are deprotonated during complexation in this particular case, had to remain untouched. Various lipophilic substituents were thus attached to the three nitrogen atoms of taci (Scheme 1). Here, we present the syntheses of a series of new *N*-alkylated derivatives of taci, namely 1,3,5-trideoxy-1,3,5-tris(ethylamino)-*cis*-inositol (L^1), 1,3,5-tris(butylamino)-1,3,5-trideoxy-*cis*-inositol (L^2), and 1,3,5-trideoxy-1,3,5-tris(hexylamino)-*cis*-inositol (L^3), and the characterization of their lanthanide complexes and those of tbci (L^4) in aqueous and methanolic solutions. The affinity towards Ln^{III} ions will be discussed as a function of ligand substituents, cation size and pH.

Results and Discussion

Ligand Syntheses

The syntheses of the three ligands L^1-L^3 are summarized in Scheme 3. As previously discussed with regard to the ligand tmaci,[22] the introduction of alkyl groups is not a routine task, mainly due to the multifunctionality of taci and the possibility of forming many amines having numerous degrees of substitution. Many procedures for the specific conversion of primary to secondary amines have been reported in the literature, but there is no universal efficient method available. However, the reductive alkylation of primary amines is one of the most useful routes to secondary amines. According to the Hegetschweiler reports,[19–21] catalytic hydrogenation using Pt as the catalyst[24] is probably the best way to prepare *N*-alkylated derivatives starting from taci. This method was then chosen for the reduction of the Schiff bases formed in situ by the treatment of taci with the appropriate carbonyl compound. Indeed, catalytic hydrogenation of the taci sulfate salt in the presence of a large excess of acetaldehyde with Pt as the catalyst, and subsequent elution by ion-exchange chromatography led to L^1 in a 62% yield. Unfortunately, the introduction of butyl substituents at the three nitrogen atoms by the same method was not successful and resulted in the formation of a crude mixture of various compounds, presumably due to the steric hindrance of the imine formed in situ. This reaction was readily driven towards the formation of the desired L^2 in a 65% yield by using sodium borohydride as the reducing agent. L^3 was obtained under the same conditions using 3.3 equivalents of the appropriate carbonyl compound in a 56% yield. As expected, the replacement of the H−N hydrogen atoms by alkyl substituents generates rather lipophilic chelates. The coordination properties of this new ligand set towards trivalent lanthanide cations can be evaluated in different media, depending on the chain length: in water for L^1 and L^2 and in water/methanol for L^2, L^3, and L^4.



Scheme 3

Characterization of Ln^{III} Complexes in Solution by ES-MS

Electrospray ionization mass spectrometry (ES-MS) has been shown to be a suitable technique to qualitatively characterize preformed ions in solution,[25] and has moreover been used for identification of supramolecular coordination complexes.[26−28] Aqueous and methanolic samples containing the ligand and europium(III) of different molar ratios were analyzed. Due to their characteristic isotopic patterns, the signals for the europium-containing species can easily be recognized, and indicate the number of Eu^{III} cations present in the detected complexes. Figure 1 shows a typical spectrum obtained from a water/methanol solution (1:1, v/v) of L^4 and $Eu(NO_3)_3$ at a molar ratio (M/L) of 1.5 in the absence of added base.

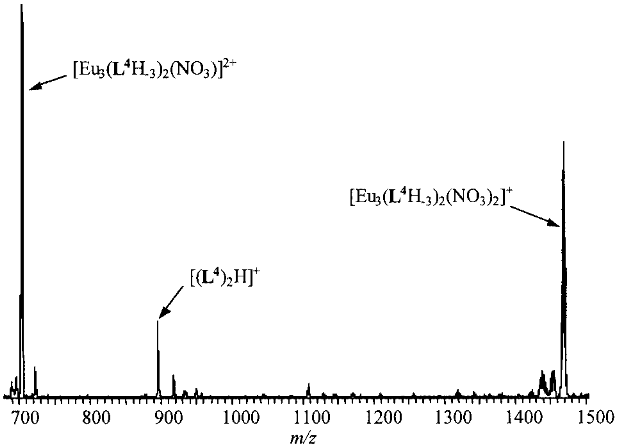


Figure 1. ES-MS spectrum of a water/methanol solution (1:1, v/v) of L^4 and $Eu(NO_3)_3$. c_L/c_M = 1:1.5; $c_L = 1\cdot10^{-3}$ M

The only Eu-containing species detected under our experimental conditions are $[Eu_3(LH_{-3})_2(NO_3)_2]^+$ and $[Eu_3(LH_{-3})_2(NO_3)]^{2+}$. The experimental and calculated isotopic patterns are identical. As an example, the peak envelope of $[Eu_3(L^4H_{-3})_2(NO_3)_2]^+$ is depicted in Figure 2.

