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NMR Study of Solution Structures and Dynamics of Lanthanide(III) Complexes of DOTA

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The low-temperature limiting NMR spectra (^{1}H and ^{13}C) of 12 LnDOTA$^-$ complexes (Ln = La, Pr, Nd, Sm, Eu, Tb, Dy, Ho, Er, Tm, Yb, and Lu) support the presence in solution of two isomeric forms. The relative abundance of the two isomers changes markedly along the lanthanide series with no apparent trend; NMR data suggest that the structure of the major isomer of LaDOTA$^-$ corresponds to that one of the minor isomer of the corresponding Lu^{3+} complex. The solution structures of the two isomers are assigned on the basis of a fitting procedure of calculated to experimental chemical shifts of the resonances of the proton spectrum of YbDOTA$^-$. The Yb^{3+}–hydrogen distances utilized in these calculations are determined by exploiting the Curie spin mechanism contribution to the longitudinal and transverse proton relaxation rates. The solution structures of the two isomers differ for the layout of the acetate arms, the cyclododecane ring conformation being identical in both species. The interconversion between the two isomers occurs as the temperature is increased and this process may be independent of the rearrangement involving the cyclododecane ring, as shown from the ^{13}C-VT NMR spectra of the Nd^{3+} complex and 2D-EXSY experiments on the Yb^{3+} complex respectively.

Introduction

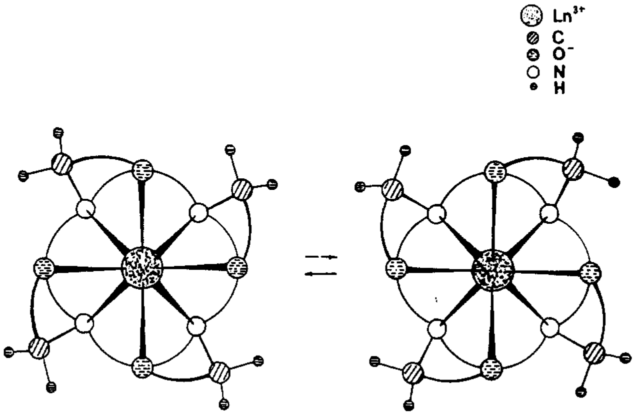
The macrocyclic ligand 1,4,7,10-tetraazacyclododecane-*N,N′,N″,N‴*-tetraacetic acid (DOTA) exhibits a very strong complexing ability toward lanthanide(III) ions because it provides a preformed internal cavity of eight donor sites well suited to wrap around the metal ions. This results in tightly packed complexes with high thermodynamic and kinetic stabilities.[1,2] The X-ray solid state structures of Eu^{3+} [3] and Gd^{3+} [4] complexes show that DOTA acts as an octadentate ligand with four nitrogen and four oxygen donor atoms arranged to describe a square antiprismatic geometry with a ninth axial coordination site occupied by a water molecule.

The ^{1}H NMR spectra of some LnDOTA$^-$ complexes (Ln = La, Lu, Eu, Yb) were already reported by Desreux in 1980,[5] who showed that the rigidity of the macrocycle ring is lost as the temperature is increased. He suggested that the dynamic process in DOTA complexes occurs through successive changes in conformations of the ethylenic groups. As shown in Scheme I, this leads to the interchange between two enantiomeric structures, which are of course indistinguishable from the NMR point of view. The concerted rotation of the ethylenic moieties along the C–C bonds and the "flip-flop" motion of the four carboxylate groups exchange the proton sites according to Scheme II.

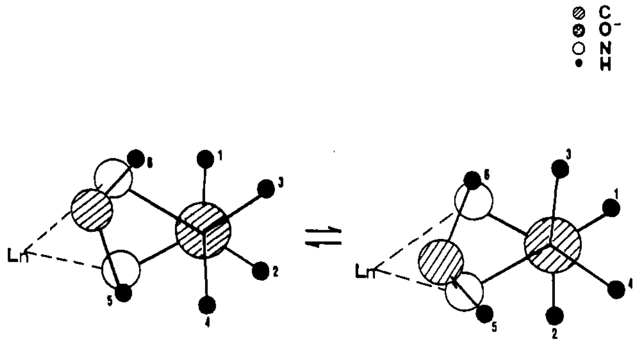
Both Eu^{3+} and Yb^{3+} complexes showed in their NMR spectra some low intensity resonances (roughly accounted for about 10–30% of the main species) which were not considered at that time.[5] In a later paper dealing with the strictly related [1*R*-(1*R**,4*R**,7*R**,10*R**)]-$\alpha,\alpha',\alpha'',\alpha'''$-tetramethyl-1,4,7,10-tetraazacyclododecanetetraacetic acid YbDOTMA$^-$ complex,[6] these additional resonances were assigned to an isomeric form of these complexes.

In order to get more insight into the solution structures and dynamics of these species we undertook a systematic NMR study of 12 LnDOTA$^-$ complexes (Ln = La, Pr, Nd, Sm, Eu, Yb, Tb, Ho, Dy, Er, Tm, Lu).

Scheme I



Scheme II



Experimental Section

The DOTA ligand was provided by Bracco Industria Chimica. Hexahydrates lanthanide chlorides were purchased from Aldrich Chemical Co.

Lanthanide complexes were prepared, at ~0.2 M concentration, from stock solutions of the corresponding chlorides following the procedure reported by Desreux.[5]

Samples (0.08 M) for NMR studies were prepared by dilution of the above solutions. Spectra below −5 °C were obtained by adding aliquots of CD$_3$OD to the aqueous solutions.

tert-Butyl alcohol was used as an internal reference.

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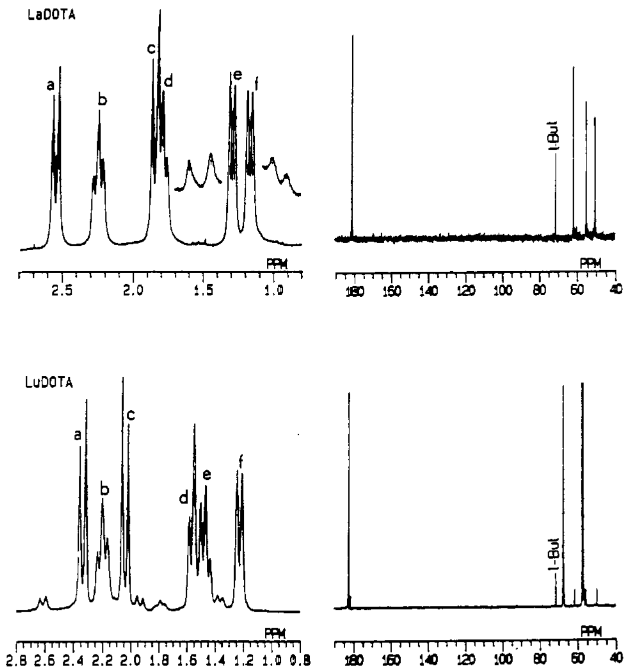

Figure 1. ^{1}H and ^{13}C NMR spectra of La- and LuDOTA$^-$ complexes recorded at 9.4 T (400 MHz) and 273 K in D_2O solvent. *tert*-Butyl alcohol was added as an internal reference.

