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Lanthanide complexes of new nonadentate imino-phosphonate ligands derived from 1,4,7-triazacyclononane: synthesis, structural characterisation and NMR studies

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The polyamino ligand 1,4,7-tris(2-aminoethyl)-1,4,7-triazacyclononane (**1**) has been used to synthesise two new ligands by Schiff-base condensation with methyl sodium acetyl phosphonate to give ligand L and methyl sodium 4-methoxybenzoyl phosphonate to give ligand L^1 in the presence of lanthanide ion as templating agent to form the complexes [Ln(L)] and [Ln(L^1)] (Ln = Y, La, Gd, Yb). Both ligands L and L^1 have nine donor atoms comprising three amine and three imine N-donors and three phosphonate O-donors and form Ln(III) complexes in which the three pendant arms of the ligands wrap around the nine-coordinate Ln(III) centres. Complexes with Y(III), La(III), Gd(III) and Yb(III) have been synthesised and the complexes [Y(L)], [Gd(L)] and [Gd(L^1)] have been structurally characterised. In all the complexes the coordination polyhedron about the lanthanide centre is slightly distorted tricapped trigonal prismatic with the two triangular faces of the prism formed by the macrocyclic N-donors and the phosphonate O-donors. Interestingly, given the three chiral phosphorus centres present in [Ln(L)] and [Ln(L^1)] complexes, the three crystal structures reported show the presence of only one diastereomer of the four possible. ^{1}H, ^{13}C and ^{31}P NMR spectroscopic studies on diamagnetic [Y(L)] and [La(L)] and on paramagnetic [Yb(L)] complexes indicate the presence in solution of all the four different diastereomers in varying proportions. The stability of complexes [Y(L)] and [Y(L^1)] in D_2O in both neutral and acidic media, and the relaxivity of the Gd(III) complexes, have also been investigated.

Introduction

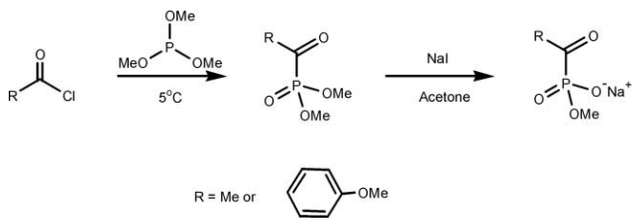
The coordination chemistry of lanthanide ions with functionalised macrocyclic ligands has been widely investigated over the last two decades because of the importance of their medicinal and biochemical applications. For example, Gd(III) complexes have been studied as contrast agents in magnetic resonance imaging,[1–3] ^{90}Y complexes in radioimmunotherapy[4] and Eu and Tb complexes as luminescent probes.[5–8] A number of poly(amino) carboxylate ligands have been studied because of their high selectivity towards lanthanide ions and because of the high thermodynamic stability and kinetic inertness of their complexes.[1–3] In the search for new and effective ligands for the complexation of lanthanide ions, the attachment of phosphonyl pendant arms onto macrocycles such as [9]aneN$_3$[9–11] or [12]aneN$_4$[12–17] has received much attention over recent years. These ligands have been studied not only as analogues of the amino-carboxylate ligands for the application in MRI and in nuclear medicine, but their complexes have also proved to be useful as paramagnetic shift reagents for biological cations having NMR-active nuclei.[2,15,18] Moreover, the presence of P-centres in these ligands allows the measurement by ^{31}P NMR spectroscopy of the intracellular concentrations of metal cations such as Mg(II).[11,14,19,20]

With 1,4,7-triazacyclononane ([9]aneN$_3$) as a macrocyclic core, the addition of pendant arms has led to the formation of hexadentate ligands which form very stable complexes with divalent and trivalent first row transition elements.[21] While 1,4,7-tris(methylenephosphonate)-1,4,7-triazacyclononane (NOTP) appears to form more stable complexes with the lanthanides than does the carboxylate N-functionalised ligand (NOTA),[9,10] the trisubstituted phosphonate monoester derivative of [9]aneN$_3$ (NOTPME) has been used for monitoring the concentration of free Mg(II) in isolated cells, although the complexes are less stable than the triphosphonate analogues ([Ln(NOTP)]).[9,18] Recently, we have reported the coordination properties of a poly(imino)carboxylate ligand derivative of [9]aneN$_3$ towards lanthanide ions (L^2, Scheme 2).[22,23] We report herein the synthesis of two new poly(imino)phosphonate ligands (L and L^1) by Schiff-base condensation of a polyamine derivative of [9]aneN$_3$ with two different alkylphosphonate monoesters in the presence of Ln(III) ion as templating agent. Methyl sodium acetyl phosphonate and methyl sodium 4-methoxybenzoyl phosphonate were the ketones used to synthesise L and L^1, respectively. L and L^1 are [9]aneN$_3$ derivatives where the arms have been extended to obtain a set of nine donor atoms: they are, therefore, capable of fully encapsulating the Ln(III) centre. The synthesis of nine-coordinate Ln(III) complexes [Ln(L)] (Ln = Y, La, Gd, Yb) and [Ln(L^1)] (Ln = Y, Gd) together with the crystal structures of [Y(L)], [Gd(L)] and [Gd(L^1)] and the NMR spectra of all the complexes except the Gd(III) ones are described. The hydrolysis of the imine bonds of [Y(L)] and [Y(L^1)] complexes in D_2O in both neutral and acidic media and the relaxivity of the Gd(III) complexes have also been assessed.

Results and discussion

Synthesis of the complexes [Ln(L)] and [Ln(L^1)]

Sodium alkylphosphonates were synthesised *via* a modified procedure first described by Karaman *et al.*[24] (Scheme 1). Dimethyl alkylphosphonates were synthesised by slow addition of trimethyl phosphite to the relevant acid chloride and purified by distillation under reduced pressure. Reaction of the dimethyl phosphonate in dry acetone with NaI affords the mono-sodium



Scheme 1 Synthesis of sodium phosphonate monoesters.

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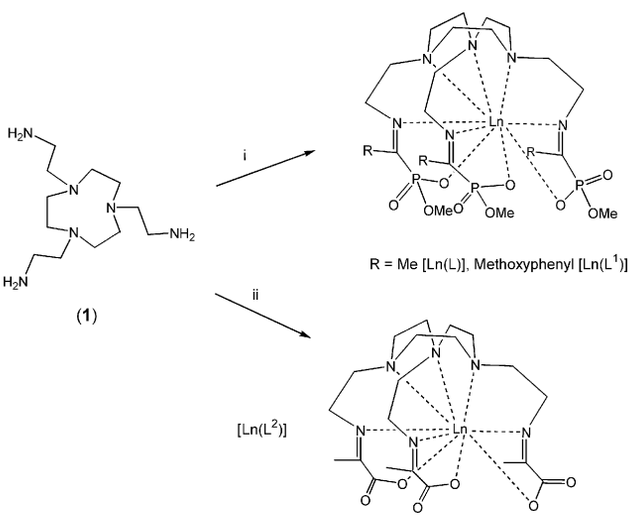
salt as an insoluble precipitate in good yield and high purity. The synthetic scheme shown in Scheme 1 was employed for two different acid chlorides for R = methyl and methoxyphenyl.