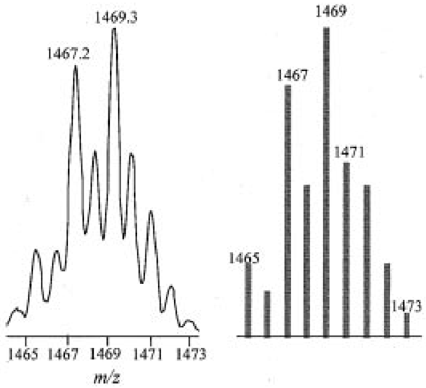


Figure 2. Experimental and calculated isotopic patterns of $[Eu_3(L^4H_{-3})_2(NO_3)_2]^+$. c_L/c_M = 1:1.5; $c_L = 1\cdot10^{-3}$ M

In the presence of triethylamine, the hydroxo complexes $[Eu_3(LH_{-3})_2(NO_3)(OH)]^+$ and $[Eu_3(LH_{-3})_2(OH)_2]^+$ are also detected. Fragmentation of the complex resulted in the complete destruction of this species. It is worth noting that whatever the Eu/L ratio, ranging from 1:2 to 2:1, the trinuclear complex is the only species observed. Finally, we have also checked that similar complexes were formed with a series of lanthanide cations including Pr^{3+}, Nd^{3+}, Sm^{3+}, Ho^{3+}, and Lu^{3+}. In all cases, only the ions of the type $[Ln_3(LH_{-3})_2]^{3+}$ have been evidenced in the ES-MS spectra, as was previously observed for the Ln^{III} ion complexation by taci.[17]

Protonation Equilibria

In order to analyze the stability of the metal complexes formed in solution, we first studied the protonation properties of each ligand using potentiometric methods. The protonation constants of ligands L^1, L^2, L^3, and L^4 obtained in water or in water/methanol (1:3, v/v) solutions are listed in Tables 1 and 2, respectively. For comparison, protonation constants of related compounds (taci and tdci) are also reported.

Table 1. Protonation constants ($\log K^H_i$) for taci, L^1, L^2, and tdci determined in water (25 °C; 0.10 M KCl, pK_w = 13.78) using the program HYPERQUAD

Equilibrium quotient	taci	L^1	L^2	tdci
[HL]/[L][H]	8.87(2); 8.90[a]	9.362(6)	9.40(1)	9.68[a]
$[H_2L]/[HL][H]$	7.38(3); 7.40[a]	7.777(6)	7.74(1)	7.62[a]
$[H_3L]/[H_2L][H]$	5.96(3); 5.95[a]	6.257(6)	6.20(1)	5.89[a]
$[H_3L]/[L][H]^3$	22.21	23.40	23.34	23.19

[a] From ref.[15]

Table 2. Protonation constants ($\log K^H_i$) for L^2, L^3, and L^4 determined in water/methanol (1:3, v/v) (25 °C; 0.10 M KCl, pK_w = 13.89) using the program HYPERQUAD

Equilibrium quotient	L^2	L^3	L^4
[HL]/[L][H]	8.44(3)	8.56(2)	7.65(3)
$[H_2L]/[HL][H]$	7.14(3)	7.25(3)	6.16(3)
$[H_3L]/[H_2L][H]$	5.80(6)	5.74(3)	4.48(6)
$[H_3L]/[L][H]^3$	21.38	21.55	18.29

In each case, three constants corresponding to the protonation of the amino groups have been calculated. The values obtained for L^1 and L^2 in water are roughly similar, and as expected the overall basicity of these two ligands (bearing secondary amines) is higher than that of taci (primary amine) and lower than that of tdci (tertiary amine). Due to their poor solubility in water, the protonation properties of ligands L^3 and L^4 have been investigated in water/methanol (1:3, v/v). For comparison, L^2 has also been studied under the same conditions. The protonation constants determined for L^3 are close to those determined for L^2, i.e. the chain length does not significantly affect the basicity of the amino groups. On the other hand, the overall basicity of L^4 is three orders of magnitude lower than that of the alkyl derivatives. Note that benzylamine, with a pK^H value of 9.62, is also known to be a weaker base than butylamine and hexylamine whose pK^H values are 10.78 and 10.64, respectively.[29]

The separation of the pK^H values is in the range 1.3−1.7 and is higher than the statistical separation (log3 = 0.48). This means that the protonation of an amino group is influenced by other amino groups that are already protonated. This is expected since the basic sites are only separated by 3 carbon atoms.[30] Besides, the ΔpK^{H} values of ca. 1.5 observed between two consecutive protonation constants are similar to those calculated for 1,3,5-triaminocyclohexane (pK^{H}: 10.16, 8.66, 7.17),[31] and are thus consistent with the expected ligand conformation in solution, i.e. the conformation in which the hydroxy groups are in the axial positions and the amino groups are in the equatorial positions due to the steric hindrance of the bulky substituents.

