Multinuclear Magnetic Resonance Study of the Structure and Dynamics of Lanthanide(III) Complexes of the Bis(propylamide) of Diethylenetriaminepentaacetic Acid in Aqueous Solution

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The structure and dynamics of the lanthanide(III) complexes of the bis(propylamide) of diethylenetriaminepentaacetate (DTPA-PA$_2$) in aqueous solution have been investigated by ^{13}C and ^{17}O NMR. With the use of the longitudinal ^{13}C relaxation times of the Nd^{III} complex it is shown that the organic ligand is bound to the lanthanide(III) ion in an octadentate fashion via the three nitrogens of the diethylenetriamine backbone, the three carboxylate groups, and the two amide oxygens. ^{17}O NMR measurements show that the coordination sphere is completed by one water ligand. The inversion of the lanthanide-bound nitrogens is precluded, and therefore four diastereomeric pairs of isomers are possible for these complexes. Low-temperature ^{13}C NMR spectra show that all these isomers occur in solution. Three dynamic processes have been identified by means of variable-temperature NMR measurements: (i) rapid rotations of the carboxylate groups, (ii) racemization at the middle N atom via interconversions between the two possible conformations of the ethylene bridges, and (iii) racemization at the terminal N atoms of the diethylenetriamine backbone via decoordination–inversion–coordination. The barriers of the interconversions between the enantiomers have been determined by line-shape analysis and from coalescence temperatures. A comparison is made with the Ln^{III} diethylenetriaminepentaacetate (DTPA) complexes.

Introduction

The rapid development of magnetic resonance imaging (MRI) has been of great importance to medical diagnosis. Although excellent soft-tissue images are obtained with this technique, early experiments showed that contrast agents might increase its diagnostic value immensely. Consequently, parallel with the development of MRI, there has been an explosive growth in interest for contrast agents.[1–3] These agents can be applied to enhance the contrast of images, allowing for example an easier recognition of abnormal tissue. It is also possible to map regions in tissue with different accessibility to these reagents as a result of varying barrier permeabilities, flow, or perfusion and to visualize vascular disorders as infarction, stroke, or hypoxic/anoxic effects.

The Gd^{III}–diethylenetriamine-N,N,N',N'',N''-pentaacetate complex [Gd(DTPA)(H$_2$O)]$^{2-}$ is the first contrast agent that has been approved for use in humans and is used nowadays on a routine basis. This paramagnetic complex contains one inner-sphere water molecule[4–7] that exchanges rapidly[8,9] with the bulk water in the body, thereby providing an efficient mechanism for the enhancement of the relaxation rates ($1/T_1$ and $1/T_2$) of the water protons. The latter parameters contribute to the intensity of the MRI signal and thus the contrast of the images.

A drawback of the Gd(DTPA) complex is that it has a negative charge, which, because it is usually administered at 0.5 M, results in a relatively high osmolality under physiological conditions and consequently undesired side effects. The adverse effects of ionic chelates are always higher than those of nonionic ones at the same concentration,[10] and therefore the neutral Gd^{III} complexes of bis(amide) analogues of DTPA (Chart I) and nonionic macrocyclic chelates derived from DOTA (1,4,7,10-tetraazacyclododecane-N,N',N'',N'''-tetraacetate) have recently been introduced as alternatives.[6,11–15] The X-ray crystal structure of the Gd^{III} complex of the bis(ethylamide) of DTPA (DTPA-EA$_2$) revealed that in the solid state Gd^{III} is coordinated to the three nitrogens, the three carboxylates, the two amide carbonyls, and one water.[12] This structure is very similar to that of the Ln^{III} complexes of DTPA, both in the solid state and in aqueous solution.[5,16–18]

This paper reports the results of a multinuclear NMR study on the structure and the dynamics of the Ln^{III} complexes of the bis(propylamide) of DTPA (DTPA-PA$_2$) in aqueous solution. 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 structural analysis of these complexes.[19,20] The Nd^{III}-induced ^{13}C relaxation rate enhancements were utilized to investigate the binding of the organic ligand,
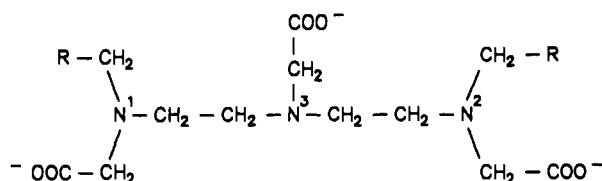
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Chart I

R — CH$_2$
     \
      N^1— CH$_2$ — CH$_2$ — N^3— CH$_2$ — CH$_2$ — N^2
     /
$^-$OOC — CH$_2$

COO$^-$
|
CH$_2$
|
CH$_2$ — R

CH$_2$ — R

CH$_2$ — COO$^-$

DTPA	:	R=COO$^-$
DTPA–A$_2$	:	R=CONH$_2$
DTPA–EA$_2$	:	R=CONHCH$_2$CH$_3$
DTPA–PA$_2$	:	R=CONHCH$_2$CH$_2$CH$_3$

whereas the various Ln^{III}-induced ^{17}O water shifts were employed to determine the water coordination number. Variable-temperature studies were performed in order to get information on the dynamics of these complexes. A comparison is made with the previously studied Ln^{III}–DTPA system.[5] Some initial results of this study were published in a preliminary communication.[21]

Experimental Section

Chemicals and Solutions. The ligand DTPA-PA$_2$ was synthesized according to Sherry et al.[11] or by a procedure analogous to that reported for the corresponding bis(ethylamide) compound.[12] DTPA-A$_2$ was prepared analogous to the latter procedure, using a solution of 25% ammonia in water. This compound was obtained as an oil, and it was used without further purification. ^{13}C NMR (100.6 MHz, D$_2$O, pH 4.5): δ 52.41, 53.81, 56.61, 59.04, 59.42, 173.50, 175.91, and 177.71.

