Inorganic Chemistry

Article

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Insight into the Dynamics of Lanthanide-DTPA Complexes As Revealed by Oxygen-17 NMR

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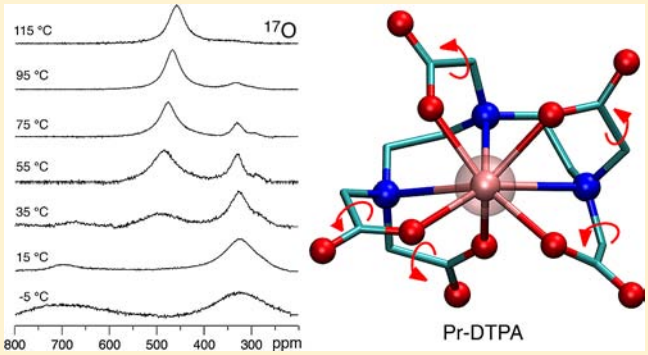
Supporting Information

ABSTRACT: DTPA chelates of various diamagnetic and paramagnetic lanthanide(III) metal ions, as well as the chemically similar DTPA chelate of Y^{3+}, were studied in aqueous solution by variable temperature ^{17}O NMR with the aim of characterizing their internal dynamics. As a consequence of poor chemical shift dispersion and fast quadrupole relaxation, no dynamic exchange process could be detected for the diamagnetic complexes nor for the Sm-DTPA complex. In contrast, the spectra recorded for the Eu-DTPA complex show chemical exchange due to the well-known racemization process and, at high temperature, feature signal broadening that reveals a fluxional process involving the interchange of the coordinated and noncoordinated oxygen atoms of the carboxylate groups. The spectra recorded for the Pr-DTPA complex feature coalescence events due to such a fluxional process, which is ascribable to the rotation of the carboxylate groups. The activation free energy barriers determined experimentally are remarkably lower than the calculated activation barriers recently reported for the rotation of the carboxylate groups of various Ln-DOTA complexes. Furthermore, the smallest activation free energy measured for the Pr-DTPA complex, about 45 kJ mol^{-1}, is significantly lower than the activation free energy characterizing the racemization process. The fluxional behavior of the carboxylate groups is, however, not expected to significantly affect the residence time of the water molecule coordinated to the metal ion.



INTRODUCTION

Lanthanide (Ln) metal ions and octadentate polyaminocarboxylate ligands, among which are the DTPA (diethylenetriaminepentaacetic acid, Figure 1A) and DOTA (tetraazacyclododecanetetraacetic acid) ligands, are known to form 1:1 complexes that exhibit high thermodynamic stability and kinetic inertness. The DTPA and DOTA complexes of gadolinium (Gd^{3+}), which are highly paramagnetic and comprise a labile coordinated water molecule, are therefore used as contrast agent for magnetic resonance imaging (MRI).[1−5] The efficiency of a positive MRI contrast agent is described by its R_1 relaxivity, i.e., the increase in the longitudinal relaxation rate of the water protons per unit concentration of contrast agent. In this respect, the residence time of the coordinated water molecule (τ_M) is a parameter of primary importance. For the contrast agents presently used in clinical MRI, τ_M is on the order of 100 ns at 25 °C, which corresponds to an activation free energy for water exchange of 35 kJ mol^{-1}, but the optimal τ_M value at 1.5 T is about 10 ns.[1]

The detailed characterization of polyaminocarboxylate chelates of Ln metal ions is an active research area of continuing interest, notably for the design of novel contrast agents with improved properties.[1−5] The structure and dynamics of Ln-DTPA complexes have been the subject of several studies by X-ray diffraction and/or nuclear magnetic resonance (NMR).[6−13] Since the Gd^{3+} metal ion is responsible for strong paramagnetic relaxation enhancement (PRE) effects, which induce severe signal broadening, both diamagnetic and weakly paramagnetic Ln-DTPA complexes were studied by solution-state NMR with the aim of indirectly characterizing the most important Gd-DTPA complex. The DTPA ligand possesses three nitrogen atoms (one central and two equivalent lateral nitrogen atoms) and five carboxylate groups (one central and four equivalent lateral groups) which are all involved in the chelation of the Ln metal ion. In the following, the coordinated oxygen atoms are referred to as O′ and the noncoordinated carbonylic oxygen atoms as O″. The generic structure of Ln-DTPA complexes is depicted in Figure 1B. The oxygen atom O_1', which belongs to the central carboxylate group, lies in the same plane as the lateral oxygen atoms O_2', O_3', and O_4', while the lateral oxygen atom O_5' lies in the same plane as the

