Lanthanide(III) and group 13 metal ion complexes of tripodal amino phosphinate ligands†

Michael S. Kovacs, Vishakha Monga, Brian O. Patrick and Chris Orvig*

Received 24th June 2005, Accepted 6th September 2005
First published as an Advance Article on the web 25th October 2005
DOI: 10.1039/b507905e

The tripodal amino-phosphinate ligands, tris(4-(phenylphosphinato)-3-benzyl-3-azabutyl)amine ($H_3ppba{\cdot}2HCl{\cdot}H_2O$) and tris(4-(phenylphosphinato)-3-azabutyl)amine ($H_3ppa{\cdot}HCl{\cdot}H_2O$) were synthesized and reacted with Al^{3+}, Ga^{3+}, In^{3+} and the lanthanides (Ln^{3+}). At 2 : 1 H_3ppba to metal ratios, complexes of the type $[M(H_3ppba)_2]^{3+}$ ($M = Al^{3+}$, Ga^{3+}, In^{3+}, Ho^{3+}–Lu^{3+}) were isolated. The bicapped $[Ga(H_3ppba)_2](NO_3)_2Cl{\cdot}3CH_3OH$ was structurally characterized and was shown indirectly by various techniques to be isostructural with the other $[M(H_3ppba)_2]^{3+}$ complexes. Also, at 2 : 1 H_3ppba to metal ratios, complexes of the type $[M(H_4ppba)_2]^{5+}$ ($M = La^{3+}$–Tb^{3+}) were characterized, and the X-ray structure of $[Gd(H_4ppba)_2](NO_3)_4Cl{\cdot}3CH_3OH$ was determined. At 1 : 1 H_3ppba to metal ratios, complexes of the type $[M(H_4ppba)]^{4+}$ ($M = La^{3+}$–Er^{3+}) were isolated and characterized. Elemental analysis and spectroscopic evidence supported the formation of a 1 : 1 monocapped complex. Reaction of 1 : 1 ratios of H_3ppa with Ln^{3+} and In^{3+} yielded complexes of the type $[M(H_3ppa)]^{3+}$ ($M = La^{3+}$–Yb^{3+}) but with Ga^{3+}, complex of the type $[Ga(ppa)]{\cdot}3H_2O$ was obtained. Reaction of 1 : 1 ratios of H_3ppa with Ln^{3+} and In^{3+} yielded complexes of the type $[M(H_3ppa)]^{3+}$ ($M = La^{3+}$–Yb^{3+}) but with Ga^{3+} a neutral complex $[Ga(ppa)]{\cdot}3H_2O$ was obtained. The formation of an encapsulated 1 : 1 complex is supported by elemental analysis and spectroscopic evidence.

Introduction

For many years, the group 13 metals (Al, Ga, In, Tl) and the lanthanides (Ln) have either been employed, or have been investigated for potential use in nuclear medicine.[1] ^{67}Ga(III) and ^{111}In(III) have been used in diagnostic agents, the former for imaging certain types of cancer, and the latter as pretargeting agents for cancer imaging and therapy, *e.g.* the use of ^{111}In-octreoscan.[2] $^{201}Tl^+$ as a myocardial imaging agent predates the use of ^{99m}Tc for this application, although $^{201}Tl^+$ imaging has been largely supplanted by Tc-based diagnostic agents such as Cardiolite®. The use of the lanthanides as therapeutic agents has received extensive attention since the US Food and Drug Administration approval of ^{153}Sm(EDTMP) for bone pain palliation in terminal cancer patients. Gd(III) has received extensive attention due to its use in MRI contrast agents.[3,4]

Efforts to explore amino-phosphinate ligands with the group 13 metals and the lanthanides have focused on DOTA-type ligands and tren-based tripodal ligands (Scheme 1). The former have been more thoroughly investigated, and a variety of work has been published on their synthesis, structures of their lanthanide complexes, solution behavior and luminescence properties.[5–11] 1 : 1 Complexes with the lanthanides have been obtained with this type of ligand system and the resulting stereochemistry has been extensively investigated.[9,12–15] In addition to the clockwise and counterclockwise wrapping isomers, six diastereomers have been characterized using a variety of NMR techniques.[9,12–15] The DOTA phosphinate ligands have also been modified to act as bifunctional chelates.[16]

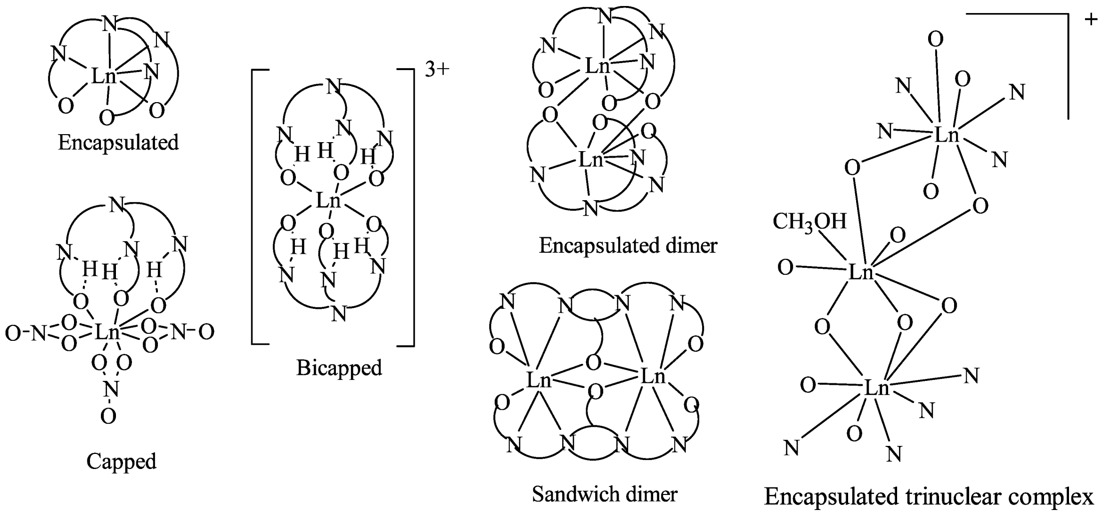
The tripodal ligand H_3ppma was found to form 2 : 1 bicapped complexes with group 13 metals and the lanthanides.[17–19] The S_6 symmetry of these bicapped complexes made unique ^{27}Al, ^{71}Ga and ^{31}P NMR spectroscopic studies amenable that allowed the determination of stability constants below the pH limit of traditional potentiometric techniques.[17] Encapsulated 1 : 1 complexes were not obtained in the tripodal amino-phosphinate system. For application in nuclear medicine, this result was a significant setback because 1 : 1 encapsulated complexes are ideal. Such a complex should have higher thermodynamic stability than would a 2 : 1 bicapped complex; the coordination sphere would contain only donors from the ligand, unlike in the monocapped case, where kinetically labile water molecules or counterions are coordinated. Encapsulated 1 : 1 complexes are also much less sensitive to entropic effects that occur at extreme dilution. Kinetically inert complexes with high thermodynamic stability are required to prevent demetallation of the complex *in vivo*.