The synthesis of the complexes [Ln(L)] (Ln = Y, Gd, Yb, La) and [Ln(L^1)] (Ln = Y, Gd) was achieved by Schiff-base condensation of 1,4,7-tris(2-aminoethyl)-1,4,7-triazacyclononane (**1**) with methyl sodium acetyl phosphonate and methyl sodium 4-methoxybenzoyl phosphonate, respectively, using Ln(III) ion as templating agent (Scheme 2). Reaction of one equivalent of **1**, one equivalent of the Ln(III) salt and three equivalents of the appropriate sodium phosphonate monoester in MeOH for 2 h, followed by precipitation of the product by addition of Et_2O, affords the desired complexes [Ln(L)] and [Ln(L^1)] as white solids. Elemental analysis and mass spectra for all the complexes are consistent with the formulations [Y(L)]·2CH_3OH, [Ln(L)]·3NaCl·nH_2O and [Ln(L^1)]·3NaCl·nH_2O (n = 1, 2 or 3).



Scheme 2 Synthetic scheme for the preparation of complexes [Ln(L)], [Ln(L^1)] and [Ln(L^2)]. Reagents and conditions: i, 3 RCOP(OMe)-OONa, LnX, MeOH, 2 h (R = methyl or methoxyphenyl); ii, 3 MeCOCOONa, LnX, MeOH 2 h.

Structural characterisation of [Ln(L)] and [Gd(L^1)]·0.5CH_3OH

Single-crystals of the complexes [Ln(L)] (Ln = Y, Gd) and [Gd(L^1)]·0.5CH_3OH were obtained by adding a ten-fold excess of Et_2O into a solution of the complexes in MeOH at room temperature. The cloudy solution formed was left to stand for two days and single crystals were obtained. Single-crystal X-ray diffraction studies confirm that in the structures [Y(L)]·CH_3OH, [Gd(L)]·1.5CH_3OH·H_2O and [Gd(L^1)]·0.5CH_3OH the lanthanide metal is nine-coordinate, using all nine donor atoms of the ligands, namely the three amino N-donors of the macrocycle, the three imino N-donors and the three phosphonate O-donors. The complexes [Ln(L)] are isostructural and the bond lengths are in the ranges 2.659(3)–2.698(5) Å for the bonds between the metal and the macrocyclic N-donors, 2.591(3)–2.684(5) Å for the bonds to the N-donors of the imine moieties and 2.289(3)–2.357(4) Å to the phosphonate O-donors (Table 1). The bond lengths between Y(III) and the donor atoms are shorter than the Gd(III)–N and Gd(III)–O bond lengths, as expected, given the different effective ionic radii for the two ions: 1.11 Å for Gd^{3+} and 1.07 Å for Y^{3+} (values are for the nine-coordinate ions).[25] Two different views of the crystal structure of [Gd(L)], as an example of the isostructural [Ln(L)] complexes, are shown in Fig. 1(a) and (b). There is a high degree of planarity in the fragments C(2)–O(7) of the pendant arms in the two structures due to the conjugation between the imine and phosphonate groups, with the mean deviation from the least squares mean plane being only 0.009–0.049 Å. As already observed for the imino-carboxylate complexes [Ln(L^2)],[22,23] the difference in the opening of the three arms can be seen by looking at the pitch angle between the plane of the macrocycle and the plane of each phosphonate. The average of the three pitch angles is 41.3° for [Y(L)] and 43.0° for [Gd(L)], values that are smaller than those observed for the [Ln(L^2)] complexes (50.6° for [Gd(L^2)] and 49.6° for [Y(L^2)]).[22,23] The coordination geometry about the lanthanide centre is a slightly distorted tricapped trigonal prism (Fig. 2) as observed for the complexes [Ln(L^2)] with the macrocyclic N-donors and the phosphonate oxygens forming the two triangular faces and the imine N-centres capping the three rectangular faces of the prism. The upper and lower triangular faces of the prism are essentially equilateral (angle range 57.4–61.8°) and parallel (the angle between the plane defined by the triangle of three O-donors and the one defined by the three N-donors is 3.4°), but the oxygen triangular faces are always slightly twisted around the three-fold axis

Table 1 Selected bond lengths (Å) in the crystal structures of [Y(L)]·CH_3OH and [Gd(L)]·1.5CH_3OH·H_2O

	[Y(L)]	[Gd(L)]
Ln–N(1)	2.659(3)	2.680(5)
Ln–N(4)	2.667(3)	2.698(5)
Ln–N(7)	2.680(3)	2.669(5)
Ln–N(3A)	2.591(3)	2.684(5)
Ln–N(3B)	2.618(3)	2.663(5)
Ln–N(3C)	2.656(3)	2.684(5)
Ln–O(7A)	2.292(2)	2.336(4)
Ln–O(7B)	2.289(3)	2.336(4)
Ln–O(7C)	2.292(3)	2.357(4)

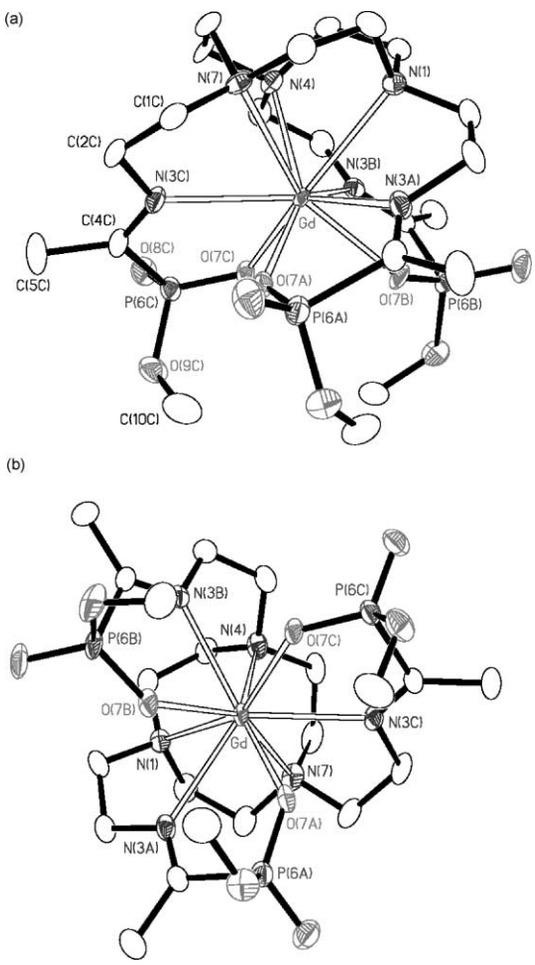


Fig. 1 (a) Ellipsoid plot of [Gd(L)] with numbering scheme adopted. Hydrogen atoms and solvent molecules have been omitted for clarity. Displacement ellipsoids are drawn at 50% probability. (b) View of the crystal structure of [Gd(L)] along the non-crystallographic three-fold axis.