Received: May 15, 2012
Published: July 20, 2012

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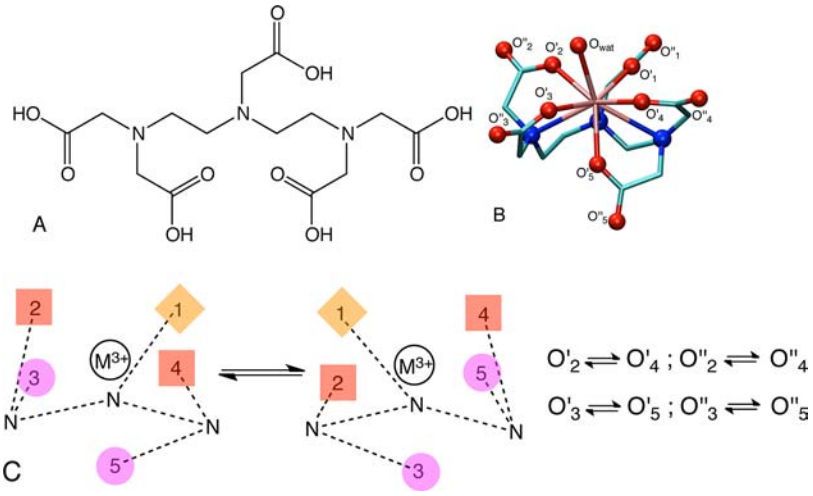

Figure 1. Structure of the DTPA ligand (A), ball-and-stick representation of a metal-DTPA complex (B), and schematic representation of the racemization process (C). In part B, the hydrogen atoms are omitted for clarity, the nitrogen atoms are shown in blue, and the oxygen atoms in red; the oxygen atoms coordinated to the metal ion are labeled as O′ and the noncoordinated carbonylic oxygen atoms as O′′. In part C, the numbering refers to the carboxylate groups, and the methylene groups are omitted.

nitrogen atoms. Ln-DTPA complexes are chiral, and ^{1}H and/or ^{13}C NMR studies have shown that they undergo a conformational rearrangement, which basically consists in shuffling the acetate groups, leading to racemization (see Figure 1C).[9−11] The environment of the oxygen atoms of the central carboxylate group (O_1' and O_1'') remains unchanged but the process is responsible for chemical exchange between the coordinated oxygen atoms of the lateral carboxylate groups (O_2' with O_4' and O_3' with O_5') as well as between the corresponding noncoordinated oxygen atoms (O_2'' with O_4'' and O_3'' with O_5''). The activation free energy of racemization, $\Delta G^{\ddagger}_{rac}$, for the complex of praseodymium (Pr^{3+}), europium (Eu^{3+}), and ytterbium (Yb^{3+}) are, respectively, 56.5, 55.4, and 49.4 kJ mol^{-1} at 25 °C.[9]

According to density functional theory (DFT) calculations, a change in the carboxylate binding mode from mono to bidentate or vice versa (the so-called carboxylate shift) is expected to play a role in the biological activity of zinc enzymes by ensuring a fast ligand exchange, including water exchange.[14] Monodentate carboxylate derivatives may also exhibit fluxionality stemming from the interchange of O′ and O′′. This process is not detectable by ^{1}H nor ^{13}C NMR but is amenable to study by ^{17}O NMR. Recently, by combining natural abundance ^{17}O dynamic NMR and DFT calculations, we showed that acetoxysilanes of the general formula $(CH_3COO)_nSi(CH_3)_{4-n}$, with n = 1−4 as well as acetoxy derivatives of hypervalent iodine, either of I(III) or I(V), are fluxional compounds as a consequence of a degenerate[1,3]-sigmatropic shift mechanism.[15−17] In these compounds, the bidentate binding mode corresponds to either a transition state or a high-energy intermediate. The activation free energy for the acetoxysilanes was measured to range from 76 to 48 kJ mol^{-1} in acetonitrile at 25 °C, decreasing for increasing number of acetoxy groups. For the Dess-Martin periodinane, the NMR measurements indicate that it is considerably lower than 43 kJ mol^{-1}, on the order of 25 kJ mol^{-1} according to DFT calculations. These data show that the activation free energy characterizing the interchange of O′ and O′′ may span a rather wide range, comprising the energy barrier that controls the exchange of the coordinated water molecule of MRI contrast agents.

A few months ago, while the present work was under progress, Mayer et al. reported on the interchange of O′ and O′′ in Ln-DOTA complexes.[18] According to DFT calculations, this exchange process occurs via the internal rotation of the carboxylate groups and the activation free energy is strongly dependent on the radius of the metal ion: it increases along the lanthanide series (i.e., for decreasing ionic radius) from about 75 kJ mol^{-1} for the DOTA complex of lanthanum (La^{3+}) to 135 kJ mol^{-1} for the twisted square antiprismatic isomer of the DOTA complex of lutetium (Lu^{3+}). These calculated energy barriers were found to be consistent with the results of variable temperature ^{17}O NMR measurements. The authors concluded that it is very likely that the rotation of the carboxylate groups and the exchange of water are processes taking place independently of each other.

The present ^{17}O NMR study investigates the internal dynamics of Ln-DTPA complexes in aqueous solution and primarily the exchange between the coordinated (O′) and noncoordinated (O′′) oxygen atoms of the carboxylate groups. This process is expected to be characterized by a lower activation barrier in Ln-DTPA complexes because (i) they are less rigid than the corresponding Ln-DOTA complexes[19] and (ii) five carboxylate groups are bound to the metal ion against four in the Ln-DOTA chelates. DTPA complexes of both diamagnetic metal ions (the lanthanide ions La^{3+} and Lu^{3+} as well as the chemically similar yttrium ion Y^{3+}) and paramagnetic metal ions (the samarium ion Sm^{3+}, Pr^{3+}, and Eu^{3+}) were studied over a wide range of temperatures using ^{17}O-enriched DTPA. It is noteworthy that the very recent work of Mayer et al.[18] and the present work are, to the best of our knowledge, the first two studies reporting on the ^{17}O NMR of complexes between Ln metal ions and polyaminocarboxylate ligands.

