Structure and Dynamics of Lanthanide(III) Complexes of the Bis(propylamide) of Diethylenetriaminepentaacetic Acid† in Aqueous Solution

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NMR shift and relaxation measurements show that the lanthanide(III) complexes of the bis(propylamide) of diethylenetriaminepentaacetic acid (H_3L) occur in at least eight isomeric forms, in which the metal ion is coordinated by a water molecule and the octadentate chelated organic ligand.

The lanthanide complex $[Gd(dtpa)(H_2O)]^{2-}$ (H_5dtpa = *N,N,N′,N″,N″*-diethylenetriaminepentaacetic acid) has found widespread application as a contrast agent for magnetic resonance imaging (MRI).[1] A drawback of this complex is that it has a negative charge, which results in a relatively high osmolality under physiological conditions. Therefore, neutral Gd^{III} complexes of bis(amide) analogues of the dtpa have been proposed as alternatives.[2,3] Here, we report some preliminary results of an NMR study on the structure and the dynamics of the lanthanide(III) complexes of the bis(amide) ligand L.

The Ln^{III}–L complexes were synthesized according to procedures previously described,[2] or by a procedure analogous to that reported recently for the corresponding bis(ethylamide) compounds.[3]‡

The Ln^{III} complexes of a particular ligand are usually almost isostructural. Therefore, one can profit from the different NMR properties of the various Ln^{III} ions in the structural analysis of these complexes.

The ^{13}C NMR spectrum of the Nd(L) complex in D_2O at 50 MHz and 85 °C showed nine signals in the carbonyl region (δ 164–187), four sets (integral ratio 2 : 2 : 2 : 1) of propyl ^{13}C signals (δ 11.3–12.4, 21.7–23.3 and 42.6–45.0), and at least eleven partially overlapping signals for the other methylene

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† H_3L = 6-carboxymethyl-3,9-bis(*N*-propylcarbamoylmethyl)-3,6,9-triazaundecanedioc acid.

‡ The complexes were obtained as hydrates $Ln(L)\cdot nH_2O$ (n = 1–3). The elemental analyses (Ln,C,H,N) were within 0.3% of the theoretical values. The FAB mass spectra showed the expected $(M + 1)^+$ cluster.

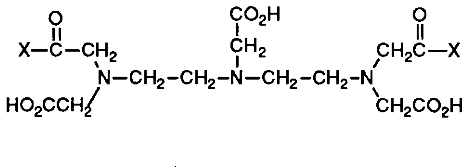
groups. At 3 °C and 100 MHz the NMR spectrum was substantially broadened and most of the signals were very weak. After dilution of the sample with CD_3OH (1 : 1 v/v) and cooling to −30 °C, eight sets of signals were observed for the β-methylene and the methyl carbons of the propylamide group. These spectra show that many types of ligand environment are present in solution.

Longitudinal relaxation measurements were performed at 85 °C and 50 MHz. Comparison of the spectra mentioned above shows that under these conditions fast exchange on the NMR time scale occurs between two sets of species, whereas the exchange within each set is slow. Assuming that there are two isomers A and B, which are in fast exchange on the NMR time scale, the observed longitudinal relaxation rate of a nucleus ($1/T_{1,\mathrm{obs}}$) is given by eqn. (1),[4] where $T_{1,\mathrm{A}}$ and $T_{1,\mathrm{B}}$ are the intrinsic relaxation times in the absence of exchange and f_A and f_B are the molar fractions of the isomers. For exchange between more than two species analogous expressions can be derived. For each isomer the longitudinal relaxation rate is related to the structure *via* the reduced Solomon–Bloembergen eqn. (2).[5,6]

$$1/T_{1,\mathrm{obs}} = f_\mathrm{A}/T_{1,\mathrm{A}} + f_\mathrm{B}/T_{1,\mathrm{B}} \qquad (1)$$

$$1/T_1 = 4/3(\mu_0/4\pi)^2(\mu^2\gamma^2\beta^2T_{1,\mathrm{e}}/r^6) \qquad (2)$$

Here $\mu_0/4\pi$ is the magnetic permeability *in vacuo*, μ is the effective magnetic moment, γ is the magnetogyric ratio, β is the Bohr magneton, and $T_{1,\mathrm{e}}$ is the electron spin relaxation time, which has been shown to be rather independent of the ligation of the $\mathrm{Ln^{III}}$ cation.[7,8] The relaxation rates obtained (see Table 1) were corrected for any diamagnetic contributions by using the corresponding relaxation rates of the diamagnetic La(L) complex. Then with the use of eqn. (2) 'averaged' distances were calculated (see Table 1). The distances obtained are similar to those obtained for the Nd(dtpa) complex[9] and are in good agreement with the distances measured in the solid state structure of the related Gd complex of the bis(ethylamide) analogue of the dtpa ligand (single isomer).[3] It can be concluded that all ^{13}C NMR signals observed can be assigned to isomers that bind to the $\mathrm{Nd^{III}}$ cation in an octadentate fashion *via* the three nitrogen atoms, the carboxylate groups and the amide oxygen atoms.



