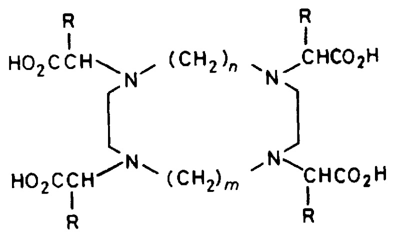
Lanthanide Complexes of 1,4,7,10-Tetra-azacyclotridecane-1,4,7,10-tetra-acetic Acid: Proton Nuclear Magnetic Resonance Studies

José R. Ascenso, Rita Delgado, and João J. R. Fraústo da Silva
Centro di Quimica Estrutural, Complexo I, Instituto Superior Técnico, Lisbon, Portugal

The conformation in solution of some lanthanide(III) complexes of 1,4,7,10-tetra-azacyclotridecane-1,4,7,10-tetra-acetic acid has been studied by ^{1}H n.m.r. techniques. The results suggest that these complexes have an approximate square-antiprism geometry in solution, with the lanthanide ion lying in a shell above the plane defined by the four nitrogens of the ligand and below that of the co-ordinated carboxylate oxygens. The tetra-aza ring in these complexes prefers a [12433] conformation, being less flexible than in the complexes of the corresponding 14-membered ring and being comparable with that of the more common 12-membered ring.

In previous papers[1,2] we reported the results of studies on the metal complexation properties of a series of tetra-aza macrocycles substituted by four pendant acetate groups, (1).



	m	n	R
(1a)	2	2	H
(1b)	2	3	H
(1c)	3	3	H
(1d)	2	2	CH$_3$

The higher values reported for the entropies of formation (ΔS°) of the complexes with alkaline-earth-metal ions relative to the complexes of the corresponding ions with non-cyclic polyaminocarboxylates[2] suggest that the ring adopts a folded conformation and forms, together with the four acetate groups, a kind of cage inside which the metal ions are trapped. Furthermore, the enthalpies of formation (ΔH°) of these complexes decrease sharply with increasing size of the ring, but no specific effect was observed due to increasing cation size.

These observations led to the conclusion that the internal diameter of the cage is sufficient to encapsulate this type of ion and that the ligand loses rigidity as the size of the tetra-aza ring increases. Furthermore, the conformation of this ring must change from ligand to ligand to account for the sharper decrease in ΔH° values.

The smaller ligands (**1a**) and (**1b**) are expected to co-ordinate lanthanide(III) ions similarly to the larger alkaline-earth-metal ions. Indeed, it has been shown that the lanthanide complexes of (**1a**)[3,4] as well as their chiral analogues formed with (**1d**)[5] are both very stable and have very rigid structures in solution, the ring conformation being the characteristic [3333] 'square' conformation of 12-membered rings.

In solution, the inversion of the ethylenediamine groups of the lanthanide complexes of (**1a**) proceeds very slowly at 0 °C and at higher temperature a free-energy barrier of 60 kJ mol^{-1} was found.[3] This energy barrier is probably higher in the case of the (**1d**) complexes for which a value higher than 77 kJ mol^{-1} was estimated[5] at 100 °C.

The insertion of CH$_2$ groups in the ring of compound (**1a**) will certainly lead to alterations in the structure of the resulting complexes and will decrease their rigidity. These effects have already been observed for complexes of Tb$^{\text{III}}$ with (**1c**),[6] where the 14-membered ring adopts a {77} folded conformation, encapsulating the lanthanide ion in a highly distorted dodecahedral cage.

Our previous studies on the tetra-aza macrocycle (**1b**), for which the internal diameter of the 13-membered ring is intermediate (1.92 Å) between those of (**1a**) (1.83 Å) and (**1c**) (2.07 Å), have shown that its behaviour cannot be predicted straightforwardly from the parent ligands and its less symmetric character may result in interesting anomalies, *e.g.* a copper complex with high absorption coefficient ($\varepsilon = 370$ l mol^{-1} cm^{-1}).[7] The study of its complexes with the lanthanide ions seemed of interest in order to determine whether anomalies also occur in these cases or whether there is only an effect of size, leading to some intermediate situation between the complexes of (**1a**) and (**1c**), or closer to one of these.