^{17}O-enrichment of the carboxylate groups of DTPA-PA$_2$ was achieved by heating the compound in 10% ^{17}O-enriched water (Icon Services, Inc., Summit, NJ) for 10 h at 90 °C, followed by evaporation of the solvent and drying the residue under vacuo over zeolite KA. It is known that under these conditions amide oxygens do not exchange with water.[22]

The La^{III}, Nd^{III}, and Dy^{III} complexes were prepared according to a procedure analogous to that described by Raymond et al. for the Gd-(DTPA-EA$_2$) complex.[12] The complexes were obtained as hydrates Ln-(DTPA-PA$_2$)·nH$_2$O (n = 1–3). The elemental analysis were within 0.3% of the theoretical values. The FAB mass spectra showed the expected (M + 1)$^+$ cluster.

Samples of the Ln^{III} complexes for the NMR measurements were prepared by dissolution of solid Ln(DTPA-PA$_2$) in D$_2$O or by mixing of equimolar solutions of DTPA-PA$_2$ and hydrated LnCl$_3$ (Aldrich Chemical Co.), followed by adjustment of the pH with a solution of NaOD in D$_2$O. The pH of the solutions was measured at room temperature with a calibrated microcombination probe purchased from Aldrich Chemical Co. The pH values given are direct meter readings.

NMR Measurements. The NMR spectra were recorded with a Nicolet NT-200 WB or a Varian VXR-400 S spectrometer. For ^{13}C NMR *tert*-butyl alcohol was used as internal standard (methyl signal at 31.2 ppm). The ^{17}O chemical shifts were determined with respect to D$_2$O as external standard. The chemical shifts of the ^{17}O signals were determined by fitting the observed signal with a Lorenzian line function. Downfield-induced shifts are denoted as positive.

Longitudinal relaxation rates were measured with the Nicolet NT-200 WB spectrometer by using a [(90°$_x$180°$_y$90°$_x$)–τ–90°–acq] inversion recovery pulse sequence. The T_1 values were calculated by using a three-parameter fit of the experimental data.[23]

Results and Discussion

^{13}C NMR Spectra. The ^{13}C NMR spectra of the diamagnetic La^{III}- and Lu^{III}–DTPA-PA$_2$ complexes in D$_2$O at 25 °C indicated that various species were present in solution. Both complexes displayed two sets of signals for the propyl group. The La^{III}
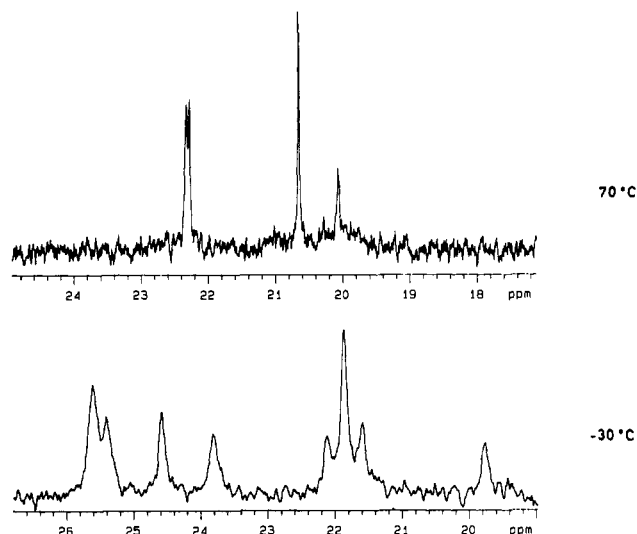

Figure 1. Influence of the temperature on the 100.6-MHz ^{13}C NMR β-methylene carbons of the Nd(DTPA-PA$_2$) complex in CD$_3$OD–D$_2$O (1:1, v/v).

complex showed five carboxylate and two amide carbonyl signals, whereas in the ^{13}C NMR spectrum of the Lu^{III} complex six carboxylate and four amide carbonyl signals could be discerned.[24] The region between 56 and 68 ppm, in which the other signals occur, was very complex due to overlap of peaks. At room temperature ^{13}C NMR spectra of the paramagnetic complexes exhibited very broad and featureless signals, usually only signals for the propyl groups could be recognized. Increasing the temperature to 75 °C resulted in an appreciable sharpening of the signals, and at this temperature good spectra for the complexes of the lighter lanthanides (Ce → Eu) with DTPA-PA$_2$ could be obtained (see supplementary material). The spectra for Ln = Tb → Yb were still very broad, and therefore, these spectra were not taken into consideration. The broadening of the spectra can be ascribed to exchange phenomena as a result of the conformational mobility of the complexes. Similar phenomena have been observed with Ln(DTPA) complexes[5,16] and with Ln^{III} complexes of macrocyclic polyamino carboxylates, such as DOTA.[25]

The spectra of the paramagnetic Ln(DTPA-PA$_2$) complexes at high temperature (>70 °C) confirmed the presence of many types of ligand environment in solution. For example, the ^{13}C NMR spectrum of the Nd(DTPA-PA$_2$) complex in D$_2$O at 100 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 groups. Upon cooling of the sample to 3 °C, substantial broadening occurred and most of the signals were very weak. A sample in CD$_3$OD (1:1 v/v) at –30 °C gave a spectrum in which each of the four signals of both the β-methylene and the methyl carbons of the propylamide group were split into two new signals (see Figure 1). Since the two propyl groups of the Nd^{III}-bound ligand may be chemically different, this implies that at least four species are present in solution.