H_5dtpa : X = OH
H_3L : X = $NHCH_2CH_2Me$

Table 1 ^{13}C NMR relaxation rates ($1/T_1$) and $\mathrm{Nd^{III}}$–C distances (r) in the isomers of Nd(L)(D_2O) (total concentration 0.16 mol dm^{-3} in D_2O) at 85 °C and pH 6.7; ^{1}H decoupling was applied

Nucleus	$(1/T_1)$/s^{-1} [a]	r/Å [b]
CO	6.07–7.49	3.08–3.18
CH_2 [c]	3.97–5.40	3.25–3.42
α-CH_2 (Propyl)	0.24–0.28	5.33–5.47
β-CH_2 (Propyl)	0.06–0.08	6.56–6.89
γ-CH_3 (Propyl)	0.09–0.15	5.91–6.44

[a] Ranges for the signals of the various isomers. Corrected for diamagnetic contributions by subtracting the corresponding relaxation rates of La(L) (0.12–0.16, 2.08–2.92, 0.89, 0.56 and 0.24 s^{-1}, respectively). [b] Calculated from the corrected relaxation rates and eqn. (2). [c] CH_2 groups of the dtpa part of the ligand.

Upon binding of the ligand L in this fashion the inversion of the three nitrogen atoms is precluded, which makes them chiral. Therefore, in principle, eight enantiomers (four diastereoisomeric pairs) are possible for this complex (see Fig. 1), which explains the number of propyl CH_2 and CH_3 signals in the ^{13}C NMR spectrum at −30 °C (see above). Previously, it has been shown for dtpa that wagging of the ethylene bridges causes racemization around the central nitrogen atom (see Fig. 1*B*).[9,10] This conformational interconversion manifested itself in isochronism of corresponding nuclei on both sides of the pseudo-mirror plane of the ligand. A similar phenomenon in the case of the ligand L explains that the four diastereoisomeric pairs here give rise to, for example, four sets of propyl ^{13}C signals at 85 °C (see Fig. 1: one set for **1**, two sets for **2**, that coincide with those for **3**, and one set for **4**).

It should be noted, however, that as a consequence of the partial double bond character of the amide C–N bond, the rotation around this bond is restricted. In the ^{13}C spectrum of the free Ligand L, separate signals for the various rotamers were not observed. Probably fast rotations around the other bonds in this compound average out the chemical shift differences. Upon binding to a lanthanide ion, as a result of the reduced ligand flexibility and of paramagnetic effects on the chemical shifts, the rotation around the two amide C–N bonds might become slow on the ^{13}C NMR time scale. This could give rise to a fourfold splitting of the various ^{13}C signals in the spectrum of the Nd(L) complex. A ^{13}C NMR spectrum of the corresponding Nd[dtpa-bis(amide)] (X = NH_2) for which the rotamers are identical, also showed, however, splitting of the various signals; at 85 °C, for example, eight carbonyl signals were observed between 162 and 188 ppm. Therefore, it can be concluded that the chirality of the lanthanide-bound nitrogens accounts for the splitting of the various signals.