Stability of the Complexes in Aqueous and H_2O/MeOH Media

The affinity of these ligands for lanthanide(III) cations was also studied by potentiometry in water or in water/methanol (1:3, v/v). The titration curves obtained for the Ln−L^1 and Ln−L^4 systems are representative of this study and are presented in Figure 3.

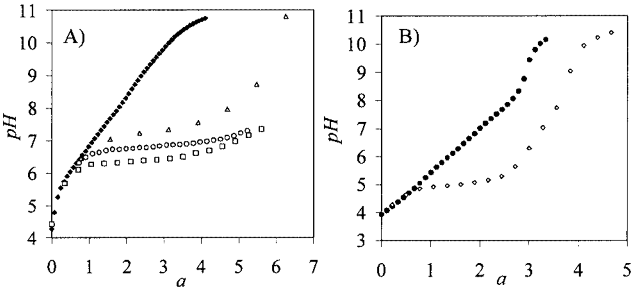


Figure 3. Potentiometric titration curves (experimental points, 25 °C, I = 0.10 M KCl) for: **A)** L^1 (◆) and different systems in water: Nd^{3+}−L^1 (Δ), Eu^{3+}−L^1 (○), Lu^{3+}−L^1 (□); c_L/c_M = 1:1.5; c_L = $1\cdot10^{-3}$ M; **B)** L^4 (●) and Eu^{3+}−L^4 (◇) system in water/methanol (1:3, v/v); c_L/c_M = 1:0.5; c_L = $0.5\cdot10^{-3}$ M. a is the number of base added per mol of ligand

The following conclusions can be drawn from the titration curves. The curves obtained for the Ln^{III}−ligand L^1, L^2, L^3, and L^4 systems share many features with the titration curves described for Ln^{III}−taci systems.[17] Each curve shows distinct regions corresponding to (i) the removal of the first proton from $[H_3L]^{3+}$, (ii) the formation of the complex characterized by the low slope of the pH curve in this range, (iii) the titration of the possible excess ligand (occurring for instance in the case of the Ln−L^4 system as shown in Figure 3, B), (iv) a further deprotonation of the complex at high pH values. These experiments unambiguously established the formation of the species $[M_3(LH_{-3})_2]^{3+}$ according to Equation (1):

$$H_3L^{3+} + 1.5\,M^{3+} + 6\,OH^- \rightleftarrows 0.5\,[M_3(LH_{-3})_2]^{3+} + 6\,H_2O \qquad (1)$$

In all cases presented here, the HYPERQUAD 2000 program gave convergence for models containing the $[M_3(LH_{-3})_2]^{3+}$ species, and in certain cases, $[M_3(LH_{-3})_2(OH)]^{2+}$ has been suggested if sufficient experimental points in the basic region were available. All other species considered, including mono- and dinuclear complexes, were systematically rejected by the program. The values of the stability constants, β_{32-6} according to Equation (2), calculated from the experimental points using the program HYPERQUAD are compiled in Tables 3 and 4. Figure 4 gives an insight into the species distribution as a function of pH for the Eu^{3+}−L^1 and Eu^{3+}−L^4 systems.

Table 3. Formation constants ($\log\beta_{32-6} = [Ln_3(LH_{-3})_2]/[Ln]^3[L]^2[H]^{-6}$) of taci, L^1, L^2, and tdci in water (25 °C; 0.10 M KCl, pK_w = 13.78)

Ion	taci	L^1	L^2	tdci
Nd^{3+}	−24.1[a]	−26.4(2)	−27.0(2)[b]	
Eu^{3+}	−17.9[a]; −18.5[c]	−21.4(1)[b]	−21.2(2)[b]	−16.8[c]
Lu^{3+}	−12.5[a]; −11.3[c]	−16.9(2)[b]	−17.6(2)[b]	

[a] From ref.[17] [b] Constants obtained using batch ("out-of-cell") method. [c] From ref.[15]