Table I. ^{13}C NMR Chemical Shifts (ppm) of Paramagnetic LnDOTA$^-$ Complexes[a]

	major isomer				minor isomer			
ions	$CH_{2\,et}$	$CH_{2\,et}$	$CH_{2\,ac}$	CO_2^-	$CH_{2\,et}$	$CH_{2\,et}$	$CH_{2\,ac}$	CO_2^-
Pr^{3+}	−18.4	−43.2	23.7	139.2				
Nd^{3+}	1.6	−11.1	41.3	146.5	−3.0	−20.4	18.4	130.7
Sm^{3+}	26.5	22.6	41.6	159.8	24.9	18.9	32.7	154.4
Eu^{3+}	66.1	40.2	85.2	176.4	57.7	55.9	53.5	162.8
Yb^{3+}	−64.5	50.8	117.8	10.1	65.1	36.6	−39.8	72.8

[a] The spectra were recorded at 400 MHz and at the following temperatures: PrDOTA$^-$, −35.0 °C in a D_2O/CD_3OD (1:4) solution; NdDOTA$^-$, −5.0 °C; SmDOTA$^-$, −7.0 °C; EuDOTA$^-$, −3.0 °C; YbDOTA$^-$, 2.5 °C.

^{1}H and ^{13}C NMR spectra were recorded at 2.1, 6.4, and 9.4 T on JEOL EX-90, GX-270/89, and EX-400 Fourier transform spectrometers, respectively.

The COSY spectra were collected with 1024 data points in F_2 and 512 data points in F_1. The data were processed by using a sine bell window function and zero filled to a 2048 × 2048 data matrix before Fourier transformation and symmetrization. EXSY spectra were collected by using the standard $90°-t_1-90°-\tau_M-90°$ (NOESY) pulse sequence and the data processed as in the COSY experiments.

The variable-temperature accessories were checked against the methyl alcohol calibration method.

Longitudinal relaxation times T_1 were measured by the inversion–recovery technique whereas spin–spin relaxation time T_2 were measured from the half-height widths ($\delta\nu_{1/2}$) of the resonances. Corrections for field inhomogeneities were made by subtracting the line width of the *tert*-butyl alcohol from the line width of the other resonances. Uncertainties in T_1 and T_2 values have been estimated to be less than 5%.

Results

NMR Spectra of the Diamagnetic LnDOTA$^-$ Complexes (Ln = La and Lu). The proton NMR spectra of both complexes were already recorded by Desreux[5] at the observation frequency of 90 MHz. We repeated the observation at 400 MHz, and through 2D-COSY experiments at low temperatures, we got an accurate assignment of the resonances.

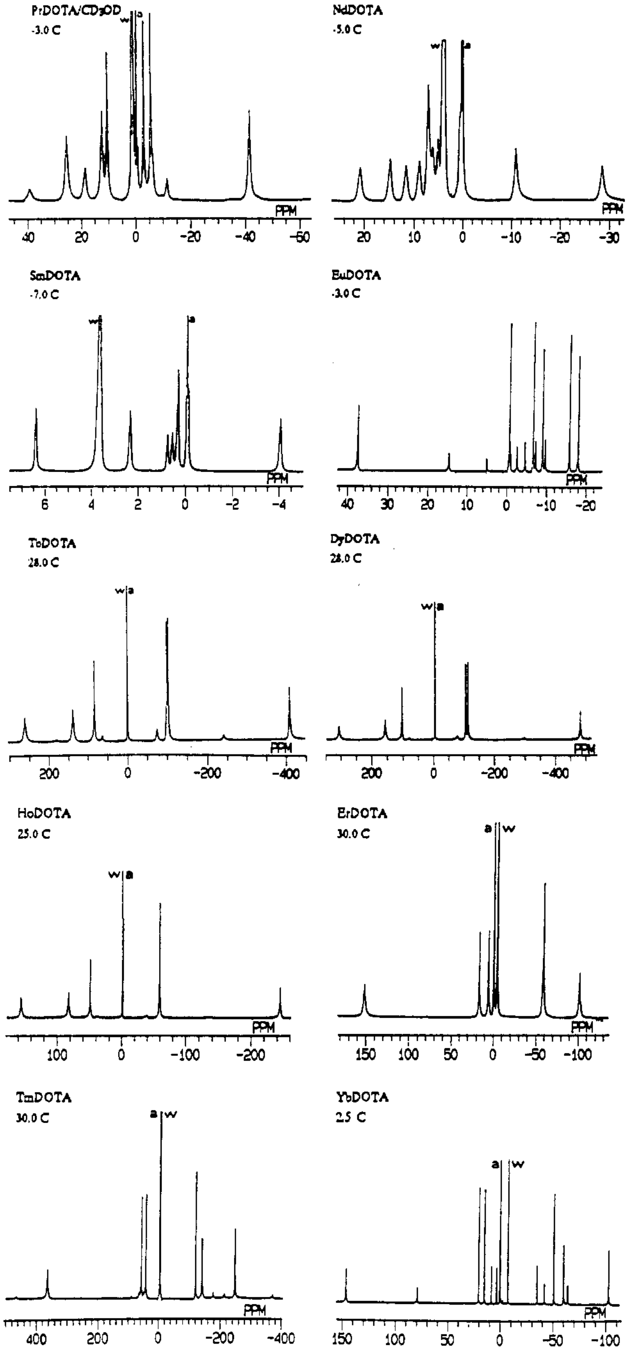

Figure 2. ^{H} NMR spectra of paramagnetic LnDOTA$^-$ complexes. EuDOTA$^-$, SmDOTA$^-$, YbDOTA$^-$, and NdDOTA$^-$ spectra were recorded at 9.4 T (400 MHz); the PrDOTA$^-$ spectrum was recorded at 6.4 T (270 MHz); DyDOTA$^-$, TbDOTA$^-$, HoDOTA$^-$, ErDOTA$^-$, and TmDOTA$^-$ spectra were recorded at 2.1 T (90 MHz).