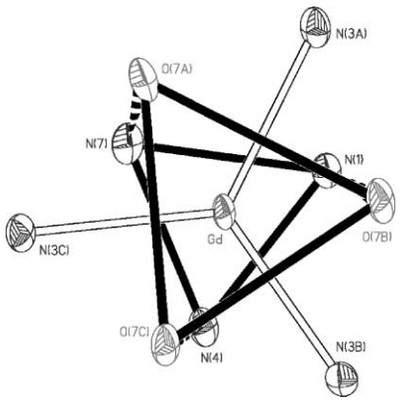


Fig. 2 Coordination geometry about the metal centre in [Gd(L)].

compared to the nitrogen triangular faces. The twist between the two triangular faces can be quantified by looking at the torsion angles formed by the four atoms of every rectangular face of the prism. In [Y(L)] the average of the three torsion angles (one for every triangular side) is 16.9° and in [Gd(L)] it is 18.4°; therefore the distortion from the trigonal prismatic geometry is more evident as the size of the encapsulated ion increases. The distortion observed for the complexes [Ln(L^2)] is more pronounced with values for the Y(III) and Gd(III) complexes of 20.2 and 21.4°, respectively.[22,23]

In [Gd(L^1)]·0.5CH_3OH (Fig. 3) the nine-coordinate Gd(III) ion shows bond lengths in the ranges 2.641(13)–2.696(13) Å for the bonds between the Gd(III) and the macrocyclic N-donors, 2.619(14)–2.701(13) Å for the bonds to the N-donors of the imine moieties, and 2.303(11)–2.350(13) Å for those to the phosphonate O-donors (Table 2). In [Gd(L^1)]·0.5CH_3OH the fragments C(2)–O(6) and C(10) are almost planar due to conjugation between the imine and phosphonate groups, with the mean deviation from the least squares mean plane being only 0.020–0.067 Å. The pitch angles between the plane of the macrocycle and the plane of each phosphonate characterise the opening of the three arms: the average of the three pitch angles for [Gd(L^1)] is 43.7°, very similar to the one observed for [Gd(L)]. Also, the methoxybenzene fragments are planar (mean deviation of 0.018–0.047 Å) and almost perpendicular to the plane formed by the imino-phosphonate fragments (79.6–106.8°). The coordination geometry about the Gd(III) centre is again slightly distorted tricapped trigonal prismatic. The macrocyclic N-donors and the phosphonate oxygens impose

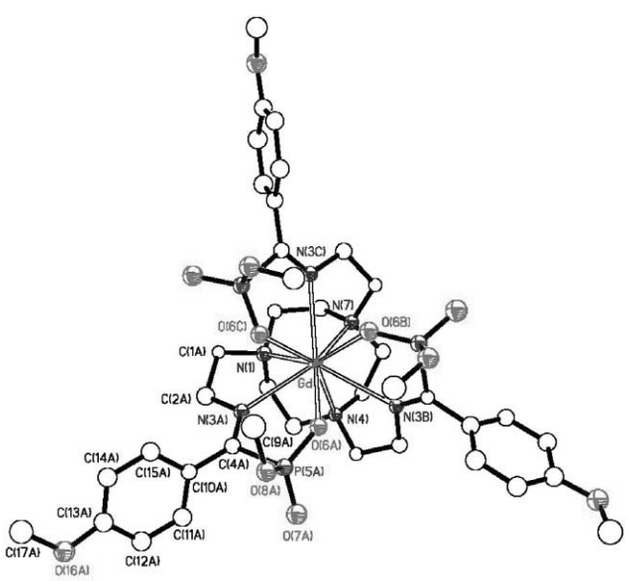


Fig. 3 Crystal structure of [Gd(L^1)]·0.5CH_3OH with numbering scheme adopted. Hydrogen atoms and CH_3OH molecules have been omitted for clarity.

Table 2 Selected bond lengths (Å) for [Gd(L^1)]·0.5CH_3OH

Gd–N(1)	2.643(14)	Gd–N(3C)	2.652(13)
Gd–N(4)	2.696(13)	Gd–O(6A)	2.303(11)
Gd–N(7)	2.641(13)	Gd–O(6B)	2.350(13)
Gd–N(3A)	2.619(14)	Gd–O(6C)	2.334(11)
Gd–N(3B)	2.701(13)		

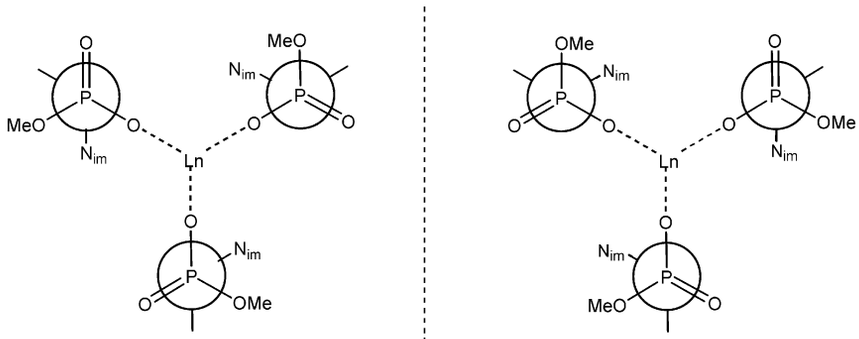
the two triangular faces and the imine nitrogens cap the three rectangular faces of the prism. The upper and lower triangular faces of the prism are essentially equilateral (angle range 59.0–60.6°) and parallel (the angle between the plane defined by the triangle of three oxygen donors and that defined by the three nitrogen donors is 1°), but the nitrogen triangular face is slightly twisted around the three-fold axis relative to the oxygen triangular face by an angle of 17.5°, quite similar to that of [Gd(L)].