Experimental

1,4,7,10-Tetra-azacyclotridecane-1,4,7,10-tetra-acetic acid (**1b**) was prepared as described previously.[1] Solutions of its lanthanide complexes, concentration 0.05 mol dm^{-3}, were prepared in 5-mm n.m.r. tubes by adding stoicheiometric amounts of the solid ligand to known volumes of stock solutions of the lanthanide chlorides. The pH was adjusted to 4.8 with diluted KOH and the solutions were heated to 100 °C to ensure completion of the reaction. This was monitored by the disappearance of the resonances of the free ligand in the ^{1}H n.m.r. spectra obtained after evaporation of the solutions to dryness under N$_2$ and redissolution of the solid in D$_2$O. The final measured pH of the solution was about 4.6.

Proton n.m.r. spectra were recorded at 300 MHz on a Bruker CXP 300 spectrometer and at 100 MHz on a JEOL JNM 100 PTF spectrometer. All spectra were obtained in the Fourier-transform mode and the chemical shifts were measured in p.p.m. using t-butyl alcohol (1.3 p.p.m. from SiMe$_4$) as internal reference.

The calibration of the temperature of the probe was done using an ethylene glycol sample, and the values of the free energy of activation $\Delta G^\ddagger$ for the conformation equilibrium of the tetra-aza ring were derived from the coalescence temperature T_c obtained by extrapolating a plot of total shift *versus* $1/T$ above and below T_c. The coalescence temperature was estimated with an error of about ±2 °C.

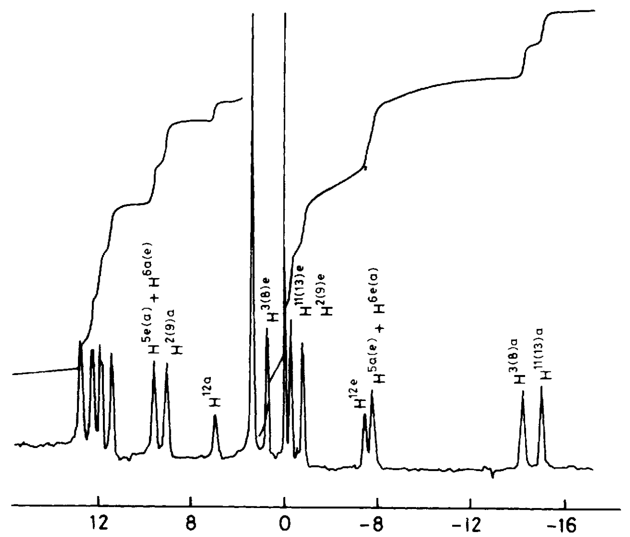


Figure 1. ^1H N.m.r. spectrum of a 0.05 mol dm^{-3} solution of the praseodymium complex of (**1b**) in D_2O at 98 °C and 100 MHz. Relative intensities of the peaks are shown, as well as the assignment of the protons in the tetra-aza cyclotridecane ring. For the numbering of atoms in the ring see Figure 3 or 4(*b*)

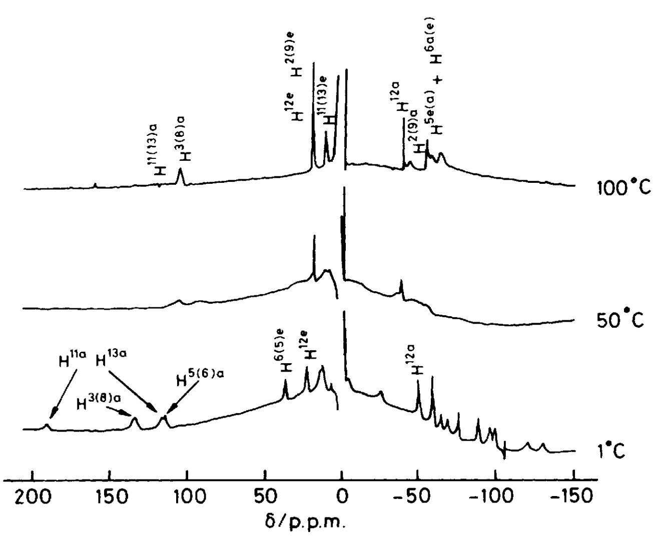


Figure 2. ^1H N.m.r. spectra of a 0.05 mol dm^{-3} solution of the ytterbium complex in D_2O at 300 MHz. The assignment of most of the proton peaks of the tetra-aza cyclotridecane ring is shown for the spectra at 1 and 100 °C. For the numbering of atoms in the ring see also Figure 3 or 4(*b*)

