Nuclear Magnetic Resonance Studies of Neutral Lanthanide(III) Complexes with Tetraaza-macrocyclic Ligands containing Three Phosphinate and One Carboxamide Co-ordinating Arms

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Novel, neutral Eu^{III}, Gd^{III} and Yb^{III} complexes have been obtained with tetraaza-macrocyclic ligands containing three phosphinate and one carboxamide co-ordinating arms. The overall results are consistent with a co-ordination geometry based on the octadenticity of these ligands. Among the possible 16 enantiomeric pairs one is largely dominant as ascertained by the high resolution ^{1}H, ^{13}C and ^{31}P NMR spectra of the Eu^{III} and Yb^{III} complexes. Partial assignment of ^{1}H and ^{13}C resonances was possible for one Eu^{III} complex on the basis of homo- and hetero-correlated two-dimensional NMR experiments. The evaluation of the Curie contribution to the longitudinal relaxation rates of the ^{31}P resonances has provided a route to the determination of the Yb–P distances. The addition of the chiral solvating agent β-cyclodextrin to a solution of the Yb^{III} complex containing benzylic substituents on the amido nitrogen allowed the chiral resolution of an enantiomeric pair by ^{31}P NMR spectroscopy. The measurement of water proton longitudinal relaxation rates of solutions of the Gd^{III} complexes indicated that these chelates have one inner-sphere co-ordinated water molecule whereas the parent tetraphosphinate complexes have none.

There is an active search for neutral Gd^{III} complexes of high thermodynamic and kinetic stability which may be used as low-osmolality contrast agents for magnetic resonance imaging (MRI). This aspect is particularly important for those new applications of MRI which require administration of high doses of contrast agent. Initially, this target was pursued by Quay and co-workers[1,2] by considering the bis(methylamide) derivative of *N*,*N*,*N*′,*N*″,*N*″-diethylenetriaminepentaacetic acid. This ligand acts as an octadentate ligand and forms charge neutral complexes with Ln^{III} (Ln = lanthanide) ions. However, some concern exists because of the relatively low stability constants of the resulting Ln^{III} complexes, which has resulted in the need to co-administer the complex, for *in vivo* use, with 5% of the labile calcium complex. An alternative route to neutral complexes involved substituting one acetate arm in the 1,4,7,10-tetraazacyclododecane-*N*,*N*′,*N*″,*N*‴-tetraacetic acid (H_4dota) ligand by a pendant group bearing an alcoholic[3] or carboxamido[4] functionality as a donor group towards the Ln^{III} ion. These Ln^{III} complexes have been shown to maintain essentially the same high kinetic stability as the parent complexes of H_4dota.

We have recently reported[5] our investigations on tetra-(methylphosphinate) and -(benzylphosphinate)–[12]aneN_4 ([12]aneN_4 = 1,4,7,10-tetraazacyclododecane) macrocyclic ligands and their complexes with Y, Gd, Eu and Yb. Surprisingly, a hydration number $q = 0$ was found for these anionic complexes both in the solid state (*i.e.* a crystal structure of the yttrium benzylphosphinate complex) and in solution (luminescence studies on Eu complexes and relaxometric data for the aqueous solutions of the Gd complexes). We thought that the substitution of one phosphinate arm for a carboxamido group in the tetra(methylphosphinate) macrocyclic ligand might allow three features to be studied: (*i*) the generation of neutral Ln^{III} complexes of potential use as low osmolality contrast agents for MRI; (*ii*) the favourable approach of one water molecule to the paramagnetic centre by releasing the steric encumbrance of the four phosphinate groups in the parent complex; (*iii*) the modulation of the lipophilicity of the complexes through an appropriate choice of the substituents on the amido nitrogen directed away from the co-ordination cage. This in turn may enhance the non-covalent binding ability of the complexes with a variety of substrates.

To this purpose we have prepared the Ln^{III} complexes of the ligands L^1–L^3.[6,7] In this paper we report the results obtained from the high-resolution ^{1}H, ^{13}C and ^{31}P NMR spectra of the Eu^{III} and Yb^{III} complexes and from the relaxometric measurement of the aqueous solution of the Gd^{III} derivatives.

Results and Discussion

Solution NMR Studies.—A representative set of ^{1}H, ^{13}C and ^{31}P NMR spectra for the Eu^{III} and Yb^{III} complexes with H_3L^2 are shown in Figs. 1 and 2. The corresponding spectra for the complexes of these metal ions with H_3L^1 and H_3L^3 do not differ markedly from those in Figs. 1 and 2, apart from the obvious differences related to the change of the substituents on the amide functionality. From the ^{31}P NMR spectra of all the six complexes it is immediately apparent that there is just one main set of three, equally intense resonances which indicates the occurrence of one, largely dominant isomer (with diastereotopic P nuclei) among several possibilities.

Before analysing the experimental results it is useful to discuss schematically what might be expected in terms of the number of isomers in solution, their spectral multiplicity and their possible interconversion processes. All of the salient structural and dynamic features of Ln^{III} complexes with H_3L^1–H_3L^3 can be drawn from preliminary considerations with H_4dota, the simplest of the octadentate macrocyclic ligands.[8–10]

A schematic representation of the solid-state square-

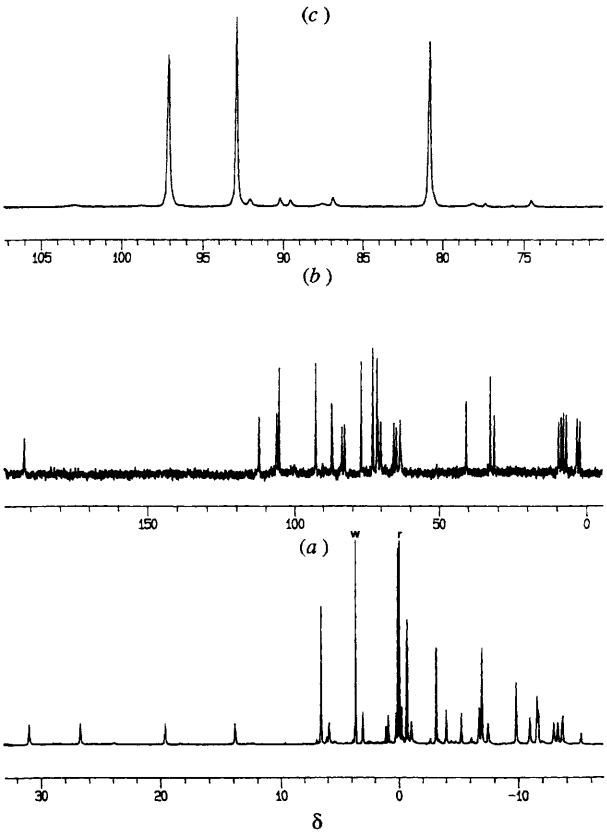
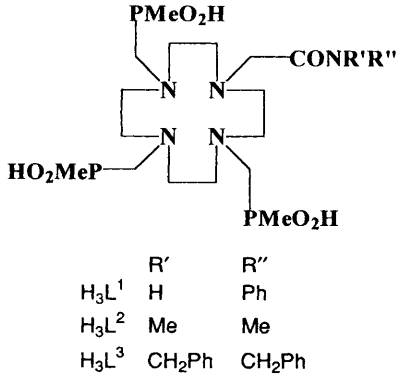