NMR spectroscopic studies

Phosphinate and phosphonate monoester donors have the advantage of a possible structural variation by changing the –R or –OR group on the P-centre, and this can allow control of lipophilicity of the complexes. However, the introduction of an alkyl or alkoxy functionality on phosphorus causes the formation of chiral centres on binding to a metal cation. Several studies have been reported on Ln(III) complexes containing chiral phosphorus centres and NMR spectra with multiple resonances have been discussed.[1,16,17] Thus, Ln(III) complexes of cyclen derivatives show the presence of two slowly interconverting diastereomers in solution due to clockwise (Δ) and counter-clockwise (Λ) rotation of the cyclododecane ring conformation as well as rotation of the methylene groups in the pendant arms (λ and δ).[26] In addition to this isomerism, phosphinate and phosphonate ester lanthanide complexes of cyclen derivatives have an asymmetric centre at each phosphorus with possible *R* or *S* configuration. From ^{19}F NMR spectroscopic studies Sherry and co-workers have observed[17] the sixteen possible ^{19}F resonances due to six different diastereomers [Δ(*RRRR*), Δ(*RRRS*), Δ(*RRSS*), Δ(*RSRS*), Δ(*RSSS*) and Δ(*SSSS*)] in the spectra of paramagnetic complexes with a fluorinated ester analogue of DOTP. An analogous study by Lukes and co-workers on the tetra(phenyl)-phosphinic acid derivative of cyclen (DOTPP) showed[16] that the orientation of the phosphinic groups in the solid state is (*RSRS*), but the ^{31}P NMR spectrum of the Lu(III) complex in solution again shows sixteen resonances due to the six diastereomers mentioned above.

Since nine-coordinate lanthanide complexes such as [Ln(L)] and [Ln(L^1)] contain three chiral phosphorus centres, four possible diastereomers, each of them with two enantiomers, can be distinguished. The three crystal structures [Y(L)]·CH_3OH, [Gd(L)]·1.5CH_3OH·H_2O and [Gd(L^1)]·0.5CH_3OH show the presence of only one diastereomer, the (*RRR*)/(*SSS*) (Scheme 3). The other three diastereomers, (*RRS*)/(*RSS*), (*RSS*)/(*RRS*) and (*RSR*)/(*SRS*), do not crystallise, probably because they comprise only small fractions of the complexes present in solution. Interestingly, this result differs from what is observed in the X-ray crystal structure of the Y(III) complex with the ligand obtained by Schiff-base condensation of tris(2-aminoethyl)amine with three molar equivalents of methyl sodium acetyl phosphonate.[27] This complex structure shows the formation of a heptanuclear cluster containing four eight-coordinate Y(III) and three Na^+ centres, with the presence of only the (*RRS*)/(*RSS*) diastereomer.[27] This is possibly due to the formation of aggregates with one phosphonate group bound also to a metal centre of an adjacent molecule, resulting in complexes which are less symmetric than [Ln(L)] and [Ln(L^1)].

NMR spectroscopic studies were carried out in order to determine whether the four different diastereomers present in solution could be distinguished. The ^1H NMR spectrum of



Scheme 3 (*RRR*)/(*SSS*) pair of enantiomers in [Ln(L)] and [Ln(L^1)] complexes.

Table 3 ^{1}H NMR chemical shifts (ppm) for the major isomer in the paramagnetic [Yb(L)] complex

	δ/ppm		δ/ppm
H_{3a}	43.4	H_{3e}	7.6
H_{4e}	22.3	H_{1e}	−12.4
H_{4a}	15.1	H_{2e}	−13.6
H_{Me1}	10.4	H_{Me2}	−16.7
H_{1a}	9.1	H_{2a}	−37.7

[Yb(L)] (300 MHz, 298 K, D_2O) has turned out to be particularly useful because the peaks are shifted over an expanded spectral region due to the paramagnetic shift allowing minor isomers to be detected. The ^{1}H NMR spectrum of [Yb(L)], shown in Fig. 4, shows ten resonances shifted in a range between 43.4 and – 37.7 ppm corresponding to the major isomer, each of them surrounded by three smaller peaks in a ratio of about 70 : 10 : 10 : 10. The resonances of the major isomeric form were assigned with the help of a 2D COSY experiment and are reported in Table 3. Since all the single crystals obtained from solution of [Ln(L)] and [Ln(L^1)] complexes show the presence of only the (*RRR*)/(*SSS*) diastereomer, there is a strong possibility that the major component in solution, which gives the highest peaks in the ^{1}H NMR spectrum, is the (*RRR*)/(*SSS*) diastereomer.

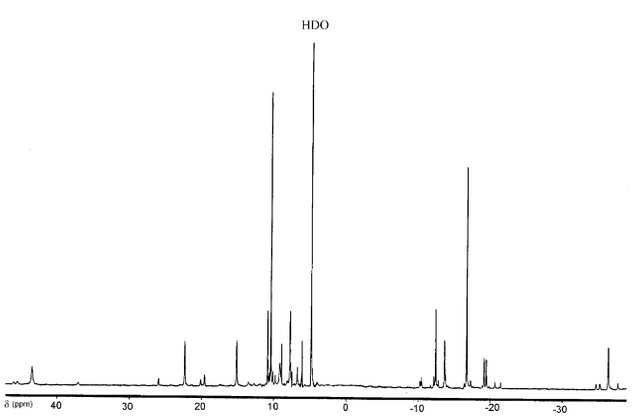


Fig. 4 ^{1}H NMR spectra of paramagnetic [Yb(L)] in D_2O at 298 K.

Further NMR spectroscopic studies were performed on Y(III) complexes of L and L^1 and on [La(L)] and compared with the studies on [Ln(L^2)].[22] The ^{1}H NMR spectra of [Y(L)] and [La(L)] show a very similar splitting pattern (Fig. 6) with a complex series of multiplets and of doublets of doublets. A 2D-COSY experiment combined with a ^{1}H–^{13}C coupling 2D experiment allowed accurate assignment of the resonances (Table 4, see Fig. 5 for labelling scheme). The ^{1}H NMR signals for [Y(L)] and [La(L)] are broader than those observed for [Ln(L^2)], and the coupling constants could only be determined for the macrocyclic protons and for the methyl groups coupled to phosphorus. The ethylenic moiety of the macrocycle shows a

Table 4 ^{1}H NMR chemical shifts (ppm) for diamagnetic [Y(L)] and [La(L)]

	[Y(L)]	[La(L)]
H_{Me1}	2.08	2.19
H_{1e}	2.53	2.58
H_{1a}	2.66	2.77
H_{3a}	2.80	2.78
H_{2e}	2.88	2.92
H_{2a}	3.33	3.44
H_{3e}	3.36	3.48
H_{Me2}	3.56	3.64
H_4 (ax. and eq.)	3.75	3.82

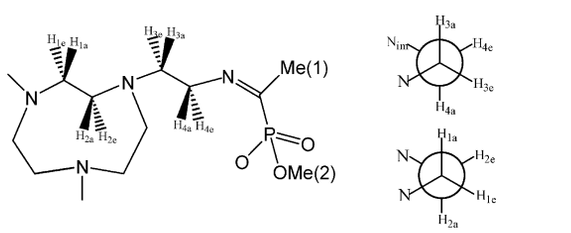


Fig. 5 (a) Labelling scheme for the phosphonate group, for the CH_2CH_2 linkers of the macrocycle and the arms and (b) their Newman projections.