Table 4. Formation constants ($\log\beta_{32-6} = [Ln_3(LH_{-3})_2]/[Ln]^3[L]^2[H]^{-6}$) of L^2, L^3, and L^4 determined in water/methanol (1:3, v/v) (25 °C; 0.10 M KCl, pK_w = 13.89) using the program HYPERQUAD

Ion	L^2	L^3	L^4
Nd^{3+}	–	−15.9(2)	−13.9(2)
Eu^{3+}	−10.3(2)	−11.8(1)	− 8.3(1)

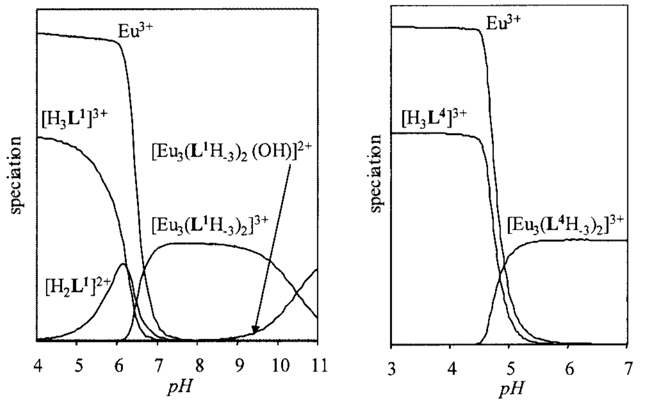


Figure 4. Species distribution as a function of pH for the Eu^{3+}−L^1 and Eu^{3+}−L^4 systems. c_L/c_M = 1:1.5; c_L = $1\cdot10^{-3}$ M. The formation constants listed in Tables 1 to 4 were used for the calculations

$$3\,Ln^{3+} + 2\,L \rightleftarrows [Ln_3L_2H_{-6}]^{3+} + 6\,H^+ \qquad (2)$$

Ligands L^1 and L^2 form stable complexes with Nd^{3+}, Eu^{3+}, and Lu^{3+} in water, with stability constants lower than those previously calculated for taci and the related cations. In water/methanol solution, Nd^{3+} and Eu^{3+} complexes formed with L^4 show a higher stability than those formed with L^2 and L^3. The plots in Figure 5, giving the calculated fraction of free Eu^{3+} versus pH for the different ligands, provide another way of comparing their complexing power. The binding ability follows the sequence $L^1 \approx L^2 <$ taci, in water, and $L^3 < L^2 << L^4$, in water/

methanol. Hence, ligand L^4 is the most effective in complexing europium in water/methanol (1:3, v/v) in the pH range 4.5−5.5, due to its relatively low basicity and high stability constant.

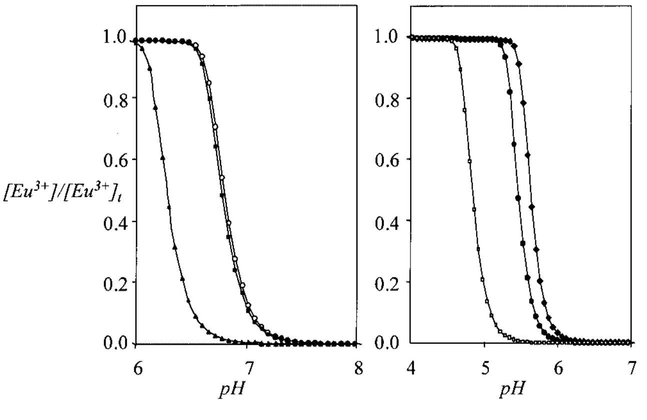


Figure 5. Fraction of calculated free europium concentration as a function of pH for taci (▲), L^1 (■), and L^2 (○) in water (left plot) and for L^2 (●), L^3 (◆), and L^4 (□) in water/methanol (1:3, v/v) (right plot). c_L/c_M = 1:1.5; $c_L = 1 \cdot 10^{-3}$ M

The differences in the Ln^{III} complex stabilities observed between taci and its *N*-functionalized derivatives may be explained by considering the effects of the basicity of the amino groups and the steric hindrance provided by the nitrogen substituent. As the Ln^{III} are very hard cations, the affinity of a family of ligands for these ions is usually correlated to their overall basicity; for a given lanthanide cation, as ΣpK^H increases, the complex stability constant also increases.[32] In this study, ligands based on the taci framework show an exceptional behavior since the more basic the amino groups are, the less effective lanthanide(III) complexation is. For taci and its derivatives, it is difficult to correlate the complexation constants with the overall ligand basicity, as has been done for several aminocarboxylic acids,[33] because the dissociation constants of the alcohol functions are not known. Under the experimental conditions used, these groups are not deprotonated in the absence of the metal, and the influence of nitrogen substitution on the alcohol dissociation constants is thus unknown. Moreover, it can obviously be assumed that the presence of the bulky groups renders the formation of the hindered sandwich-type complexes less favorable, and as a consequence the corresponding stability constant values decrease. Hence, the ligands L^1 and L^2 form less stable complexes than the unsubstituted taci in water. The same conclusion can be reached to explain the lower stability of the complexes formed with L^3 than those formed with L^2 in water/methanol solution.