Fig. 1 The ^{1}H (*a*), ^{13}C-{^{1}H} (*b*) and ^{31}P-{^{1}H} (*c*) NMR spectra (298 K, D_2O, 9.4 T) of the Eu–L^2 complex. The labels **w** and **r** indicate the solvent and Bu^{t}OH (1%, internal reference) peaks, respectively



	R′	R″
H_3L^1	H	Ph
H_3L^2	Me	Me
H_3L^3	CH_2Ph	CH_2Ph

antiprismatic structure of $[Ln(dota)]^-$ complexes is shown in Fig. 3 (structure **A**). The inverted square-antiprismatic geometry of the second isomer present in the aqueous solution can be obtained either through a concerted rotation of the acetate arms (Fig. 3, **B**) or through an inversion of configuration of the macrocyclic ring by keeping the acetate groups fixed in their positions (Fig. 3, **C**). These axially symmetric complexes **B** and **C** are enantiomers and therefore are not distinguishable in their NMR spectra. The concomitant occurrence of both acetate group rotation and ring inversion leads to another square-antiprismatic structure (**D**), which is the mirror image of **A**. Finally, in the NMR spectra each enantiomeric pair is characterized by: (*a*) six distinct resonances in the low-temperature limiting proton spectrum, corresponding to four ring protons and two acetate protons; (*b*) four resonances in the carbon spectrum, corresponding to two ethylenediamine carbons, one methylenic and one carboxylate carbon.

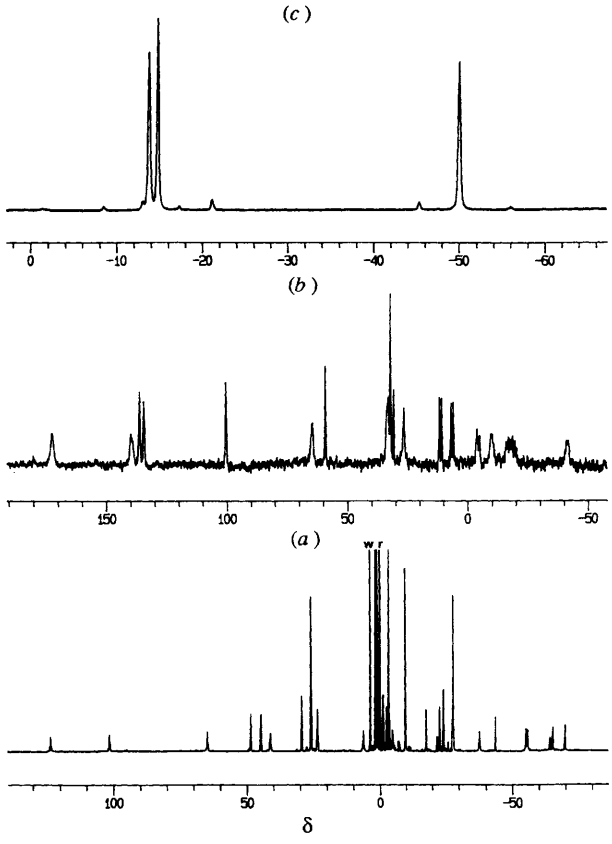


Fig. 2 The ^{1}H (*a*), ^{13}C-{^{1}H} (*b*) and ^{31}P-{^{1}H} (*c*) NMR spectra (298 K, D_2O, 9.4 T) of the Yb–L^2 complex. Labels as for Fig. 1

The neutral lanthanide(III) chelates considered in this work represent a much more complicated case since: (*i*) the three phosphorus atoms of the ligands engender three chiral centers in the complexes and from this the possible existence of eight stereoisomers follows; (*ii*) each stereoisomer may adopt, in principle, one of the two structural arrangements depicted in Fig. 3 as **A** and **B** (or **D** and **C**) and therefore the number of stereoisomers is raised to 16; (*iii*) moreover, the presence of chiral centres makes the structural pairs **A**/**D** and **B**/**C** no longer enantiomeric and thus the number of possible isomers has to be doubled, to give a total number of 32! (*iv*) the lack of axial symmetry removes the signal degeneracy in the NMR spectra and separate signals for each P, C and H atom of the ligands are to be expected, with a resulting considerable spectral complication.

A scheme of the 32 possible stereoisomers divided into eight main groups corresponding to the eight possible combinations of the configurations for the three chiral centres is given in Fig. 4. Within each group there are four isomers corresponding to the four structural models **A**–**D** in Fig. 3. The arrows connect 16 enantiometric pairs. Figs. 5–8 show the schematic structures for the 16 diastereoisomers of the groups **1**–**4**, divided according to the co-ordination geometries **A**, **B**, **C** and **D**, respectively.

As anticipated above in solution, fortunately, one diastereoisomer predominates, although NMR signals from four other minor species are clearly detectable in the ^{31}P NMR spectra. The high complexity of the proton (16 peaks for the ring protons, eight peaks for the methylenic protons of the side arms, three methyl signals and the resonances associated with the N-substituents) and carbon NMR spectra precludes any sound structural inference from the analysis of the data. However, by simply considering steric factors it might be suggested that the most probable isomer in solution has a structure that minimizes the repulsive steric interactions within these bulky ligands. From this point of view structures **1D**/**8A**