To investigate the possibility of isolating 1 : 1 encapsulated complexes containing group 13 metals or the lanthanides, modifications to the tripodal amino-phosphinate ligands are described herein. Attempts were made to prepare new ligands with modifications occurring at the phosphinate R group and/or the amine R group. Although modification at the phosphinate R group proved difficult, synthesis of the benzylated amino-phosphinate ligand tris(4-(phenylphosphinato)-3-benzyl-3-azabutyl)amine (H_3ppba) was successful. Two distinct classes of 2 : 1 complexes, and one class of 1 : 1 complex were prepared and characterized with the group 13 metal ions (Al^{3+}, Ga^{3+}, In^{3+}) and the lanthanides. H_3ppba

---

Medicinal Inorganic Chemistry Group, Department of Chemistry, University of British Columbia, 2036 Main Mall, Vancouver, B.C., V6T 1Z1, Canada. E-mail: orvig@chem.ubc.ca

† Electronic supplementary information (ESI) available: Experimental section. See http://dx.doi.org/10.1039/b507905e



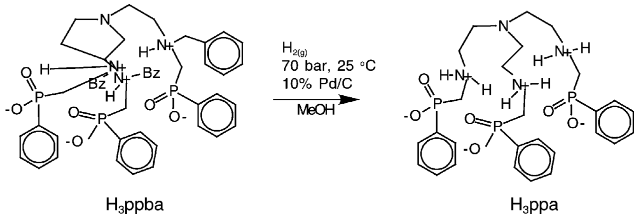
Scheme 1

was also used as a synthetic precursor to obtain the unique amino-phosphinate ligand tris(4-(phenylphosphinato)-3-azabutyl)amine (H_3ppa) by N-debenzylation. H_3ppa contains a secondary amine, a functionality that has been elusive in amino-phosphinate systems until this report.

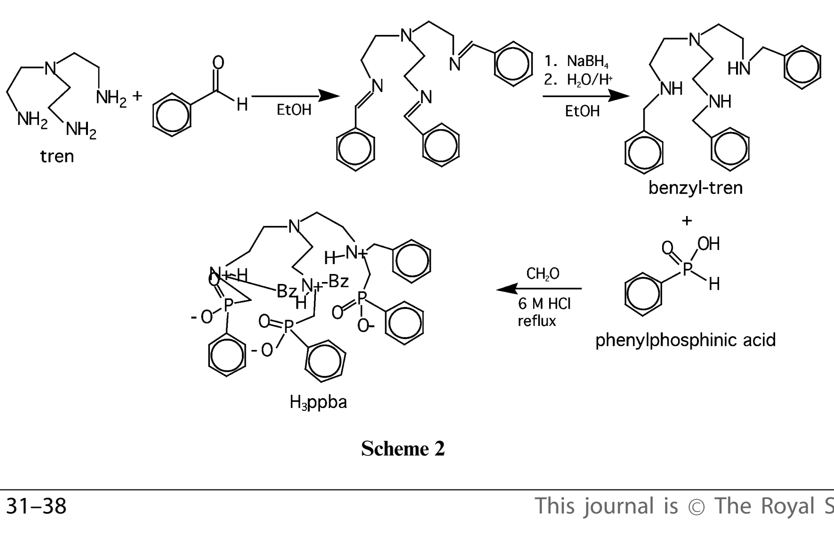
Results and discussion

The synthesis of new amino-phosphinate ligands was accomplished by adapting the Moedritzer–Irani reaction[20] to react phenylphosphinic acid with tris(2-benzylaminoethyl)amine in the presence of formaldehyde (Scheme 2). The synthesis of tris(2-benzylaminoethyl)amine (the benzylated derivative of tren) was accomplished by standard methods.[21] Recrystallization of the product from the reaction of benzylated tren and phenylphosphinic acid affords pure tris(4-(phenylphosphinato)-3-benzyl-3-azabutyl)amine ($H_3ppba{\cdot}2HCl{\cdot}H_2O$) in good yield. The ligand was found to be soluble in methanol, hot ethanol, hot isopropanol, DMSO and DMF.

The possibility of modification at the amine was also investigated. It was expected that the presence of the three bulky benzyl groups would discourage 1 : 1 encapsulated complex formation. Removal of these groups by catalytic hydrogenation, however, afforded the novel secondary amine tripod tris(4-(phenylphosphinato)-3-azabutyl)amine ($H_3ppa{\cdot}HCl{\cdot}H_2O$) (Scheme 3). The reaction is easily monitored by the loss of the methylene resonance of the benzyl group in the ^1H NMR spectrum at 4.45 ppm. Catalytic hydrogenation of N-benzyl groups is known to be difficult because of the propensity of free amines to poison the Pd catalyst.[22] High pressure and a large excess of Pd catalyst were required for this reaction to proceed. Hydrogenation reactions are known to produce pure products in high yield; the products of the reaction are H_3ppa and toluene, and the problem of purifying the zwitterionic product from the Moedritzer–Irani reaction is avoided. H_3ppa is highly water-soluble; the ligand is also soluble in alcohols such as methanol and ethanol.



Scheme 3



Scheme 2

Complexes of the ligand H_3ppma were clearly shown to be 2 : 1 bicapped complexes of the type $[M(H_3ppma)_2](NO_3)_3$, where M = Al^{3+}, Ga^{3+}, In^{3+} and Ln^{3+}.[17–19] Therefore, the first step of this study was to prepare 2 : 1 ligand : metal complexes for comparison. All complexes were prepared under similar conditions, but two distinct classes of 2 : 1 bicapped complexes were identified.

Reaction of one equivalent of $Ga(NO_3)_3\cdot 6H_2O$ with two equivalents of $H_3ppba\cdot 2HCl\cdot H_2O$ in methanol results in the formation of the 2 : 1 bicapped complex $[Ga(H_3ppba)_2](NO_3)_2Cl\cdot 3CH_3OH$ (**1**). Indicating that complex formation occurs in methanol solution, the ^{31}P NMR singlet of H_3ppba shifted upfield from 23.2 to 14.4 ppm for the complex, but little other information is obtained from NMR spectroscopy. A number of metal salts were tried, including chloride, triflate and perchlorate, but only the mixed nitrate/chloride product formed crystals that were amenable to X-ray structural analysis and had consistent composition. Reactions with Al^{3+}, In^{3+}, and the lanthanides Ho^{3+} through Lu^{3+} formed the same type of tricationic complex. Isolated yields ranged from 31 to 84%. In the case of the lanthanides, the complexes appeared to have somewhat higher solubility, and yields were difficult to improve. Any attempt to improve the yields by removing the solvent resulted in the formation of glassy solids with inconsistent compositions according to their elemental analyses.