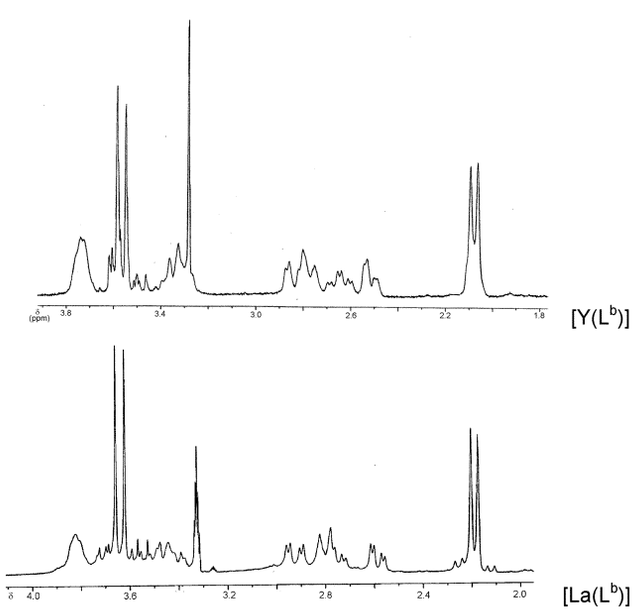


Fig. 6 ^{1}H NMR spectra of [Y(L)] (above) and [La(L)] (below) at 298 K in D_2O and CD_3OD, respectively.

series of multiplets, and the 2D-COSY experiment allowed us to assign the equatorial proton at 2.53 ppm as geminal to the axial proton at 2.66 ppm (and H_{eq} at 2.88 geminal to H_{ax} at 3.33 ppm). Only one geminal coupling constant between axial and equatorial protons of the same CH_2 group could be observed

Table 5 ^{13}C NMR chemical shifts (ppm) for [Y(L)] and [Y(L^1)]

	[Y(L)]	[Y(L^1)]
$CH_3C{=}N$	16.7	—
$CH_2N{=}C$	51.1	36.1
NCH_2 (arm)	52.9	50.8
NCH_2 (ring)	57.6	49.5
CH_3OP	48.2	55.5
CH_3OAr	—	54.0
C(Ar)	—	113.6, 114.4, 114.7, 127.8, 131.0, 132.3
C=N	175.2	160.7

(13.0 Hz) and the *trans* coupling constants between axial and equatorial protons of adjacent CH_2 groups are 4.6 and 4.8 Hz. The H–P coupling constants are 9.1 Hz for [Y(L)] (8.6 Hz for [La(L)]) for the methyl group next to the imine bond (H_{Me1}) and 9.7 Hz for [Y(L)] (11.1 Hz for [La(L)]) for the methyl of the methoxy group (H_{Me2}). In the ^{1}H NMR spectrum of [La(L)] (recorded in CD_3OD), the equatorial proton at 2.58 ppm assigned to the ethylenic moiety of the macrocycle is geminal to the axial proton at 2.77 ppm (J_{gem} = 13.1 Hz) and H_{eq} at 2.92 geminal to H_{ax} at 3.44 ppm (J_{gem} = 16.3 Hz). The *trans* (eq–ax) coupling constants between the CH_2 groups of the ethylenic moiety of the macrocycle are 4.1 and 4.6 Hz, respectively. While the ^{1}H NMR spectrum of [Y(L)] does not clearly show the presence of different isomers, the ^{1}H NMR spectrum of [La(L)] provides evidence of the presence of two minor isomers near the doublet at 2.19 ppm corresponding to H_{Me1} (Fig. 6). In contrast, only in the ^{31}P NMR spectrum of [Y(L)] can more than one peak corresponding to the other diastereomers be observed, while the ^{31}P NMR spectrum of [La(L)] shows only one singlet at 14.5 ppm. The ^{31}P NMR spectrum of [Y(L)] (Fig. 7) shows one dominant doublet at 14.67 ppm which results from the H–P coupling (J_{HP} = 8.8 Hz) and three minor doublets (one of them overlapped at 14.74) at 14.51 and 13.75 ppm (J_{HP} = 8.9 and 8.6 Hz, respectively) corresponding to the three minor diastereomers. The ^{13}C NMR spectrum of [Y(L)] (75.5 MHz, 298 K, D_2O) shows the expected signals which are assigned with the help of a ^{1}H–^{13}C coupling experiment and reported in Table 5. Interestingly, the coupling constant between ^{13}C and ^{31}P observed in this spectrum is quite large: the carbon resonance at 175.2 ppm, assigned to the imine carbon, appears as a doublet with J_{CP} of 187.4 Hz and the carbons of the two methyl groups, one next to the imine carbon and the other one of the methoxy group, appear as two doublets with J_{CP} of 23.4 and 22.9 Hz, respectively.

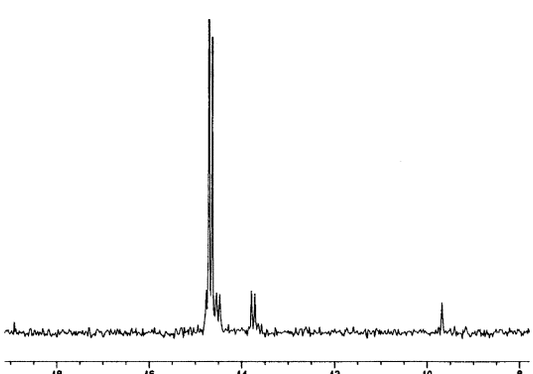
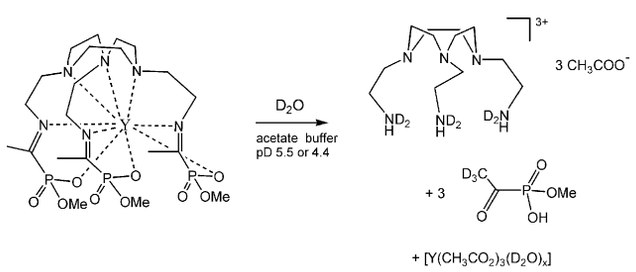


Fig. 7 ^{31}P NMR spectrum of [Y(L)] in D_2O at 298 K.

The ^{1}H NMR spectrum of [Y(L^1)] (300 MHz, 298 K, D_2O) is not as clear as the spectra described above, all the CH_2 groups next to the N-atoms giving a broad multiplet between 2.73 and 3.88 ppm; the methyl group of the methoxybenzene unit gives a singlet at 3.91 ppm and the methoxy group on the phosphorus forms a doublet at 3.57 ppm (J_{HP} = 12.0 Hz). The proton on the benzene ring gives two doublets at 7.17 and 7.51 ppm (J_{HH} = 8.5 and 8.6 Hz, respectively). The expected resonances in the ^{13}C NMR spectrum of [Y(L^1)] are reported in Table 5. The ^{31}P NMR spectrum of the same complex again shows a coupling between ^{1}H and ^{31}P, for the major isomer at 11.7 ppm (J_{HP} = 9.1 Hz) and for the other three isomers at 11.5, 10.7 and 9.7 ppm, with coupling constants of 8.9, 8.5 and 8.8 Hz, respectively.