RESULTS AND DISCUSSION

Diamagnetic Complexes. ^{17}O NMR spectra of the DTPA complexes of La^{3+}, Lu^{3+}, and Y^{3+} in aqueous solution were recorded at 14.1 T and various temperatures ranging between 5 and 95 °C (Figure 2 and the Supporting Information). In the whole temperature range, the spectra of these three chelates show a single signal at about 280−290 ppm, which can be

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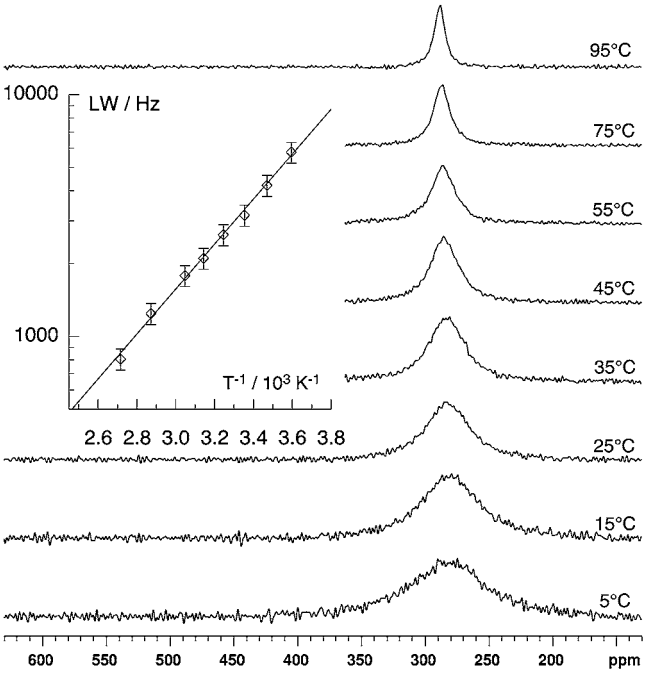

Figure 2. Variable temperature ^{17}O NMR spectra recorded at 14.1 T for the La-DTPA complex in aqueous solution. No apodization of the free induction decay was used. The variation of the full line width at half-height versus the inverse temperature is shown as a semi-logarithmic plot in the inset; the confidence intervals correspond to ±10% (twice the estimated relative standard error); the plain line is the result of the best-fit analysis according to eq 1.

properly represented by a single Lorentzian line (see the Supporting Information). The chemical shift slightly increases for increasing temperatures while the signal becomes significantly sharper.

The spectra recorded by Mayer et al. for the La-DOTA complex also show a single signal, at 295−302 ppm, for temperatures ranging between 25 and 147 °C and magnetic fields up to 18.8 T; the authors concluded that the rotation of the carboxylate groups is fast on the NMR spectral time scale.[18] As mentioned above, the DTPA ligand possesses four equivalent lateral carboxylate groups and one central carboxylate group. If both the racemization and the exchange between the coordinated and noncoordinated oxygen atoms are in the slow exchange regime, the ^{17}O spectrum of the DTPA complexes is expected to show 10 resonance lines (O_{1-5}' and O_{1-5}'') of equal integrated intensities. If both these dynamic processes are in the fast exchange regime, the spectrum is expected to show three resonance lines, with integrated intensities in the ratio 1:2:2 (2:4:4), corresponding to the average signals of (i) O_1' and O_1'', (ii) O_2', O_2'', O_4' and O_4'', (iii) O_3', O_3'', O_5' and O_5'' (see Figure 1C). Hence the signal observed for the La-DTPA, Lu-DTPA, and Y-DTPA complexes is the superimposition of, at least, three resonance lines; its characteristics must therefore be regarded as apparent values.

The observed full line width at half-height, shortly referred to as line width (LW) in the following, ranges from about 6×10^3 Hz for the complex La-DTPA at 5 °C to 6×10^2 Hz for Lu-DTPA at 95 °C (see inset of Figure 2 and the Supporting Information). The temperature dependence is properly accounted for by an Arrhenius-type variation, eq 1, where the pre-exponential factor is the apparent line width at 298 K, E_a is the apparent activation energy, R is the gas constant, and T is the absolute temperature. The observed LW variation corresponds to the temperature dependence expected for the natural line width due to quadrupole relaxation (the line width decreases for increasing temperatures mainly as a consequence of the shortening of the overall rotational correlation time). No additional broadening that would reveal an exchange process is detected and, therefore, no kinetic data can be extracted. The results of the nonlinear best-fit of eq 1 to the experimental line width data are given in Table 1. The LW_a^{298} values are consistent with the transverse relaxation rate data, $1/T_{2,B}^{298}$, reported by Mayer et al. for the DOTA complexes ($\pi LW_a^{298} = 1/T_{2,B}^{298}$).[18] The apparent activation energy is similar for the three chelates, corroborating that quadrupole relaxation is the major contribution to the observed overall line width. Furthermore, these activation energy data are in close agreement with the activation energy for the rotational correlation time of the Gd-DTPA complex as determined by simultaneous analysis of electron paramagnetic resonance (EPR), NMR, and nuclear magnetic relaxation dispersion (NMRD) measurements.[20−22]