An X-ray structural analysis was performed on a crystal of **1** isolated from the reaction of H_3ppba with Ga^{3+} (Fig. 1, Table 1). The Ga^{3+} ion is clearly bicapped by two H_3ppba ligands; examination of the bond lengths and a difference map indicate that each of the three arm N atoms are protonated on each H_3ppba ligand. The ligands are best regarded as neutral zwitterions, thus, the complex has an overall +3 charge. The Ga^{3+} ion is coordinated only by the phosphinato O atom donors with one symmetry-imposed Ga–O bond length of 1.9501(13) Å. The two H_3ppba ligands are related to each other through a crystallographic inversion center at the Ga^{3+} ion. Although the portion of the unit cell containing $[Ga(H_3ppba)_2]^{3+}$ is well established, large void spaces exist where satisfactory modeling of mixed NO_3^-, Cl^- and CH_3OH was not possible. Correction of the disordered data in the void spaces resulted in $R1 = 0.048$ and no peak in the difference map exceeding 0.87 e^- $Å^{-3}$. The elemental analyses for the Ga^{3+} and other H_3ppba complexes strongly support the proposed composition.

Table 1 Selected bond lengths (Å) and bond angles (°) in $Ga(H_3ppba)_2](NO_3)_2Cl\cdot 3CH_3OH$ (**1**)

Ga(1)–O(1)	1.9501(13)	C(3)–P(1)	1.8355(19)
O(1)–P(1)	1.5051(13)	C(4)–P(1)	1.796(2)
O(2)–P(1)	1.4923(14)		
P(1)–O(1)–Ga(1)	143.83(8)	O(2)–P(1)–O(1)	120.24(8)
O(1)–Ga(1)–O(1*)[a]	88.85(6)	O(1)–P(1)–C(3)	104.05(8)
O(1)–Ga(1)–O(1*)[a]	91.15(6)	O(1)–P(1)–C(4)	110.32(9)
O(1)–Ga(1)–O(1*)[a]	180.00(7)	O(2)–P(1)–C(3)	110.76(9)
C(4)–P(1)–C(3)	99.51(9)	O(2)–P(1)–C(4)	109.84(9)

[a] The O atoms are related to each other by symmetry.

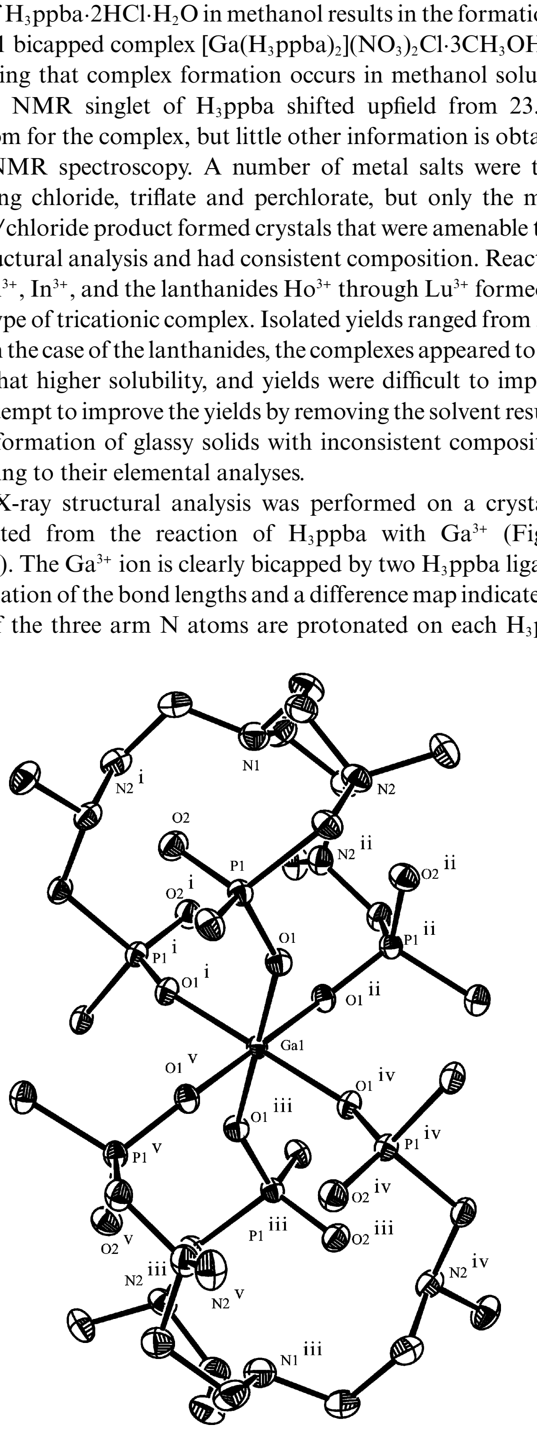


Fig. 1 ORTEP diagram of the $[Ga(H_3ppba)_2]^{3+}$ cation with the solvent molecules and the aromatic rings removed for clarity; 50% thermal probability ellipsoids are shown. Symmetry labels: i: $-y$, $x - y$, z; ii: $-x + y$, $-y$, z; iii: $-x + 1/3$, $-y + 2/3$, $-z + 2/3$; iv: $y + 1/3$, $-x + y + 2/3$, $-z + 2/3$; v: $x - y + 1/3$, $x + 2/3$, $-z + 2/3$.

Analogous to the structurally characterized $[In(H_3ppma)_2]^{3+}$ or $[Lu(H_3ppma)_2]^{3+}$ complexes,[17,19] there is nearly perfect S_6 symmetry around the Ga^{3+} ion. In the case of $[In(H_3ppma)_2]^{3+}$, the crystallographic symmetry imposed perfect 90 and 180° angles between the O atoms of the phosphinato ligands.[17] The 180° angles in $[Lu(H_3ppma)_2]^{3+}$ are crystallographically imposed, and the 88.72(6) and 91.28(6)° angles are extremely close to 90°.[19] The unique bond angles in **1** are 180.00, 91.15(6) and 88.85(6)°, therefore, the structure is also an octahedral complex with nearly perfect S_6 symmetry. The bond lengths in each of the three complexes are comparable when the ionic radii are corrected for the three different metals.

Also analogous to the two known H_3ppma complexes, the coordination of each phosphinato O atom introduces a chiral center at each P atom.[17,19] In the crystal structure of **1**, only the *RRRSSS* diastereomer is observed. In order to accommodate the bulk of the phenyl rings on the phosphinate group, the only other diastereomer that is chemically possible is the *RRSSSR*.[17] There is no evidence for the presence of this diastereomer in the solid state in any of the studies to date.

Mass spectral (+LSIMS) data for the entire series of complexes demonstrate clearly that 2 : 1 complexes are formed (see ESI†). Peaks are seen in each case corresponding to the monocationic 2 : 1 and 1 : 1 complexes. Since the ligand peak at 879 is also observed in every case, it is reasonable to conclude that the 1 : 1 complex is formed by fragmentation in the mass spectrometer.

IR spectroscopy shows that complexes of H_3ppba with Al^{3+}, Ga^{3+}, In^{3+} and the lanthanides Ho^{3+} through Lu^{3+} are completely isostructural (Fig. 2). The IR spectra have several notable features in the region shown. The peak around 1450 cm^{-1} is attributed to ν(P–Ph); the sharp peak at 1383 cm^{-1} arises from $\nu(NO_3)$; the three large peaks at *ca.* 1190, 1130, 1070 cm^{-1} are attributed to ν(P–O); and the peaks around 700 cm^{-1} are due to ν(P–C) and ν(P–Ph).