The trend in the stability constants across the lanthanide series follows the well-known electrostatic trend,[34] i.e. $\log\beta_{32-6}$ increases from Nd^{III} to Lu^{III} and/or Eu^{III}, as seen in Figure 6. Lanthanide(III) complexation in water can be decomposed in two steps: the first step corresponds to dehydration, and the second step, to the reaction between the desolvated species. The compensation effect assumes that the free energy of the first step is negligible,[35] and thus the free energy of the global process reflects the second step, i.e. the interaction between the ligand and the metal ion, leading to an increase in the stability constants from La^{III} to Lu^{III}.

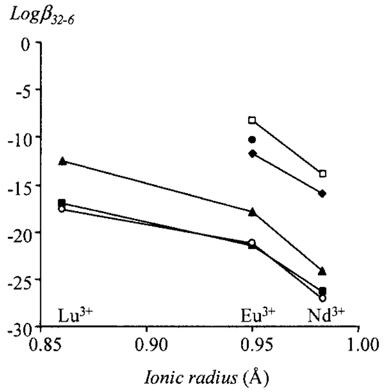


Figure 6. Variation of the $\log\beta_{32-6}$ values as a function of ionic radius for taci (▲), L^1 (■), and L^2 (○) in water and for L^2 (●), L^3 (◆), and L^4 (□) in water/methanol (1:3, v/v)

The great increase in the affinity from La^{III} to Lu^{III}, already observed with the ligand taci,[17] is also seen for the derivatives L^1-L^4. The difference in $\log\beta_{32-6}$ from Eu^{III} to Nd^{III} is 6.2 for taci, and ranges from 4.1 to 5.8 for L^1 to L^4. The simulation of the fraction of free Ln^{3+} in solution in the presence of L^4 as a function of pH clearly shows that the europium cations are totally complexed at pH 5.1, while at the same pH, the neodymium cations remain free in solution. Note that it does not mean that ligand L^4 would be able to selectively complex Eu^{3+} in the pH range 4.6 to 5.1. It would then be necessary to consider the formation of heterotrinuclear complexes, namely $[Eu_2Nd(LH_{-3})_2]^{3+}$ and $[EuNd_2(LH_{-3})_2]^{3+}$. We have already demonstrated the existence of such compounds with taci.[36]

NMR Analysis

In order to gain an insight into the solution structure of these complexes, a ^1H NMR study was undertaken. Solutions containing the water-soluble ligand L^1 and $Eu(OTf)_3$ at a molar ratio (M/L) of 1.5 were analyzed at pD values ranging from 4.70 to 8.21 at 278 K. Addition of small amounts of base (NaOD) clearly show the disappearance of the signals assigned to the ligand, and the appearance of numerous resonances within the 0 to −23 ppm region. As in the complex, each nitrogen atom becomes an asymmetric center, a mixture of diastereoisomers exists in solution and a further analysis of this region is not obvious. At pD 8.21, the spectrum of the sample only shows the resonances assigned to the complex, indicating that the ligand has totally been converted to the Eu^{III} complex. NMR spectra were also recorded at variable temperatures as seen in Figure 7, which represents the spectra of $[Eu_3(L^1)_2H_{-6}]^{3+}$ at 348 K and 278 K. A better resolution of the series of multiplets is obtained at 278 K, but it does not provide suitable information to confirm the solution structure of the complex. At 348 K, the signals scattered within 0 and −26 ppm merge into two broad signals centered at $\delta = -14.2$ ppm and −6.3 ppm. Considering the fact that the spectrum of the europium complex with taci only exhibits two signals at $\delta = -21.72$ ppm and −14.49 ppm, assigned to the protons H^N and H^O,[17] the two broad signals may represent the average of all the "H^N" and "H^O" protons. This last result is consistent with the pseudo D_{3h} symmetry of the complex when interconversion around the nitrogen atom is fast. Similar observations were made for europium complexes formed with L^2, L^3, and L^4 in methanol.