As shown in Figure 1, LaDOTA$^-$ shows six resonances at −3 °C as expected on the basis of the solid-state structure. The acetate protons (a and c) appear as a pair of doublets (J = 16.6 Hz) at 2.55 and 1.88 ppm, respectively. The ethylenic moiety affords two triplets (b and d at 2.25 and 1.80 ppm, respectively) for the axial protons and two doublets (e and f at 1.30 and 1.17 ppm, respectively) for the equatorial protons. The geminal couplings is 13.2 Hz and the trans (ax–eq) coupling is 14.2 Hz. A 2D-COSY experiment allowed us to assess that the equatorial proton at 1.17 ppm is geminal to the axial resonances at 1.80 ppm (and H_{eq} at 1.30 ppm to H_{ax} at 2.25 ppm, respectively). This low-temperature limiting spectrum shows a few very low intensity peaks assignable to the second isomer. This species was not previously detected, probably because of its very low concentration and because of the fact that it is involved in an exchange process with the major species which is already occurring at temperatures close to 0 °C and at the observation frequency of 400 MHz.

The ^{13}C NMR spectrum of LaDOTA$^-$ at −3 °C (Figure 1) shows the expected four resonances assigned as follows: 181.4

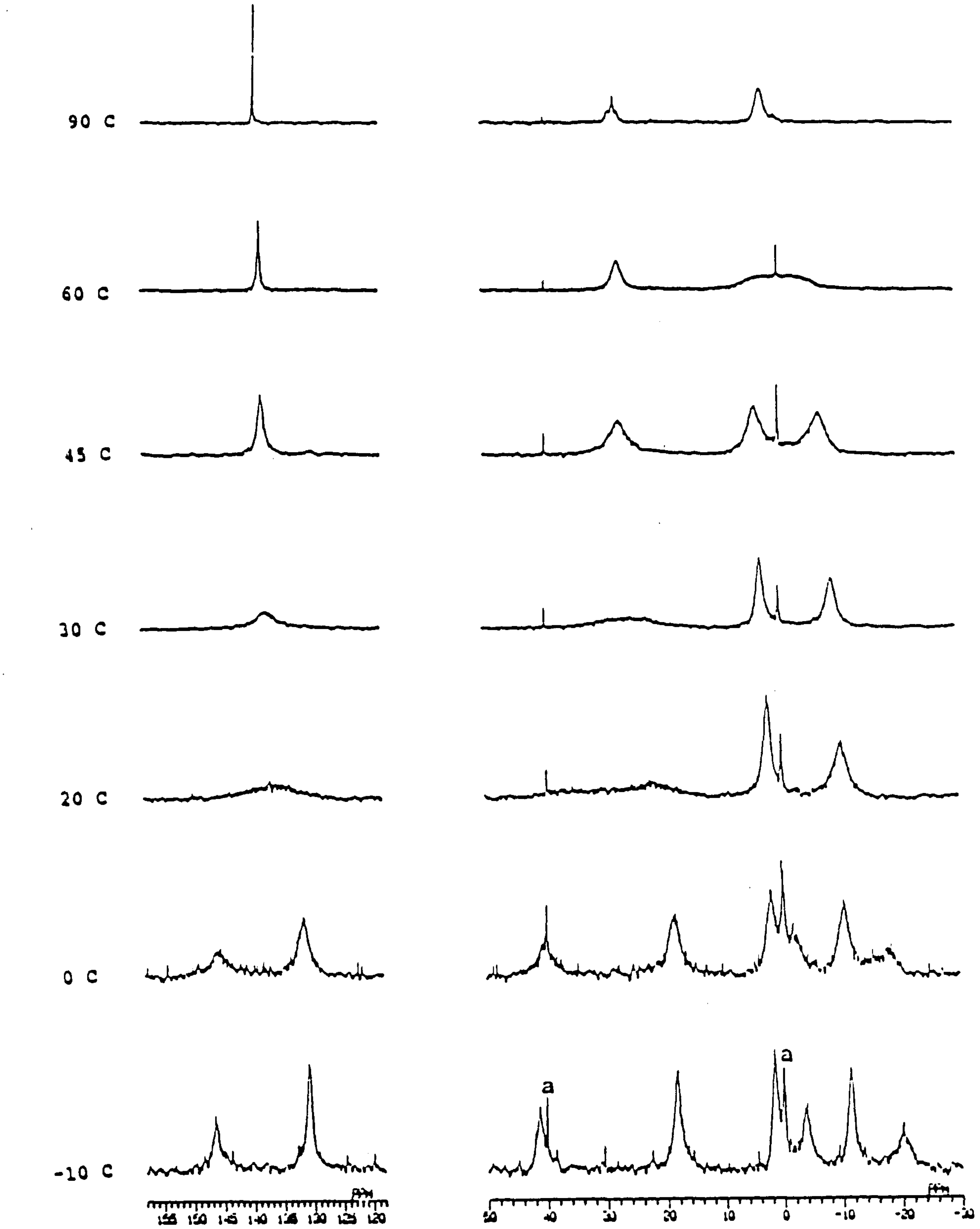

Figure 3. Variable-temperature ^{13}C NMR spectra of the NdDOTA$^-$ complex in D_2O (pH = 7.3), recorded at 9.4 T (400 MHz). The a-labeled resonances indicate *tert*-butyl alcohol added as an internal reference.

ppm to the carboxylate functionalities, 62.1 ppm to the methylenic carbons of the acetate arms, and 55.9 and 50.9 ppm to the ethylenic carbons in the tetraazamacrocycle.

The ^1H and ^{13}C NMR spectra of LuDOTA$^-$ show more clearly the presence of the two isomers. The proton spectrum (Figure 1) of the major isomer shows a spectral pattern analogous to that observed for LaDOTA$^-$ with significant shifts of some resonances: the methylenic protons of the acetate groups (a and c) resonate at 2.35 and 2.05 ppm, respectively (J_{gem} = 16.8 Hz), whereas the axial ethylenic resonances (b and e) fall at 2.20 and 1.46 ppm with their equatorial counterparts at 1.57 and 1.22 ppm, respectively. The coupling constants inside the ethylenic moiety are quite similar to those found for LaDOTA$^-$ affording a J_{gem} value of 13.7 Hz and a J_{trans} value of 13.4 Hz.