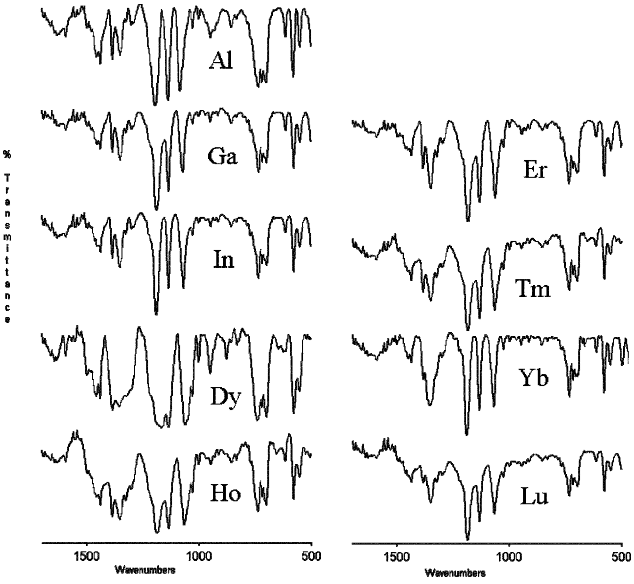


Fig. 2 IR spectra of [M(H$_3$ppba)$_2$](NO$_3$)$_2$Cl, M as indicated.

The intensity and position of all of these peaks remains relatively unchanged in all of the spectra, except in that of Dy^{3+}, which appears to show some additional spectral features (*vide infra*).

For the series of lanthanides La^{3+} through Dy^{3+}, however, the IR spectra of the complexes were found to differ greatly from the "Ga^{3+} type" structures. The elemental analyses (see ESI†) of the Eu^{3+}, Gd^{3+} and Tb^{3+} complexes indicate that complexes of the type [Ln(H$_4$ppba)$_2$]$^{5+}$ are formed wherein the apical nitrogen of each ligand is protonated to afford a +5 complex. Obtaining good elemental data for this class of complex was difficult. Isolated yields were quite low (10–15%), and only Eu^{3+}, Gd^{3+} and Tb^{3+} complexes were isolated in pure form. Satisfactory elemental analyses for the La–Sm^{3+} and Dy^{3+} complexes were never obtained. Lying on the border between the +5 and +3 complexes, it is possible that Dy^{3+} formed a mixture of both complex types. The appearance of new features in the IR spectrum of the Dy^{3+} complex supports this hypothesis.

Despite the fact that pure complexes could not be obtained for all of the early Ln^{3+} series, the +LSIMS data and IR spectroscopy indicate that these complexes have similarities to the Eu^{3+}, Gd^{3+} and Tb^{3+} complexes. The large shift in frequency of the IR bands associated with P and O bonding may be attributed to a change in the intramolecular H-bonding involving the protonated N atoms. If this is the case, the positions of the transitions in the IR spectra are a remarkably sensitive probe of the intramolecular H-bonding. Although the Sm^{3+} complex has an identical IR spectrum to those of the Gd^{3+} and Tb^{3+} complexes, strangely the Eu^{3+} complex does not, even though its elemental analysis supports its formulation as [Eu(H$_4$ppba)$_2$]$^{5+}$. The Nd^{3+} spectrum is identical to the Eu^{3+} spectrum. The early Ln^{3+} may have a propensity to form a mixture of 2 : 1 and 1 : 1 complexes (*vide infra*). This may explain why satisfactory elemental analyses could not be obtained for La^{3+}–Sm^{3+}, and may also explain the presence of the 2 : 1 peaks in the +LSIMS spectra.

From the reaction mixture of Gd^{3+} and H$_3$ppba, a single crystal was obtained and was used in an X-ray structural analysis (Fig. 3, Table 2). The complex has a bicapped structure similar to that found in **1**. Each arm of the tripod is related to the other arms by six-fold crystallographic symmetry. Both the pendant amines and the apical amines are protonated to afford the product complex as [Gd(H$_4$ppba)$_2$](NO$_3$)$_4$Cl·3CH$_3$OH (**2**). The geometry around Gd^{3+} is nearly octahedral, with unique bond angles of 180.00, 87.52(6) and 92.48(6)° between the O phosphinato donor atoms. As in **1**, the P atoms in **2** have a *RRRSSS* configuration and this is the only diastereomer seen in the solid state. The presence of the [M(H$_4$ppba)$_2$]$^{5+}$ complex in the unit cell is very clear, but the six-fold symmetry of the $R\bar{3}$ unit cell complicated the identification of the five counterions and the CH$_3$OH in the large void spaces of the unit cell. This disorder was modeled with help from the analytical data and was refined to $R1 = 0.034$.

Table 2 Selected bond lengths (Å) and bond angles (°) in [Gd(H$_4$ppba)$_2$](NO$_3$)$_4$Cl·3CH$_3$OH (**2**)

Gd–O(2)	2.2841(17)	P(1)–C(1)	1.797(3)
P(1)–O(1)	1.500(2)	P(1)–C(7)	1.845(3)
P(1)–O(2)	1.5104(16)		
Gd–O(2)–P(1)	143.85(10)	O(1)–P(1)–C(1)	112.67(11)
O(2)–Ga–O(2*)^a	87.52(6)	O(1)–P(1)–C(7)	108.17(10)
O(2)–Ga–O(2*)^a	92.48(6)	O(2)–P(1)–C(1)	107.45(11)
O(2)–Ga–O(2*)^a	180.00	O(2)–P(1)–C(7)	107.94(10)
O(1)–P(1)–O(2)	117.45(11)	C(1)–P(1)–C(7)	101.97(12)

^{a} The O atoms are related to each other by symmetry.

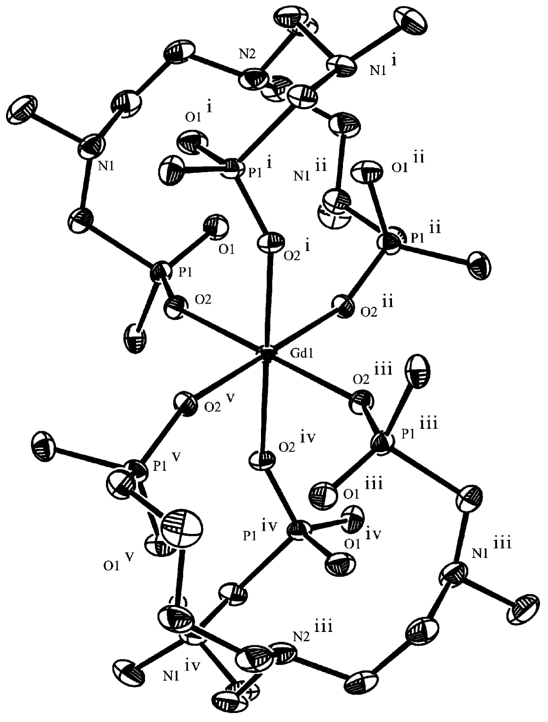


Fig. 3 ORTEP diagram of the [Gd(H$_4$ppba)$_2$]$^{5+}$ cation with the solvent molecules and the aromatic rings removed for clarity; 50% thermal probability ellipsoids are shown. Symmetry labels: i: $-y, x - y, z$; ii: $-x + y, -x, z$; iii: $-x, -y, -z$; iv: $y, -x + y, -z$; v: $x - y, x, -z$.