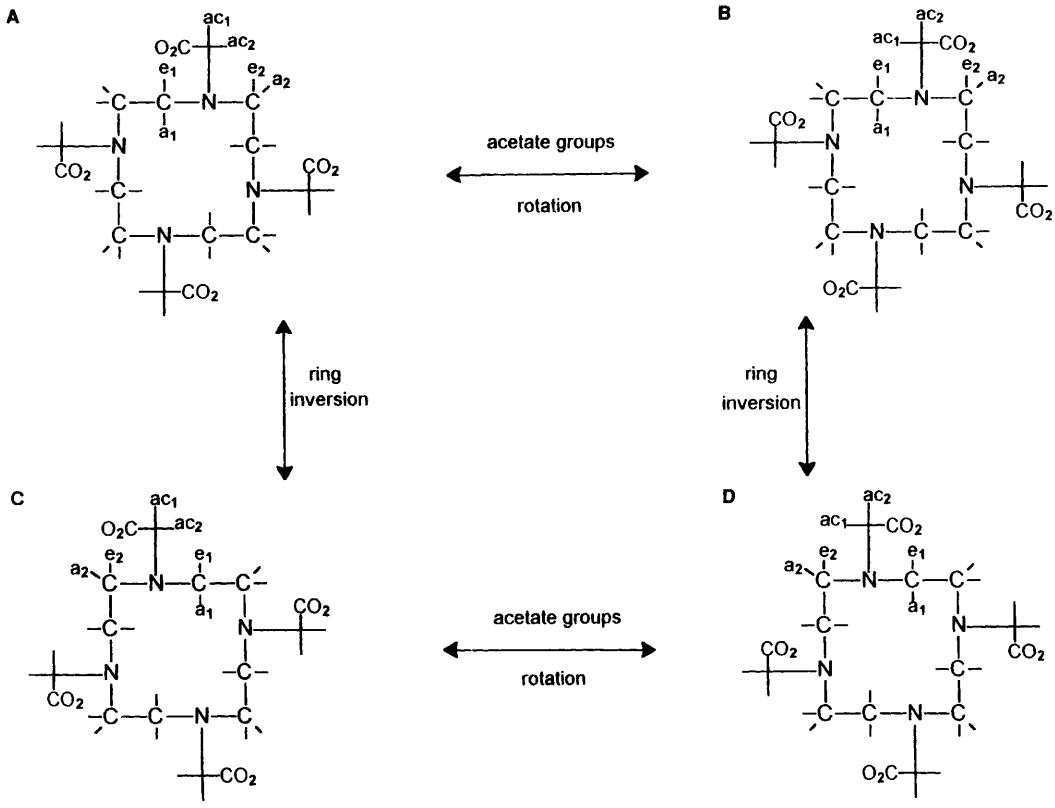


Fig. 3 Schematic representation of the two co-ordination geometries adopted by Ln–dota complexes in solution and their interconversion paths

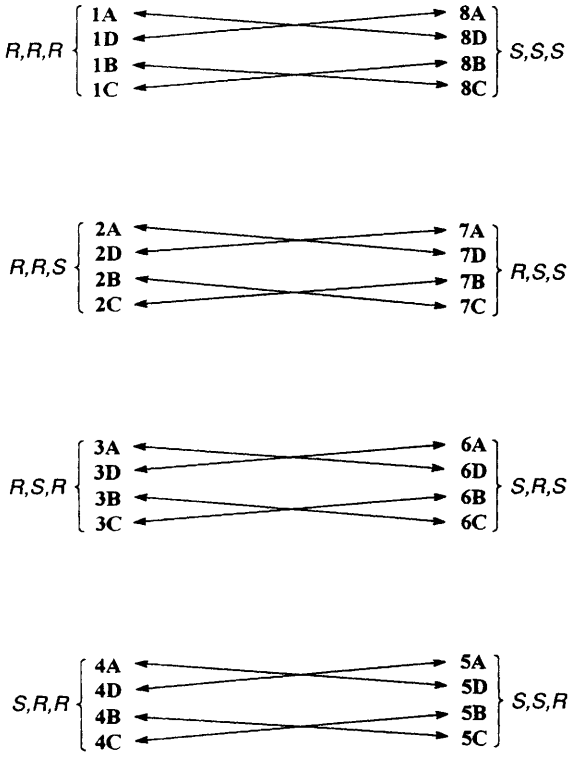


Fig. 4 Symbolic representation of the 32 possible stereoisomers for the Ln^{III} complexes with H_3L^1–H_3L^3. The arrows connect enantiomeric pairs

and **1B**/**8C** (*R*,*R*,*R* or *S*,*S*,*S* at phosphorus), where the P-methyl groups are directed outside the co-ordination cage, should represent the best candidates. Since a single species is predominant, it follows that one of the two basic co-ordination geometries is favoured and, as found for the tetra(benzylphosphinate) complexes,[5] we think that it is the inverted square antiprism,[8–10] *i.e.* the enantiomeric pair **1B**/**8C**.

The variable-temperature ^1H and ^{31}P NMR spectra indicate that an exchange process involving the different isomers takes place in the range 293–363 K. There are two distinct possibilities: (1) if the Ln–O bonds are inert, then the exchange can only occur among the members of each subset (*R*,*R*,*R*; *R*,*R*,*S*; . . .) through a sliding motion of the acetate arms or configuration inversion of the ring, as depicted in Fig. 3; (2) if the Ln–O bonds are labile, then through a bond-breaking and reforming process the exchange may involve all the possible isomers.

The experimental data, owing to the very low concentration of the minor species and the high spectral complexity, do not enable a clear distinction between the two cases. Nevertheless, data accumulated over the last few years on structurally related complexes are indicative of kinetically *inert* Ln–O bonds,[9,11,12] so that the pathways depicted in Fig. 3 are more likely.

Whereas it appears to be very difficult to establish unambiguously the structure of the isomeric species present in solution, a partial assignment of the proton and carbon NMR spectra for the major diastereoisomer was accomplished for the Eu^{III} complexes. It is well known that Eu^{III} complexes are particularly suitable for high resolution NMR investigation since they combine the expanded chemical shift range, typical of paramagnetic compounds, with a limited line broadening. In fact, as shown in Fig. 9(*a*), in the low magnetic field (90 MHz) ^1H NMR spectrum of the Eu complex with H_3L^2 the multiplets are clearly detectable. The spectrum consists of eight triplets, attributable to the eight axial protons of the macrocyclic ring, a number of doublets corresponding to the eight equatorial protons of the ring and to the methylenic protons (actually some of them appear as triplets due to the P coupling) of the side arms, three doublets of relative intensity 3 corresponding to

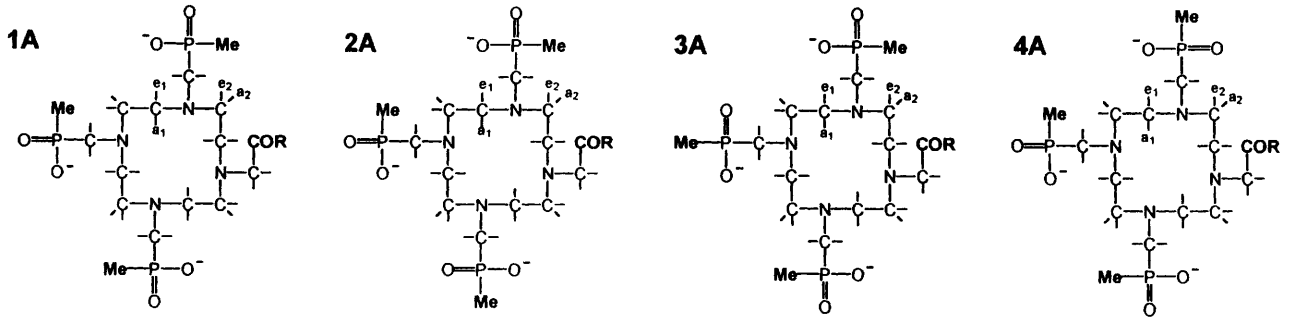


Fig. 5 Schematic representation of the four distinct stereoisomers characterized by an **A**-type structural model