Four resonances of the minor isomer can be clearly detected in the 1D-spectrum; furthermore, 2D-COSY experiment allowed us to assess that two more resonances of the minor isomer are buried under peaks b and e of the major isomer. The assignment

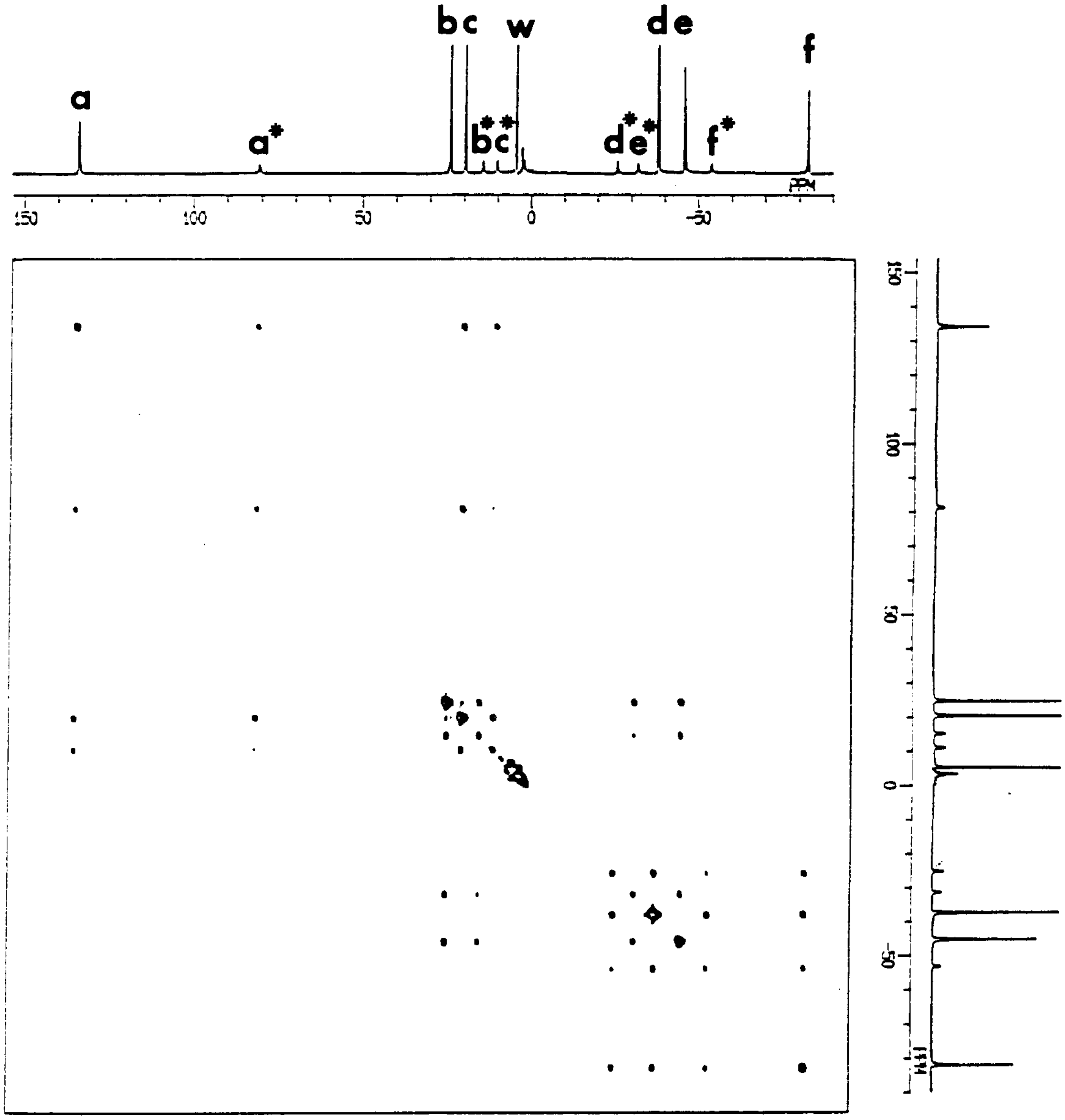

Figure 4. Proton EXSY spectrum of YbDOTA$^-$ (80 mM) in D_2O at 400 MHz and 25 °C. Mixing time (τ_M) was 5 ms. The water signal has been labeled with "W". Assignments of the resonances: a and e, axial protons; b and c, equatorial protons; d and f, acetate protons. The signals marked by the asterisks are due to the minor isomer.

of the proton resonances of the minor LuDOTA$^-$ isomer is then as follows: acetate protons at 2.62 and 1.94 ppm; axial ethylenic protons (triplets) as ~2.20 ppm (below b) and 1.80 ppm; equatorial ethylenic protons (doublets) at 1.35 ppm and ~1.45 ppm (under e).

The ^{13}C NMR spectrum of LuDOTA$^-$ clearly shows two set of resonances corresponding to the two isomers. The resonances of the major one fall at 182.7 ppm (CO_2^-), 67.3 ppm (CH_2 acetate), and 57.6 and 56.6 ppm (CH_2 ethylenic); the minor isomer affords the following resonances: 181.7 ppm (CO_2^-), 61.4 (CH_2 acetate), and 55.8 and 50.1 ppm (CH_2 ethylenic).

NMR Spectra of Paramagnetic LnDOTA$^-$ Complexes. The low-temperature limiting ^1H NMR spectra of 10 paramagnetic LnDOTA$^-$ complexes are reported in Figure 2. The number and the relative intensities of the observed resonances in each spectrum (except ErDOTA$^-$) are consistent with the presence of two isomers whose relative ratio changes along the series.

As expected on the basis of the large differences among the effective magnetic moments of lanthanide ions,[7] the chemical shift range shown by the various complexes is quite different. It goes from about 10 ppm for SmDOTA$^-$ to several hundred ppm for TmDOTA$^-$.

At 400 MHz the proton resonances of all 10 complexes appear too broad to allow for the detection of any coupling pattern. This paramagnetic broadening may be reduced when the spectra are recorded at lower magnetic field strength as we verified in the case of EuDOTA$^-$. The magnetic properties of the Eu ion are such that the proton spectrum shows a chemical shift range large enough (ca. 60 ppm) to allow the observation of separated resonances for all the chemically different protons, but at the same time, they cause only a small magnetic field-induced line broadening. Thus, at low magnetic field strength, it is possible to detect the coupling pattern. The *J* values of the resonances of both species, obtained from a spectrum recorded at 0 °C and 90 MHz, are very similar, thus suggesting the same conformation of the tetraaza ring in the two isomers.