The switch from [M(H$_4$ppba)$_2$]$^{5+}$ (M = La^{3+}–Tb^{3+}) to [M′(H$_3$ppba)$_2$]$^{3+}$ (M′ = Al^{3+}, Ga^{3+}, In^{3+}, Ho^{3+}–Lu^{3+}) is an interesting phenomenon that was not observed in the H$_3$ppma system. It is possible that the size of the metal ion and the nature of the H-bonding network in the uncoordinated upper part of the tripodal ligand have some role in this behavior. It is a well-known fact that early lanthanide trivalent metal ions are larger than late lanthanide trivalent metal ions. The angles between the phosphinate O donors in **1** have two unique angles of 88.88(6) and 91.12(6)°, whereas the unique angles in the **2** are 87.52(6) and 92.48(6)°. It is possible that the larger Ln^{3+} ions can tolerate this compression of the bond angles better than the smaller Ln^{3+} and group 13 metal ions. As a result of the compression at the bottom of the tripod, the upper tripod can open up and a rearrangement of the H-bonding network can occur (including the apical N proton) to produce the observed +5 complex. This explanation is also supported by the dramatic change in the P=O and P–O stretching frequencies in the IR spectra of the complexes.

In order to investigate further the strange behavior of the 2 : 1 La^{3+}–Sm^{3+} complexes, including the possibility of 1 : 1 complex formation, a study of the system in 1 : 1 ratios was initiated. Under similar conditions to those which produced the 2 : 1 complexes, 1 : 1 ratios of $M(NO)_3$ (M = La^{3+}–Lu^{3+}) and H_3ppba were reacted in methanol. These reactions afforded complexes of the type $[M(H_4ppba)]^{4+}$ in 14–34% yield. Upon mixing of the starting materials, a finely-divided precipitate immediately formed for most of the lanthanides. Towards the end of the series (Tm^{3+}–Lu^{3+}), no precipitate formed and prismatic crystals appeared corresponding to the $[M(H_3ppba)_2]^{3+}$ complexes over a period of 48 h. This was verified crystallographically for the Yb^{3+} complex (the full solution of the structure was not completed once this was discovered).

Unlike those of the 2 : 1 complexes, the +LSIMS mass spectra of the 1 : 1 complexes show no substantial evidence of 2 : 1 peaks. In some of the complexes, 2 : 1 peaks were observed at trace levels (20× gain). The possibility exists that a small excess of ligand may have been present in these cases. Lanthanide nitrate salts are very hygroscopic and the excess water would not have been accounted for if it were present.

The IR spectra of the 1 : 1 complexes La^{3+}–Er^{3+} are remarkably similar. The $\nu(NO_3)$ peak is at 1384 cm^{-1}, which is the same frequency as that seen in the 2 : 1 complexes. With the exception of complexes of La^{3+} Sm^{3+}, and Er^{3+} which have an additional peak at 1238 cm^{-1}, all the other complexes share similar features in the ν(PO) region of the spectrum (1303, 1181, 1134, 1054 cm^{-1}). The IR spectrum of the Ho^{3+} complex has a peak at 1238 cm^{-1} which is seen as a small shoulder on the broad peak at 1181 cm^{-1}. The fact that this same peak is seen the 2 : 1 Nd^{3+} and Eu^{3+} IR spectra (see electronic supplementary information) supports the possibility that a 1 : 1 complex may be present depending on the exact conditions of preparation of the early lanthanide 2 : 1 complexes. The IR spectra of the late lanthanide 2 : 1 complexes (Fig. 2) demonstrate that these metals have no propensity to form 1 : 1 complexes under these conditions.

With a small variation in hydration, the elemental analyses for the 1 : 1 complexes are very consistent. All the complexes appear to have the formulation $[M(H_4ppba)](NO_3)_3Cl\cdot xH_2O$. As expected, the carbon content is much lower than in any of the 2 : 1 complexes, and the nitrogen content is much higher, owing to the lack of a second carbon-rich ligand. The analyses of the Ho^{3+} and Er^{3+} complexes appear to have slightly higher levels of carbon, perhaps because of the preference of the late Ln^{3+} to form 2 : 1 complexes in this system.

Because all the 1 : 1 complexes precipitate as highly insoluble powders, no crystals suitable for an X-ray structural analysis could be obtained. The complexes only have limited solubility, even in solvents such as DMSO; after dissolution they are unrecoverable. Given that the elemental analysis supports the formulation $[M(H_4ppba)]^{4+}$, wherein all four N atoms are protonated, it seems highly unlikely that an encapsulated complex is formed. The $\nu(NO_3)$ in the IR spectra is identical to that of the two structurally characterized 2 : 1 complexes, therefore, it is unlikely that the NO_3^- ligands are coordinated to Ln^{3+} in the 1 : 1 complexes. Given this combined evidence, the most reasonable assumption is that the complexes are monocapped, with 3–5 H_2O molecules completing the coordination sphere.

Reaction of tris(4-(phenylphosphinato)-3-azabutyl)amine ($H_3ppa\cdot HCl\cdot H_2O$) with $Ga(NO_3)_3\cdot 6H_2O$ in methanol at a 1 : 1 molar ratio results in the formation of a finely-divided white precipitate after standing for 48 h. Elemental analysis of this precipitate gives the composition $[Ga(ppa)]\cdot 3H_2O$ (**6**). Clearly, this is a very interesting result because it is possible that an encapsulated 1 : 1 complex has formed. The lack of counterions strongly suggests that the pendant N donors are not protonated NH_2^+, but rather the neutral NH. Unlike the $[M(H_4ppba)]^{4+}$ complexes described previously, the formation of an encapsulated 1 : 1 complex is a distinct possibility. The +LSIMS data support the formulation as 1 : 1; a large peak at *m/z* 675 corresponding to $[Ga(Hppa)]^+$ is seen. Only a trace peak is seen at *m/z* 1285 corresponding to the 2 : 1 complex $[GaH_4(ppa)_2]^+$. In order to investigate further this behavior and to compare the reactivity of lanthanides with H_3ppa, similar reactions were carried out with indium and lanthanide (M = La^{3+}–Yb^{3+}) nitrate salts. A study of the system in 1 : 1 ratios of $M(NO_3)_3$: H_3ppa in methanol was initiated to explore the possibility of 1 : 1 complex formation. These reactions afforded complexes of the type $[M(H_3ppa)]^{3+}$, just as the lanthanide complexes with H_3ppba in good yields (50–83%). Upon mixing of the starting materials, a finely-divided precipitate immediately formed for the indium complex and most of the lanthanides. It was interesting to note that the indium complex with this ligand forms complexes resembling the lanthanides rather than gallium.