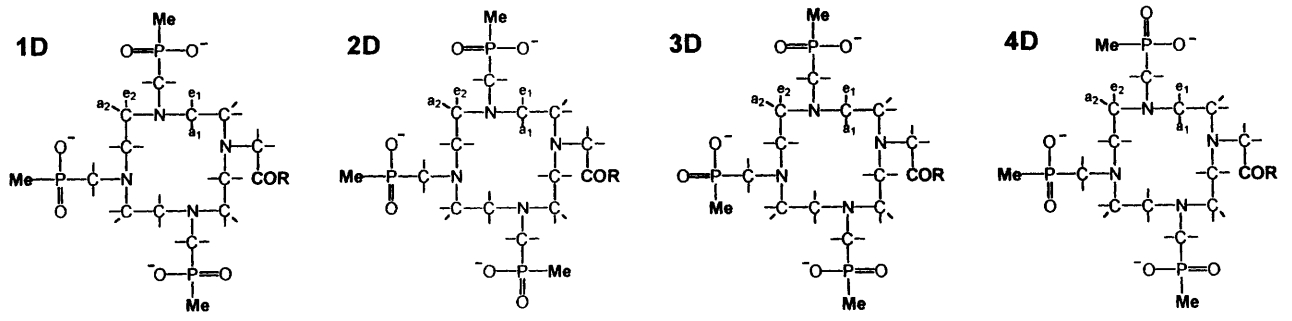


Fig. 6 Schematic representation of the four distinct stereoisomers characterized by a **D**-type structural model

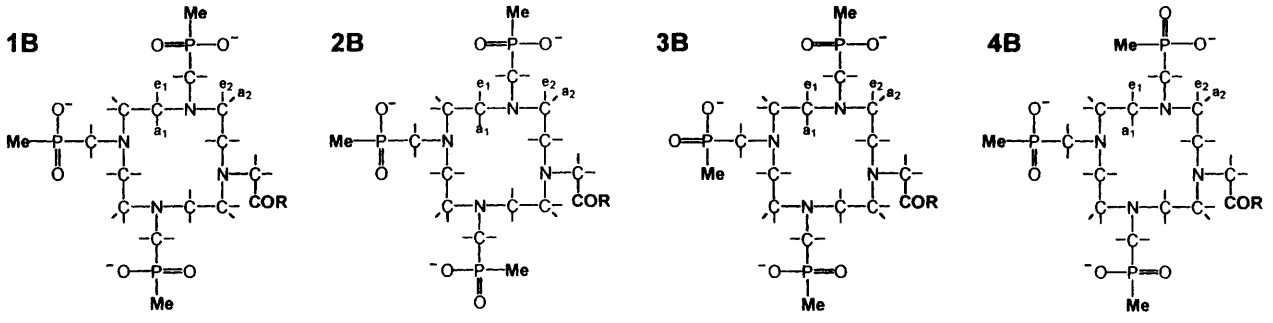


Fig. 7 Schematic representation of the four distinct stereoisomers characterized by a **B**-type structural model

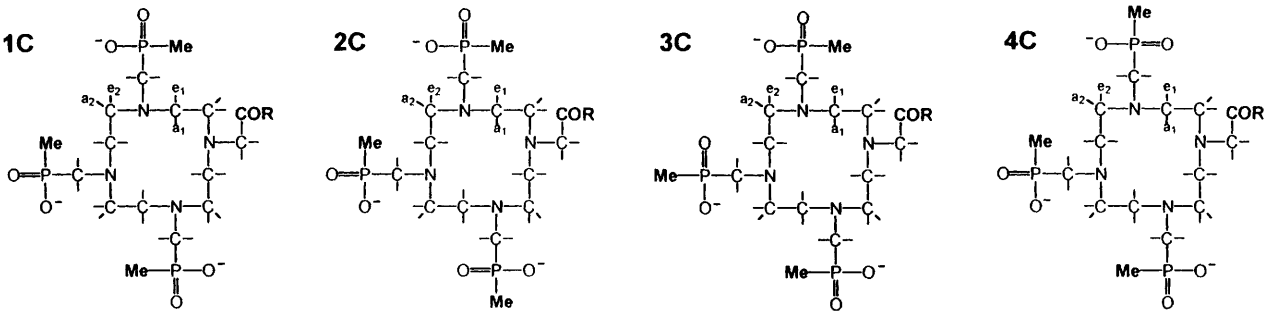


Fig. 8 Schematic representation of the four distinct stereoisomers characterized by a **C**-type structural model

the P-coupled methyl groups and two singlets (at δ 6.4 and −0.1) for the NMe_2 functionality. The two isotropically shifted resonances for the N-methyl groups unambiguously indicate that the carboxamido group is firmly bound to the lanthanide(III) ion. Each axial proton is coupled to an equatorial and to another axial proton of the same ethylenediamine group. A homonuclear two-dimensional correlation spectroscopy (COSY) experiment (Fig. 10) recorded at room temperature and at the same magnetic field strength enabled us to draw the proton connectivities and then to assign the resonances within each of the four ethylenediamine groups. A heteronuclear C–H COSY experiment, recorded at 9.4 T, confirmed the above proton assignments and also allowed the attribution of the carbon resonances.

The analysis of the NMR data of the Yb^{III} complex is more difficult because the resonances are affected by a much shorter T_2 value and as a consequence neither coupling patterns in the one-dimensional spectra nor a complete set of crosspeaks in the two-dimensional experiments were detected. Only a rough assignment of the proton spectrum was undertaken on the basis of the analogy with corresponding spectra for structurally related complexes with H_4dota[8,9] and its tetraphosphonate[13] and tetra(benzylphosphinate)[5] analogues. This direct comparison is possible for the Yb^{III} complexes because the paramagnetic shifts are essentially 'pseudo-contact' in origin and therefore may be strictly related to the polar coordinates of the nuclei. Very similar results, as expected, were obtained for the other complexes, to show that changing the N