$$LW = LW_a^{298}\, e^{E_a/R\left[\frac{1}{T}-\frac{1}{298}\right]} \quad (1)$$

Paramagnetic Complexes. Enhanced resolution of the ^{17}O NMR signals of Ln-DTPA chelates could, in principle, be achieved by taking advantage of the so-called lanthanide-induced-shift (LIS). Therefore, variable temperature ^{17}O NMR spectra were recorded at 14.1 T for the DTPA complexes of the paramagnetic metal ions Sm^{3+}, Pr^{3+}, and Eu^{3+}. Among the paramagnetic Ln metal ions, Sm^{3+} is characterized by the smallest magnetic susceptibility.[23] Similarly to the diamagnetic DTPA complexes, the Sm-DTPA complex gives rise to superimposed ^{17}O NMR resonances at 260−250 ppm for temperatures ranging between −5 °C up to 115 °C (see Figure 3). This differs from the spectra recorded by Mayer et al. at 18.8 T for the Sm-DOTA complex which show two signals of equal intensities at 245−215 ppm (O′) and 290−295 ppm (O″) in the temperature range of 25−150 °C.[18] The overall signal observed for the Sm-DTPA chelate can properly be represented by a single Lorentzian line (see the Supporting Information). For this complex, the chemical shift slightly decreases for increasing temperatures and, as expected, the signal narrows. The temperature dependence of the observed line width is fittingly described by an Arrhenius-like variation

Table 1. Results of the Best-Fit of Equation 1 to the ^{17}O NMR Linewidth Data[a]

	La-DTPA	Lu-DTPA	Y-DTPA	Sm-DTPA
LW_a^{298} (kHz)	3.34 ± 0.08	2.57 ± 0.06	3.11 ± 0.07	3.12 ± 0.07
E_a (kJ mol^{-1})	17.9 ± 0.6	18.9 ± 0.6	19.3 ± 0.6	16.3 ± 0.6

[a]See text for parameter definitions. The errors were estimated from the analysis of 500 pseudo-experimental data sets obtained by adding random errors generated from Gaussian distributions and using an absolute standard error of ±1 K on the temperature and a relative standard error of ±5% on the linewidth.

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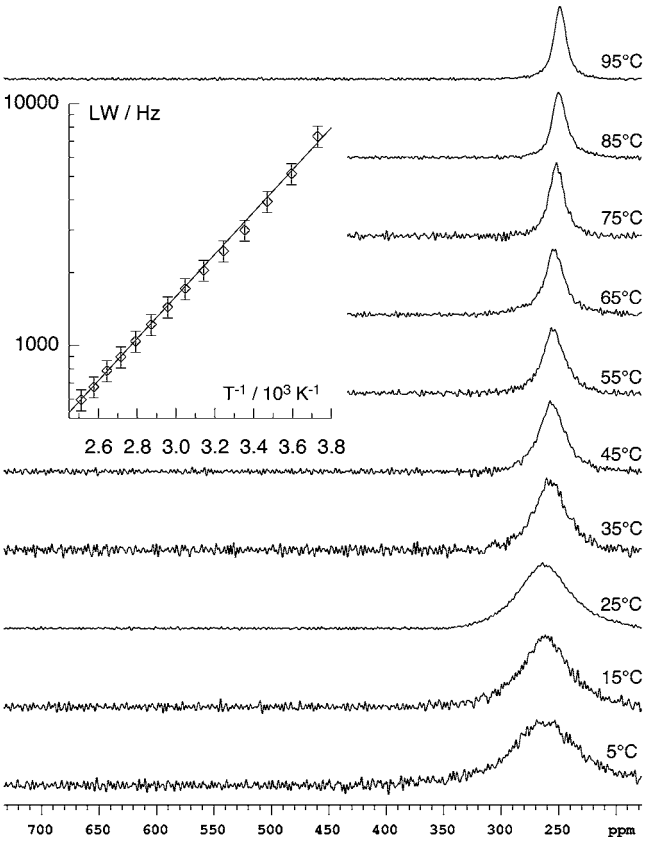

Figure 3. Variable temperature ^{17}O NMR spectra recorded at 14.1 T for the Sm-DTPA complex in aqueous solution. No apodization of the free induction decay was used. The variation of the full line width at half-height versus the inverse temperature is shown as a semi-logarithmic plot in the inset; the confidence intervals correspond to ±10% (twice the estimated relative standard error); the plain line is the result of the best-fit of eq 1.

