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^{17}O NMR Study of Diamagnetic and Paramagnetic Lanthanide(III)−DOTA Complexes in Aqueous Solution

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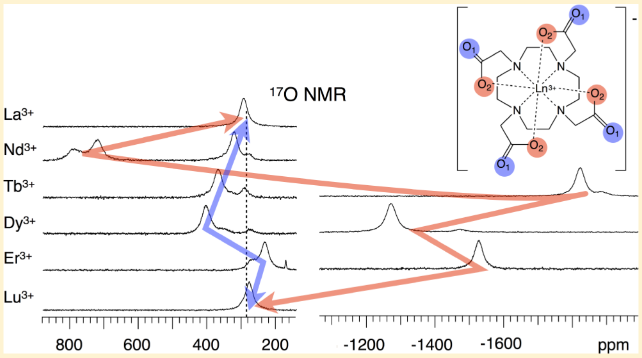
S *Supporting Information*

ABSTRACT: The complexes between the polyaminocarboxylate DOTA ligand and the whole series of stable lanthanide(III) metal ions, except Gd^{3+}, were studied in aqueous solution by ^{17}O NMR. For all of the paramagnetic systems, the ^{17}O NMR signals of both the nonchelating (O_1) and chelating (O_2) oxygen atoms could be detected, and for some of them, the signals of both the SAP and TSAP (TSAP′) conformational isomers were also observed. Line width data analysis reveals that signal broadening is not dominated by paramagnetic relaxation enhancement, as it was believed to be. The data indicate that quadrupole relaxation and, for some complexes, chemical exchange between the SAP and TSAP isomers are the major contributions to the ^{17}O NMR line width at 25 °C. Besides, the Fermi contact and pseudocontact contributions to the observed lanthanide-induced shifts could be extracted. The ^{17}O hyperfine coupling constants determined for O_2 in the SAP and TSAP isomers are similar to each other and to the values reported for several Gd(III) complexes comprising fast-exchanging ligands. Interestingly, the results suggest that ^{17}O NMR should prove to be useful for the study of highly paramagnetic Gd(III) complexes of nonlabile ligands.



■ INTRODUCTION

The DOTA (tetraazacyclododecanetetraacetic acid, see Figure 1) and DTPA (diethylenetriaminepentaacetic acid) complexes of Gd^{3+}, which exhibit high thermodynamic stability and kinetic inertness, are currently used as contrast agents for clinical magnetic resonance imaging. Indeed, these chelates comprise a water molecule coordinated to the metal ion, which undergoes fast exchange with surrounding water molecules and, consequently, is responsible for effective positive contrast.[1−3]

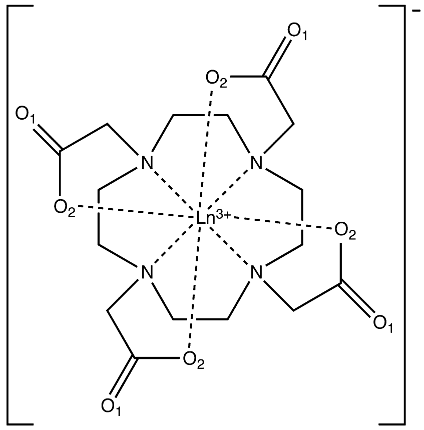


Figure 1. Schematic structure of [Ln-DOTA]$^-$ complexes. The coordinated water molecule is not represented.

Owing to extreme signal broadening induced by paramagnetic relaxation enhancement (PRE), Gd-based complexes cannot be studied by conventional solution-state NMR approaches, and therefore, the corresponding complexes of the other paramagnetic Ln^{3+} ions, which are all characterized by much faster electron spin relaxation, or the complexes of diamagnetic metal ions (the lanthanide La^{3+} and Lu^{3+} as well as the chemically similar Y^{3+} ion) are commonly used as model systems.[4−8] Hence, ^{1}H and ^{13}C NMR studies have shown that lanthanide(III)−DOTA complexes (Ln-DOTA) exist in a dynamic equilibrium between square antiprismatic (SAP) and twisted square antiprismatic (TSAP or TSAP′) geometries, the TSAP form being favored with the four lightest members of the Ln series (La−Nd). With the four heaviest Ln^{3+} ions (Er−Lu), the minor twisted square antiprismatic form does not involve coordination of water and is therefore referred to as TSAP′.[9]