The methylene carbons of the diethylenetriamine group and the central glycine unit of the Ln(DTPA-PA$_2$) complexes (Ln = La → Eu) gave, depending on the Ln^{III} ion, broad signals or clusters of signals at roughly the same chemical shifts as those of the corresponding Ln(DTPA) complexes (see Table I), which suggests that there is similarity among the various species of the Ln(DTPA-PA$_2$) complexes and between these complexes and

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Table I. Comparison of ^{13}C Chemical Shifts[a] of Ln(DTPA-PA$_2$)[b] with Those of Ln(DTPA)[c] Complexes

complex	N^{1}CH$_2$CH$_2$N^3	N^{1}CH$_2$CH$_2$N^3	N^{3}CH$_2$CO$_2$
La(DTPA)	59.11	57.71	66.57
La(DTPA-PA$_2$)	58.4–59.0	57.3	65.5
Ce(DTPA)	46.06	36.10	53.17
Ce(DTPA-PA$_2$)	47.5	39.1–40.8	57.0–58.1
Pr(DTPA)	30.18	13.45	45.99
Pr(DTPA-PA$_2$)	30.1	16.7	49.2
Nd(DTPA)	32.60	24.59	52.88
Nd(DTPA-PA$_2$)	31.9	24.0	54.8–55.3
Sm(DTPA)	58.23	56.68	66.69
Sm(DTPA-PA$_2$)	57.4–58.2	57.4–58.2	65.5
Eu(DTPA)	99.48	114.82	96.07
Eu(DTPA-PA$_2$)	98.2	114.8	93.8–94.1

[a] In ppm; in D$_2$O at pD 7 and 73 °C; internal standard *tert*-butyl alcohol (CH$_3$: 31.20 ppm). The terminal and the middle N-atoms are denoted as N^1 and N^3, respectively. [b] Measured from 0.16 M samples. At the chemical shifts given, several signals or a broad signal was observed. [c] Measured from samples obtained upon adding Ln^{III} to a 0.13 M solution of Li$_5$(DTPA) in D$_2$O. Molar ratio Ln^{III}/DTPA = 0.7.

Table II. Longitudinal ^{13}C Relaxation Times (T_1) of Nd(DTPA-PA$_2$) and of La(DTPA-PA$_2$) in D$_2$O at 85 °C and 50.3 MHz, Measured in 0.16 M Solutions of the Complex

δ (ppm)	T_1 (s)	assgnt	δ (ppm)	T_1 (s)	assgnt
		Nd(DTPA-PA$_2$)			
186.38	0.132	CO	44.47	0.870	α-CH$_2$ (propyl)
182.95	0.137	CO	43.37	0.854	α-CH$_2$ (propyl)
177.04	0.136	CO	42.58	0.883	α-CH$_2$ (propyl)
175.99	0.160	CO	33.11	0.136	N^{1}CH$_2$CH$_2$N^3
172.68	0.161	CO	25.08	0.145	N^{1}CH$_2$CH$_2$N^3
170.84	0.143	CO	23.34	1.597	β-CH$_2$ (propyl)
168.07	0.143	CO	23.17	1.626	β-CH$_2$ (propyl)
164.70	0.131	CO	22.15	1.555	β-CH$_2$ (propyl)
70.67	0.134	CH$_2$CO	21.70	1.577	β-CH$_2$ (propyl)
67.24	0.143	CH$_2$CO	12.36	3.008	γ-CH$_3$ (propyl)
61.18	0.139	CH$_2$CO	12.11	2.941	γ-CH$_3$ (propyl)
55.57	0.134	CH$_2$CO	11.60	2.802	γ-CH$_3$ (propyl)
45.02	0.853	α-CH$_2$ (propyl)	11.31	2.559	γ-CH$_3$ (propyl)
		La(DTPA-PA$_2$)			
181.64	7.67	CO	62.36	0.479	CH$_2$CO
180.82	8.03	CO	58.8	0.342	N^{1}CH$_2$CH$_2$N^3 [a]
176.91	7.88	CO	57.3	0.348	N^{1}CH$_2$CH$_2$N^3 [a]
176.17	6.39	CO	43.19	1.12	α-CH$_2$ (propyl)
65.70	0.390	CH$_2$CO	22.83	1.80	β-CH$_2$ (propyl)
64.01	0.383	CH$_2$CO	11.87	4.11	γ-CH$_3$ (propyl)

[a] These assignments may be interchanged.

the Ln(DTPA) complexes. Attempts to fit the spectra to calculated ones for various models failed, due to the complexity of the spectra as a result of the large number of species present in solution, which hampered a full assignment of the spectra.

As a consequence of the partial double-bond character of the amide C–N bond, the rotation around this bond is restricted, which could give rise to a 4-fold splitting of the ^{13}C signals. However, in the ^{13}C and ^1H spectra of the free DTPA-PA$_2$ ligand, separate signals for the various rotamers were not observed, as probably fast rotations around the other bonds in this compound average out the chemical shift differences. Upon binding of the ligand to a paramagnetic Ln^{III} ion, as a result of the reduced ligand flexibility and of paramagnetic effects on the chemical shifts, the rotation around the amide C–N bonds might become slow on the ^{13}C NMR time scale. This could give rise to a 4-fold splitting of the various ^{13}C signals. However, the ^{13}C NMR spectrum of the Nd^{III} complex of DTPA–bis(amide) (DTPA-A$_2$) for which the rotamers are identical, showed an analogous 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 slow rotations around the amide C–N bonds cannot explain the occurrence of multiple sets of signals in the ^{13}C NMR spectra of the Ln–DTPA-PA$_2$ complexes.