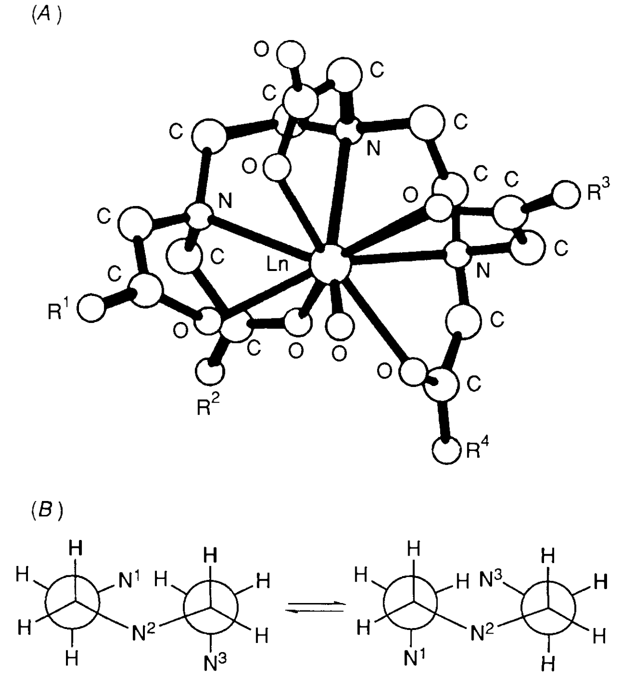


Fig. 1 (*A*) Schematic representation of the Ln(L) (H_2O) complex in aqueous solution. Since the inversion of the nitrogen atoms is precluded, eight enantiomers are possible; **1**; $R^1 = R^3$ = PA, $R^2 = R^4$ = O, **2**; $R^1 = R^4$ = PA, $R^2 = R^3$ = O, **3**; $R^2 = R^3$ = PA, $R^1 = R^4$ = O, **4**: $R^2 = R^4$ = PA, $R^1 = R^3$ = O (PA = $NHCH_2CH_2Me$). 'Wagging' of the diethylenetriamine backbone leads to interconversion of these enantiomers with the mirror images of **1**, **3**, **2**, and **4**, respectively. (*B*) Conformation interconversion in the diethylenetriamine backbone of Ln(L) complexes.

Table 2 Lanthanide induced ^{13}C shifts[a] of Ln(L)[b] and Ln(dtpa) complexes[c] in D_2O at pH 7

Complex	N^1–CH_2–CH_2–N^2	N^1–CH_2–CH_2–N^2	N^2–CH_2–CO_2
Nd(L)	−25.9	−32.3	−10.3
Nd(dtpa)	−26.5	−33.1	−13.7
Pr(L)[d]	−28.9	−41.3	−16.9
Pr(dtpa)	−28.9	−44.3	−20.6

[a] ^{13}C chemical shifts with respect to those of the diamagnetic analogues [La(L) and La(dtpa), respectively]. The terminal and the central N-atoms of the diethylenetriamine group are denoted as N^1 and N^2, respectively. [b] At 85 °C. [c] At 73 °C.[9] [d] Sample prepared by dissolution of equimolar amounts of $PrCl_3 \cdot 6H_2O$ and $Na_3(L)$ in D_2O.

The Dy^{III}-induced ^{17}O shift of water in the presence of the Dy(L) complex (0.05 mol dm^{-3}, pH 7.4, 25 °C), extrapolated to a molar ratio Dy(L)/D_2O of 1 is −2103 ppm. With the use of the procedure described previously,[11–13] it is deduced that 1 (±0.5) water molecule completes the first coordination sphere, which is in agreement with the conclusions based on previous relaxivity measurements.[2]

The magnitudes of the paramagnetic lanthanide induced shifts of the methylene carbons of the diethylenetriamine group and the central glycine unit of the Ln(L) complexes are almost the same as those of the corresponding Ln(dtpa) complexes (see Table 2), which confirms the structural similarity between these complexes.

Additional information on the dynamics of the system could be obtained from variable temperature ^{13}C NMR spectra of the diamagnetic La(L) complex. At 50 °C and 100 MHz, six carboxy and two amide carbonyl ^{13}C signals could be discerned. Increasing the temperature caused coalescence of two pairs of carboxylate signals of about equal intensity. From the coalescence temperatures and the chemical shift differences, the $\Delta G^{\ddagger}$ for the exchange process concerned was estimated to be about 75 kJ mol^{-1}. This barrier is higher than those reported for intramolecular rearrangements *via* 'wagging' processes.[10] Furthermore, it is somewhat larger than the difference in stability between corresponding octadentate and pentadentate bound polyaminopolycarboxylates as estimated from their stability constants.[14] Therefore, this barrier could be explained by inversion of the terminal diethylenetriamine nitrogen atoms, which requires partial decoordination of the ligand. At temperatures below 30 °C broadening of various signals again occurred, probably owing to slowing of the wagging process of the ethylene bridges and, consequently, of the inversion of the central nitrogen atom, with respect to the NMR time scale. All dynamic NMR phenomena reported were independent of the complex concentration (0.02–0.16 mol dm^{-3}), confirming the intramolecular nature of the rearrangements.

A more detailed analysis of the structures of the various forms of the Ln(L) complexes, both in solution and in the solid state, is in progress.

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