Analogous to the 1 : 1 M^{3+} : H_3ppba complexes, the +LSIMS and ESIMS mass spectra of the 1 : 1 M^{3+} H_3ppa complexes show no substantial evidence of 2 : 1 peaks (see ESI†). In some of the complexes, 2 : 1 peaks were observed at trace levels (20× gain). Lanthanide nitrate salts are very hygroscopic and the excess water would not have been accounted for if it were present. With a small variation in hydration, the elemental analyses for the 1 : 1 complexes are very consistent. All the Ln complexes appear to have the formulation $[M(H_3ppa)](NO_3)_3Cl\cdot xH_2O$ whereas the In complex was isolated as $[In(H_3ppa)](NO_3)_3Cl\cdot 2CH_3OH$.

Because all of the In and Ln complexes precipitate as highly insoluble powders, crystals suitable for an X-ray structural analysis could not be obtained. The complexes only have limited solubility, even in solvents such as DMSO; after dissolution they are unrecoverable. Given that the elemental analysis supports the formulation $[M(H_3ppa)]^{3+}$, wherein three of the N atoms are protonated, it seems highly unlikely that an encapsulated complex is formed. The $\nu(NO_3)$ in the IR spectra is identical to that of the two structurally characterized 2 : 1 complexes of these metal ions with H_3ppba, therefore, it is unlikely that the NO_3^- ligands are coordinated to In^{3+} and Ln^{3+} in the 1 : 1 complexes. Given this combined evidence, the most reasonable assumption is that the complexes are monocapped, with 3–5 H_2O molecules (or CH_3OH in case of In) completing the coordination sphere.

The IR spectra of the H_3ppa ligand and the Ga, In and Ln complexes have several notable features. One of the *ν*(PO) bands shifts from 1188 to 1181 cm^{-1} upon complex formation. The band at 954 cm^{-1} in the free ligand disappears completely. Unlike all other complexes with H_3ppa, there is no indication of a free nitrate in the IR spectrum of the gallium complex at *ca.* 1385 cm^{-1}. The broad *ν*(NH) peak shifts from 3414 cm^{-1} in the free uncomplexed ligand to 3421 cm^{-1} in the complexes, which may indicate that the N donors are involved in complex formation. The seemingly unusual strengthening of the N–H bond upon coordination may occur because the N atom is first deprotonated from NH_2^+ to NH, then is subsequently coordinated to Ga^{3+}. Since this is a two-step process, it is difficult to state with absolute certainty that the N donors are coordinated to Ga^{3+} on the basis of IR spectroscopy alone. With respect to the free ligand and the gallium complex, the IR spectra of all other complexes show more distinct features in the fingerprint region.

The ^{31}P NMR spectrum of **6** in methanol is complicated and contains at least seven resonances between 23.7 and 24.9 ppm, shifted downfield from the ligand in which it is seen as a singlet at 21.1 ppm. Unlike the gallium complex, the ^{31}P NMR resonances of In and La complexes shifted upfield to 16.1–19.2 ppm. The ^1H NMR spectra of the complexes and the free ligand demonstrate significant shifts of the CH_2 groups compared to the free ligand. Although the speciation in solution is complicated, the shifts of the pendant CH_2 arms are strongly indicative of pendant N atom coordination to the metal. It is plausible to regard the complex as encapsulated, but in the absence of X-ray structural data, it can not be stated for certain.

Conclusions

In order to obtain 1 : 1 complexes of the group 13 metals Al^{3+}, Ga^{3+}, In^{3+} and the lanthanides, two new amino-phosphinate tripod ligands were synthesized. H_3ppba was synthesized by the Moedritzer–Irani reaction of tris(2-benzylaminoethyl)amine, formaldehyde and phenylphosphinic acid to afford tris(4-(phenylphosphinato)-3-benzyl-3-azabutyl)amine ($H_3ppba\cdot 2HCl\cdot H_2O$) in good yield. The reaction of $H_3ppba\cdot 2HCl\cdot H_2O$ with H_2 at 70 bar with a 10% Pd on C catalyst yielded tris(4-(phenylphosphinato)-3-azabutyl)amine (H_3ppa), a water soluble tripodal aminophosphinate ligand containing three secondary amine functional groups. $H_3ppba\cdot 2HCl\cdot H_2O$ was reacted with Al^{3+}, Ga^{3+}, In^{3+} and Ln^{3+} in 2 : 1 ratios and was found to form bicapped complexes of the type $[M(H_3ppma)_2]^{3+}$ ($M = Al^{3+}$, Ga^{3+}, In^{3+}, Ho^{3+}–Lu^{3+}) or $[M(H_4ppma)_2]^{5+}$ ($M = La^{3+}$–Tb^{3+}). Crystal structures were obtained for $[Ga(H_3ppba)_2]^{3+}$ and $[Gd(H_4ppba)_2]^{5+}$, and a combination of IR spectroscopic, mass spectrometric and elemental analytical data were used to infer the structures of the remaining metal complexes. The bicapped geometry is formed by a pair of ligands coordinating to the metal centre through its phosphinate O atoms only. Either three or four of the nitrogen atoms on each ppba unit are protonated, and an H-bonded network is formed in the empty space of the tripod. 1 : 1 complexes of the type $[M(H_4ppba)_2]^{4+}$ ($M = La^{3+}$–Er^{3+}) were obtained by the reaction of $H_3ppba\cdot 2HCl\cdot H_2O$ and the appropriate metal salts at 1 : 1 molar ratios. Although an X-ray structure was not obtained, the combination of IR spectroscopic, mass spectrometric and elemental analysis data strongly support the formation of a monocapped complex wherein the nitrate counterions are not coordinated to the metal centre. 1 : 1 molar ratios of $H_3ppa\cdot HCl\cdot H_2O$ and $Ga(NO_3)_3\cdot 6H_2O$ in methanol afford the 1 : 1 complex $[Ga(ppa)]\cdot 3H_2O$. Although ^1H and ^{31}P NMR spectroscopies, IR spectroscopy, +LSIMS and elemental analysis support the formation of a 1 : 1 encapsulated complex, the exact nature of the complex can not be ascertained without an X-ray structural analysis. The reaction of $H_3ppa\cdot HCl\cdot H_2O$ with various lanthanides and $In(NO_3)_3$ in a 1 : 1 molar ratio afforded complexes of the type $[M(H_3ppa)]^{3+}$ ($M = In^{3+}$, La^{3+}–Yb^3.

Experimental

Materials

All solvents were of HPLC grade and were obtained from Fisher. When anhydrous solvents were required they were dried using conventional procedures.[23] Ligand syntheses were carried out under Ar; metal complexes were prepared in air and were found to be completely air and moisture stable. HPLC grade methanol (Fisher), tris(2-aminoethyl)amine (W.R. Grace & Co.), benzaldehyde (Aldrich), $NaBH_4$ (Fisher), 37% aqueous formaldehyde (Fisher), concentrated HCl (Fisher), phenylphosphinic acid (Aldrich), 10% Pd on C (Aldrich), and prepurified $H_{2(g)}$ (Praxair) were all obtained from commercial sources and were used without further purification. Tris(2-benzylaminoethyl)amine was synthesized by published methods.[21] All hydrated metal salts were used as received and were obtained from Johnson Matthey.