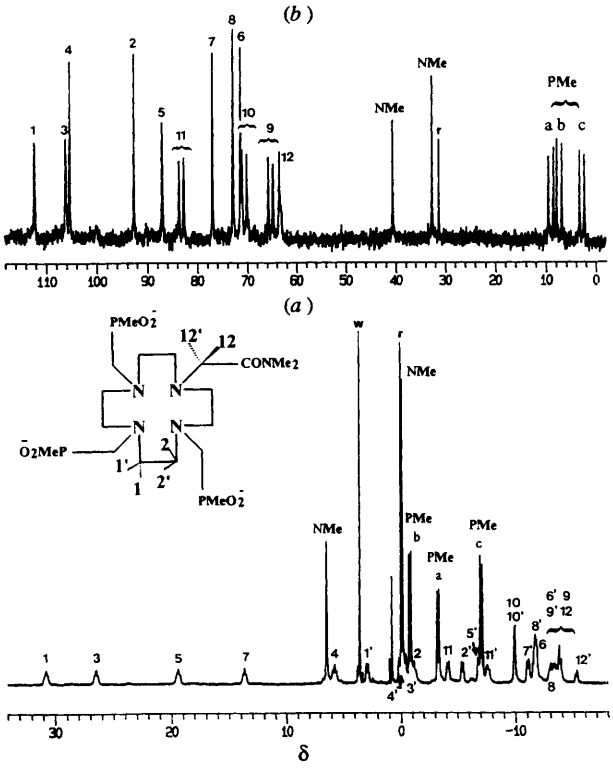


Fig. 9 The 90 MHz ^{1}H (*a*) and 100.6 MHz ^{13}C-{^{1}H} (*b*) NMR spectra (298 K, D_2O) of the Eu complex with H_3L^2 with partial assignment of the resonances. In (*a*) the primed numbers indicate equatorial hydrogen atoms, unprimed numbers axial hydrogen atoms. In (*b*) only the region of the protonated carbon atoms is shown. Peaks 1–8 and 9–11 correspond to the macrocyclic and to the methylenephosphinic carbon atoms, respectively. The resonances labelled with **w** and **r** refer to the solvent and Bu^{t}OH ($\delta_H = 0$, $\delta_C = 31.3$), respectively

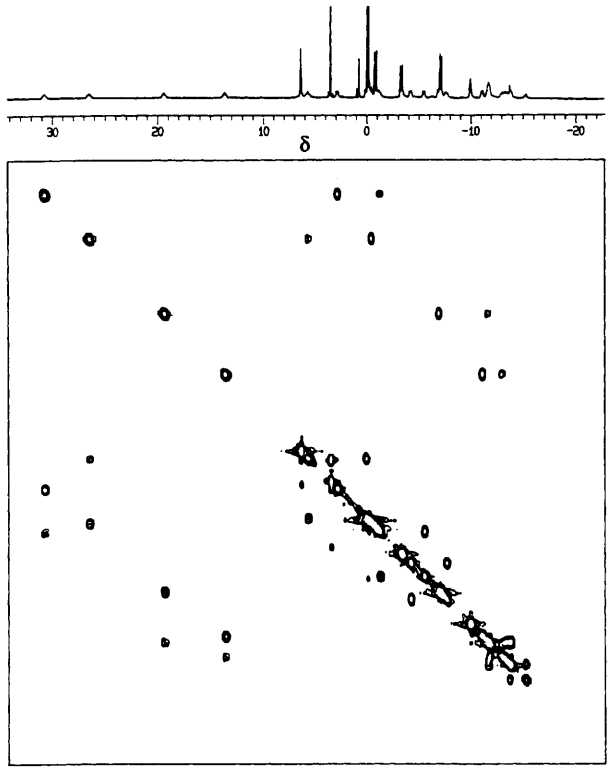


Fig. 10 The 90 MHz ^{1}H–^{1}H two-dimensional COSY spectrum (298 K) of the Eu complex with H_3L^2

substituents has little effect on the structural and magnetic properties of these lanthanide complexes. Further insight into the solution structures of these complexes was obtained by additional experiments on the Yb complexes using ^{31}P NMR spectroscopy.

Determination of Yb–P *Distances by* T_1 *Measurements*.—In the complexes the phosphorus atoms are inequivalent and therefore three distinct resonances are present in the NMR spectra. Moreover two P atoms are *cis* to the carboxamido group, whereas one is *trans*. Indeed in the spectrum of the Yb complex with H_3L^2 two resonances are very close and are separated by 35 ppm from the other one. As mentioned above, in the Yb complexes the paramagnetic shift of non-metal bound ligand atoms is mainly dipolar in origin and therefore is closely related to their geometrical coordinates. This implies that the small chemical shift difference among the three resonances could well be due to small differences in the P–Yb distances (and angles). This may be a consequence of a certain distortion of the co-ordination cage due to the presence of the carbonyl group. Since X-ray structural data are not yet available, we have calculated the P–Yb distances for the three complexes by measuring the ^{31}P T_1 relaxation time as a function of magnetic field (36.4, 109.3 and 162 MHz). In this case the structural information content can be extracted by exploiting the magnetic field dependence of the Curie-spin relaxation mechanism.[11,14] In fact, the longitudinal relaxation rate, R_1, can be written as the sum of three contributions [equation (1)]

$$R_1 = R_{1d} + R_{1dip} + R_{1Curie} \quad (1)$$

where R_{1d} represents the diamagnetic component, corresponding to the relaxation rate measured for the Y^{III}, La^{III} or Lu^{III} derivatives; R_{1dip} is the contribution corresponding to the electron-nuclear dipolar interaction and R_{1Curie} is the Curie-spin term. The difference $(R_1 - R_{1d})$ represents the paramagnetic contribution R_{1p} to the measured relaxation rate and has the functional form shown in equation (2) where τ_S

$$R_{1p} = \frac{20}{15}\frac{\gamma_p^2 g_j^2 \beta^2 J(J+1)}{r^6}\tau_S + \frac{6}{5}\frac{\omega_p^2 g_j^4 \beta^4 J^2 (J+1)^2}{r^6 (3kT)^2}\left[\frac{\tau_r}{1+\omega_p^2\tau_r^2}\right] \quad (2)$$

and τ_r represent the electronic relaxation time for the metal ion ($\sim 10^{-13}$ s) and the reorientational correlation time of the complex, respectively. The other terms have their usual meaning and for Yb^{III} $g_j = \frac{8}{7}$ and $J = \frac{7}{2}$. Equation (2) can be rewritten in a more schematic form as equation (3).

$$R_{1p} = D_1\tau_S + \frac{\chi_1 f(\tau_r) H_0^2}{r^6} \quad (3)$$

It follows that by plotting the relaxation rates as a function of the square of the applied magnetic field a straight line is obtained. From the slope of the line the distance value r is calculated, provided that a good estimate of the reorientational correlation time is available, and from the intercept the value of the electronic relaxation time may be obtained. The experimental results for the three resonances of the Yb^{III} complex with H_3L^3 are shown in Fig. 11. The distances reported in Table 1 have been obtained from equation (3) by using a τ_r value of 100 ps, as derived from the analysis of the nuclear magnetic relaxation dispersion profiles of Gd^{III} complexes of similar size[12,15] and are in the range 3.32–3.82 Å. These values, despite the approximate value of the reorientational correlation time utilized, are in very good agreement with the value of 3.35 Å derived from the X-ray crystal data for the tetra(benzylphosphinate) yttrium complex.[5] The results seem then to indicate