Results and Discussion

The Spectrum of the Tetra-aza Ring.—The ^1H n.m.r. spectrum of the praseodymium(III) complex of (**1b**) at 98 °C, Figure 1, shows a well resolved set of fourteen signals; integration of this spectrum reveals that twelve of these signals have equal intensities and that the two at 6.01 and −6.87 p.p.m. have half the intensity of the former resonances. It is immediately apparent from the 1:1 stoicheiometry of the complex that each of the signals of the set of twelve corresponds to two equivalent protons and each signal of the second set corresponds to a single proton.

The presence of only fourteen resonances in the spectrum can be taken as an indication that, at high temperature, the tetra-aza ring of the ligand is folded and undergoes a fast internal rearrangement. The effects of this process are clearly seen in the spectrum of the ytterbium complex at three temperatures, Figure 2. At 50 °C all resonances become very broad except for the two proton resonances of half intensity at 14.70 and −30.46 p.p.m. in the spectrum at 100 °C, for which the linewidth is not affected by the rate of the internal rearrangement. The slight changes observed in the linewidths of these protons are due only to the effect of temperature on the broadening induced by the paramagnetic ytterbium(III) ions.

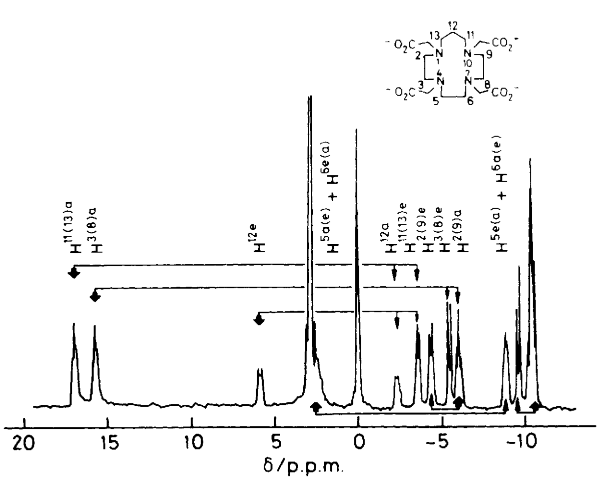


Figure 3. ^1H N.m.r. spectrum of a 0.05 mol dm^{-3} solution of the europium complex in D_2O at 98 °C and 100 MHz. The assignment of the peaks of the protons in the tetra-aza cyclotridecane ring is shown; the bars and the arrows connect proton resonances found to be spin–spin coupled. Bolder arrows indicate the positions irradiated. The numbering of the atom positions is also shown

The spectrum of the europium complex at 98 °C, Figure 3, also shows two sets of resonances, one set being twice as intense as the other. Since in this case there is practically no paramagnetic broadening caused by Eu^{III}, the fine structure is observed, enabling the use of simple decoupling experiments for the assignments. The results are shown in Figure 3, in which the proton resonances that are spin–spin coupled are indicated with bars and arrows.

The two peaks of one-proton intensity at 5.90 and −2.36 p.p.m. are readily assigned as belonging to the β protons of the propane chain from the values of their relative areas and the collapse of the multiplet for each resonance upon decoupling one proton from the other. Irradiation of the multiplet at −2.36 p.p.m. also produces collapse of the lowest-field triplet at 17.01 p.p.m.; however, no significant effect on the two low-field triplets was observed upon irradiating the peak of the β-propane proton at 5.90 p.p.m. Moreover, irradiation of the triplet at 15.76 p.p.m. revealed that these protons are coupled only to the protons of the doublet at −5.47 p.p.m. and to those of the higher-field triplet at −6.00 p.p.m.