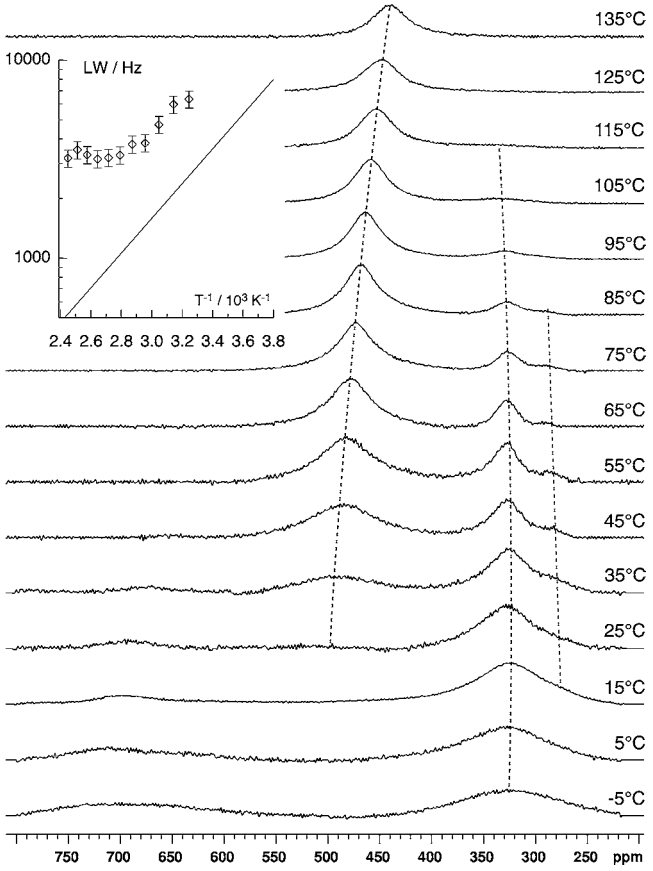

Figure 4. Variable temperature ^{17}O NMR spectra recorded at 14.1 T for the Pr-DTPA complex in aqueous solution. No apodization of the free induction decay was used. The dotted lines are guides for the eye emphasizing chemical shift variations. The variation of the full line width at half-height versus the inverse temperature (35−135 °C) is shown for the signal at 500−450 ppm as a semilogarithmic plot in the inset; the confidence intervals correspond to ±10% (twice the estimated relative standard error). For comparison purpose, the best-fit of eq 1 to the Sm-DTPA line width data is shown as a plain line.

(see inset of Figure 3), indicating that no kinetic information can be obtained for this chelate. The results of the nonlinear best-fit of eq 1 to the experimental line width data are given in Table 1. The apparent line width at 298 K and the apparent activation energy are similar to the corresponding values determined for the diamagnetic DTPA complexes, indicating that the PRE induced by the Sm^{3+} ion are weak compared to quadrupole relaxation.

In contrast to the Sm-DTPA complex, both the Pr-DTPA and Eu-DTPA complexes give rise to several ^{17}O NMR signals at 14.1 T (see Figures 4 and 5). The assignment of the ^{17}O NMR spectra is definitely less straightforward than the assignment of ^{1}H or ^{13}C spectra. Indeed, scalar couplings and nuclear Overhauser effects cannot be exploited and proper integrated intensity measurements may be tricky, notably as a consequence of low signal-to-noise ratio, signal broadening, signal overlapping, possible baseline distortions, and/or nonuniform excitation. The assignment was primarily based (i) on chemical shift data, which were compared to the values reported for Ln-DOTA complexes[18] and (ii) on the effects of the exchange processes. Relative integrated intensities that could be trustfully estimated by deconvolution analysis were used with the purpose to check whether the spectra are compatible with the interpretation. The main characteristics exploited for the assignments are presented in the following. With the Pr^{3+} and Eu^{3+} metal ions, the signals of the coordinated oxygen atoms (O′) experience a large positive or negative LIS (hundreds of ppm). The chemical shift of these signals is thus quite different from the values observed for the diamagnetic complexes. The detection of these signals is hampered by significant broadening due to PRE effects, which may also prevent the observation of the individual O′ resonance lines. In constrast, the signals of the noncoordinated (O′′) oxygen atoms experience a much smaller LIS (tens of ppm) and weaker PRE effects. Hence, individual resonance lines are more easily observed in the O′′ chemical shift range, i.e., between 100 and 300 ppm, which is similar to the chemical shift range for the diamagnetic complexes. The LW of both the O′ and O′′ signals is expected to decrease for increasing temperatures, unless chemical exchange occurs. Both the racemization and the interchange of the carboxylate oxygen atoms are so-called equipopulated two-site exchange processes. As the temperature increases, they may be responsible for signal broadening, coalescence events, disappearance of resonance lines, and observation of new average signals. The determination of the temperature for which a coalescence event occurs (T_c) allows the estimation of the free energy of activation characterizing the underlying dynamic process (see the Supporting Information). As mentioned above, the racemiza-