The ^{13}C NMR spectra were also recorded for some of these paramagnetic LnDOTA$^-$ complexes (Ln = Pr, Nd, Sm, Eu, Yb) (Table I). An aid to distinguish between acetate and ethylenic carbons comes from the coalescence behavior of the ethylenic carbons with the increase of the observed temperature as previously

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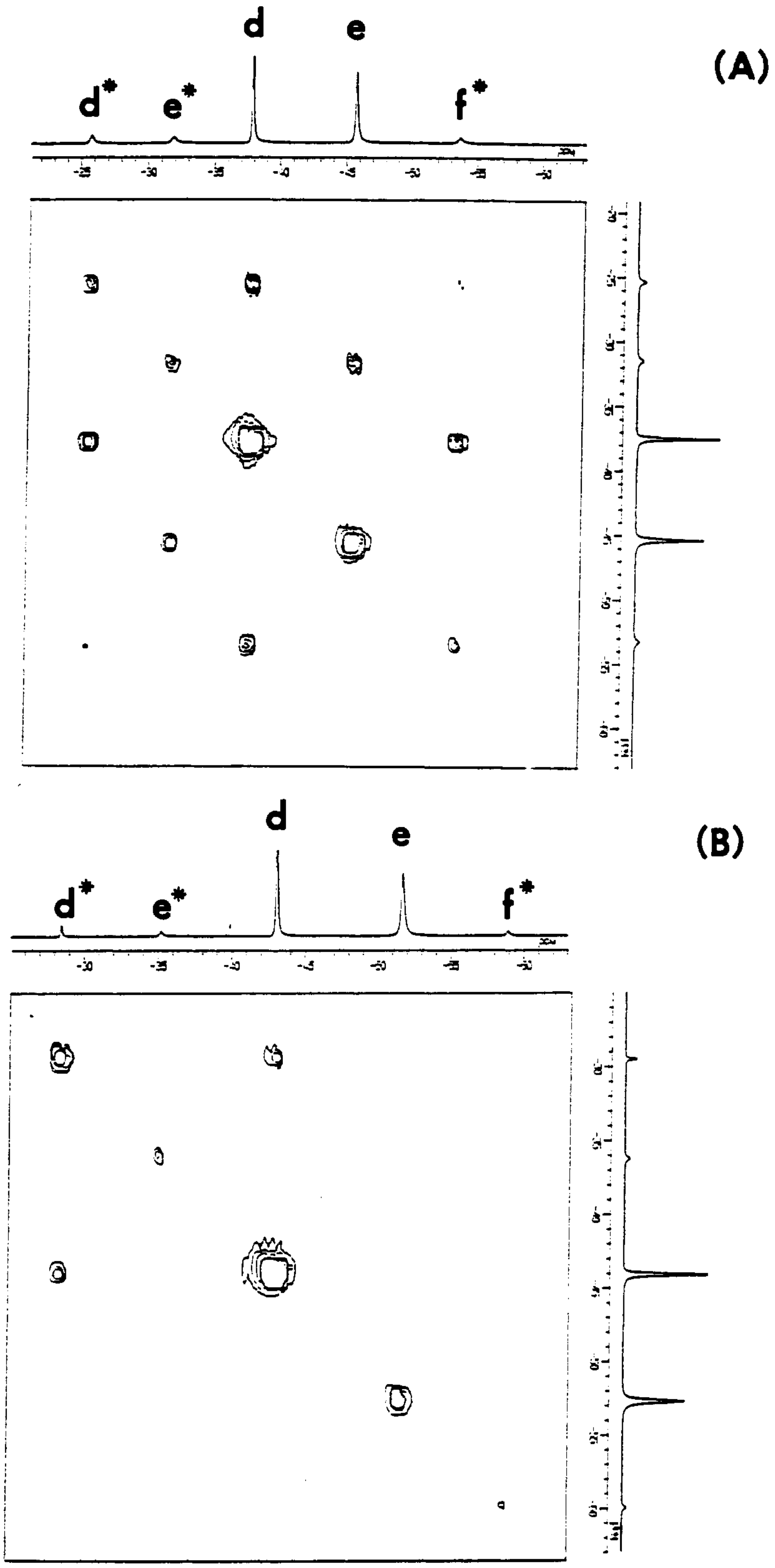

Figure 5. Expanded region (−20 to −65 ppm) of the proton EXSY spectrum for YbDOTA$^-$ at 400 MHz and 25 (A) and 0 °C (B). Mixing time was 5 ms.

shown by Desreux.[5] Not reported in the table are the corresponding spectra of Tb^{3+}, Dy^{3+}, Ho^{3+}, Er^{3+}, and Tm^{3+} complexes because no useful assignment of their broad and featureless resonances can be made.

Variable Temperature NMR Spectra. By changing the temperature, two dynamic processes have been detected through changes in the ^{1}H and ^{13}C NMR spectra. These processes are clearly separated in the variable-temperature ^{1}H NMR spectra of PrDOTA$^-$ and in the VT-^{13}C NMR spectra of NdDOTA$^-$, respectively. For the latter complex, at −10 °C, reported in Figure 3, the position and the relative intensities of the eight resonances are consistent with a mixture of the two isomers in the ratio 1:2. As the temperature is increased, all the resonances broaden, collapse, and then merge to afford a spectrum of four resonances all of equal intensity near 45 °C. The observed behavior is consistent with an exchange process which averages out pairs of corresponding resonances for the two isomers. The observation of two ethylenic resonances in the spectrum at 45 °C indicates

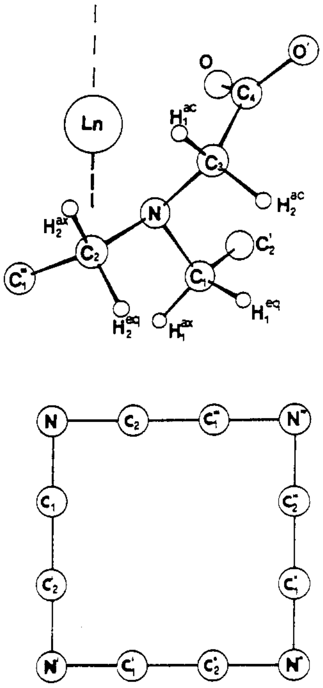

Figure 6. Sketched views of the basic fragment and of the tetraazacyclododecane ring in LnDOTA$^-$ complexes.

that the rigidity of the macrocycle is maintained at this temperature. As the temperature is further increased, an averaging process involving the two ethylenic resonances takes place.

The VT ^1H NMR spectra of PrDOTA$^-$ parallels this behavior on passing from 12 proton resonances (actually some peaks of the minor isomer were not resolved) at low temperature to six signals of equal intensity at 40 °C as a result of a coalescence process involving pairs of proton resonances on the two isomers. At higher temperature, once the isomerization process becomes fast on the NMR time scale, a second dynamic process takes place which averages the resonances of the acetate protons and of two pairs of axial and equatorial protons on adjacent ethylenic carbons.

In the other complexes the two processes are not so clearly distinguishable although it is clear enough that the isomerization process always occurs before or simultaneously with the motion involving the cyclododecane ring.