Nd^{III}-Induced Relaxation Rate Enhancements. Among the lighter Ln^{III} ions (Ln = Ce → Eu) Nd^{III} has the longest electron relaxation times[26] and, therefore, this lanthanide was selected for a study of the coordination of the DTPA-PA$_2$ ligand by means of ^{13}C NMR longitudinal relaxation rates. The measurements were performed at 85 °C and 50.3 MHz. From the variable-temperature spectra of the Nd(DTPA-PA$_2$) complex (see above), it can be concluded that under these conditions fast exchange on the NMR time scale occurs between several ligand nuclei, which probably can be ascribed to exchange between species. Assuming that there are two species A and B, which are in fast exchange on the NMR time scale, the observed longitudinal relaxation rate of a nucleus ($1/T_{1,obs}$) is given by[27,28]

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

where $T_{1,A}$ and $T_{1,B}$ are the intrinsic relaxation times in the absence of exchange and f_A and f_B are the molar fractions of A and B. For exchange between more than two species analogous expressions can be derived. For each isomer the relaxation rate can be related to its structure via the reduced Solomon–Bloembergen equation:[26,29]

$$1/T_1 = {}^4/_3(\mu_0/4\pi)^2(\mu^2\gamma^2\beta^2 T_{1,e}/r^6) \qquad (2)$$

Here $\mu_0/4\pi$ is the magnetic permeability under vacuum, μ is the effective magnetic moment of the lanthanide ion, γ is the magnetogyric ratio, β is the Bohr magneton, $T_{1,e}$ is the electron spin relaxation time, and r is the distance between the ^{13}C nucleus in question and the lanthanide ion.

The relaxation rates obtained for the various ^{13}C signals are compiled in Table II. It can be seen that the magnitudes of the relaxation rates for corresponding nuclei of the various species are about the same. In order to obtain a correction for diamagnetic effects the relaxation rates of the La(DTPA-PA$_2$) complex were measured as well (see Table II). In Table III the ranges of corrected relaxation rates for the various nuclei are given. It has been shown that T_{1e} usually is rather independent of the ligation of the Ln^{III} cation.[30,32] For example, the values of T_{1e} for Gd(DTPA)$^{2-}$ and Gd(DTPA–bisamide) as obtained from solution EPR measurements are very similar.[33] For lanthanides other than Gd, large deviations from T_{1e} would be expected only for complexes with very rigid and symmetric macrocyclic ligands.[34] By use of the data reported by Alsaadi et al. on Nd^{III} complexes of DTPA and related amino polycarboxylate ligands,[30] $T_{1,e}$ for the Nd(DTPA-PA$_2$) complexes at 85 °C is estimated to be 0.9 × 10^{-13} s. Then "averaged" distances r were calculated from the corrected relaxation rates and eq 2. The distances obtained are given in Table III. From these distances it can be concluded that the DTPA-PA$_2$ ligand is bound to the Ln^{III} ion via the three carboxylate groups (in a monodentate fashion), the two amide oxygens, and the three N atoms of the diethylenetriamine unit. The presence of significant amounts of isomers, in which one of the carboxylate or amide groups is not coordinated to Ln^{III}, can be excluded because, according to eq 2, this would have been reflected in relative large values for $1/T_1$ for the concerning ^{13}C nuclei. The structure of the Nd(DTPA-PA$_2$) complex is analogous to those of the previously reported Nd(DTPA) complex in solution[5] and the solid-state structure of Gd(DTPA-EA$_2$).[12] For com-

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Table III. Nd^{III}-Induced ^{13}C Relaxation Rate Enhancements $(1/T_1)$ and Nd^{III}–C Distances in the Isomers of Nd(DTPA-PA$_2$): Comparison with Distances in the Nd(DTPA)$^{2-}$ Complex[5] and in the Solid-State Structure of Gd(DTPA-EA$_2$)[12]

nucleus	$1/T_1$ (s^{-1})[a]		r (Å)		
	Nd(DTPA-PA$_2$) (soln)	Nd(DTPA) (soln)[b]	Nd(DTPA-PA$_2$) (soln)	Nd(DTPA) (soln)[b]	Gd(DTPA-EA$_2$) (X-ray)[c]
CO	6.07–7.48	5.99–6.53	3.08–3.19	3.15–3.20	3.25–3.31
CH$_2$CO	4.40–5.39	e	3.25–3.37	e	3.40–3.56
N^{1}CH$_2$CH$_2$N^3	3.96–4.02	5.89	3.42–3.43	3.21	3.46–3.54
N^{1}CH$_2$CH$_2$N^3	4.42–4.47	3.61	3.36–3.36	3.48	3.46–3.51
α-CH$_2$ (propyl)	0.24–0.28		5.33–5.47		5.13–5.23
β-CH$_2$ (propyl)	0.06–0.09		6.46–6.89		5.26–6.45
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 relaxation rates of the corresponding La^{III} complex. Soln = solution. [b] Calculated from the corrected relaxation rates and eq 2. [c] Reference 5. [d] Reference 12. [e] Not measured, because of overlapping signals.
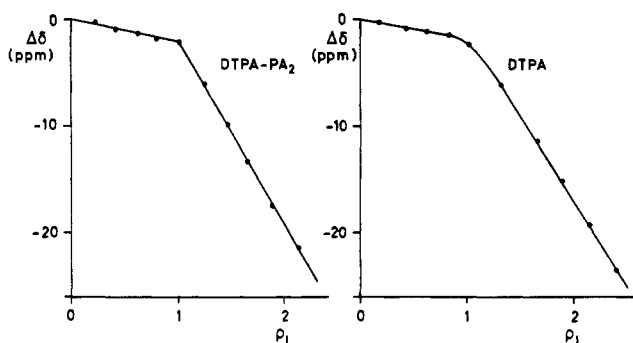
Figure 2. Plot of the Dy^{III}-induced water ^{17}O shift versus the molar ratio Dy^{III}/organic ligand (ρ_L) for 0.05 M solutions of DTPA-PA$_2$ and DTPA in D$_2$O at 25 °C.

parison Ln^{III}–C distances in the latter complexes are included in Table III. It can be seen that they are in agreement with the distances obtained now for the Nd(DTPA-PA$_2$) complex. The inversion of the three N atoms in the diethylenetriamine backbone of DTPA-PA$_2$ is precluded upon binding to Nd^{III}. Then these N atoms are chiral, and in principle eight enantiomeric forms (four diastereomeric pairs) are possible for the Ln^{III}-bound ligand, which explains the large number of ^{13}C NMR signals observed for these complexes.