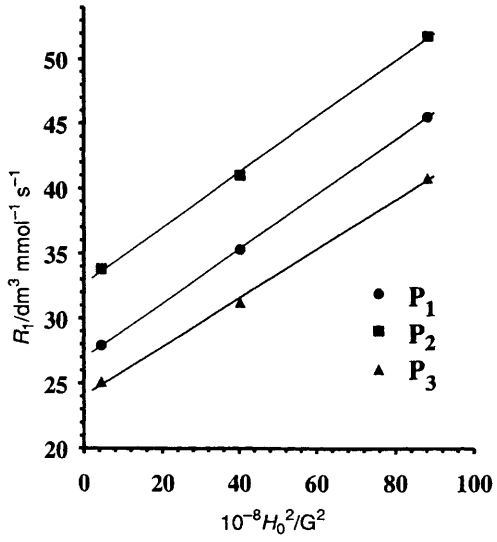


Fig. 11 Plot of the longitudinal relaxation rates R_1 of the ^{31}P resonances for the Yb complex with H_3L^3 *versus* the square of the magnetic field strength. Data taken at 2.1, 6.3 and 9.4 T and 298 K; G = 10^{-4} T

a certain degree of distortion in the co-ordination polyhedron induced by the presence of the carboxamido group, which is particularly pronounced in the case of the complex with H_3L^2.

Spectral Resolution of the Enantiomeric Complexes.—As discussed above, each of the Ln^{III} complexes considered in this work is actually present in aqueous solution as a mixture of enantiomeric pairs which of course cannot be distinguished by NMR spectroscopy. However, their occurrence may be indirectly revealed if these species are allowed to interact with an enantiomerically pure substrate.[16] The presence of benzylic groups in Ln^{III} chelates with H_3L^3 suggested the possible formation of reversible adducts in solution with the chiral solvating agent β-cyclodextrin.[17,18] The interaction of each enantiomeric pair in the aqueous solution of Yb–L^3 affords two diastereoisomeric inclusion complexes characterized in principle by a different set of resonances. This effect is particularly clear for the ^{31}P spectrum. As shown in Fig. 12 the addition of β-cyclodextrin to a solution of the Yb complex with H_3L^3 results in the splitting (and shifting) of the three ^{31}P resonances, thus allowing the chiral resolution of the two enantiomeric forms corresponding to the major isomeric form of the complex.

Relaxometric Investigations of the Gadolinium Complexes with H_3L^1–H_3L^3.—The long electronic relaxation time associated with the Gd^{III} ion prevents any possibility of analysing the high resolution NMR spectra of its complexes. However, we may safely assume that the complexes of this metal ion with H_3L^1–H_3L^3 display the same octadenticity found for the complexes of the lighter Eu^{III} and the heavier Yb^{III} ions. The measurement of the longitudinal relaxation rate of solvent water protons, at 20 MHz and 25 °C, affords values of relaxivity[19] R_{1p} of 3.09 and 3.08 dm^3 mmol^{-1} s^{-1} for complexes with H_3L^1 and H_3L^3 respectively, which are significantly higher than the relaxivities found for the analogous tetra(methylphosphinate) (2.44) and tetra(benzylphosphinate) (1.85 dm^3 mmol^{-1} s^{-1}) derivatives,[5] thus supporting the view that the substitution of a phosphinate by an acetamide group decreases the steric encumbrance and allows a water molecule to enter the inner co-ordination sphere of the paramagnetic metal ion. However the observed relaxivities appear markedly lower than those of other Gd^{III} complexes of similar size which contain one bound water molecule[14,15,19] in the inner co-ordination sphere. The observation of a decrease in relaxivity upon increasing

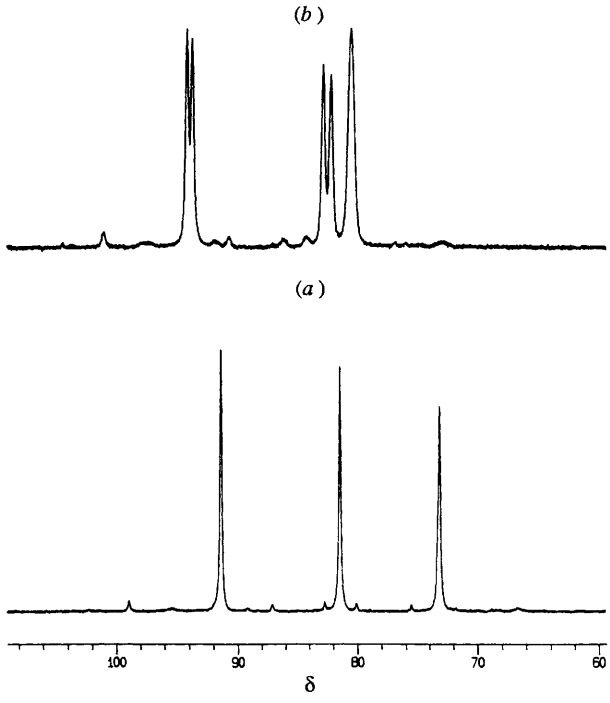


Fig. 12 The ^{31}P NMR spectra (9.4 T, 298 K) of an Yb–L^3 solution (0.01 mol dm^{-3}) in D_2O in the absence (*a*) and in the presence (*b*) of a little excess of β-cyclodextrin

Table 1 Phosphorus-31 NMR chemical shifts[a] and calculated[b] metal–phosphorus distances (Å) of Yb^{III} complexes with H_3L^1–H_3L^3

	H_3L^1		H_3L^2		H_3L^3	
	δ_P	r	δ_P	r	δ_P	r
P_1	−34.3	3.46	−13.7	3.43	−25.0	3.35
P_2	−40.4	3.51	−14.8	3.61	−35.2	3.32
P_3	−43.0	3.38	−50.3	3.82	−41.3	3.40

[a] Data measured in aqueous solution at 9.4 T and 298 K and referenced to 85% H_3PO_4. [b] From data measured at 2.1, 6.3 and 9.4 T.

temperature leads us to rule out the involvement of a long exchange lifetime of the co-ordinated water molecule among the possible causes of the limited relaxation efficiency.[20] This feature is not clearly understood at this stage and may be related to the fact that in the type of complexes considered in this work the bound water molecule is maintained, on average, at a distance which is longer than that commonly found (3.0–3.2 Å). An alternative explanation is that minor isomers with a hydration number of zero may be present in solution, although the NMR studies of the Eu and Yb complexes indicate that there is one major species in solution. The resolution of this point must await further studies which are currently in progress.