In order to better highlight the exchange processes we utilized the two dimensional (2D) proton exchange spectroscopy (EXSY) technique by recording the spectra for Yb(DOTA)$^-$. This technique represents a powerful tool for the study of chemical exchange by allowing the direct observation in a single experiment of cross peaks between mutually exchanging protons under the condition of slow exchange. Despite the problems arising from the fast nuclear relaxation rates and the large range of chemical shifts of paramagnetic systems, this technique has been successfully utilized in the study of paramagnetic complexes.[8-10]

Shown in Figure 4 is the 400-MHz EXSY spectrum of YbDOTA$^-$ recorded at 25 °C. The spectrum is very clear and indicates all the cross-peaks between pairs of protons undergoing mutual chemical exchange and provides a partial assignment of the resonances (vide infra).

The dynamic process occurring inside each isomeric form of YbDOTA$^-$ is easily deduced by the cross signals between a and c, b and e, and d and f.

The spectrum also indicates the occurrence of an exchange between the two isomers since each resonance of a species is correlated to two signals of the other isomer: one is the consequence of the isomerization process while the other represents a correlation between signals through both the inversion of the ethylenic groups and the isomerization process. Even if the two exchange mechanisms have similar activation energies, the inversion of the ethylenic group presents a higher activation barrier, as shown by the VT-^{13}C NMR study of NdDOTA$^-$, and in fact it could be frozen out by lowering the temperature. Figure 5 shows the −20 to −65 ppm region of the EXSY spectrum of YbDOTA$^-$ recorded at 25 °C (part a) and 0 °C (part b). In the low-temperature spectrum only the isomerization process is present leaving only cross peaks between the acetate resonances of the two isomers. This dynamic process exchanges d with d* and f with f*, and this observation therefore suggests that a concerted motion of the acetate groups must be involved in the exchange mechanism.

Table II. Internal Coordinates of the LnDOTA$^-$ Complex Labeled According to Figure 6[c]

	X-ray	major	minor
	Distances (Å)		
Ln–N	2.7 ± 0.2	2.61	2.61
N–C_3	1.5 ± 0.1	1.53	1.53
N–C_2	1.5 ± 0.1	1.50	1.50
N–C_1	1.5 ± 0.1	1.50	1.50
C_3–C_4	1.5 ± 0.1	1.53	1.53
C_4–O	1.24[a]	1.24	1.24
C_4–O′	1.21[a]	1.21	1.21
C–H	1.09[b]	1.09	1.09
	Bond Angles (deg)		
Ln–N–C_3	111 ± 3	111.3	111.3
Ln–N–C_1	111 ± 3	111.5	111.5
Ln–N–C_2	111 ± 3	107.1	107.1
N–C_3–C_4	112 ± 3	112.1	112.1
N–C_3–H_1^{ac}	109[b]	107.6	107.6
N–C_3–H_2^{ac}	109[b]	108.3	108.3
C_3–C_4–O	120[a]	120.0	120.0
C_3–C_4–O′	120[a]	120.0	120.0
N–C_1–H_1^{ax}	109	108.0	108.0
N–C_1–H_1^{eq}	109	105.7	105.7
N–C_2–H_2^{ax}	109	111.9	111.9
N–C_2–H_2^{eq}	109	105.3	105.3
	Dihedral Angles (deg)		
$LnNC_1H_1^{ax}$	*b*	159.3	159.3
$LnNC_1H_1^{eq}$	*b*	−81.4	−81.4
$LnNC_2H_2^{ax}$	*b*	160.5	160.5
$LnNC_2H_2^{eq}$	*b*	−79.3	−79.3
$LnNC_3C_4$	−34 ± 2	−31.6	37.8
$LnNC_3H_1^{ac}$		88.8	158.2
$LnNC_3H_2^{ac}$		−153.2	−83.8
NC_3C_4O		8.9	−28.3
NC_3C_4O'		−171.1	151.7

[a] Carbonylic groups were positioned on a geometrical basis. [b] Protons were positioned on a geometrical basis with a C–H distance of 1.09 Å. [c] In the first column we report the mean values of the internal coordinates obtained from X-ray structure determination of EuDOTA$^-$ [3] with relative deviations from maximum to minimum values; the second and third columns report the internal coordinates of the two isomers as obtained from the fitting procedure of the experimental to calculated isotropic proton shifts of YbDOTA$^-$.

Discussion

The similarity found between the ^1H and ^{13}C chemical shifts for the principal isomer of LaDOTA$^-$ and for the minor isomer of LuDOTA$^-$ suggests that they have the same solution structure. If this is the case, then this means that an inversion of the relative stabilities of the two isomeric structures occurs at the extreme of the lanthanide row. No regular trend in the relative ratio of the two species is detected along the series. We have no explanation for the observed behavior, but it is clear enough that it is not a simple consequence of the lanthanide contraction.

The close correspondence observed among the coupling patterns inside the ethylenic moieties of La^{3+}, Lu^{3+}, and Eu^{3+} and the

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(9) Jenkins, B. G.; Lauffer, R. B. *J. Magn. Reson.* **1988**, *80*, 328.
(10) Ming, L-J.; Jang, H. G.; Que, L. *Inorg. Chem.* **1992**, *31*, 359.

Table III. Comparison between Selected Internal Coordinates Obtained from X-ray Data for EuDOTA$^-$ [3] (First Column) and from the Computed Model (Second Column) Relevant to the Assessment of the Tetraazadodecane Ring Conformation

	X-ray	calcd
	Distance (Å)	
C_1–C_2'	1.5 ± 0.1	1.52
	Bond Angles (deg)	
N–C_2–C_1''	113 ± 6	111.1
N–C_1–C_2'	111 ± 3	113.1
	Dihedral Angles (deg)	
$NC_1C_2'N'$	−59 ± 5	−57.4
$C_1NC_2C_1'''$	−79 ± 5	−79.5
$C_2'C_1NC_2$	164 ± 2	164.3

Table IV. Lanthanide-Induced Shift Parameters, Calculated Isotropic Shifts, and Yb–Proton Distances Evaluated by the Curie Contribution to the Longitudinal and Transverse Relaxation Times for the Major Isomer at 0 °C

	r^{calcd} [a]	θ^{calcd} [a]	$\delta\nu^{\text{calcd}}$ [a]	r^{Curie} [b]	$\delta\nu^{\text{exptl}}$ [c]
H^{ax}_1	3.74	23.3	153.5	3.49	153.7
H^{eq}_2	4.40	46.4	24.8	4.40	25.6
H^{eq}_1	4.40	47.1	22.6	4.33	21.1
H^{ac}_1	4.32	72.0	−48.4	4.23	−47.9
H^{ax}_2	3.77	67.1	−55.8	3.64	−56.0
H^{ac}_2	3.73	85.4	−101.6	3.78	−101.5
R^d			0.009		
D_1^e			5300 ± 24		
std dev			±0.9	±0.06	

[a] Distances (Å) Yb–H(r^{calcd}), angles (deg) between magnetic axis and protons (θ^{calcd}), and shifts ($\delta\nu^{\text{calcd}}$) are reported for the best fit to data calculated from the major isomer model, with Yb^{3+} representing the origin of the coordinate system. [b] Distances (Å) Yb–H calculated by the evaluation of the Curie contribution to the proton relaxation rates. [c] Experimental shifts after subtraction of the diamagnetic contribution as evaluated from the shifts of the LaDOTA$^-$ complex. [d] R is the agreement factor as defined in eq 3. [e] D_1 (ppm Å^3) is the dipolar coefficient in eq 1.