Ln^{III}-Induced Water ^{17}O Shifts. Upon addition of Dy^{III} to a solution of DTPA-PA$_2$ in D$_2$O, the water ^{17}O shift decreases linearly as the molar ratio Dy^{III}/DTPA-PA$_2$ (ρ_L) increases. The exchange of water between the Dy^{III} complex and the bulk is fast on the ^{17}O NMR time scale. At $\rho_L = 1.0$, a steep increase in the magnitude of the (negative) induced shift occurred; the slope of the line at $\rho_L > 1.0$ was 8.4 times as large as that of the line at $\rho_L < 1.0$ and equal to the slope of the line, obtained when the experiment was performed in the absence of DTPA-PA$_2$ (see Figure 2). The sharp change in the slope of the curve at $\rho_L = 1.0$ is in agreement with the high stability constants of the Ln–DTPA-PA$_2$ complexes (log $K = 16.23$ for Ln = Gd).[11] Previously, we have shown that the Dy^{III}-induced ^{17}O water shift is almost independent of the other ligands coordinated to the Dy^{III} ion.[35-38] Consequently the slope of the plot of the Dy^{III}-induced shift versus the molar ratio Dy^{III}/water (ρ_w) can be used to determine the hydration numbers of Dy^{III} complexes. If it is assumed that in the absence of organic ligands Dy^{III} in D$_2$O is coordinated by 8 or 9 water ligands, then it can be concluded that one Dy^{III}-bound water is present in the Dy(DTPA-PA$_2$) complexes. The total coordination number is therefore 9, which is the most common value for aqueous systems with this type of ligands. The plot of

the Dy^{III}-induced shift verus ρ_L for the system Dy^{III}-DTPA (see Figure 2) is analogous, with exception of the change of the slope of the curve at $\rho_L = 1.0$, which was not sharp but gradual. The stability constants of the Ln(DTPA) complexes (log $K = 22.26$ for Ln = Gd)[11] are however much higher than those for the DTPA-PA$_2$ complexes. The different shape of the curve around $\rho_L = 1$ has to be ascribed to the binding of Dy^{III} ions to the carboxylate groups in the second coordination sphere of the [Dy(DTPA)]$^{2-}$ complex, which has been shown to occur previously.[5] Apparently, the affinity of the neutral Dy(DTPA-PA$_2$) complex for Dy^{III} cations is much smaller.

In order to obtain the number of inner-sphere water molecules in the other Ln(DTPA-PA$_2$) complexes, a more rigorous treatment of the Ln^{III}-induced water ^{17}O shifts is required. The induced shifts (Δ) are a combination of diamagnetic (Δ_d), contact (Δ_c), and pseudocontact shifts (Δ_p). The value of Δ_d can be estimated from an interpolation of the induced shifts for La^{III} and Lu^{III}. The contact contribution results from a through-bond transmission of unpaired spin density of the Ln^{III} cation in question, whereas the pseudocontact shift arises from a through-space dipolar interaction between the magnetic moments of the unpaired electrons of the Ln^{III} ion and the ^{17}O nucleus. Both Δ_c and Δ_p can be written as the product of a term that is characteristic of the Ln^{III} ion but independent of the complex structure ($\langle S_z \rangle$ and C^D, respectively) and a second term that is characteristic of the complex but that is independent of the Ln^{III} ion (F and G, respectively):[39,40]

$$\Delta' = \Delta - \Delta_d = \Delta_c + \Delta_p = \langle S_z \rangle F + C^D G \qquad (3)$$

Values for $\langle S_z \rangle$ and C^D are tabulated in the literature.[39-43] When the various Ln^{III} complexes are isostructural, eq 3 can be rearranged in a linear form:[44]

$$\Delta'/C^D = \langle S_z \rangle F/C^D + G \qquad (4)$$

So, when a series of Ln^{III} complexes yields a linear plot of Δ'/C^D versus $\langle S_z \rangle/C^D$, this is an indication that they are isostructural.[44,45]

The water ^{17}O shifts obtained for the various Ln–DTPA-PA$_2$ systems at 73 °C were extrapolated to $\rho_w = 1$ (see Table IV). The values obtained correspond to $n\Delta$, where n is the number of Ln^{III}-bound waters in the concerning complex. A plot of these shifts according to eq 4 gives a straight line (see Figure 3), which shows that no change of the number of inner-sphere waters occurs along the lanthanide series. By means of a multiple regression method[46] the values of nF and nG were determined to be –68 and 8.56,

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Table IV. Lanthanide-Induced Water ^{17}O Shifts (ppm) for 0.16 M Ln^{III}(DTPA-PA$_2$) Complexes in D$_2$O at pD 7 and 73 °C