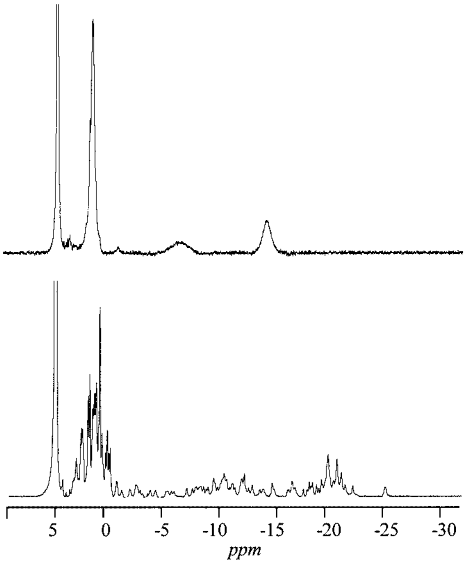


Figure 7. 400 MHz ^{1}H NMR spectra of the $Eu^{3+}-L^1$ system in D_2O (pD = 8.21) at 348 K (top) and 278 K (bottom). c_L/c_M = 1:1.5; $c_L = 1\cdot10^{-2}$ M

Conclusion

The new ligands L^1, L^2, and L^3, synthesized via alkylation of taci with various carbonated chains, as well as the trisbenzyl derivative L^4 show similar complexation properties towards lanthanide(III) cations as the ligand taci. The only species evidenced by electrospray ionization spectrometry and potentiometry is the trinuclear complex $[Ln_3L_2H_{-6}]^{3+}$. In the complex, the coordination of the nitrogen atoms to the lanthanide cations leads to several chiral centers, and thus a more detailed NMR analysis is prevented by the observation of numerous diastereoisomers in solution.

The stability constants of the lanthanide complexes of the four ligands show the well-known electrostatic trend, i.e. an increase from lanthanum to lutetium. Moreover, although ligands L^1-L^4 are more basic than taci, they give less stable complexes with Ln^{III}, indicating that the steric hindrance is the determining factor in the formation of the sandwich complex $[Ln_3L_2H_{-6}]^{3+}$. The ligands may be classified according to their Ln^{III} affinity: $L^1 \approx L^2 <$ taci, in water, and $L^3 < L^2 << L^4$, in water/methanol, and thus among this set of ligands, L^4 appears to be the most effective in binding 4f cations. The striking increase in affinity across the series, previously seen with the ligand taci, is maintained for the lipophilic derivatives L^1-L^4.

Experimental Section

General Information: All solvents and reagents were obtained from commercial suppliers and used without further purification. The precursor taci, used as the sulfate salt, and the ligand tbci (L^4) were prepared according to literature procedures.[21,23] Catalytic hydrogenation was performed within a TOP 80 reactor with controlled hydrogen pressure, temperature and rotation speed. Melting points were measured with an Electrothermal IA93000 and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a Varian Mercury 400 spectrometer. Chemical shifts are reported in ppm with solvent as the internal reference. When necessary, pD was adjusted with a sodium deuteroxide solution (pD = pH_{read} + 0.41).[37] Mass spectra were acquired on a LCQ-ion trap (Finnigan-Thermoquest, San Jose, USA) equipped with an electrospray source. Electrospray full scan spectra in the range m/z = 100−1500 were obtained by infusion through a fused silica tubing at 2−10 μL/min. The solutions were analyzed in the positive mode. The LCQ calibration (m/z = 50−2000) was achieved according to the standard calibration procedure from the manufacturer (mixture of caffeine, MRFA and Ultramark 1621). The temperature of the heated capillary for the LCQ was set to 85 °C, the ion-spray voltage was in the range 1−6 kV and the injection time was 5−200 ms. Samples for ES-MS were prepared by dissolving the ligand (10^{-3} M) and the lanthanide salt in water or in water/methanol solution, the pH was then adjusted to the desired value if necessary by adding triethylamine. Elemental analyses were performed by the Service Central d'Analyses (Vernaison-69)