^{17}O NMR is commonly used to characterize complexes comprising a paramagnetic Ln metal ion and fast-exchanging ligands. In particular, the number of inner-shell water molecules,[10,11] as well as their residence time,[12,13] can be determined via relaxation time and lanthanide-induced shift (LIS) measurements. The observed LIS depends on both the Fermi contact and pseudocontact contributions. The former is due to the electron-spin density transmitted on the ligand nuclei through the bonds, while the latter results from the

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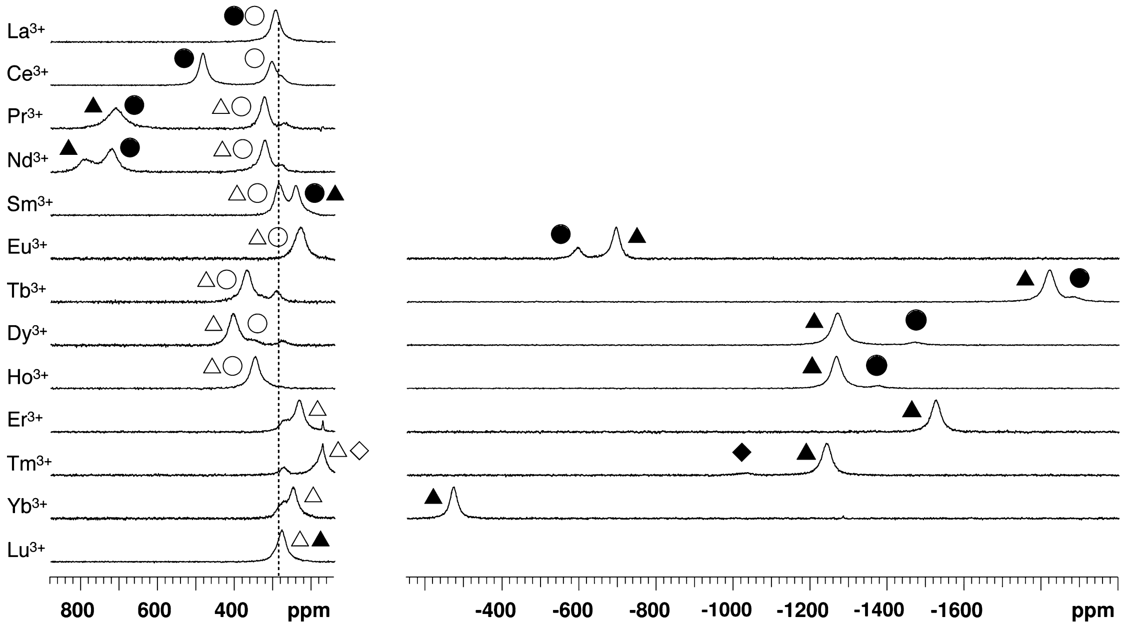

Figure 2. ^{17}O NMR spectra recorded at 25 °C and 14.1 T for $[\text{Ln-DOTA}]^-$ complexes in aqueous solution. The dashed line highlights the chemical shift of the free DOTA ligand, while the symbols indicate the signals of the complex: (○) TSAP O_1, (△) SAP O_1, (◇) TSAP′ O_1, (●) TSAP O_2, (▲) SAP O_2, and TSAP′ O_2 (◆). The chemical shift scale is referenced to the signal of neat D_2O at 25 °C (0 ppm). The processing of the free induction decay comprised exponential apodization with a line broadening factor of 30 Hz.

through-space dipolar interaction between the electronic and nuclear magnetic moments. The LIS observed for an oxygen atom directly coordinated to a paramagnetic Ln metal ion is expected to be largely due to the Fermi contact term.[14−16] Hence, it mainly depends on the isotropic hyperfine coupling constant ($A/\hbar$ or HFCC), which was found to not vary significantly along the lanthanide series and to be rather insensitive to the nature of the ligand. Indeed, HFCC data, measured by ^{17}O NMR for the fast-exchanging water molecule coordinated to many different small Gd^{3+} systems, among which are the Gd-DOTA and Gd-DTPA complexes, are in the range of $3.9 \pm 0.3 \times 10^6$ rad s^{-1} (0.57−0.67 MHz).[17,18] Similar values were also found for the coordinating oxygen atom of a variety of fast-exchanging groups, e.g., carboxyl, carbonyl, hydroxyl, ether, and phosphate functional groups.[16]