Experimental

Column chromatography was carried out using neutral alumina pretreated with ethyl acetate. Solvents were dried from an appropriate drying agent where required and water was purified by the Milli-Q system. The IR spectra were recorded with a Perkin-Elmer 1600 FT-IR spectromer, ^{1}H, ^{13}C-{^{1}H} and ^{31}P-{^{1}H} NMR spectra with JEOL EX-400, Bruker AC250, JEOL GX-270 and JEOL EX-90 spectrometers operating at 9.4, 5.87, 6.34 and 2.11 T respectively. Proton and carbon chemical shifts are referenced to the resonance of internal *tert*-butyl alcohol (one drop; δ_H 0, δ_C 31.3). The two-dimensional COSY spectrum for [EuL^2] (pD 7.2) was recorded at 90 MHz

and 25 °C. Data were collected with 512 points in F_2 (128 scans over 6000 Hz) and 256 points in F_1 and by using a delay between pulses of 0.5 s. Data were processed using a shifted sine square-bell function in F_2 and F_1. Phosphorus-31 NMR spectra are referenced to 85% phosphoric acid contained in a capillary inside the NMR tube. Proton solvent longitudinal relaxation times were measured at 20 MHz and 25 °C on a Stelar SpinMaster spectrometer (Stelar, Mede-PV, Italy) by means of the inversion–recovery technique (16 experiments, 4 scans). The reproducibility in T_1 measurements was ± 0.4%.

All coupling constants are in Hz. Mass spectra were recorded with a VG 7070E spectrometer operating in desorption chemical ionisation (DCI) (ammonia) or FAB (glycerol matrix) modes.

Synthesis of H_3L^1.—*N-Phenyl-2-chloroethanamide*. Triethylamine (2.45 g, 0.024 mol) was added to a solution of aniline (2.0 g, 0.02 mol) in dry diethyl ether (100 cm^3). The mixture was cooled to −60 °C and chloroacetyl chloride (2.9 g, 0.024 mol) added dropwise. The mixture was allowed to warm to room temperature and washed with dilute hydrochloric acid (2 × 100 cm^3) followed by water (2 × 100 cm^3). Removal of solvent under reduced pressure gave a white crystalline solid, yield 2.9 g (85%), m.p. 126–127 °C (Found: C, 56.9; H, 4.60; N, 7.95. C_8H_8ClNO requires: C, 56.6; H, 4.70; N, 8.25%). NMR: $\delta_H(CDCl_3)$ 4.19 (2 H, s, $ClCH_2$), 7.20 (1 H, t, ^3J 7.2, C_6H_5 *p*-H), 7.36 (2 H, m, C_6H_5 *m*-H), 7.54 (2 H, d, *J* 7.9, C_6H_5 *o*-H), 8.27 (1 H, br s, NH); ^{13}C-{^1H} ($CDCl_3$), δ 42.8 ($ClCH_2$); 120.1, 125.3, 129.1 (C_6H_5 o-, m-, p-C); 136.6 (C_6H_5 *ipso*-C); 163.8 (C=O).

1-(*Phenylcarbamoylmethyl*)-1,4,7,10-*tetraazacyclododecane*. 1,4,7,10-Tetraazacyclododecane (1.50 g, 8.8 mmol) in dibutyl ether (40 cm^3) was heated to 70 °C and hexacarbonyl molybdenum (2.30 g, 8.8 mmol) added. The mixture was heated to reflux under argon for 2 h, giving a bright yellow precipitate of the 1,4,7,10-tetraazacyclododecane–molybdenum–tricarbonyl complex, which was filtered under argon and dried under vacuum. The yellow complex was heated in dry degassed dimethylformamide with anhydrous potassium carbonate (excess) at 80 °C under argon and *N*-phenyl-2-chloroethanamide (1.50 g, 8.8 mmol) added. Heating (80 °C) was continued for a further 2 h and the solvent then removed under reduced pressure with mild heating. The resulting brown residue was taken up in aqueous hydrochloric acid (1 mol dm^{-3}) and the mixture stirred open to the air for 18 h. The pH of the solution was raised to 14 with potassium hydroxide pellets with cooling and the dark green molybdenum residues filtered off giving a clear yellow solution. Extraction into dichloromethane followed by removal of solvent under reduced pressure gave a yellow-brown oil, yield 1.33 g (50%). NMR: $\delta_H(CDCl_3)$ 2.66–2.93 (19 H, br m, CH_2CH_2, NH ring), 3.25 (2 H, s, NCH_2CO), 7.06 (1 H, t, ^3J 7.4, C_6H_5 *p*-H), 7.29 (2 H, m, C_6H_5 *m*-H), 7.69 (2 H, d, ^3J 8.1, C_6H_5 *o*-H), 10.10 (1 H, br s, HNPh); ^{13}C-{^1H} ($CDCl_3$), δ 45.7, 47.1, 47.9 (CH_2CH_2); 59.6 (NCH_2CO); 119.4, 123.7, 128.8 (C_6H_5, *o*-, *m*-, *p*-C); 138.4 (C_6H_5, *ipso*-C); 170.0 (C=O). *m/z* (DCI) 306 (100%, $M^+ + 1$).

Triethyl 10-(*phenylcarbamoylmethyl*)-1,4,7,10-*tetraazacyclododecane*-1,4,7-*triyltrimethylenetri*(*methylphosphinate*). The monosubstituted cycle (1.33 g, 4.4 mmol) was heated to 80 °C in anhydrous tetrahydrofuran under argon and paraformaldehyde (0.60 g, 19.6 mmol) followed by diethoxy(methyl)-phosphine (2.67 g, 19.6 mmol) were added. The solution was heated to reflux under argon for 18 h over molecular sieves (Soxhlet). The excess paraformaldehyde was filtered off and the solvent removed under vacuum giving a brown oil. The product was purified by alumina column chromatography, (gradient elution from dichloromethane to 2% methanol–dichloromethane; R_f = 0.4, 5% methanol–dichloromethane), giving a yellow-brown oil, yield 1.6 g (55%). NMR: $\delta_H(CDCl_3)$ 1.25 (9 H, t, ^3J 7.3, OCH_2CH_3), 1.37 (3 H, d, ^2J 13.5, PCH_3), 1.47 (6 H, d, ^2J 13.5, PCH_3), 2.69–3.2 (24 H, br m, CH_2CH_2, NCH_2P, NCH_2CO), 4.05 (6 H, m, OCH_2CH_3), 7.06 (1 H, t, ^3J 7.3, C_6H_5 *p*-H), 7.30 (2 H, m, C_6H_5 *m*-H), 7.68 (2 H, d, ^3J 8.6, C_6H_5 *o*-H), 9.93 (1 H, br, *H*NPh). ^{31}P-{^1H} ($CDCl_3$), δ 52.2, 51.8, 51.4; ^{13}C-{^1H} ($CDCl_3$), δ 13.9 (d, ^1J 90, PCH_3); 16.6 (OCH_2CH_3); 53.5, 53.7, 54.0, 54.4, 54.9, 55.0, 55.2, 55.8 (CH_2N ring, NCH_2P, $POCH_2CH_3$); 60.0 (NCH_2CO); 119.4, 123.6, 128.7 (C_6H_5, *o*-, *m*-, *p*-C); 138.5 (*ipso*-C); 169.8 (C=O). *m/z* (DCI) 666 (91, $M^+ + 1$), 546 (41%, M^+ − PhNCO).