These results make it possible to assign the triplet at 17.01 p.p.m. to the protons attached to carbons C^{11} and C^{13}, whereas the triplet at 15.76 p.p.m. is assigned to the protons attached to carbons C^3 and C^8. The resonance at 2.48 p.p.m., partially hidden by the solvent peak, is coupled only to the poorly resolved quartet at −8.92 p.p.m. For this reason these two resonances are assigned to the protons attached to C^5 and C^6. For the numbering of atom positions in the macrocyclic ring see Figures 3 and 4(*b*).

The peaks in the spectra of the complexes of metals other than Eu^{III} are too broad at high temperature to allow their assignment through decoupling experiments; only in the case of Pr^{III} was it possible to assign some of the narrower peaks using this technique. Still, in spite of the changes in the sign of the pseudo-contact shifts, the spectra of these complexes at high temperature are sufficiently similar to that of the europium complex to allow the assignment of the peaks by analogy, Figures 1 and 2.

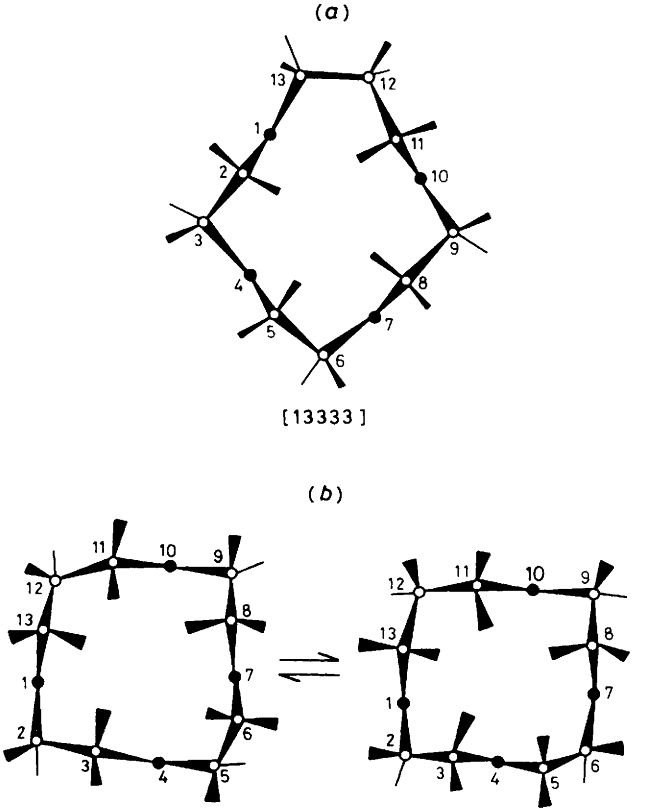
The Spectrum of the Acetate Protons.—The assignment of the acetate resonances is simplified by the cage structure of these complexes which results in the four acetate groups and the axial protons, $H^{11(13)a}$ and $H^{3(8)a}$, being on opposite sides of the tetra-aza ring. For this reason, the highest-field doublet and multiplet of the spectrum of the europium complex, Figure 3, corresponding to eight protons, are assigned to the acetate protons. The splitting of the doublet, $J = 17$ Hz, is characteristic of this type of proton.[8] For the same reason, the four lowest-field peaks in the spectrum of the praseodymium complex are assigned to two different acetate AB patterns. It should be noted that the conformation equilibrium undergone by the cyclotridecane tetra-aza ring at high temperature averages the acetate groups on the two halves of the macrocyclic ring and reduces the number of acetate AB patterns from four to two.

Conformational Behaviour of the Tetra-aza Ring.—The previous assignments confirm the existence of an internal rearrangement which at high temperature is sufficiently fast to average the two halves of the molecule of the complex, leaving unchanged the geometric position of the H^{12} protons of the propanediamine ring; a more detailed analysis of the nature of this process requires an examination of the most stable conformations that a 13-membered macrocyclic ring can adopt.