Hydrolysis experiments

In previous work we have studied the possibility of using lanthanide complexes of the ligand obtained by Schiff-base condensation of tren with sodium pyruvate in the targeting of *in vivo* regions of low pH by exploiting the instability of the C=N bonds at acidic pH.[28] As observed in the hydrolysis studies carried out on the complex [La(L^2)], [Y(L)] was found to be stable in D_2O at neutral pH. Hydrolysis experiments were carried out at acidic pH to determine the hydrolysis rate of the imine bonds in this complex. The hydrolysis of [Y(L)] was investigated in two separately buffered solutions at pD = 4.4 and 5.5 (acetate buffer). In both cases the hydrolysis was complete in less than 2 h. Therefore, it appears that [Y(L)] is much less stable under acidic conditions than [La(L^2)] where hydrolysis is only complete after 100 h.[23] The products of the hydrolysis of [Y(L)] are the protonated ligand $[H_3L]^{3+}$, $[Y(D_2O)_x]^{3+}$ and only one phosphorus-containing product (presumably the methyl acetylphosphonic acid) as confirmed by ^{31}P NMR spectroscopy (Scheme 4). The relatively low stability under acidic conditions of these phosphonate monoester complexes may be due to ineffective conjugation between the imine and the phosphonate group in [Y(L)] compared to the imine and carboxylate groups in [La(L^2)]. This explanation is supported by quantum mechanical calculations on dimethyl-benzoyl phosphonate which show a very low energy barrier to rotation about the C–P bond.[24] Confirmation of the low stability of phosphonate monoester complexes comes from the complex [Y(L^1)] which was found to be unstable in D_2O at neutral pH and at room temperature. The imine bond hydrolyses completely within five days and the course of the hydrolysis could not be interpreted quantitatively by ^{1}H or ^{31}P NMR because of the complexity of the spectra. Indeed, the products of the hydrolysis are not only the amine L, the free lanthanide ion and the starting methoxybenzoyl phosphonate, but also another product present in both the ^{1}H and ^{31}P NMR spectra, which could be identified as methoxybenzyl phosphonate coordinated to Y(III).



Scheme 4 Scheme showing the hydrolysis of [Y(L)] in D_2O at pD 5.5 and 4.4.

Relaxivity of [Gd(L)]·3NaCl·3H_2O and [Gd(L^1)]·3NaCl·3H_2O

Relaxivities of [Gd(L)]·3NaCl·3H_2O and of [Gd(L^1)]·3NaCl·3H_2O at 300 MHz and 37°C were measured as 1.64 ± 0.08 and 1.54 ± 0.08 mM^{-1} s^{-1}, respectively. These values, only slightly higher than the value of 1.26 (5) mM^{-1} s^{-1} observed for the imino-carboxylate analogue [Gd(L^2)],[23] suggest that no water molecules are bound to the Gd(III) centres and only the second-sphere and outer-sphere terms contribute to the relaxivity. Furthermore, the X-ray crystal structure determination confirmed that [Gd(L)] and [Gd(L^1)] have no water molecule coordinated to the paramagnetic metal centre and this feature of the structure is likely to be maintained in solution.

Conclusions

Two new ligands have been formed by metal template Schiff-base condensation of a macrocyclic triamine with methyl sodium acetyl phosphonate to give ligand L and methyl sodium 4-methoxybenzoyl phosphonate to give ligand L^1. The complexes [Y(L)], [Gd(L)] and [Gd(L^1)] show slightly distorted tricapped trigonal prismatic geometry with the two triangular faces of the prism formed by the macrocyclic N-donors and the phosphonate O-donors. Interestingly, given the three chiral phosphorus centres present in [Ln(L)] and [Ln(L^1)] complexes, the three crystal structures reported show the presence of only one diastereomer of the four possible, although ^{1}H, ^{13}C and ^{31}P NMR spectroscopic indicate the presence in solution of all the four different diastereomers in varying proportions. The complexes [Y(L)] and [Y(L^1)] in D_2O are relatively unstable in both neutral and acidic media, and relaxivity of the Gd(III) complexes confirm only second- and outer-sphere term contributions.

Experimental

Spectra were recorded on a Bruker DPX 300 spectrometer (^{1}H and ^{13}C NMR) or on a Perkin-Elmer 1600 spectrometer (FTIR, KBr discs). Elemental analytical data were obtained by the Microanalytical Service (Perkin-Elmer 240B analyser) at the University of Nottingham. FAB (Fast Atom Bombardment) mass spectra were obtained by the EPSRC National Mass Spectrometry Service at the University of Swansea. 1,4,7-Tris(2-aminoethyl)-1,4,7-triazacyclononane (**1**)[22] and methyl sodium acetyl phosphonate[24] were prepared as described in the literature. All starting materials were obtained from Aldrich Chemical Co. and were used without further purification.

Synthesis of [Y(L)] and [Gd(L)]

1,4,7-Tris(aminoethyl)-1,4,7-triazacyclononane (**1**) (22.2 mg, 0.086 mmol) dissolved in MeOH (10 cm^3) was added to a solution of methyl sodium acetyl phosphonate (41.3 mg, 0.258 mmol) and the appropriate Ln(III) chloride in MeOH (30 cm^3). The resulting colourless solution was heated under reflux for 2 h. After cooling, the solvent volume was reduced, Et_2O was added and a white solid was obtained. The solid was filtered off and dried under reduced pressure. Single crystals suitable for X-ray structural analysis were obtained from a Et_2O–MeOH (10 : 1) solution of the complex at room temperature.

[Y(L)]·2CH$_3$OH. Obtained 46.8 mg of crystalline material, 0.061 mmol, yield 70.9%. Mass spectrum (FAB, glycerol–MeOH–H_2O matrix) *m*/*z* 727 (M^+ [$C_{21}H_{42}N_6O_9P_3Y$ + Na^+]). Elemental analysis: found (calc. for $C_{21}H_{42}N_6O_9P_3Y$·2CH_3OH): C, 36.07 (35.95); H, 6.64 (6.56); N, 10.68% (10.94%). IR (KBr disk), cm^{-1}: 2940w, 2854w, 1637s ($\nu_{C=N,\ C=O}$), 1458w, 1212m, 1075m, 785m, 553m.

[Gd(L)]·3NaCl·3H$_2$O. Obtained 47.2 mg, 0.047 mmol, yield 54.8%. Mass spectrum (FAB, glycerol–MeOH–H_2O matrix) *m*/*z* 796 (M^+ [$C_{21}H_{42}N_6O_9P_3Gd$ + Na^+]) Elemental analysis: found (calc. for $C_{21}H_{42}N_6O_9P_3Gd$·3NaCl·3H_2O) C, 25.32 (25.17); H, 4.95 (4.83); N, 8.48% (8.39%). IR (KBr disk), cm^{-1}: 2949w, 2852m, 1629s ($\nu_{C=N,\ C=O}$), 1473w, 1359w, 1208s, 1110m, 1071s, 783m, 588m.