10-(*Phenylcarbamoylmethyl*)-1,4,7,10,-*tetraazacyclododecane*-1,4,7-*triyltrimethylenetri*(*methylphosphinic acid*). The monoamide triester was dissolved in a solution of potassium deuteroxide in deuterium oxide and stirred for 12 h at room temperature. The ^1H NMR spectrum of the reaction mixture showed resonances due to ethanol and the required product. The solution was acidified with dilute hydrochloric acid, the water removed under reduced pressure and the residue extracted into absolute ethanol giving ligand H_3L^1 in quantitative yield. NMR: $\delta_H(D_2O)$ 1.02 (9 H, d, ^2J 13.9, PCH_3), 2.37–2.62 (24 H, br m, CH_2CH_2, NCH_2P, NCH_2CO), 6.9–7.1 (5 H, m, C_6H_5); ^{31}P-{^1H} (D_2O), δ 42.8, 41.8; ^{13}C-{^1H} (D_2O), δ 16.4 (d, ^1J 88, PCH_3); 51.7, 52.2, 52.7 (NCH_2 ring); 55.9 (d, ^1J 99, NCH_2P); 57.3 (NCH_2CO); 122.1, 125.6, 129.2 (C_6H_5, *o*-, *m*-, *p*-C); 137.0 (C_6H_5, *ipso* C); 173.6 (C=O). The related macrocycles H_3L^2 and H_3L^3 were prepared in a similar manner and as reported previously.[7]

Synthesis of the Europium, Gadolinium and Ytterbium Complexes with H_3L^1–H_3L^3. [EuL^1]. The macrocycle H_3L (200 mg, 0.35 mmol) was dissolved in water (10 cm^3) and the pH adjusted to 2 with dilute hydrochloric acid. Europium oxide (61 mg, 0.18 mmol) was added and the solution heated to reflux for 3 h giving a clear solution. The pH was raised to 6 with aqueous potassium hydroxide and heating continued for a further 3 h. The solution was filtered through 0.45 μm (Millipore) filters and the water was removed under reduced pressure. The product was purified by alumina column chromatography (10% methanol–dichloromethane; R_f = 0.7, 25% methanol–dichloromethane) to give a colourless solid, yield 150 mg (60%). ^{31}P-{^1H} NMR (D_2O): δ 67.0, 86.1, 101.1. IR (KBr): 3396s (br), 2977s, 2871s, 1626s, 1596s, 1571s, 1454m, 1425m, 1327m, 1294s, 1137s, 1070m, 1034s, 891m, 810m, 743m, 526m. *m/z* (FAB) 732 (82%, $M^+ + 1$) (Found: C, 33.4; H, 5.90; N, 8.75. $C_{22}H_{39}EuN_5O_7P_3 \cdot 3H_2O$ requires C, 33.7; H, 5.75; N, 8.90%).

[YbL^1]. The ytterbium complex was prepared from H_3L^1 and ytterbium oxide by an identical procedure to that described for the Eu complex. ^{31}P-{^1H} NMR (D_2O): δ −60.7, −43.2, −32.0. IR spectrum identical to that of [EuL^1]. *m/z* (FAB) 753 (100%, $M^+ + 1$) (Found: C, 30.8; H, 5.7; N, 8.0. $C_{22}H_{39}N_5O_7P_3Yb \cdot 6H_2O$ requires C, 30.7; H, 5.9; N, 8.05%).

The complexes with H_3L^2 and H_3L^3 were prepared in an analogous manner.

[EuL^2] ^{31}P-{^1H} NMR (D_2O): δ 80.7, 93.1, 97.1. IR (KBr): 3406s (br), 2360m, 2341m, 1625s, 1460m, 1426m, 1294m, 1228m, 1144s, 1071m, 1030s, 976m, 892m, 743m, 524m. *m/z* (FAB) 684 (10, $M^+ + 1$) (Found: C, 27.3; H, 6.5; N, 8.5. $C_{18}H_{39}EuN_5O_7P_3 \cdot 6H_2O$ requires C, 27.3; H, 6.5; N, 8.8%).

[YbL^2]. ^{31}P-{^1H} NMR (D_2O): δ −50.3, −14.8, −13.7. IR spectrum identical to that of [EuL^2]. *m/z* (FAB) 705 (11%, $M^+ + 1$) (Found C, 27.5; H, 6.3; N, 8.5. $C_{18}H_{39}N_5O_7P_3Yb \cdot 5H_2O$ requires C, 27.2; H, 6.2; N, 8.8%).

[EuL^3]. ^{31}P-{^1H} NMR (D_2O): δ 71.8, 90.5, 98.4. IR (KBr): 3406s (br), 2867m, 1602s, 1454m, 1297m, 1228m, 1144s, 1073m, 1030s, 890m, 805m, 741m, 702m, 518m. *m/z* (FAB) 836 (69%, $M^+ + 1$) (Found: C, 41.1; H, 6.05; N, 7.8. $C_{30}H_{47}EuN_5O_7P_3 \cdot 3H_2O$ requires C, 40.5; H, 5.99; N, 7.9%).

[YbL^3] ^{31}P-{^1H} NMR (D_2O): δ −41.3, −35.2, −25.0. IR spectrum identical to that of [EuL^3]. *m/z* (FAB) 857 (100%, $M^+ + 1$) (Found: C, 39.2; H, 6.4; N, 7.4. $C_{30}H_{47}N_5O_7P_3Yb \cdot 4H_2O$ requires C, 38.8; H, 5.99; N, 7.6%).

The complexes of gadolinium were prepared as described in ref. 7.

GdL[1]. IR spectrum identical to that of [EuL[1]]. *m/z* (FAB) 737 (90%, $M^+ + 1$) (Found: C, 31.6; H, 5.80; N, 8.05. $C_{22}H_{39}GdN_5O_7P_3 \cdot 5H_2O$ requires: C, 31.9; H, 5.95; N, 8.45%).

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