Although the cyclotridecane tetra-aza ring is larger than the cyclododecane tetra-aza ring, its size is insufficient to accommodate the large lanthanide ions in its central cavity and, as in the cases of the complexes with (**1a**)[4] and (**1c**),[6] the ring is constrained to adopt a folded conformation with the four nitrogens facing the lanthanide ion, which lies, as in a shell, bound to these four nitrogens and to the carboxylate groups. This conformation, also found to occur in other complexes of large cations with other medium and large tetra-aza[9] and tetra-oxa rings,[10,11] results in the two protons attached to each carbon of the tetra-aza ring being in different geometrical positions relative to the lanthanide ion.* For this reason, the dipolar shifts,[12] which depend on geometric factors (distance and angles) relating the position of the lanthanide to that of the hydrogen nuclei, are different and can even be of opposite sign for the same lanthanide.

There is still insufficient knowledge about the conformational properties of large odd-membered rings. Some structural studies have been reported for complexes of 13-membered tetra-aza rings with Ni^{II}[13] and Co^{III},[14] in which the ring, more or less strained, seems to fit the size of the ions. Recent force-field calculations for cyclotridecane and other odd-membered cycloalkane rings yielded the strain energies for the most stable conformations of these molecules.[15]

When compound (**1b**) is formed from cyclotridecane by replacement of four carbon atoms by four nitrogens and these are forced to be on the same side of the molecule to satisfy the co-ordination requirements of the lanthanide ion, only the conformations [13333] and [12433] are satisfactory, Figure 4. The latter is a little higher in energy in the case of cyclotridecane.[15,16] Space-filling molecular models for (**1b**) also show these two conformations to be the most favourable for simultaneous co-ordination of the four nitrogens to a lanthanide ion.



[12433]

Figure 4. Conformations of the tetra-aza cyclotridecane ring as derived from cyclotridecane. The equilibrium shown between the two enantiomeric [12433] conformations explains the internal rearrangement of the tetra-aza ring at high temperature. ●, Nitrogen atoms; ○, carbon atoms

Whether the [13333] or the [12433] conformation is actually adopted in the present chelates can be deduced from the spectra, noting that a conformation equilibrium between two [13333] enantiomeric conformers, that leaves the position of the H^{12} protons unchanged, would give rise in the spectrum of the europium complex at high temperature to three peaks shifted to very low field, assigned to an average of the chemical shifts of the protons in axial positions at carbons C^{11} and C^{13}, C^{2} and C^{9}, and C^{3} and C^{8}. The same type of equilibrium for the conformation [12433] would give rise, in the same spectrum, only to two triplets shifted to very low field, assigned to an average of the chemical shifts of the axial protons at carbons C^{11} and C^{13}, and C^{3} and C^{8}, resulting mainly from a high geminal coupling constant and a high *trans* coupling constant for these protons with the corresponding vicinal protons.

The presence of only two peaks at very high or very low field, depending on the sign of the pseudo-contact shift and the fact that these peaks are triplets, Figure 3, leads to the conclusion that the tetra-aza ring in the present complexes prefers the [12433] conformation. This fact enables the complete identification of all proton peaks in Figure 3.

Further support for this conformation of (**1b**) in its lanthanide complexes is derived from the behaviour of 13-membered tetrathioethers in complexes with Cu^{II} whose structure was published recently.[17] In this case, the large size of the sulphur atom forces the tetrathio ring to adopt a non-planar conformation to encompass the copper(II) ion; this conform-

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* To distinguish each pair of protons in the ring, those nearer to the metal are called axial (a) and those more distant equatorial (e). For axial protons, the bond to carbon is approximately parallel to the axis passing through the lanthanide and the middle of the ring; the C–H bonds of the equatorial protons point away from the ring.

ation may also be considered of [12433] type in the wedge notation, and folding of the ligand molecule through a line going from the β carbon of the six-membered ring to one of the carbons of the chelate ring opposite to it is also observed. Despite the differences between the tetrathio and the tetra-aza rings, it appears that (**1b**) is co-ordinated to the lanthanide ions in the same fashion, with the metal ion lying above the four nitrogens and below the carboxylate groups, which results in an approximate square-antiprism symmetry for the complexes.