In contrast, ^{17}O NMR has scarcely been used to characterize the coordination between paramagnetic Ln metal ions and nonlabile ligands, probably because LIS and, even more so, line broadening are expected to be significant drawbacks,[16,19] and this in addition to rather low intrinsic sensitivity and baseline distortion issues. The only few ^{17}O NMR studies reported so far for such paramagnetic Ln−polyaminocarboxylate complexes concern the cations Pr^{3+}, $Sm^{3+,}$ or Eu^{3+}, which are responsible for relatively weak PRE effects.[20] These studies focused on (i) water coordinated to the $[\text{Eu-DOTAM}]^{3+}$ complex dissolved in acetonitrile,[13] (ii) water coordinated to the Eu^{3+} complex of a DOTA tetraamide derivative in aqueous solution,[21] (iii) the carboxylate groups of the Sm- and Pr-DOTA complexes in aqueous solution,[22,23] or (iv) the carboxylate groups of the Sm-, Pr- and Eu-DTPA complexes in aqueous solution.[24] Previous attempts to observe the ^{17}O NMR signals of the DTPA or DOTA complexes of heavy paramagnetic Ln metal ions were unsuccessful.[25,22] In particular, it was reported that no signal could be detected for the ^{17}O-enriched DOTA complexes of Dy^{3+}, Ho^{3+}, or Yb^{3+}.

The present study reports on the ^{17}O NMR spectra of the negatively charged $[\text{Ln-DOTA}]^-$ species existing in aqueous solution around neutral pH. It deals with the whole series of stable, i.e. nonradioactive, lanthanide(III) metal ions except Gd^{3+} and is aimed at addressing the following issues: (i) ability to detect ^{17}O NMR signals for nonlabile ligands of paramagnetic Ln complexes, (ii) magnitude and origin of the ^{17}O signal broadening for such systems as well as (iii) magnitude and origin of the ^{17}O LIS.

RESULTS AND DISCUSSION

^{17}O NMR Signal Detection and Assignment. Aqueous samples of ^{17}O-enriched $[\text{Ln-DOTA}]^-$ complexes (Ln $\neq$ Pm^{3+}, Gd^{3+}; a total of 13 systems) were prepared, considering a small excess of the DOTA ligand to preclude the presence of free Ln^{3+} ions (see Experimental Section). High-quality ^{17}O NMR spectra could be obtained using the RIDE pulse sequence[26] and optimized acquisition parameters, minimizing baseline distortion and water excitation. Spectra recorded at 14.1 T and 25 °C are shown in Figure 2. The signal of the free DOTA ligand is expected at about 290 ppm[22,23] and could be detected in most of the samples.[27] The spectra recorded for the diamagnetic $[\text{La-DOTA}]^-$ and $[\text{Lu-DOTA}]^-$ complexes show a single signal at about 296 and 283 ppm, respectively, i.e. slightly shifted with respect to the signal of free DOTA. Both these spectra, as well as those of the weakly paramagnetic $[\text{Pr-DOTA}]^-$ and $[\text{Sm-DOTA}]^-$ complexes, are in agreement with literature.[22,23]

The ^{17}O NMR spectra of the paramagnetic DOTA complexes (11 systems) exhibit distinct resonance lines for the nonchelating (O_1) and chelating (O_2) oxygen atoms. Hence, for all of these systems, the rotation of the carboxylate groups is a rather slow process at 25 °C, and this corroborates the results of recent dynamic-NMR and computational studies of some Ln-DOTA systems.[22,23] For the $[\text{Pr-DOTA}]^-$ and $[\text{Sm-DOTA}]^-$ complexes, O_1 versus O_2 signal assignment was based on literature,[22,23] while for the ^{17}O spectra of those

Table 1. $\langle S_z \rangle$ and C^D Values for the Lanthanide(III) Metal Ions[20] and ^{17}O Chemical Shift Data (δ) of the Corresponding $[Ln\text{-}DOTA]^-$ Complexes[a]