Synthesis of [Yb(L)] and [La(L)]

A solution of 1,4,7-tris(aminoethyl)-1,4,7-triazacyclononane (**1**) (0.20 mmol) in MeOH (10 cm^3) was added to 3 molar equivalents of methyl sodium acetyl phosphonate and the appropriate $LnCl_3$ dissolved in MeOH (30 cm^3). The resulting colourless solution was heated under reflux for 2 h. After cooling, the solvent volume was reduced, Et_2O was added and a white solid was obtained. The solid was filtered off and dried *in vacuo*.

[Yb(L)]·3NaCl·3H$_2$O. Obtained 140.5 mg, 0.138 mmol, yield 68.9%. Mass spectrum (FAB, glycerol–MeOH–H_2O matrix) *m*/*z* 812 (M^+ [$C_{21}H_{42}N_6O_9P_3Yb$ + Na^+]). Elemental analysis: found (calc. for $C_{21}H_{42}N_6O_9P_3Yb$·3NaCl·3H_2O): C, 24.88 (24.78); H, 4.91 (4.75); N, 8.40% (8.26%). IR (KBr disk), cm^{-1}: 2952w, 2918w, 2852w, 1634s ($\nu_{C=N,\ C=O}$), 1475w, 1360w, 1216s, 1111m, 1076s, 784m, 763m, 551m.

[La(L)]·3NaCl·3H$_2$O. Obtained 139.6 mg, 0.142 mmol, yield 70.8%. Mass spectrum (FAB, 3-NOBA matrix) *m*/*z* 777 (M^+ [$C_{21}H_{33}N_6O_9P_3La$ + Na^+]). Elemental analysis: found (calc. for $C_{21}H_{42}N_6O_9P_3La$·3NaCl·3H_2O): C, 25.81 (25.64); H, 4.90 (4.92); N, 8.41% (8.54%). IR (KBr disk), cm^{-1}: 2959m, 2928m, 2857w, 1628s ($\nu_{C=N,\ C=O}$), 1465m, 1382m, 1285s, 1226m, 1068m, 1033m, 793m, 640m.

Synthesis of methyl sodium 4-methoxybenzoyl phosphonate

Methyl sodium 4-methoxybenzoyl phosphonate was synthesised using a modified procedure of that described by Karaman *et al.*[24] Thus trimethyl phosphite (12.79 g, 0.1 mol) was added dropwise to *p*-anisoyl chloride (17.23 g, 0.1 mol) at 25 °C. During the addition of trimethyl phosphite, the mixture was cooled to 5 °C with an ice-bath. After this addition, the cooling bath was removed and the solution was left to stir at ambient temperature for 12 h affording a pale yellow solution which was purified by vacuum distillation to produce dimethyl 4-methoxybenzoyl phosphonate (10.05 g, 47.6 mmol, yield 48%). ^{1}H NMR ($CDCl_3$): δ 3.84 (6H, t, $P(OCH_3)_2$), 3.87 (3H, d, 4-CH_3O), 6.92 (2H, d, $(CH)_2C$=O), 8.21 (2H, d, $(CH)_2$COMe) ppm. ^{13}P NMR ($CDCl_3$): δ 0.21 (sept) ppm. ^{13}C NMR ($CDCl_3$): δ 54.04 ($P(OCH_3)_2$), 55.65 (CH_3C), 114.28 ($(CH)_2CC$=O), 129.48 (CC=O), 132.51 ($MeOC(CH)_2$), 165.14 (COMe), 195.88 (C=O) ppm. A solution of sodium iodide (7.14 g, 47.6 mmol) in dry acetone (32 cm^3) was added to a solution of dimethyl 4-methoxybenzoyl phosphonate (10.05 g, 47.6 mmol) in dry acetone (50 cm^3). The solution was left to stir for 12 h to produce a milky solution, which was filtered, washed with dry acetone and dried under vacuum to produce the desired product as an off-white solid (6.59 g, 55%). ^{1}H NMR (D_2O): δ 3.65 (3H, d, $POCH_3$), 3.88 (3H, s, $COCH_3$), 7.06 (2H, d, $C(CH)_2$), 8.17 (2H, d, $MeOC(CH)_2$) ppm. ^{31}P NMR (D_2O): δ 2.81 (s) ppm. ^{13}C NMR (D_2O): δ 53.17 ($P(OCH_3)$), 55.87 (CH_3C), 114.44 ($(CH)_2CC$=O), 129.43 (CC=O), 132.31 ($MeOC(CH)_2$), 164.49 (COMe), 206.02 (C=O) ppm. Mass spectrum (FAB, 3-NOBA matrix): *m*/*z* 275 (M^+ [$(C_9H_{10}O_5PNa)$ + $Na]^+$), 526 [$(C_9H_{10}O_5PNa)_2$ + $Na]^+$, 778 [$(C_9H_{10}O_5PNa)_3$ + $Na]^+$, 1031 [$(C_9H_{10}O_5PNa)_4$ + $Na]^+$. IR (KBr disc): 2947w, 1602s, 1256s, 1089s, 1060s, 834m, 762w, 557m cm^{-1}.

Synthesis of [Y(L^1)] and [Gd(L^1)]

1,4,7-Tris(aminoethyl)-1,4,7-triazacyclononane (**1**) (0.20 mmol) dissolved in MeOH (10 cm^3) was added to a solution of methyl sodium 4-methoxybenzoyl phosphonate (3 molar equivalents) and the appropriate $LnCl_3$ in MeOH (30 cm^3). The resulting colourless solution was heated under reflux for 2 h. After cooling, the solvent volume was reduced and, by addition of Et_2O, a white solid was obtained. The solid was filtered off and dried *in vacuo*.

[Y(L^1)]·3NaCl·3H$_2$O. Obtained 164.1 mg, 0.136 mmol, yield 67.8%. Mass spectrum (FAB, 3-NOBA matrix) *m*/*z* 1004 (M^+ [$C_{39}H_{54}N_6O_{12}P_3Y$ + Na^+]). Elemental analysis: found (calc. for $C_{39}H_{54}N_6O_{12}P_3Y$·3NaCl·3$H_2O$): C, 38.44 (38.71); H, 5.16 (5.00); N, 7.08% (6.95%). IR (KBr disk), cm^{-1}: 2954w, 2848w, 1606s ($\nu_{C=N,\ C=O}$), 1509s, 1456m, 1418w, 1299m, 1253m, 1211s, 1082s, 1052s, 785m, 560m.