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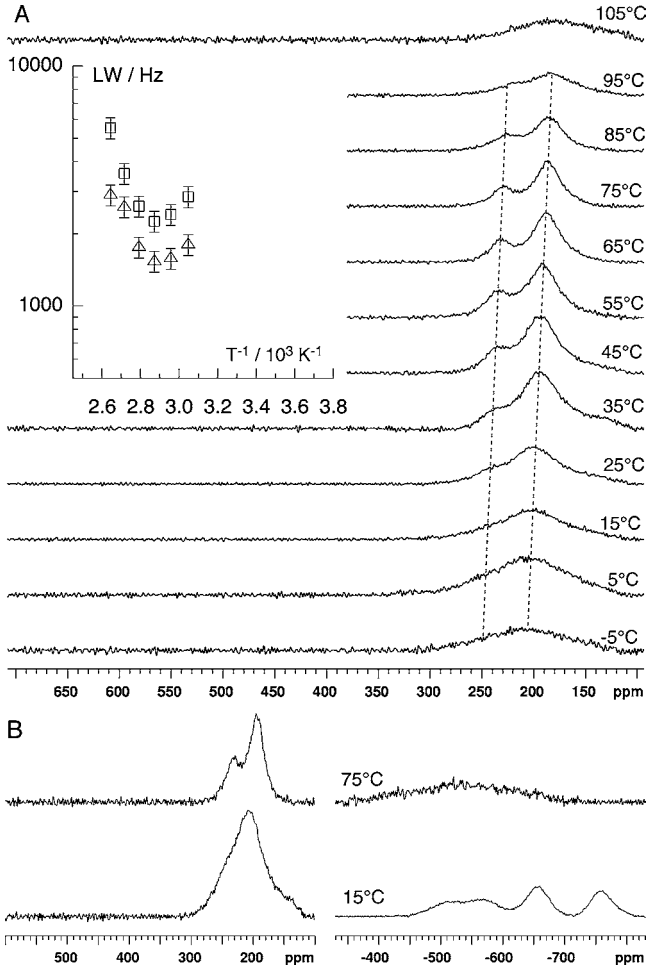

Figure 5. Variable temperature ^{17}O NMR spectra recorded at 14.1 T for the Eu-DTPA complex in aqueous solution. (A) Region of the O′′ signals. No apodization of the free induction decay was used. The dotted lines are guides for the eye emphasizing chemical shift variations. The inset shows a semilogarithmic plot of the variation of the full line width at half-height of the signals at about 190 ppm (□) and 230 ppm (Δ) versus the inverse temperature (55−105 °C); the confidence intervals correspond to ±10% (twice the estimated relative standard error). (B) Regions of the O′′ signals (left) and O′ signals (right) from spectra of an independent sample recorded at 15 and 75 °C. Exponential multiplication of the free induction decay with a line-broadening factor of 50 Hz was used for these spectra.

tion process is responsible for exchange between pairs of oxygen atoms of the same type (see Figure 1C). In particular, it is thus responsible for the coalescence of signals within the chemical shift range of about 100−300 ppm (the coalescence of the O_2'' and O_4'' signals, on the one hand, and the coalescence of the O_3'' and O_5'' signals, on the other hand). The chemical environment of the central carboxylate group is not affected by the racemization process. Hence, the O_1'' signal does not broaden nor disappear as a consequence of this process. In contrast to the racemization process, the interchange of the carboxylate oxygen atoms is responsible for exchange between pairs of oxygen atoms of different type (between O′ and O′′). In particular, it is responsible for the disappearance of signals in the chemical shift range between 100 and 300 ppm and for the observation of a new average signal at a totally different chemical shift (at the average value between $\delta_{O'}$ and $\delta_{O''}$).

At the lowest investigated temperatures, the spectra of Pr-DTPA show two broad signals (Figure 4, see also the Supporting Information). The signal at low field is assigned to coordinated oxygen atoms ($\delta_{O'} \approx 700$ ppm) because a rather large LIS is observed. Conversely, the signal at high field is assigned to noncoordinated oxygen atoms ($\delta_{O''} \approx 300$ ppm). These chemical shift data are consistent with the values reported for the O′ and O′′ signals of the Pr-DOTA complex.[18] The spectra evolve intricately as the temperature increases: (i) the low-field signal is hardly or not detected at all; (ii) the spectra show two signals at high field ($\delta_{O''} \approx 280$ and 320 ppm) for temperatures ranging between 35 and 95 °C, but a single broad signal is detected at higher temperatures up to approximately 115 °C (see also the Supporting Information); (iii) at 35 °C and higher temperatures, a rather intense signal is observed at 500−450 ppm. Furthermore, the line width of the signal at 320 ppm decreases in the temperature range of 35−75 °C and increases at higher temperatures. The line width of the signal at 500−450 ppm is significantly larger than the line width measured for the Sm-DTPA complex (see the inset of Figure 4); it decreases for increasing temperatures up to about 95 °C and is essentially constant between 95 and 135 °C.