			δ (ppm)					
Ln	$\langle S_z \rangle$	C^D	O_1 TSAP	O_2 TSAP	O_1 SAP	O_2 SAP	O_1 TSAP′	O_2 TSAP′
La^{3+}	–	–	296	296	–	–	–	–
Ce^{3+}	−0.98	−6.3	305	485	–	–	–	–
Pr^{3+}	−2.97	−11	326	712	326	712	–	–
Nd^{3+}	−4.49	−4.2	335	722	335	788	–	–
Sm^{3+}	0.06	−0.7	286	242	286	242	–	–
Eu^{3+}	10.68	4.0	230	−592	230	−692	–	–
Tb^{3+}	31.82	−86	372	−1884	372	−1818	–	–
Dy^{3+}	28.55	−100	353	−1470	404	−1268	–	–
Ho^{3+}	22.63	−39	347	−1376	347	−1267	–	–
Er^{3+}	15.37	33	–	–	233	−1524	–	–
Tm^{3+}	8.21	53	–	–	174	−1239	174	−1026
Yb^{3+}	2.59	22	–	–	249	−271	–	–
Lu^{3+}	–	–	–	–	283	283	–	–

[a] δ values were measured in aqueous solution at 25°C and are given with respect to external neat D_2O.

paramagnetic systems that are reported for the first time, it relies on the reasonable assumption that the noncoordinated O_1 atom experiences smaller LIS than O_2 (in absolute value). The assignment shown in Figure 2 is supported by the analysis of the LIS presented further below.

At 25 °C, distinct O_2 resonance lines are observed for the SAP and TSAP (TSAP′) isomers of six paramagnetic complexes, i.e. for the DOTA complexes of Nd^{3+}, Eu^{3+}, Tb^{3+}, Dy^{3+}, Ho^{3+}, and Tm^{3+}.[28] After careful inspection, even the O_1 resonance lines of the SAP and TSAP conformations could be distinguished for the $[Dy\text{-}DOTA]^-$ complex (see the Supporting Information [SI]). SAP versus TSAP (TSAP′) signal assignment was based on the observed, or expected, relative integrated intensities. The integral ratios that could be determined by deconvolution analysis were found to be in excellent agreement with the molar proportions reported in the literature (see the SI).[9]

^{17}O NMR Signal Broadening. For diamagnetic systems, the ^{17}O NMR line width is typically due to quadrupole relaxation, but in some cases, significant broadening may arise from chemical exchange.[29,30] As can be seen in Figure 2, the line width observed for the diamagnetic and paramagnetic $[Ln\text{-}DOTA]^-$ complexes is of the same order of magnitude, suggesting that signal broadening due to PRE is not as important as believed.[16] The full line width at half-height (LW) observed for the O_2 signals was determined by Lorentzian deconvolution analysis and found to range between about 2 and 4 kHz at 25 °C (see the SI). These LW data do not exhibit a positive correlation with the effective magnetic moment of the Ln metal ions. On the contrary, the broadest O_2 signals belong to the DOTA complexes of Pr^{3+} and Nd^{3+}, which are characterized by a relatively small magnetic moment. Actually, in addition to intrinsic quadrupole relaxation and to some PRE, the O_2 line width of these two complexes is significantly affected by the exchange between the SAP and TSAP conformations. Indeed, the O_2 resonance lines feature coalescence at about 25 °C for the $[Pr\text{-}DOTA]^-$ complex[23] and at about 40 °C for the $[Nd\text{-}DOTA]^-$ complex (see the SI). On this basis, the activation free energy ($\Delta G^\ddagger$) characterizing the exchange between the TSAP and SAP forms of the $[Nd\text{-}DOTA]^-$ complex is estimated to be 53 kJ/mol, i.e. somewhat larger than the corresponding data previously reported for the $[Pr\text{-}DOTA]^-$ complex ($\Delta G^\ddagger \simeq 50$ kJ/mol).[23] These results, together with the observation of distinct TSAP and SAP O_2 signals at 25 °C for the DOTA complexes of Nd^{3+}, Eu^{3+}, Tb^{3+}, Dy^{3+}, and Ho^{3+}, suggest that the activation barrier increases along the Ln series.

^{17}O NMR chemical shift and LIS data. The chemical shift (δ) data measured at 25 °C are gathered in Table 1. The O_1 chemical shift takes only positive values, between about 170 and 410 ppm. On the contrary, the O_2 chemical shift varies between +800 and −1900 ppm, taking positive values with the lightest paramagnetic metal ions (Ce–Sm) and negative values for the others (Eu–Yb). The LISs measured for the coordinated O_2 oxygen atoms of the DOTA complex of Eu^{3+} are similar to the corresponding values reported for the DTPA complex.[24] In addition, they are similar to the values reported for the inner-sphere water molecule of the $[Eu\text{-}DOTAM]^{3+}$ complex in acetonitrile and of the complex between Eu^{3+} and a DOTA tetramide derivative in aqueous solution.[13,21]