Instrumentation

Mass spectra were obtained with either a Kratos MS 50 (electron impact ionization, EIMS) or a Kratos Concept II H32Q instrument (Cs^+-LSIMS with positive ion detection). Infrared (IR) spectra in the range 4000–500 cm^{-1} were recorded as KBr disks with a Mattson Galaxy Series 5000 FTIR spectrophotometer. Microanalyses for C, H, N, and Cl were performed by Mr P. Borda in this department. ^1H NMR spectra were recorded on Bruker AC-200E (200 MHz) or Bruker AV-300 (300 MHz) NMR spectrometers with δ referenced downfield from external TMS. $^{13}C\{^1H\}$ NMR spectra were recorded on a Bruker AC-200E (50 MHz) spectrometer with δ referenced downfield from external TMS. $^{31}P\{^1H\}$ NMR spectra were recorded on a Bruker AV-300 (121.5 MHz) NMR spectrometer with δ referenced to external 85% aqueous phosphoric acid. A Parr model 4753 pressure vessel and a model 4316 gauge block assembly equipped with a 140 bar burst plate were used for the hydrogenation reaction.

Preparation of compounds

Tris(4-(phenylphosphinato)-3-benzyl-3-azabutyl)amine, $H_3ppba\cdot 2HCl\cdot H_2O$. Tris(2-benzylaminoethyl)amine (2.0 g, 4.8 mmol) was dissolved in 10 mL methanol. Concentrated HCl (20 mL) was added dropwise, followed by phenylphosphinic acid (2.1 g, 15 mmol). The temperature was raised to reflux; 37% aqueous formaldehyde was added dropwise over a 30 min period, and the reaction was refluxed for a further 5 h. After cooling, acetone was added to the creamy yellow-coloured suspension to precipitate the product completely. The product was recovered by filtration and was recrystallized from boiling ethanol to afford the pure white product (yield = 3.8 g, 81%). Anal. Calc. (found) for $C_{48}H_{57}N_4O_6P_3\cdot 2HCl\cdot H_2O$: C, 59.44 (59.44); H, 6.34 (6.18); N, 5.78 (5.95). (+)LSIMS: m/z 879 ([M + H]$^+$). ^{1}H NMR (CD_3OD, 300 MHz) δ 7.75–7.15 (overlapped multiplets, 30H), 4.45 (s, 6H), 3.63 (s, 6H), 3.39 (s, 12H). ^{31}P NMR (CD_3OD) δ 23.2 (s).

Tris(4-(phenylphosphinato)-3-azabutyl)amine, $H_3ppa\cdot HCl\cdot H_2O$. $H_3ppba\cdot 2HCl\cdot H_2O$ (500 mg, 0.510 mmol) was dissolved in 50 mL methanol, to which 10% Pd on C (300 mg, 0.282 mmol) was added as an ethanol suspension. The mixture was stirred at room temperature and reacted with $H_{2(g)}$ (70 bars, 48 h). The catalyst was removed by filtration on a fine frit, the solvent was removed, and the hygroscopic white product was recrystallized from a hot ethanol–acetone mixture (yield 150 mg, 44%). Anal. Calc. (found) for $C_{27}H_{39}N_4O_6P_3\cdot HCl\cdot H_2O$: C, 48.91 (49.18); H, 6.38 (6.38); N, 8.45 (7.95). (+)LSIMS: $m/z = 609$ ([M + H]$^+$). ^{1}H NMR (CD_3OD, 300 MHz) δ 7.87 (s, 6H), 7.50 (s, 9H), 3.16 (s, 12H), 2.95 (s, 6H). ^{31}P NMR (CD_3OD, 121.5 MHz) δ 21.1 (s).

Synthesis of metal complexes

Detailed procedures are given for representative examples of $[M(H_3ppba)_2]^{3+}$ (M = Al^{3+}, Ga^{3+}, In^{3+}, Ho^{3+}–Lu^{3+}), $[M(H_4ppba)_2]^{5+}$ (M = Ln^{3+}–Tb^{3+}), $[M(H_4ppba)]^{4+}$ (M = La^{3+}–Tm^{3+}) and $[M(H_3ppa)]^{3+}$ (M = La^{3+}–Yb^{3+}, In^{3+}) complexes. Characterization data for all compounds prepared are listed in the ESI.†

General preparative method for the synthesis of $M(H_3ppba)_2]$-$(NO_3)_2Cl\cdot 3CH_3OH$ (M = Ga^{3+}), (1). To a solution of $H_3ppba\cdot 2HCl\cdot H_2O$ (100 mg, 0.103 mmol) in 5 mL CH_3OH was added a solution of $Ga(NO_3)_3\cdot 6H_2O$ (18.7 mg, 0.052 mmol) in 0.5 mL CH_3OH. Upon standing for 48 h at room temperature, colourless prismatic crystals formed, of which one was extracted for X-ray structural analysis. The remaining crystals were recovered by filtration (yield 90 mg, 84%).

General preparative method for the synthesis of $[M(H_4ppba)_2]$-$(NO_3)_4Cl\cdot 3CH_3OH$ (M = Gd^{3+}), (2). To a solution of $H_3ppba\cdot 2HCl\cdot H_2O$ (100 mg, 0.103 mmol) in 5 mL CH_3OH was added a solution of $Gd(NO_3)_3\cdot 6H_2O$ (23.2 mg, 0.0515 mmol) in 0.5 mL CH_3OH. During one week of standing at room temperature, colourless hexagonal plates formed, one of which was extracted for X-ray structural analysis. The remaining crystals were recovered by filtration (yield 15 mg, 13%.).

General preparative method for the synthesis of $[M(H_4ppba)]$-$(NO_3)_3Cl\cdot 3H_2O$ (M = Gd^{3+}), (3). To a solution of $H_3ppba\cdot 2HCl\cdot H_2O$ (100 mg, 0.103 mmol) in 5 mL CH_3OH was added a solution of $Gd(NO_3)_3\cdot 6H_2O$ (46.4 mg, 0.103 mmol) in 0.5 mL CH_3OH. A precipitate immediately formed out of the mixture and a finely-divided white powder was isolated by filtration (yield 45 mg, 33%). The insolubility of the white powder made it impossible to obtain crystals for X-ray structural analysis.

General preparative method for the synthesis of $[M(H_3ppa)]$-$(NO_3)_3Cl\cdot xH_2O$ (M = Eu^{3+}), (4). To a solution of $H_3ppa\cdot HCl\cdot H_2O$ (38 mg, 0.058 mmol) in 5 mL CH_3OH was added a solution of $Eu(NO_3)_3\cdot 6H_2O$ (25.7 mg, 0.058 mmol) in 0.5 mL CH_3OH. A precipitate immediately formed out of the mixture and a finely-divided white powder was isolated by filtration (yield 45 mg, 80%). The insolubility of the white powder made it impossible to obtain crystals for X-ray structural analysis.