The appearance of a signal at about 500 ppm, i.e., a value which is the average of the chemical shift of O′ and O′′, indicates that the carboxylate groups undergo a dynamic process which is fast with respect to the NMR spectral time scale. Considering the work of Mayer et al.,[18] it is assumed in the following that the interchange of O′ and O′′ in the Ln-DTPA complexes occurs as a consequence of the rotation of the carboxylate groups. As mentioned above, this average signal appears at 35 °C and is rather intense. At 35 °C, the fast exchange regime thus prevails for several carboxylate groups but not for all of them since two signals are still observed at high field. This observation indicates that three carboxylate groups have similar properties, possibly the three lateral carboxylate groups lying in the oxygen atom plane (numbered 2, 3, and 4 in Figure 1B). Hence, the average signal at about 500 ppm is tentatively assigned to the O′ and O′′ atoms of these three groups. The chemical shift difference, $\Delta\delta = \delta_{O'} - \delta_{O''}$, is on the order of 400 ppm and, since the average signal is clearly detected at 35 °C, T_c is estimated to be 25 °C or somewhat lower. The activation free energy characterizing the rotation of these carboxylate groups, $\Delta G^{\ddagger}_{rot}$, is thus estimated to be approximately 45 kJ mol^{-1} or somewhat less (see the Supporting Information). This activation free energy barrier is significantly lower than the activation barrier characterizing the racemization of the Pr-DTPA complex ($\Delta G^{\ddagger}_{rac} = 56.5$ kJ mol^{-1} at 25 °C).[9]

The two high-field signals that are still observed at temperatures above 35 °C ($\delta \approx 280$ and 320 ppm) are assigned to the O′′ atom of the fourth lateral carboxylate group (possibly O_5'', according to the numbering in Figure 1B) and to the O′′ atom of the central carboxylate group (O_1''). The corresponding O′ signals are not detected, probably as a consequence of severe broadening due to PRE. The rotation of these two carboxylate groups is responsible for further coalescence in the temperature range of 115−135 °C (see the Supporting Information). The concomitant broadening of the signal at about 450 ppm indicates that all of the average signals are superimposed, which is consistent with the spectra of the diamagnetic complexes. This allows the estimation of the chemical shift difference and thus the activation free energy at the coalescence temperature ($T_c \approx 125$ °C), which is found to

dx.doi.org/10.1021/ic3010085 | Inorg. Chem. 2012, 51, 8455−8461

be on the order of 60 kJ mol^{-1} (see the Supporting Information). This activation free energy barrier is larger than the activation free energy characterizing the racemization of the Pr-DTPA complex.

The variable temperature ^{17}O NMR spectra of the Eu-DTPA complex exhibit several signals between 100 and 300 ppm, which are ascribable to the noncoordinated oxygen atoms, but no signal at lower field (Figure 5A). Signals of the coordinated oxygen atoms could be detected between −900 and −300 ppm, however. At 15 °C, the spectrum shows four signals at $\delta_{O'} \approx$ −510, −570, −660, and −760 ppm (Figure 5B). Such large negative chemical shifts agree with the sign of the contact interaction, which is opposite for the Eu^{3+} and Pr^{3+} metal ions, and with the strength of this interaction, which is stronger for the Eu^{3+} ion.[23,24] These O′ signals are assigned to the lateral carboxylate groups (numbered 2−5 in Figure 1B) because they are affected by the racemization process. Indeed, at 75 °C the spectrum exhibits a single broad signal at about 540 ppm. Attempts to detect the signal of O_1' at higher field, or in the vicinity of the signal of water, were unsuccessful.

The spectrum region corresponding to the noncoordinated oxygen atoms shows a single broad signal at low temperature ($\delta_{O''} \approx$ 200 ppm; Figure 5A) but two signals are clearly observed for temperatures ranging between 55 and 95 °C ($\delta_{O''} \approx$ 190 and 230 ppm). The LW of these two signals first decreases, then increases, for increasing temperatures (inset of Figure 5A). The less intense signal observed at about 230 ppm is assigned to O_1'' because it is detected up to 95 °C (it is not affected by the racemization process). Deconvolution analysis using Lorentzian functions indicates that the spectra are consistent with two signals of integrated intensities in the ratio 4:1 (see the Supporting Information). The main signal at about 190 ppm is thus assigned to the O″ atoms of the four lateral carboxylate groups. In this temperature range, the racemization process is fast on the NMR spectral time scale, and this signal is the superimposition of two average resonance lines ($O_{2,4}''$ and $O_{3,5}''$). All of the O″ oxygen atoms are thus detected up to 95 °C and probably at 105 °C as well. The signal broadening observed at high temperature is the consequence of the rotation of the carboxylate groups which interchanges O″ and O′. Although coalescence of the O″ and O′ signals was not reached at 105 °C, significant exchange broadening is observed and the activation free energy characterizing the carboxylate rotation can be estimated to be on the order of 60 kJ mol^{-1} (see the Supporting Information). Finally, it is noteworthy that the spectrum recorded at 35 °C shows a signal at about 130 ppm which is not detected at 55 °C (Figure 5A). Since the central O_1'' atom is observed at about 230 ppm (vide supra), this signal is assigned to the O″ atom of one lateral carboxylate group. Its intensity is rather low because the excitation is less efficient at the borders of the spectral window, but also as a consequence of significant broadening due to chemical exchange (racemization process). At 35 °C, the main signal at about 200 ppm thus corresponds to three lateral O″ atoms. Using $T_c \approx$ 55 °C and $\Delta\delta \approx$ 70 ppm, $\Delta G_{rac}^{\ddagger}$ is estimated to be 55 kJ mol^{-1}, which is in excellent agreement with the value reported in the literature (55.4 kJ mol^{-1} at 25 °C).[9]