$[Ln\text{-}DOTA]^-$ complexes are suitable molecular systems for a detailed analysis of LIS data. Indeed, they are axially symmetric, nearly isostructural along the Ln series and, as shown in the present study, the ^{17}O chemical shift is sensitive to the nature of the metal ions. The LIS (Δ') can be estimated by subtracting the diamagnetic contribution (Δ_d) from the observed chemical shift (eq 1). This estimation is straightforward for nonlabile ligands, at least to the extent that intramolecular exchange processes are slow on the NMR chemical shift time scale. In the present case, Δ_d can be taken as the chemical shift observed for the $[La\text{-}DOTA]^-$ or $[Lu\text{-}DOTA]^-$ diamagnetic complexes. As mentioned above, Δ' is the sum of the contact (Δ_c) and pseudocontact (Δ_p) contributions (eq 2). Both these terms can be expressed as the product of a Ln-dependent factor, i.e. $\langle S_z \rangle_j$ or C_j^D where j stands for the Ln metal ion, and a ligand-dependent factor, F_i or G_i where i refers to a specific site of the ligand (O_1 or O_2 in the present case). Theoretically calculated $\langle S_z \rangle$ and C^D values, which are the expectation value of the electronic spin and the Bleaney's constant respectively, can be found in the literature and are given in Table 1.[20,31−35] Hence, F and G can in principle be determined by regression analysis of LIS data measured for a series of isostructural complexes, i.e. assuming constant F and G values along the series.[16,19,36]

$$\Delta' = \delta - \Delta_d \qquad (1)$$

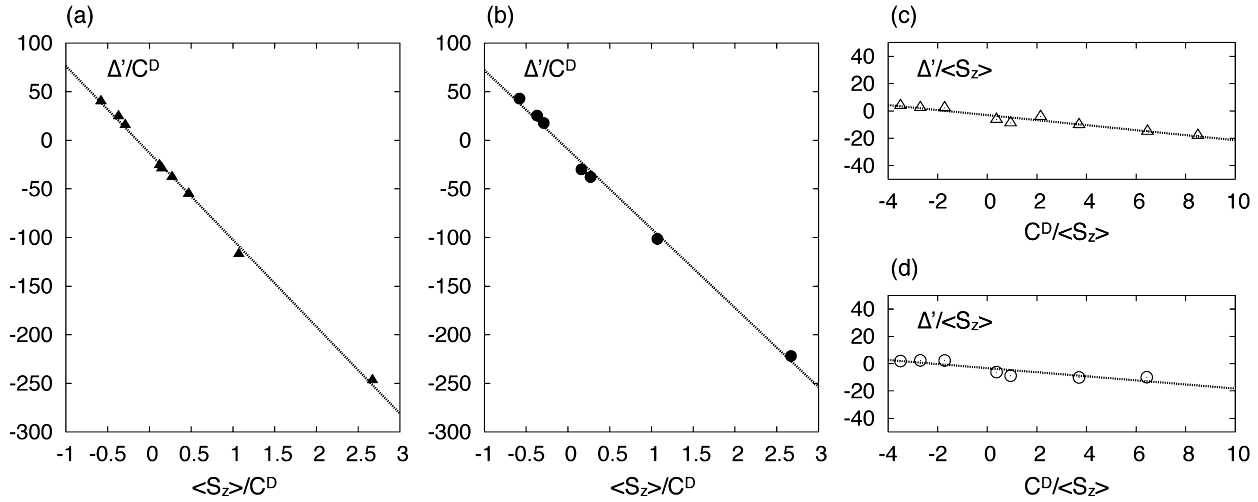

Figure 3. Regression analysis of the ^{17}O LIS data measured at 25 °C for several $[\text{Ln-DOTA}]^-$ complexes in aqueous solution. (a, ▲) and (b, ●): O_2 data for, respectively, the SAP and TSAP isomers analyzed according to eq 3 (method ***A***). (c, Δ) and (d, ○): O_1 data for, respectively, the SAP and TSAP isomers analyzed according to eq 4 (method ***B***).