Ligands Synthesis

1,3,5-Trideoxy-1,3,5-tris(ethylamino)-*cis*-inositol (L^1): A solution of the sulfate salt of taci (1.00 g, 3.08 mmol) in H_2O (160 mL) was hydrogenated under hydrogen pressure (12 bars) in the presence of PtO_2 (0.070 g, 0.31 mmol) and acetaldehyde (4.0 mL; 70.9 mmol) at room temperature for 7 days. Two additional portions of acetaldehyde (2 × 4.0 mL; 2 × 70.9 mmol) were added after 2 and 3 days. After filtration through a pad of Celite and concentration in vacuo, the crude product was purified by crystallization from H_2O/EtOH, yielding the sulfate salt of compound L^1 (0.924 g, 65%) as a white solid. ^{1}H NMR (400 MHz, D_2O, 298 K): δ (ppm) = 1.36 (t, J = 7.2 Hz, 9 H, CH_3), 3.25 (q, J = 7.3 Hz, 6 H, NCH_2),. 3.57 (t, J = 3.0 Hz, 3 H, HC_{cycle}-NH,), 4.61 (t, J = 2.9 Hz, 3 H, HC_{cycle}-OH) ppm. $C_{12}H_{30}N_3O_3\cdot SO_4\cdot HSO_4$ (457.51): calcd. C 31.5, H 6.8, N 9.1; found C 31.5, H 7.1, N.8.7.

The sulfate salt of ligand L^1 (0.924 g, 2.02 mmol) was dissolved in H_2O (50 mL) and subjected to ion-exchange chromatography (Amberlite IR 45, OH^- form). H_2O was removed under reduced pressure to afford the free base ligand L^1 (0.573 g, 96%) as a white solid. M.p. 160−161 °C (decomposition). ^{1}H NMR (400 MHz, D_2O, 298 K): δ (ppm) = 1.16 (t, J = 7.2 Hz, 9 H, CH_3), 2.83 (q, J = 7.3 Hz, 6 H, NCH_2), 2.85 (s broad, 3 H, HC_{cycle}-NH), 4.27 (t, J = 2.9 Hz, 3 H, HC_{cycle}-OH) ppm. ^{13}C NMR (100 MHz, D_2O, 298 K): δ (ppm) = 15.1 (CH_3). 41.7 (NCH_2), 59.2 (HC_{cycle}-NH), 70.0 (HC_{cycle}-OH). ES-MS: 262.2 $[M + H]^+$.

1,3,5-Tris(butylamino)-1,3,5-trideoxy-*cis*-inositol (L^2): The sulfate salt of taci (1.00 g, 3.08 mmol) in MeOH (75 mL) was refluxed with

KOH (0.675 g, 12.02 mmol) for 30 min. Butanal (1.8 mL, 20.3 mmol) was added dropwise and the solution was stirred for 3 h. The solution was then cooled to 0 °C and sodium borohydride (1.516 g, 40.08 mmol) was added in small portions. After stirring overnight at room temperature, the reaction was quenched by adding concentrated HCl. The solution was concentrated to dryness and the residue was taken up in H_2O (300 mL). The mixture was extracted with CH_2Cl_2 (150 mL) to remove excess butanal. The aqueous layer was made alkaline (pH ca. 10) by adding KOH pellets and extracted with Et_2O (8×200 mL). The solvent was removed in vacuo and the residue was purified by crystallization from CH_3CN, yielding compound L^2 (0.693 g, 65%) as a white solid with m.p. 117 °C. ^1H NMR (400 MHz, D_2O, 298 K): $\delta = 0.89$ (t, $J =$ 7.3 Hz, 9 H, CH_3,), 1.33 (sext, $J = 7.3$ Hz, 6 H, CH_2-CH_3), 1.48 (quint, $J = 7.6$ Hz, 6 H, -CH_2-), 2.61 (s broad, 3 H, HC_{cycle}-NH), 2.66 (t, $J = 7.4$ Hz, 6 H, NCH_2), 4.21 (s broad, 3 H, HC_{cycle}-OH) ppm. ^{13}C NMR (100 MHz, D_2O, 298 K): $\delta = 15.6$ (CH_3). 22.3 (CH_2-CH_3), 33.2 (NCH_2-CH_2), 46.9 (NCH_2), 59.8 (HC_{cycle}-NH), 71.4 (HC_{cycle}-OH). ES/MS: 346.5 $[M + H]^+$, 368.3 $[M + Na]^+$. $C_{18}H_{39}N_3O_3$ (345.53): calcd. C 62.6, H 11.4, N 12.2; found C 62.3, H 11.4, N 12.2.