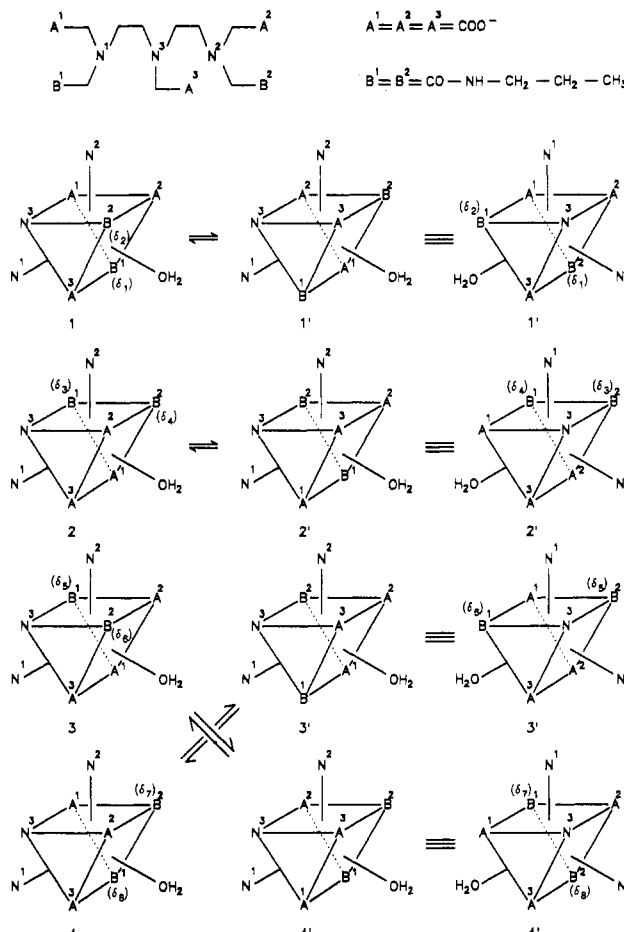| Ln^{III}	δ (ppm)^a	Ln^{III}	δ (ppm)^a
La	338	Dy	−1960
Ce	381	Ho	−1051
Pr	511	Er	−238
Nd	648	Tm	464
Sm	297	Yb	314
Eu	−320	Lu	421
Tb	−1901		

^{a} The shifts were obtained using plots analogous to that given in Figure 2. The values are extrapolated to a molar ratio of Ln^{III}/water (ρ_w) = 1. The relative errors are 5%.
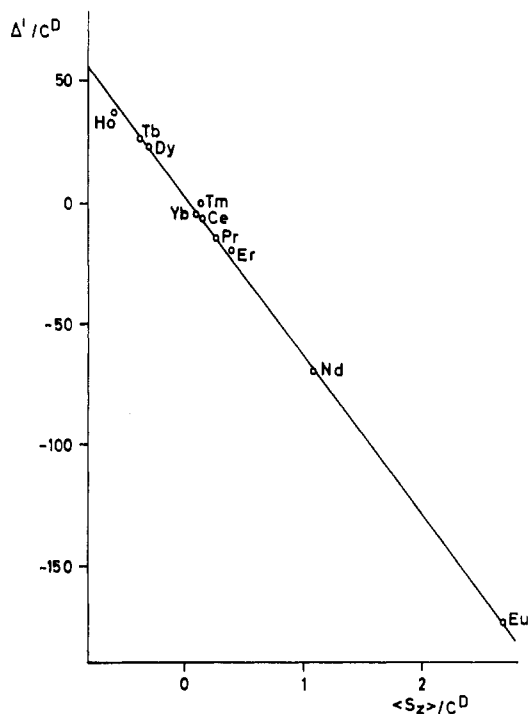
Figure 3. Plot of Δ'/C^D versus $\langle S_z \rangle /C^D$ for the ^{17}O signal in the Ln–DTPA-PA$_2$ system at 73 °C.

respectively. Previously, it has been observed that the values of F for Ln^{III}-bound oxygens are in a rather small range of −70 ± 11 at 73 °C.[35-37] Therefore from the value of nF obtained it can be concluded that $n = 1$ for all Ln^{III}–DTPA-PA$_2$ complexes, which is in agreement with the results of previous fluorescence and relaxivity measurements.[6]

Chemical Exchange between the Various Ln(DTPA-PA$_2$) Isomers. From the results of the ^{13}C relaxation rate measurements and the Ln^{III}-induced water ^{17}O measurements it can be concluded that the Ln(DTPA-PA$_2$) complexes are nine-coordinate with DTPA-PA$_2$ bound in an octadentate fashion and with one water molecule in the first coordination sphere. The coordination polyhedron of nine-coordinate Ln^{III} compounds can usually be described by a distorted tricapped trigonal prism or by a distorted monocapped square antiprism.[47] These two geometries are closely related[48] and often a particular structure can be described by both geometries equally well. The X-ray structure of the Gd-(DTPA-EA$_2$) complex can be best described by a tricapped trigonal prism,[12] and therefore, we will discuss the solution structure also in terms of this polyhedron. A similar discussion can, however, be given for a monocapped square antiprism.