Table 2. Results of the Analysis of the ^{17}O LIS Data Measured at 25 °C for Several $[\text{Ln-DOTA}]^-$ Complexes in Aqueous Solution (see text and eqs 1−5)[a]

	F	G	$A/\hbar$ (10^6 rad/s)	$A/\hbar$ (MHz)	method
O_1 TSAP	−3.3 ± 2.3	−1.5 ± 0.7	0.16 ± 0.11	0.025 ± 0.018	***B***
O_1 SAP	−3.0 ± 1.7	−1.8 ± 0.4	0.15 ± 0.08	0.023 ± 0.013	***B***
O_2 TSAP	−81 ± 5	−10 ± 5	3.9 ± 0.2	0.63 ± 0.04	***A***
O_2 SAP	−89 ± 3	−13 ± 3	4.3 ± 0.2	0.69 ± 0.02	***A***

[a] The confidence intervals correspond to twice the fitting error.

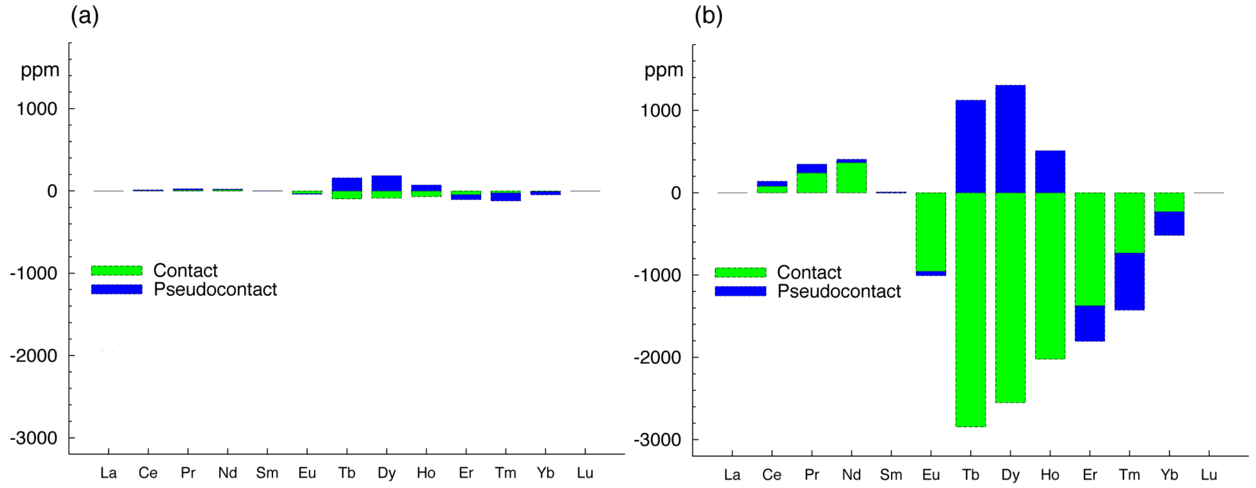

Figure 4. Contact (Δ_c) and pseudocontact (Δ_p) contributions to the LIS experienced by (a) the O_1 and (b) the O_2 oxygen atoms of $[\text{Ln-DOTA}]^-$ complexes in aqueous solution at 25 °C. Δ_c and Δ_p were calculated via eq 2 using the $\langle S_z \rangle$ and C^D values reported in Table 1 together with the F and G values given in Table 2 for the most abundant conformational isomer, i.e. the TSAP form for the lighter metal ions, up to Nd^{3+}, and the SAP form for the others.

$$\Delta' = \Delta_c + \Delta_p = \left\langle S_z \right\rangle_j F_i + C_j^D G_i \tag{2}$$

$$\frac{\Delta'}{C_j^D} = \frac{\left\langle S_z \right\rangle_j}{C_j^D} F_i + G_i \tag{3}$$

$$\frac{\Delta'}{\left\langle S_z \right\rangle_j} = F_i + \frac{C_j^D}{\left\langle S_z \right\rangle_j} G_i \tag{4}$$

$$F_i = \frac{\beta}{3kT\gamma_O} \frac{A_i}{\hbar} \times 10^6 \tag{5}$$

$$\text{PD} = \frac{|\Delta_p|}{|\Delta_c| + |\Delta_p|} \times 100 \tag{6}$$

Regression analysis of LIS data is usually performed according to either eq 3 (method ***A***) or eq 4 (method ***B***), which are both obtained from eq 2.[37−40] Method ***A*** is suitable for LIS data dominated by the Fermi contact term, while conversely, method ***B*** is better adapted if the dipolar term is the major contribution. Hence, method ***A*** is expected to provide better results for the coordinated O_2 oxygen atoms of the $[Ln\text{-}DOTA]^-$ complexes and method ***B*** for the noncoordinated O_1 atoms. The corresponding data are shown in Figure 3a,b and Figure 3c,d, respectively.[41] It can be seen that linear relationships are indeed observed, which sustains the proper choice of the method and the underlying assumptions (see also the SI).