Table V. Lanthanide-Induced Shift Parameters, Calculated Isotropic Shifts, and Yb–Proton Distances Evaluated by the Curie Contribution to the Longitudinal and Transverse Relaxation Times for the Minor Isomer at 0 °C

	r^{calcd} [a]	θ^{calcd} [a]	$\delta\nu^{\text{calcd}}$ [a]	r^{Curie} [b]	$\delta\nu^{\text{exptl}}$ [c]
H^{ax}_1	3.74	23.3	87.1	3.49	86.3
H^{eq}_2	4.40	46.4	13.9	4.38	11.2
H^{eq}_1	4.40	47.1	8.7	4.33	9.9
H^{ac}_1	3.68	80.4	−62.6	3.88	−61.9
H^{ax}_2	3.77	67.1	−36.4	3.69	−38.3
H^{ac}_2	3.73	85.4	−33.7	3.76	−33.9
R^d			0.035		
D_1^e			3127 ± 54		
std dev			±2.0	±0.06	

[a] Distances (Å) Yb–H(r^{calcd}), angles (deg) between magnetic axis and protons (θ^{calcd}), and shifts ($\delta\nu^{\text{calcd}}$) are reported for the best fit to data calculated from the minor isomer model, with Yb^{3+} representing the origin of the coordinate system. [b] Distances (Å) Yb–H calculated by the evaluation of the Curie contribution to the proton relaxation rates. [c] Experimental shifts after subtraction of the diamagnetic contribution evaluated measuring the shifts of the LaDOTA$^-$ compex. [d] R is the agreement factor as defined in eq 3. [e] D_1 (ppm Å^3) is the dipolar coefficient in eq 1.

EXSY spectrum of Yb^{3+} suggests that the cycle maintains the same staggered conformation in the two isomeric forms along the series. It follows then that the structural differences between the two isomers arise likely from the layout of the acetate arms.

An accurate assessment of the differences between the solution structures of the two isomers may be gained through a detailed quantitative study of the NMR proton spectrum of YbDOTA$^-$.

In this complex the paramagnetic induced shift on the proton resonances (obtained by subtracting the diamagnetic coordination shift from the observed shift) may be considered as entirely dipolar[11] and then, on the basis of the axial symmetry, simply given by[12]

$$\delta\nu_i = D_1 \frac{3\cos^2(\theta_i - 1)}{r_i^3} \tag{1}$$

where D_1 is the magnetic susceptibility factor and θ_i and r_i are the polar coordinates of a ligand nucleus i with respect to the magnetic susceptibility principal axis of the complex.

The Yb–H_i distances r_i, can be evaluated for the solution structure by exploiting the Curie contribution to the relaxation rates of the proton resonances of the ligand. From the established theory of the paramagnetic relaxation, the difference between the transverse and the longitudinal relaxation rate is given by[13]

$$\frac{1}{T_2} - \frac{1}{T_1} = \frac{1}{5}\frac{\gamma^2\mu^4_{\text{eff}}H_0^2}{(3KT)^2r^6}\left(4\tau_r - \frac{3\tau_r}{1+\omega^2\tau_r^2}\right) \tag{2}$$

where γ is the nuclear gyromagnetic ratio, μ_{eff} is the effective magnetic moment of the Yb^{3+} ion, H_0 is the applied magnetic field strength (in gauss), r is the distance between the proton and the paramagnetic ion, τ_r is the molecular reorientational correlation time, and the other symbols have their usual meanings.

Once τ_r is known from independent experiments, r distances may be easily determined through the measurements of the transverse and longitudinal relaxation rates. More accurate results are obtained at high magnetic fields owing to the quadratic field dependence of the $1/T_2 - 1/T_1$ difference (eq 2).

τ_r values for LnDOTA$^-$ complexes at 25 °C were already obtained from the analysis of the $1/T_1$ NMRD profile of GdDOTA$^-$ [14] (72 ps) and from ^{13}C-T_1 and NOE measurements of the ethylenic carbons of tetraazacyclododecane ring of the diamagnetic La^{3+} [15] (73 ps) and Lu^{3+} [16] (80 ps) derivatives. In this work we used a τ_r value of 80 ps.

Since the method is based on a comparison of the experimental shifts to the shifts calculated from eq 1 using geometrical factors extracted from model structures, first we established a procedure capable of modifying in a systematic way the internal coordinates of the structural model in order to get the best agreement between calculated and experimental shifts.

The quality of the obtained model is then tested through the agreement factor R[17]

$$R = \frac{\sum_i(\delta\nu_i^{\text{calcd}} - \delta\nu_i^{\text{DIP}})^2}{(\sum_i\delta\nu_i^{\text{DIP}})^2} \tag{3}$$

where $\delta\nu_i^{\text{calcd}}$ is the chemical shift value calculated by eq 1 for a given proton for each computed structural model.

First, we applied this procedure to determine the solution structure of the main isomer of YbDOTA$^-$. As for all the complexes considered in this study, the observed pattern of resonances is consistent with the occurrence of a quaternary axis

