Structure and Dynamics of Lanthanide Complexes of Triethylenetetramine-$N,N,N',N''-hexaacic Acid (H₄thta) and of Diamides H₄thta(NHR) Derived from H₄thta as Studied by NMR, NMRD, and EPR

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Dedicated to Professor André E. Merbach on the occasion of his 65th birthday

A multinuclear NMR study on [Ln(thta)]³⁻ and [Ln(thta(NHR))₂]³⁻ complexes (R = Et, CH₂(CHOH)₄-CH₂OH) shows that coordinating groups of the organic ligands in these complexes are occupying all coordination sites of the metal ions, leaving no space for coordination of H₂O molecules (H₄thta = triethylenetetramine-$N,N,N',N''-hexaacic acid). The lanthanides of the first half of the series bind the thta-type ligands in a decadent fashion, while the complexes formed with the smaller ions of the second half of the lanthanide series are nonadentate. One carboxylate group of the ligand remains unbound in the latter complexes. In principle, the thta complexes can exist in six enantiomeric forms. Only one of the pair of diastereoisomers can interconvert without decoordination of the ligand. This pair of isomers seems to be predominant in solution. For the [Ln(thta(NHR))₂]³⁻ complexes, the number of chiral centers is larger, resulting in 32 possible enantiomeric forms of the complexes. The NMR spectra of [Nd(thta(NHEt))₂]³⁻ indicate that two dynamic processes occur between the isomers in solution. The NMRD curves of [Gd(thta)]³⁻, [Gd(thta(NHEt))₂]³⁻, and [Gd(thta(NHgluca))₂]³⁻ (NHgluca = γ-glucamine) show significant differences with the previously determined outer-sphere contributions to the NMRD profiles of the corresponding [Gd(dppt(NHR))]³⁻ complexes, which can be ascribed to differences in the parameters determining the electronic relaxation.

1. Introduction. – Lanthanide complexes of polyaminopolycarboxylates have been studied intensively over the last decades because of their application as contrast agents for magnetic resonance imaging (MRI) [1]. Lanthanide complexes of thta (H₄thta = triethylenetetramine-$N,N,N',N''-$hexaacic acid = 3,6,9,12-tetraakis(carboxymethyl)-3,6,9,12-tetraazaatetradecanedioic acid), particularly [Dy(thta)]³⁻ and [Tm(thta)]³⁻, have also found applications as NMR-shift reagents for monovalent and divalent cations [2].

The complexes based on dtpta (H₄dtpta = diethylentriamine-$N,N,N',N''-$pentaacic acid = 3,6,9-bis[2-[bis(carboxymethyl)amino]ethyl]glycine] have been characterized in detail [1], while the thta analogues have received far less attention. The various lanthanide complexes of thta are not isostructurale in solution. Holz et al. [3] have suggested different coordination modes for the [La(thta)]³⁻ and [Lu(thta)]³⁻ complexes. Also for the solid state, different coordination modes have been reported
for various lanthanide complexes of thta [4–7]. The crystal structures show a ten- (La, Nd) or nine-fold (Gd, Dy) coordination geometry. This variation in coordination number can be ascribed to the lanthanide contraction along the series. Similar phenomena have been reported for Ln³⁺ complexes of other polyanionic carboxylates, e.g., of the ega ligand (H₄ega = 3,12-bis(carboxymethyl)-6,9-dioxo-3,12-diazatetradecanedioic acid) [8].

The efficiency of MRI contrast agents [1] is generally expressed as the relaxivity, r₁, which is the enhancement of the H₂O ¹H relaxation rate expressed in s⁻¹ mm⁻¹. The relaxation-rate enhancement arises from: i) an inner-sphere contribution due to protons of H₂O molecules directly coordinated to the Gd³⁺ ion and in exchange with the bulk water, and ii) an outer-sphere contribution as a result of H₂O molecules freely diffusing along the paramagnetic center. Sometimes, a third contribution is considered, which is referred to as the second-sphere contribution [9]. It concerns H₂O molecules that are not directly coordinated to the Gd³⁺ ion but that are bound to the paramagnetic complex through, e.g., H-bonds. In the literature, there is general agreement that, for [Ln(thta)³⁻] complexes, the inner coordination sphere of the metal ion is fully occupied by donating groups of the ligand, leaving no space for the coordination of H₂O molecules. Consequently, the H₂O ¹H relaxation enhancement has no inner-sphere contribution; it is determined exclusively by the outer-sphere and the second-sphere relaxation. Therefore, the [Gd(thta)]³⁻ complex is an interesting model to study these relaxation mechanisms.