The results of the best-fit analysis are reported in Table 2 together with the HFCC values as calculated using eq 5, where β is the Bohr magneton, k is the Boltzmann constant, T is the absolute temperature, γ_O is the ^{17}O magnetogyric ratio, and where the HFCC $A/\hbar$ is expressed in rad/s.[16] Chemical shift data could be obtained distinctively for the TSAP and SAP conformations of several $[Ln\text{-}DOTA]^-$ complexes (see Figure 2 and Table 1). However, considering the fitting errors, the F (G) parameters determined for each isomer, including systems for which the TSAP and SAP signals are not resolved, are unfortunately not significantly different. For O_2, the results clearly show that F is much larger than G, and the corresponding HFCC is found to lie in the range of values reported for the coordinated oxygen atom of several fast-exchanging ligands.[16−18] On the other hand, for O_1, the results suggest that F is somewhat larger than G and clearly show that the HFCC is much weaker, as expected.

It is now possible to back-calculate the contact and pseudocontact contributions. This was completed using eq 2, the $\langle S_z \rangle$ and C^D values given in Table 1 together with the F and G values determined in this work for the most abundant isomer. The Δ_c and Δ_p terms are depicted in Figure 4, and the percent of dipolar contribution (PD), as calculated according to eq 6,[39] is given in Table 3. Following the sign of $\langle S_z \rangle$, Δ_c is positive for the $[Ln\text{-}DOTA]^-$ complexes of Ce^{3+}, Pr^{3+}, and Nd^{3+}, while it takes negative value for the heavier paramagnetic ions. Similarly, following the sign of C^D, Δ_p is positive for the complexes of Ce^{3+}, Pr^{3+}, Nd^{3+}, Sm^{3+}, Tb^{3+}, Dy^{3+}, and Ho^{3+}; it is negative for the others (Eu^{3+}, Er^{3+}, Tm^{3+}, and Yb^{3+}). The metal ion Tb^{3+} is responsible for the largest negative contact shift, whereas the largest positive pseudocontact shift is induced by Dy^{3+}. The rather large and opposite Δ_c and Δ_p that are induced by Dy^{3+} and Ho^{3+} compensate each other, leading to identical O_2 chemical shift values for the SAP form ($\delta \simeq -1270$ ppm). The O_2 chemical shift observed for the SAP form of the $[Tm\text{-}DOTA]^-$ complex is similar ($\delta \simeq -1240$ ppm) but not as a consequence of compensation between the Δ_c and Δ_p terms, which are both negative in this case. The relatively weak LIS observed for O_1 is dominated by the pseudocontact contribution for all of the systems except the DOTA complexes of Nd^{3+} and Eu^{3+}, for which PD is estimated to be about 30 and 18%, respectively. In contrast, the LIS observed for O_2 is typically dominated by the contact shift, as expected. However, PD values ranging between 40 and 50% are found with Ce^{3+} and Tm^{3+}, while the pseudocontact term is even the major contribution with Yb^{3+} (PD of about 55%).

Table 3. Percent of Dipolar Contribution (PD) to the LIS Experienced by the O_1 and the O_2 Oxygen Atoms of $[Ln\text{-}DOTA]^-$ Complexes in Aqueous Solution at 25°C[a]

	PD O_1 (%)	PD O_2 (%)
Ce^{3+}	**74**	43
Pr^{3+}	**63**	30
Nd^{3+}	30	10
Eu^{3+}	18	5
Tb^{3+}	**62**	28
Dy^{3+}	**68**	34
Ho^{3+}	**51**	20
Er^{3+}	**56**	24
Tm^{3+}	**80**	49
Yb^{3+}	**84**	**55**

[a] Values larger than 50% (i.e. $|\Delta_p| > |\Delta_c|$) are underlined and indicated in bold.

CONCLUSIONS

High-quality ^{17}O NMR spectra of $[Ln\text{-}DOTA]^-$ complexes were recorded in aqueous solution for the whole series of stable lanthanide(III) metal ions except Gd^{3+}. For all of the paramagnetic systems, the signals of the oxygen atoms not coordinated (O_1) and coordinated (O_2) to the metal ion were observed. For some of these systems, signals pertaining to the SAP and TSAP (TSAP′) conformational isomers could also be observed with, in addition, integrated intensities in excellent agreement with the expected molar proportions.