An inspection of molecular models shows that DTPA-PA$_2$ can only be arranged around a Ln^{III} ion when the middle nitrogen

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$A^1 = A^2 = A^3 = COO^-$

$B^1 = B^2 = CO-NH-CH_2-CH_2-CH_3$

Figure 4. Coordination polyhedrons of the eight enantiomers of the Ln-(DTPA-PA$_2$) complex, assuming that the geometry is a tricapped trigonal prism. The interconversions via the "wagging" process are indicated. Between parentheses are fictitious chemical shifts of corresponding nuclei in the amide groups (see text). It should be noted that no discrimination can be made between A^1 and A^2, B^1 and B^2, and N^1 and N^2. These groups are labeled in order to be able to follow them during the rearrangements.
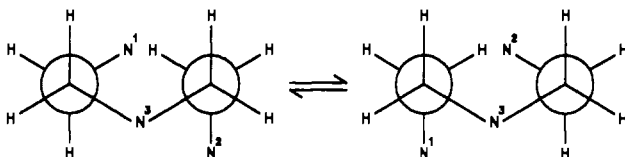
Figure 5. Conformational interconversion in the diethylenetriamine backbone of Ln(DTPA-PA$_2$) complexes.

atom (N^3; see Figure 4) is on a "prismatic" position, whereas the terminal N-atoms (N^1 and N^2) and the water ligand have to occupy the capping positions. The eight possible enantiomers of the bound ligand give rise to the complex geometries depicted in Figure 4. Geometries **1'**–**4'** are the mirror images of **1**–**4**. Thus for each nucleus in the DTPA-PA$_2$ ligand in principle four signals can be expected. The paramagnetic properties of the Ln^{III} ion magnify the chemical shift differences between these signals. This is in agreement with the observation of, for example, eight peaks for the methylene carbons of the two propyl groups of the Nd–DTPA-PA$_2$ complex at −30 °C. The molecular models also suggest that two different staggered ethane conformations are possible on either side of the middle N-atom (N^3). For the corresponding Ln(DTPA) complexes, it has been shown that a "wagging" between these conformations occurs (Figure 5). This process requires a rearrangement of the coordination polyhedron, during which the groups A^1/B^1 and A^2/B^2 interconvert between a rectangular and a triangular edge of the tricapped trigonal prism (see Figure 4). For isomers **1** and **2** the "wagging" causes

an interconversion with the mirror images **1'** and **2'**, respectively. Structure **3**, however, is interconverting with the mirror image of **4** (**4'**), and similarly **4** is exchanging with **3'** via the "wagging" process. This leads to a reduction of the number of NMR signals, when these interconversions become rapid on the NMR time scale. Consider, for example, corresponding nuclei in the amide groups B^1 and B^2. If these nuclei have chemical shifts δ_1 and δ_2, respectively, in isomer **1**, then in **1'** the chemical shifts have been interchanged to δ_2 and δ_1, respectively (see Figure 4). When the exchange is fast on the NMR time scale, these nuclei will coalesce to a single signal with chemical shift $(\delta_1 + \delta_2)/2$. Similar phenomena occur upon exchange between **2** and **2'**. For isomers **3** and **4** the situation is different. If in isomer **3** the amide nuclei B$_1$ and B$_2$ have chemical shifts δ_5 and δ_6, respectively, then after the rearrangement to **4'** the chemical shifts will have different values, say δ_7 and δ_8. So in the case of rapid exchange two new signals are obtained at $(\delta_5 + \delta_7)/2$ and $(\delta_6 + \delta_8)/2$, respectively. Since **4** is the mirror image of **4'**, the chemical shifts of B$_1$ and B$_2$ in the former isomer are δ_8 and δ_7, respectively. Similarly, it can be seen that the shifts of these nuclei in **3'** are δ_6 and δ_5. The exchange between **4** and **3'** leads then again to signals at $(\delta_5 + \delta_7)/2$ and $(\delta_6 + \delta_8)/2$, in the case of fast exchange on the NMR time scale. Thus the two signals of the interconverting couple **3** ⇌ **4'** are coinciding with those of the couple **4** ⇌ **3'**. Altogether, the number of signals for the nuclei concerned in B$_1$ and B$_2$ decreases from 8 to 4 upon going from the slow to the fast exchange region of the "wagging" process. This is in agreement with the observations in the ^{13}C spectra between –30 and +70 °C (see Figure 2). From the coalescence temperatures it can be estimated that $\Delta G^{\ddagger}_{283} = 53$ kJ/mol for this rearrangement. This is about the same as the value found for Ln(DTPA) complexes (for example, Pr(DTPA)$^{2-}$: $\Delta G^{\ddagger}_{298} = 56.5$ kJ/mol).[16] Replacement of two carboxylate groups by the relatively weak coordinating amide groups has no influence on the activation barrier. Probably, this barrier is determined by the eclipsing in the ethylene bridges in the diethylenetriamine backbone at the transition state. This is in line with the higher barriers observed for a similar process in lanthanide complexes of macrocyclic ligands, such as DOTA,[25] where two more ethylene groups are eclipsing in the transition state.

The chemical shift differences between corresponding nuclei in the various isomers are considerably smaller in the diamagnetic La^{III} and Lu^{III} complexes of DTPA-PA$_2$. This allowed the identification of a dynamic process with a higher barrier. Upon increasing of the temperature from 10 to 90 °C, a substantial increase of the line widths was observed in the ^{13}C spectra of these complexes, and some of the signals were coalescing. If it is assumed that exchange associated with the lines that broaden but do not coalesce in the temperature range mentioned is slow on the NMR time scale, then the exchange rate (k) can be calculated from the observed line widths ($\Delta\nu_{1/2}$) with[49]