CONCLUSIONS

The internal dynamics of the Y-DTPA chelate and various Ln-DTPA chelates were investigated in aqueous solution by variable temperature ^{17}O NMR. As a consequence of poor chemical shift dispersion and fast quadrupole relaxation, no kinetic data could be obtained for the chelates of the diamagnetic La^{3+}, Lu^{3+}, and Y^{3+} metal ions nor for the chelate of the weakly paramagnetic Sm^{3+} ion. However, the apparent activation energy characterizing the overall rotational dynamics, as determined from the temperature dependence of the line width, were found to be in excellent agreement with the literature data. The ^{17}O NMR spectra show several signals for the Pr-DTPA and Eu-DTPA complexes and reveal that these compounds are fluxional as a consequence of both the racemization process and the interchange of the coordinated and noncoordinated oxygen atoms of the carboxylate groups. Experimental estimations of the activation free energy characterizing this interchange process are provided for the first time. The free energy barriers determined for both the Pr-DTPA and Eu-DTPA complexes are remarkably lower than the calculated values recently reported by Mayer et al. for a series of Ln-DOTA complexes.[18] They are somewhat larger than the activation free energy characterizing the racemization of these DTPA chelates, i.e., on the order of 60 kJ mol^{-1}, with the exception of three lateral carboxylate groups of the Pr-DTPA complex, for which the activation free energy is estimated to be 45 kJ mol^{-1}. These values are significantly higher than the activation free energy characterizing the exchange of the water molecule coordinated to the metal ion, suggesting that the two processes are independent.

EXPERIMENTAL SECTION

DTPA (100%) was purchased from Chematech. $LaCl_3$, $LuCl_3$, YCl_3, $SmCl_3$, $PrCl_3$, and $EuCl_3$ were obtained as hydrates from Sigma-Aldrich. D_2O was purchased from Euriso-Top and ^{17}O-enriched water (10%) from Cortecnet. These chemicals were used as received.

The ^{17}O enrichment of DTPA was performed according to a protocol adapted from the literature.[18] About 200 mg of DTPA was dissolved in 1 g of ^{17}O-enriched water, two drops of concentrated HCl (36%) were added, and the solution was stirred at 90 °C for 24 h. The solution was cooled down to room temperature, and the pH was adjusted to 7.2 using aqueous NaOH. The solution was then freeze-dried, providing the product as a white powder. The ^1H NMR spectrum was identical to the spectrum of the starting material.

The chelates were prepared in 5 mm NMR tubes by dissolving equimolar amounts of ^{17}O-enriched DTPA and metal chloride in D_2O. The concentration of the samples was 20 mM (La-DTPA, Lu-DTPA, and Y-DTPA), 40 mM (Sm-DTPA), 100 mM (Pr-DTPA), or 130 mM (Eu-DTPA). The samples were flame-sealed in order to record NMR spectra at temperatures higher than 100 °C.

The NMR spectra were recorded lock-on, without sample spinning, on a Varian VNMRS spectrometer operating at 14.1 T (600 MHz for ^1H and 81.4 MHz for ^{17}O ; software VNMRJ 2.2C) 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 15 min. A ^1H NMR spectrum was recorded to check the static magnetic field homogeneity. The ^{17}O NMR spectra were recorded using the RIDE pulse sequence, which strongly reduces baseline distortions due to acoustic ringing,[25] with a relaxation delay of 5 ms and an acquisition time of 5 ms as well. The number of transients was adapted according to the signal-to-noise ratio. The processing comprised the correction of the first 3 points of the free induction decay (FID) by backward linear prediction and two levels of zero filling prior to Fourier transform, phase, and baseline corrections. Unless otherwise stated, no apodization of the FID was used. The signal of the solvent was used for chemical shift referencing (D_2O, δ = 0 ppm; see the Supporting Information). Deconvolution analysis was carried out using homemade programs in Excel and/or Gnuplot.

dx.doi.org/10.1021/ic3010085 | Inorg. Chem. 2012, 51, 8455−8461

■ ASSOCIATED CONTENT

Supporting Information

Additional experimental information; ^{17}O NMR spectra of various DTPA complexes obtained without backward linear prediction and no baseline correction; ^{17}O NMR spectra of the Lu-DTPA and Y-DTPA chelates; examples of Lorentzian fitting for the La-DTPA, Lu-DTPA, Y-DTPA, and Sm-DTPA chelates; ^{17}O NMR spectra of the Pr-DTPA chelate recorded at −5 °C and two different transmitter frequencies; ^{17}O NMR spectra of the Pr-DTPA chelate recorded at high temperature; deconvolution of the O″ and O′ signals of the Eu-DTPA chelate; overall scheme of the chemical exchange processes; and estimation of the activation barriers. 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.

■ ACKNOWLEDGMENTS

L.F. and M.L. thank Prof. Luce Vander Elst and Dr. Sophie Laurent (University of Mons-Hainaut, Belgium) for stimulating discussions, the "Fonds de la Recherche Scientifique" (F.R.S.-FNRS) and the Université Libre de Bruxelles (ULB) for financial support. L.F. and F.M. thank Prof. Giovanni Cerioni (Università di Cagliari, Italy) for helpful discussions.

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