$[In(H_3ppa)](NO_3)_3Cl\cdot xH_2O$ (5). To a solution of $H_3ppa\cdot HCl\cdot H_2O$ (47 mg, 0.069 mmol) in 5 mL CH_3OH was added a solution of $In(NO_3)_3\cdot H_2O$ (22 mg, 0.069 mmol) in 0.5 mL CH_3OH. A precipitate immediately formed out of the mixture and a finely-divided white powder was isolated by filtration (yield 46 mg, 71%). The insolubility of the white powder made it impossible to obtain crystals for X-ray structural analysis.

$[Ga(ppa)]\cdot 3H_2O$ (6). To a solution of $H_3ppa\cdot HCl\cdot H_2O$ (50 mg, 0.071 mmol) in 5 mL CH_3OH was added a solution of $Ga(NO_3)_3\cdot 6H_2O$ (25.8 mg, 0.071 mmol) in 0.5 mL CH_3OH. A fine white powder formed over 48 h at room temperature and was isolated by filtration (yield 29 mg, 56%). Anal. Calc. (found) for $C_{27}H_{36}N_4O_6P_3Ga\cdot 3H_2O$: C, 44.47 (44.89); H, 5.80 (5.83); N, 7.68 (7.81). (+)LSIMS: m/z 675 ([M + H]$^+$). The IR spectrum and the ^{1}H and ^{31}P NMR spectra are given in the ESI.†

X-Ray crystallographic analyses of 1 and 2

Please refer to the ESI for experimental details, and for complete tables of bond lengths and bond angles.

Compound 1. $C_{96}H_{114}GaN_8O_{12}P_6$: FW = 1827.49, crystal system: trigonal, space group $R\bar{3}c$, $a = b = 23.9800(7)$, $c = 32.5706(9)$ Å, $\alpha = \beta = 90$, $\gamma = 120°$, $V = 16220.1(8)$ Å^3, $T = 173$ K, $Z = 6$, $\mu = 0.399$ mm^{-1}, total no. of reflections collected = 46807, no. unique reflections = 4271, $R_{int} = 0.031$, R_1 ($I > 2\sigma(I)$) = 0.046, wR_2 (all data) = 0.134.

Compound 2. $C_{96}H_{116}GdN_{12}O_{24}P_6Cl$: FW = 2200.53, crystal system: trigonal, space group = $R\bar{3}$, $a = b = 14.9142(4)$, $c = 44.202(2)$ Å, $\alpha = \beta = 90$, $\gamma = 120°$, $V = 8514.4(5)$ Å^3, $T = 198$ K, $Z = 3$, $\mu = 0.762$ mm^{-1}, total no. of reflections collected = 18646, no. unique reflections = 4368, $R_{int} = 0.045$, R_1 ($I > 2\sigma(I)$) = 0.034, wR_2 (all data) = 0.093.

CCDC reference numbers 275600 and 275601.

See http://dx.doi.org/10.1039/b507905e for crystallographic data in CIF or other electronic format.

Acknowledgements

We thank the Natural Sciences and Engineering Research Council (NSERC) of Canada and DuPont Pharmaceuticals, Inc. for financial support.

References

1 F. Rosch and E. Forssell-Aronsson, *Met. Ions Biol. Syst.*, 2004, **42**, 77.
2 C. J. Anderson and M. J. Welch, *Chem. Rev.*, 1999, **99**, 2219.
3 P. Caravan, J. J. Ellison, T. J. McMurry and R. B. Lauffer, *Chem. Rev.*, 1999, **99**, 2293.
4 M. J. Allen and T. J. Meade, *Met. Ions Biol. Syst.*, 2004, **42**, 1.
5 C. J. Broan, E. Cole, K. J. Jankowski, D. Parker, K. Pulukkody, B. A. Boyce, R. A. B. Nigel, K. Millar and A. T. Millican, *Synthesis*, 1992, 63.
6 E. Cole, R. C. B. Copley, J. A. K. Howard, D. Parker, G. Ferguson, J. F. Gallagher, B. Kaitner, A. Harrison and L. Royle, *J. Chem. Soc., Dalton Trans.*, 1994, 1619.

7 S. Aime, M. Botta, D. Parker and J. A. G. Williams, *J. Chem. Soc., Dalton Trans.*, 1996, 17.
8 E. Huskowska, C. L. Maupin, D. Parker, J. A. G. Williams and J. P. Riehl, *Enantiomer*, 1997, **2**, 381.
9 S. Aime, A. S. Batsanov, M. Botta, R. S. Dickins, S. Faulkner, C. E. Foster, A. Harrison, J. A. K. Howard, J. M. Moloney, T. J. Norman, D. Parker, L. Royle and J. A. G. Williams, *J. Chem. Soc., Dalton Trans.*, 1997, 3623.
10 S. Aime, M. Botta, R. S. Dickins, C. L. Maupin, D. Parker, J. P. Riehl and J. A. G. Williams, *J. Chem. Soc., Dalton Trans.*, 1998, 881.
11 J.-C. G. Bunzli, *Metal Ions Biol. Syst.*, 2004, **42**, 39.
12 J. P. Pulukkody, T. J. Norman, D. Parker, L. Royle and C. J. Broan, *J. Chem. Soc., Perkin Trans. 2*, 1993, 605.
13 S. Aime, A. S. Batsanov, M. Botta, J. A. K. Howard, D. Parker, K. Senanayake and J. A. G. Williams, *Inorg. Chem.*, 1994, **33**, 4696.
14 A. D. Sherry, *J. Alloys Compd.*, 1997, **249**, 153.
15 W. D. Kim, G. E. Kiefer, J. Huskens and A. D. Sherry, *Inorg. Chem.*, 1997, **36**, 4128.
16 S. Liu and D. S. Edwards, *Bioconjugate Chem.*, 2001, **12**, 7.
17 M. P. Lowe, S. J. Rettig and C. Orvig, *J. Am. Chem. Soc.*, 1996, **118**, 10446.
18 P. Caravan, M. P. Lowe, P. W. Read, S. J. Rettig, L. W. Yang and C. Orvig, *J. Alloys Compd.*, 1997, **249**, 49.
19 M. P. Lowe, P. Caravan, S. J. Rettig and C. Orvig, *Inorg. Chem.*, 1998, **37**, 1637.
20 K. Moedritzer and R. R. Irani, *J. Org. Chem.*, 1966, **31**, 1603.
21 A. Naiini, W. M. P. B. Menge and J. G. Verkade, *Inorg. Chem.*, 1991, **30**, 5009.
22 T. W. Greene and P. G. M. Wuts, *Protective Groups in Organic Synthesis*, John Wiley & Sons, Inc., New York, 1999.
23 D. D. Perrin, W. L. F. Armarego and D. R. Perrin, *Purification of Laboratory Chemicals*, Pergamon Press, Oxford,1980.