$$k = \pi(\Delta\nu_{1/2} - \Delta\nu_{1/2}(0)) \tag{5}$$

where $\Delta\nu_{1/2}(0)$ is the line width in the absence of exchange. Then from the slope and the intercept of an Eyring plot, $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ can be calculated. In Figure 6 the Eyring plot for one of the carboxylate signals is given as an example. Using the line widths of eight ^{13}C signals of the La(DTPA-PA$_2$) complex and five signals of the Lu(DTPA-PA$_2$) complex, the activation parameters compiled in Table V were obtained. These values were in good agreement with the $\Delta G^{\ddagger}$ values estimated from the coalescence temperatures of some other lines in the spectra. The difference in the parameters between the La^{III} and the Lu^{III} complex is negligible. These dynamic phenomena were independent of the complex concentration (0.02–0.16 M), which indicates that the concerning complex rearrangements are intramolecular. The
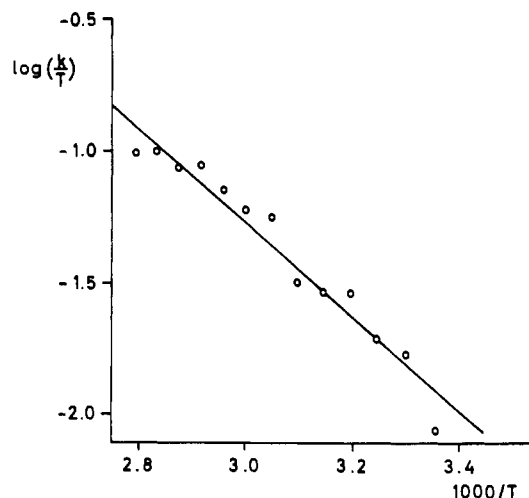

Figure 6. Eyring plot for the rearrangements in the La(DTPA-PA$_2$) complex. The data were obtained at 100.6 MHz from the line widths of the carboxylate signal at 182.8 ppm.

Table V. Kinetic Data for Rearrangements in Ln(DTPA-PA$_2$) Complexes^a

dynamic process	Ln	$\Delta G^{\ddagger}_{283}$ (kJ/mol)	$\Delta H^{\ddagger}$ (kJ/mol)	$\Delta S^{\ddagger}$ (J/mol K)	k_{283} (s^{-1})
racemization at N^1,N^2	La^b	71(1)	47(8)	–84(25)	0.7
	Lu^c	67(1)	42(8)	–88(20)	2.4
racemization at N^3 ("wagging")	Nd^d	53(1)			3.5 × 10^2
rotation COO groups	La^e	<43			>9.6 × 10^3

^{a} Measured with 0.16 M solutions in D$_2$O. ^{b} From ^{13}C NMR line shapes (100.6 MHz). Average of the results of eight lines. Exchange rates are estimated from extrapolations of Eyring plots. ^{c} As in b. Average of the results of five lines. ^{d} From coalescence temperatures of ^{13}C NMR signals (at 100.6 MHz). ^{e} From ^{17}O NMR measurements (at 54.2 MHz; see text).

barriers obtained are somewhat higher than the difference in stability between corresponding octadentate and pentadentate bound polyamino polycarboxylates as estimated from their stability constants.[50] Therefore, this barrier can be explained by inversion of the terminal diethylenetriamine N-atoms (N$_1$ and N$_2$), which requires partial decoordination of the ligand, thus by the exchanges **1** ⇌ **3**, **1'** ⇌ **3'**, **1** ⇌ **4**, **1'** ⇌ **4'**, **2** ⇌ **3**, **2'** ⇌ **3'**, **2** ⇌ **4**, and **2'** ⇌ **4'** (see Figure 4).

In the diamagnetic Ln(DTPA) complexes no line broadening was observed in the ^{13}C spectra upon increasing the temperature from 20 to 90 °C, which nicely demonstrates the difference in coordination strength between a carboxylate and an amide function.

A sample of a La(DTPA-PA$_2$) complex in which the carboxylate groups were about 5% enriched with ^{17}O showed at 54.2 MHz and 90 °C an ^{17}O spectrum with broad lines at 280 and 290 ppm with an integral ratio of 1:2. These lines are assigned to the middle and the terminal carboxylate groups, respectively. Since the carboxylate groups are bound to the Ln^{III} ion in a monodentate fashion, the oxygens within each carboxylate group are chemically inequivalent. Apparently, the exchange between these oxygen atoms is rapid on the ^{17}O NMR time scale as a result of rotation. The slow-exchange region could not be reached by cooling to 10 °C. In ^{17}O spectra of Al^{III} complexes of various carboxylates the carboxylate rotation has been observed to be slow on the NMR time scale.[51] In those cases peaks were observed at about 220 and 300 ppm for the Al^{III}-bound oxygens and the

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noncoordinated oxygens of the carboxylate groups, respectively. If we assume that, under slow-exchange conditions, the chemical shift difference in the case of La(DTPA-PA$_2$) complexes is about the same and that the coalescence temperature of these signals is below 10 °C, then using standard methods[49] the upper limit of $\Delta G^{\ddagger}$ for the rotation of the carboxylate groups in the La-(DTPA-PA$_2$) complex can be estimated to be 43 kJ/mol.

Conclusions

In conclusion we have shown that DTPA-PA$_2$ is coordinated to Ln^{III} ions in an octadentate fashion via the three N atoms of the diethylenetriamine backbone, three carboxylate oxygens, and the two amide oxygens. All Ln^{III} complexes contain one inner-sphere water molecule. The four possible diastereomeric pairs all occur in aqueous solution. This is, for example, illustrated by the observation of eight signals for the β- and for the γ-^{13}C nuclei of the two propyl groups of the Nd(DTPA-PA$_2$)(H$_2$O) complex at –30 °C.

The conformational mobility of the ethylene bridges leads to an exchange between the enantiomers, a mechanism which is similar to that observed in the corresponding Ln(DTPA) complexes.[5,16] The barrier of these exchanges is determined by the eclipsing in the ethylene bridges at the transition state. As a result of relatively weak coordinating strength of the amide group with respect to carboxylate, a racemization process at the terminal N-atoms could be observed, which involves decoordination and N-inversion. In the DTPA complexes this process is too slow to be observed by line-shape analysis.

Supplementary Material Available: ^{13}C NMR spectra of Ln^{III} complexes of DTPA-PA$_2$ (Ln = La, Ce, Pr, Nd, Sm, Eu) (6 pages). Ordering information is given on any current masthead page.