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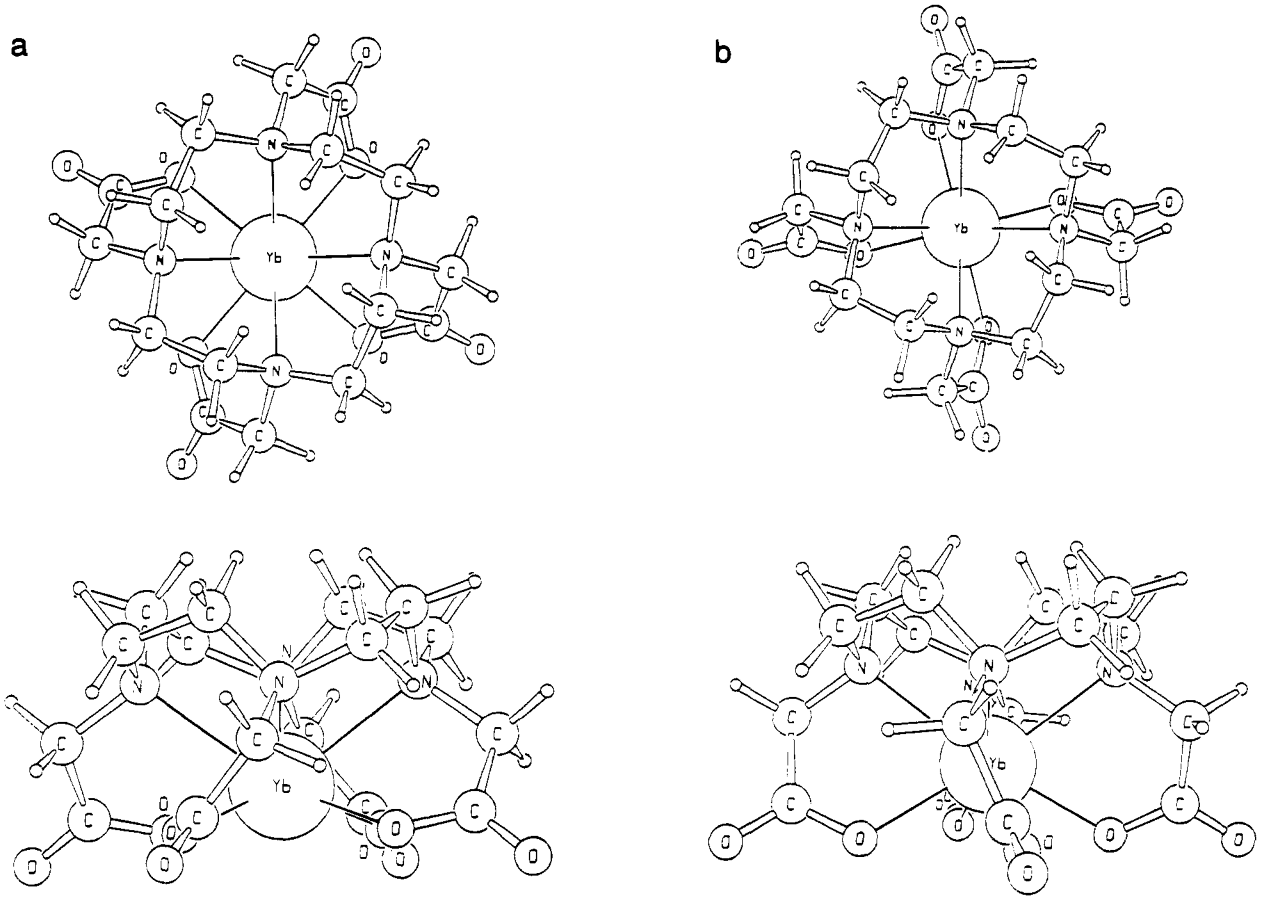


Figure 7. Top and side views of the structures for the major (a) and minor (b) isomers as obtained by analysis of the dipolar shifts for the YbDOTA$^-$ complex.

of symmetry which coincides with the magnetic axis. All the relevant structural features may then be obtained from a single basic fragment (Figure 6) which contains the lanthanide ion, a nitrogen atom with its acetate arm, and the two methylenic moieties adjacent to it.

The minimization of the agreement factor has been pursued by allowing the internal coordinates to change within a relatively narrow range around the average values obtained from crystallographic data (Table II). In doing so, particular attention has been devoted to make a judicious choice of constrain conditions in order to accomplish the combination of dihedral and bond angles which permit the closure of the ring (Table III).

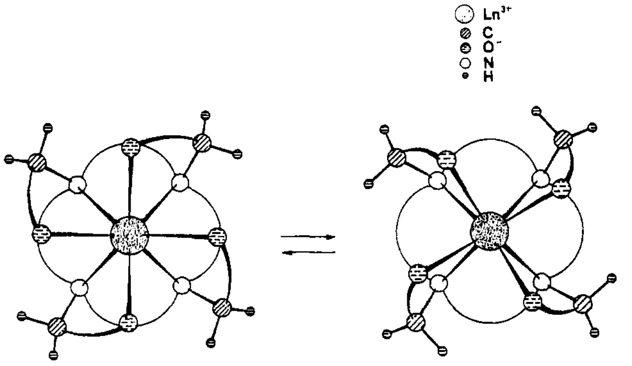
For the main isomer, the computed model showing the best agreement factor corresponds quite closely to the solid state structure determined for Eu and GdDOTA$^-$ complexes (Table IV).

The structural model of the main isomer then represents the starting point in the search of a structural model for the minor isomer.

As we discussed above, some NMR evidence suggests that the differences between the two isomers arise from a change in the layout of the acetate arms, the conformation of the ring being unchanged.

This prompted us to search for the best agreement factor through the stepwise modification of the torsional Ln–N–C_3–C_4 angle. Through this motion the methylenic protons of the acetate arms drastically change their positions with respect to the magnetic axis: H_1^{ac}(d in Figure 4), which is less shifted than H_2^{ac}(f in Figure 4) in the principal isomer, becomes markedly more shifted in the minor isomer. Besides the boundary conditions employed in the search of the structural model for the main isomer, we further imposed the constraint that the rotation of the carboxylate functionalities has to maintain Ln–O distances (2.4 Å) analogous to those found for the major isomer.

Scheme III



The results of our fitting procedure led to an antiprismatic monocapped structure containing an inverted layout of the acetate arms with respect to the principal isomer, with an unchanged conformation of the cycle (Tables V).

To pinpoint the structural differences between the minor and the major isomers of YbDOTA$^-$, we report in Figure 7 two different views of their molecular structures as obtained following the above-described procedure.

Whereas the structure of the major isomer is fully consistent with the X-ray results on Eu and GdDOTA$^-$ complexes,[3,4] and with the solution structure found by Desreux et al.[5] for the same species, the structure herein found for the minor isomer does not support the previously reported conclusion.[6]

Actually the antiprismatic polyhedron of the minor isomer is somewhat distorted toward a prismatic arrangement. It is likely that a regular prismatic polyedron may represent the activated state to be reached in the interconversion process between the two isomers.

It follows that the exchange between the two isomers may be envisaged as occurring through a concerted sliding motion of the four oxygen donor atoms on the surface of the lanthanide ion, as depicted in Scheme III. Conversely, the motion of the acetate arm could involve the exchange of the coordinated oxygen atoms. This latter mechanism can be ruled out on the basis of the low-temperature EXSY spectrum for YbDOTA$^-$, since it implies the possibility of free rotation of the unbound acetate arms and therefore the mutual exchange of the corresponding protons, which would result in the appearance of three cross-peaks for each acetate proton. These results suggest a remarkable nonlability of the Ln–O bonds for the LnDOTA$^-$ chelates as also found recently by Desreux et al.[18] in a kinetic study.

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