1,3,5-Trideoxy-1,3,5-tris(hexylamino)-*cis*-inositol (L^3): Following the same procedure as above, treatment of the sulfate salt of taci (0.300 g, 0.925 mmol) with KOH (0.202 g, 3.608 mmol), hexanal (0.37 mL, 3.053 mmol) and sodium borohydride (0.455 g, 12.02 mmol) and crystallization from ethyl acetate yielded compound L^3 (0.222 g, 56%) as a white solid with m.p. 104 °C. ^1H NMR (400 MHz, $CDCl_3$, 298 K): $\delta = 0.89$ (t, $J = 6.7$ Hz, 9 H, CH_3), 1.32 (m, 18 H, $(CH_2)_3CH_3$), 1.58 (m, 6 H, CH_2), 2.54 (s broad, 3 H, HC_{cycle}-NH), 2.76 (t, $J = 7.2$ Hz, 6 H, NCH_2,), 4.17 (s broad, 3 H, HC_{cycle}-OH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 298 K): $\delta = 14.2$ (CH_3), 22.8 (CH_2), 27.2 (CH_2), 30.2 (CH_2), 31.9 (CH_2), 47.3 (NCH_2), 59.5 (HC_{cycle}-NH), 69.7 (HC_{cycle}-OH). ES/MS: 430.5 $[M + H]^+$. $C_{24}H_{51}N_3O_3$ (429.69): calcd. C 67.1, H 12.0, N 9.8; found C 67.3, H 12.0, N 9.9.

Potentiometric Measurements

Reagents and Solutions: Solutions of titrants, support electrolyte (KCl), metal ions and ligands were prepared in water (obtained by Millipore/Milli-Q system) or in water/methanol (1:3, v/v); methanol was of analytical grade. Carbonate-free solutions of KOH were prepared from standardized solutions and were discarded when the amount of carbonate was about 1% of the total amount of base. HCl solutions were prepared from standardized solutions. Metal ions solutions were prepared with a concentration of about $1 \cdot 10^{-2}$ M, from the chloride salts of the metals and standardized by titration with H_2Na_2edta. Ligand solutions were prepared at a concentration of ca. 10^{-3} M.

Equipment and Working Conditions: All potentiometric titrations were carried out at 25.0±0.1 °C. Potential values were measured with a Metrohm combined glass electrode. Atmospheric CO_2 was excluded from the cell during the titration by passing Ar across the top of the experimental solution in the reaction cell. The titrant solutions were dispensed from a Metrohm 751 piston burette. For the titrations carried out in water/methanol (1:3, v/v), the glass electrode was previously treated by soaking it in the solution for one week to prevent erratic responses.

Measurements: The $[H^+]$ of the solutions was determined by measurement of the electromotive force of the cell, $E = E'^\circ + Q \log [H^+] + Ej$; E'°, and Q was obtained from previous calibrations.[38] The liquid-junction potential, Ej, was negligible under the experimental conditions used. The value of $K_w = [H^+][OH^-]$ was $10^{-13.78}$ in water. In water/methanol (1:3, v/v), K_w was determined from the alkaline region of the titration curve and was found to be equal to $10^{-13.85}$ under our experimental conditions. The potentiometric equilibrium measurements were made on 30 mL solutions containing 25−50 μmol of the ligand and at an ionic strength of 0.10 M.

For the study of Ln^{III} complexes in water, a batch ("out-of-cell") method was used: solutions of metal ion and ligand with a final concentration of about 10^{-3} M were prepared in separate vials of 2 mL, in which small volumes of standard KOH solution (0.10 M) were added. The [M]/[L] ratios used were 1.5:1 for the Ln^{III}/$\mathbf{L^1}$ systems, 0.5:1 and 1.5:1 for the Ln^{III}/$\mathbf{L^2}$ systems. The ionic strength of the solutions was kept at 0.10 M with KCl. Measurements were carried out after stabilization of the pH, which occurred within 12 h.

For the study of the Ln^{III} complexes in water/methanol (1:3, v/v) solution, [M]/[L] ratios were 0.5:1 and under such conditions, stabilization occurred within 4500 s, allowing automatic titrations to be performed. To check if complete equilibration had been achieved during titration, a back titration with HCl (0.10 M) was performed. In all the cases presented here, no hysteresis was observed.

Calculation of Equilibrium Constants: Protonation constants $K^H{}_i = [H_iL]/[H_{i-1}L][H]$ were calculated by fitting the potentiometric data obtained for the ligand using the program HYPERQUAD.[39,40] Stability constants of the various species formed in solution were obtained from the experimental data using the same program. The initial results were obtained in the form of overall stability constants.

$$\beta_{M_mH_hL_l} = \frac{[M_mH_hL_l]}{[M]^m[H]^h[L]^l}$$

The errors quoted correspond to the standard deviations estimated by Hyperquad 2000, multiplied by a factor of 3.

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