In this respect, compound (**1b**) is less flexible than (**1c**), which is able to fold in such a way as to encapsulate completely the lanthanide ions in a dodecahedral environment,[6] and therefore more closely resembles (**1a**) which co-ordinates these ions also in a square-antiprism geometry.[4]

The determination of the activation parameters for the internal rearrangement of the tetra-aza ring is important in order to quantify the effect of the increase in ring size on the stability and rigidity of the complexes. We have determined a free energy of activation of $\Delta G^{\ddagger} = 55$ kJ mol $^{-1}$ for this process from the coalescence temperature ($T_c = 357$ K) of the H^{11a} and H^{13a} resonances in the spectrum of the ytterbium complex of (**1b**). This value is lower than those found by Desreux[3,5] for lanthanide complexes of (**1a**) and (**1d**).

The smaller free-energy barrier found for the chelates of (**1b**) shows that the rigidity of the lanthanide complexes formed with cyclic tetra-azatetra-acetates decreases as the internal cavity of the ligand increases, in spite of differences in the conformation of the ligands. A similar trend was also found for the enthalpies and free energies of formation of complexes with alkaline-earth-metal ions,[1,2] supporting the assumed similarity of the complexes formed by these two series of metal ions with this class of ligand.

Symmetry of the Complexes.—The ratios of the paramagnetic shifts induced by the lanthanide ions may provide useful information on the symmetry and structure of these complexes in solution. When the ratios R_{ij} of observed paramagnetic shifts $\delta_{\mathrm{obs.}}$ of two nuclei *i* and *j* in the same molecule are independent of the lanthanide, then the shifts are purely pseudo-contact in origin, the series is isostructural, and the complexes have effective axial symmetry.

At 1 °C the spectrum of the ytterbium complex of (**1b**), Figure 2, shows that the rate of flipping of the tetra-aza ring is sufficiently slow on the n.m.r. time-scale to enable the observation of the spectrum of the frozen complex. This spectrum consists of a set of 18 peaks whose approximate areas correspond to the 26 protons of the ligand, indicating a very asymmetric structure for the frozen chelate molecule in solution with the 26 protons in non-equivalent positions relative to the lanthanide ion. This situation approaches that found in the solid state, in which most of the molecules of the lanthanide chelates are known to be very asymmetric.[18]

However, at 98 °C the experimental shift ratios for the present complexes (Table) relative to the shift of the axial protons H^{13} and H^{11} are approximately constant along the series. The variations observed in the shift ratios of the protons, especially those of H^{12a} and H^{12e}, are mainly due to the contribution of the contact interaction to the shifts. Such effects were also observed on the proton shift ratios of lanthanide complexes of (**1a**).[3] This observation is somewhat surprising given the results obtained at low temperature, but it just shows that at higher temperature the complexes are less rigid and that the rate of processes such as flipping of the tetra-aza ring or exchange of the positions of acetate groups in the co-ordination sphere of the lanthanide ion becomes sufficiently high to produce an effective axial symmetry for the complex on the n.m.r. time-scale. This conclusion is in accord with our previous results[19] on lanthanide complexes of ethylenediamine- and 1,2-propylenediamine-tetra-acetate as well as with other results obtained by different authors on several lanthanide complexes, and provides an excellent example of the importance of averaging mechanisms[20] in determining the effective symmetry of the complexes in solution.

Table. Experimental shift ratios for the protons of 1:1 complexes of lanthanide ions with (**1b**) relative to the protons $H^{11(13)a}$ at 98 °C

Lanthanide	H^{12e}	H^{12a}	$H^{3(8)a}$	$H^{5e(a)} + H^{6a(e)}$
Ce	0.33	−0.23	0.85	−0.59
Pr	0.31	−0.27	0.92	−0.51
Eu	0.35	−0.14	0.92	−0.52
Yb	0.17	−0.33	0.86	−0.46

Further insight into this problem may be possible after the determination of the structures in the solid state by *X*-ray diffraction, but the use of high-resolution luminescence techniques to study the complexes of terbium(III) and europium(III) may also afford some interesting information on the number and symmetry of the complex species in solution.

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