Table 6 Details of single crystal structure determinations on [Y(L)]·CH_3OH, [Gd(L)]·1.5CH_3OH·H_2O and [Gd(L^1)]·0.5CH_3OH

Compound	[Y(L)]·CH_3OH	[Gd(L)]·1.5CH_3OH·H_2O	[Gd(L^1)]·0.5CH_3OH
Formula	$C_{21}H_{42}N_6O_9P_3Y$·CH_3OH	$C_{21}H_{42}N_6O_9P_3Gd$·1.5CH_3OH·H_2O	$C_{39}H_{54}N_6O_9P_3Gd$·0.5CH_3OH
M/g mol^{-1}	736.47	838.84	1065.06
Crystal system	Orthorhombic	Monoclinic	Monoclinic
Space group	$Pna2_1$	$P2_1/n$	$P2_1/c$
a/Å	13.590(2)	16.129(2)	22.570(3)
b/Å	13.071(2)	10.9177(14)	11.0602(13)
c/Å	17.506(3)	20.047(3)	19.798(2)
β/°	90	106.462(2)	111.791(2)
U/Å^3	3109.7(8)	3385(4)	4505(2)
T/K	150(2)	150(2)	150(2)
Z	4	4	4
D_c/g cm^{-3}	1.573	1.646	1.570
μ(Mo-Kα)/ mm^{-1}	2.091	2.164	1.646
Unique reflections, R_{int} [a]	7072, 0.068	5910, 0.076	7726, 0.078
Observed reflections [$F_o \geq 4\sigma(F_o)$]	4514	4747	5923
R_1, wR_2	0.0395, 0.0565	0.0383, 0.0896	0.111, 0.234
Flack parameter	0.007(4)	—	—

[a] Following absorption corrections.

[Gd(L^1)]·3NaCl·3H_2O. Obtained 190.4 mg, 0.149 mmol, yield 74.5%. Single crystals suitable for X-ray structural analysis were obtained from a Et_2O–MeOH (10 : 1) solution of the complex at room temperature. Mass spectrum (FAB, 3-NOBA matrix) m/z 1072 (M^+ [$C_{39}H_{54}N_6O_{12}P_3Gd$ + Na^+]) Elemental analysis: found (calc. for $C_{39}H_{54}N_6O_{12}P_3Gd$·3NaCl·3$H_2O$): C, 37.05 (36.64); H, 4.85 (4.73); N, 6.81% (6.57%). IR (KBr disk), cm^{-1}: 2953w, 2850m, 1634s ($\nu_{C=N,\ C=O}$), 1505m, 1370w, 1255s, 1213m, 1090m, 1052s, 779m, 561m.

Hydrolysis experiments

Buffer solutions at pD 5.5 and at pD 4.4 were formulated using the following general procedure: potassium acetate (0.10 g) and acetic acid (0.28 cm^3) (0.32 cm^3 for the buffer at pD 4.4) were dissolved in D_2O (5 cm^3). The pH of the buffer solution was measured, and the pD was calculated using the formula pD = $pH_{measured}$ + 0.4. Two samples of [Y(L)]·2CH_3OH (5.6 and 5.2 mg, respectively) were dissolved in the two acidic buffer solutions (0.6 cm^3) at pD 4.4 and 5.5. The resulting clear solutions were transferred into an NMR tube and the ^{1}H NMR spectra were acquired at time intervals (t/h). Both the hydrolyses occurred in less than two hours and no quantitative measurement on the integrals was carried out. [Y(L^1)]·3NaCl·3H_2O (5.0 mg) was dissolved in D_2O (0.6 cm^3) and the resulting clear solution was transferred into an NMR tube and the ^{1}H NMR spectra were acquired at time intervals (t/h). In this case the course of the hydrolysis could not be followed easily because of the complexity of the ^{1}H NMR spectra.

Relaxivities of [Gd(L)] and [Gd(L^1)]

Five samples of [Gd(L)]·3NaCl·3H_2O and of [Gd(L^1)]·3NaCl·3H_2O were weighed and dissolved in 0.70 cm^3 of D_2O before transferring into an NMR tube. The transverse relaxation times (T_1) of the HDO peak at 4.707 ppm were measured using a 180–τ–90 pulse sequence at 37 °C with a Bruker 300 MHz NMR spectrometer. For [Gd(L^1)], which was found to hydrolyse slowly in D_2O, the delay between dissolving the sample in D_2O and completing the T_1 measurement was less than 15 min, a time interval over which hydrolysis of the complex is thought to be minimal. Plots of T_1^{-1}/s^{-1} against concentration of [Gd(L)] and of [Gd(L^1)]/mM give appropriate straight lines with correlation coefficients of 0.994 and 0.995, respectively. The intercept with the y axis is the relaxation rate (T_1^{-1} = 0.058 s^{-1}) of the HDO peak without the presence of the paramagnetic metal complex (concentration = 0). The relaxivities for the two complexes were calculated from the gradient of the two graphs as 1.64 ± 0.08 mM^{-1} s^{-1} for [Gd(L)] and 1.54 ± 0.08 mM^{-1} s^{-1} for [Gd(L^1)].

Crystal structure determinations

Crystal data, data collection and refinement details for compounds [Ln(L)] [Ln = Y(III) and Gd(III)] and [Gd(L^1)] are given in Table 6, with selected bond lengths in Tables 1 and 2. Data for [Y(L)]·CH_3OH and [Gd(L)]·1.5CH_3OH·H_2O and [Gd(L^1)]·0.5CH_3OH were collected on a Bruker SMART1000 CCD area detector diffractometer equipped with a low-temperature device, using graphite-monochromated Mo-Kα radiation (λ = 0.71073 Å). Multi-scan absorption corrections were applied. For [Gd(L)]·1.5CH_3OH·H_2O data were also corrected for absorption using the program XABS.[29] All the structures were solved by direct methods,[30] apart from [Gd(L)]·1.5CH_3OH·H_2O which was solved using the heavy atom method,[30] and completed by iterative cycles of ΔF syntheses and full-matrix least-squares refinement.[31] All the non-H atoms, except those in disordered groups, were refined anisotropically. The crystal structure of [Gd(L^1)]·0.5CH_3OH was not refined as a fully anisotropic model. Only the Gd atom could be refined anisotropically: attempts to extend this to lighter atoms led to their displacement parameters assuming large or physically impossible values, and even the application of rigid-bond restraints did not overcome these problems. We attribute this failure to severe limitations in the quality of the available crystals. Despite these difficulties the structure of the complex is clear and unambiguous.

In all the structures, the H atoms on MeOH molecules were placed from ΔF syntheses and refined as part of a rigid rotating group. All the other H atoms were placed in calculated positions and refined using a riding model. In [Gd(L)]·1.5CH_3OH·H_2O, H atoms on the disordered H_2O molecule and on one partly occupied MeOH molecule were omitted. The disordered H_2O molecule was modelled using partial occupancy models over two sites (occupancy factors 0.70 and 0.30). Appropriate restraints to bond distances were applied in all the disordered molecules. In all the structures the largest residual electron density features lay near the heavy atom.

CCDC reference numbers 234542–234544.

See http://www.rsc.org/suppdata/dt/b4/b404425h/ for crystallographic data in CIF or other electronic format.

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