Hence, our results contrast with those of Mayer et al.[22] (who reported that ^{17}O NMR signals could not be detected for several paramagnetic Ln-DOTA complexes) and, more generally, with the idea that the NMR signal of a coordinated site is extensively broadened by PRE if the exchange between the free and bound state is slow on the NMR time scale.[16,19,22,25] The LW of the O_1 and O_2 signals of $[Ln\text{-}DOTA]^-$ complexes ($Ln \neq Pm^{3+}$, Gd^{3+}) is not dominated by PRE effects. It depends on several contributions which are quadrupole relaxation, chemical exchange due to the SAP-TSAP equilibrium around room temperature and to the carboxylate rotation at higher temperatures,[23] and finally PRE.

The ^{17}O hyperfine coupling constants are similar for both isomers. The values determined for O_2 agree with the data reported for the coordinating oxygen atom of fast-exchanging ligands (0.57−0.67 MHz). The hyperfine coupling constants determined for O_1 are about 30 times smaller. Even though the contact shift is generally dominating the LIS of the coordinated oxygen atoms, the pseudocontact shift is often not negligible. For instance, in the case of the $[Dy\text{-}DOTA]^-$ complex, the contact shift accounts for only 66% of the total LIS, while the expected value was larger than 85%.[10,15,16] Finally, the rather small hyperfine coupling constant determined for O_1 suggests that, even for complexes characterized by a large magnetic moment and/or a long electronic relaxation time, the ^{17}O NMR signal of nonchelating oxygen atoms of slow-exchanging ligands should be barely affected by PRE. Thus, it should be possible to directly detect Gd(III) complexes by ^{17}O NMR. This is currently under investigation.

EXPERIMENTAL SECTION

DOTA (100%) was purchased from Chematech, all the $LnCl_3$ hydrates, DCl (35%) and NaOD (40%) from Sigma-Aldrich. D_2O was purchased from Euriso-Top and ^{17}O-enriched water (10%) from Cortecnet. These chemicals were used as received.

All the ^{17}O-enriched DOTA samples were prepared by dissolving the $LnCl_3$ salt with a small excess of DOTA (30 mg, 74 μmol), in 400 μL of D_2O and 150 μL 10% ^{17}O-enriched water. After the addition of 1.5 equiv of DCl 35%, the samples were left at 90 °C for 24 h. NaOD was then used to adjust the pH in the range 7.0 ± 1.6, and the samples were transferred into 5 mm NMR tubes.

The NMR spectra were recorded lock-on, without sample spinning, on a spectrometer operating at 14.1 T (600 MHz for ^{1}H and 81.4 MHz for ^{17}O) and equipped with a 5 mm broadband probe. The samples were left to reach equilibrium at the desired temperature within the magnet for at least 10 min. A ^{1}H NMR spectrum was recorded to check the static magnetic field homogeneity. The formation of the complex was checked by ^{1}H NMR spectroscopy, and the observed resonance lines were found to be in agreement with literature.[5,42]

The ^{17}O NMR spectra were recorded using the RIDE pulse sequence, which strongly reduces baseline distortions due to acoustic ringing.[26] Depending on the system, the inversion pulse was either a nonselective hard pulse or a square 180n shaped pulse in order to mainly excite the O_1 and O_2 resonance lines while reducing the intensity of the water signal. The relaxation delay and the acquisition time comprised between 5 and 25 ms; the number of transients was adapted according to the signal-to-noise ratio. The processing comprised exponential multiplication of the free induction decay with a line broadening factor of 30 Hz, correction of the first three points by backward linear prediction and zero filling prior to Fourier transform, phase, and baseline corrections. The chemical shift scale was referenced to the signal of external neat D_2O at 25 °C (0 ppm).

■ ASSOCIATED CONTENT

Supporting Information

Deconvolution analysis of the ^{17}O NMR spectra of DOTA complexes of Nd^{3+}, Eu^{3+}, Tb^{3+}, Dy^{3+}, Ho^{3+}, and Tm^{3+}, estimations of the TSAP/SAP/TSAP′ proportions, full linewith at half-height of the O_2 signals, analysis of the ^{17}O LIS data, variable temperature ^{17}O NMR spectra of [Nd-DOTA]$^-$, and estimation of the activation free energy characterizing the TSAP-SAP exchange process of the [Nd-DOTA]$^-$ complex. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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