Measurement of the magnetic-field dependence of the H₂O ¹H longitudinal relaxation rate as a function of the magnetic field (NMRD) is important for the evaluation of parameters governing the relaxivity of potential MRI contrast agents [1]. The [Gd(thta)]³⁻ complex has been used as a model for the sum of the outer- and second-sphere contributions to the total relaxivity (r₁) of acyclic polyniminopolycarboxylates [10]. By subtracting the relaxivity of [Gd(thta)]³⁻ from the observed r₁ of a Gd³⁺ complex of an acyclic polyniminopolycarboxylate, the inner-sphere contribution can be calculated, provided that the relaxivity of [Gd(thta)]³⁻ is a reasonable estimation of outer-sphere and second-sphere relaxivity of the complex under investigation [10][11]. However, the NMRD data of [Gd(dtpa(NHgluca)₂)] (NHgluca = D-glucamine = D-glue-2,3,4,5,6-pentahydroxyhexamine) [12] could not be fitted with the Solomon–Bloembergen–Morgan equations [13–15] by using this estimation for the outer- and second-sphere contribution to the relaxivity [12]; so the question arises whether [Gd(thta)]³⁻ is a suitable model for outer-sphere relaxation in Gd³⁺ complexes of dtpa derivatives.

Here we report on an NMR and EPR study on the solution structures and dynamics of the lanthanide complexes of thta and thta(NHET)₂. The NMRD profiles of the Gd³⁺ complexes of thta, thta(NHET)₂, and thta(NHgluca)₂ (see Fig. 1 for chemical structures) are analyzed and compared with literature data on the corresponding dtpa derivatives.

2. Results and Discussion. – 2.1. Synthesis of the Ligands. The diamide ligands H₄thta(NHR)₂ (derived from H₄thta) used in this study (Fig. 1) were synthesized starting from H₄thta. Heating a solution of this compound in Ac₂O and pyridine gave exclusively the dianhydride with the anhydride moieties at the terminal N-atoms.
Reactions with the appropriate amines (ethanamine or D-glucamine) gave the diamides H$_2$thta(NHEt)$_2$ and H$_2$thta(NHgluc)$_2$.

2.2. Determination of the Hydration Number of the Lanthanide(III) Complexes. Upon stepwise addition of DyCl$_3$·6H$_2$O to an aqueous solution of H$_2$thta, H$_2$thta(NH-HEt)$_2$, or H$_2$thta(NHgluc)$_2$, at pH 6 – 6.5, the $^{17}$O-NMR chemical shift of H$_2$O hardly changed up to $\rho_h = 1$ ($\rho_h = [\text{Ln}^{3+}]/[\text{organic ligand}]$). At $\rho_h = 1$, the curve of $\delta$(O) vs. $\rho_h$ showed a sudden break and at $\rho_h > 1$, the absolute value of $\delta$(O) of H$_2$O steeply increased. In that region, the $\delta$(O) of H$_2$O changed linearly with the concentration of the metal ion. These phenomena indicate that for all compounds, 1:1 Ln/ligand complexes are formed.

Previously, it has been shown that the lanthanide-induced shifts (LIS) for a Ln$^{3+}$-bound O-atom are mainly of contact origin and that the hyperfine coupling constant does not vary significantly along the lanthanide series [16]. This may be exploited for the determination of the number of Ln$^{3+}$-bound H$_2$O molecules ($q$) in the Ln$^{3+}$ complexes, particularly for Ln = Dy$^{3+}$, since for that ion, the contact contribution to the shift is predominant. From the induced shift of a solution of [Dy(D$_2$O)$_6$]$^{3+}$, the LIS value at $\rho_h = 1$ ($\rho_h = [\text{Ln}^{3+}]/[\text{D$_2$O}]$) has been determined to be $-19830$ ppm. Therefore, the LIS value per Dy$^{3+}$-bound H$_2$O is $-2479$ ppm ($-19830/8$), under the conditions applied. The initial slope of the LIS as a function of $\rho_h$ (at $\rho_h < 1$) was close to zero for all thta derivatives studied, indicating that no H$_2$O molecules are present in the first coordination sphere of the complexes of both thta and thta(NHR)$_2$. This is in agreement with previously reported X-ray structures, luminescence, and relaxivity studies on [Ln(thta)]$^{3+}$ complexes [3][7][17]. Table 1 compares the LIS of the water $^{17}$O-NMR resonance signals for several complexes of thta derivatives with those of the corresponding dtpa complexes. The latter have one H$_2$O molecule in the inner coordination sphere, which is reflected in the much larger absolute LIS values. The small LIS that is measured for the thta derivatives at $\rho_h = 1$ is originating from second- and outer-sphere H$_2$O molecules, and is of purely pseudo-contact origin. Since these H$_2$O molecules are located at a relatively large distance from the paramagnetic center and the pseudo-contact shift has a $r^{-3}$ dependence on the distance, the resulting shift is rather small. Moreover, the H$_2$O molecules of the outer-sphere are not positioned on fixed locations with respect to the paramagnetic center and, therefore, induced shifts are averaged out.

The signs of the slopes of the titration curves at $\rho_h > 1$ correspond to the relative signs of the $\langle S_i \rangle$ values of the Ln$^{3+}$ ions, which supports that the LIS value is mainly of contact origin (see Table 2). The slope of the LIS value of H$_2$O vs. $\rho_h$ in the presence of
Table 1. Lanthanide-Induced Water $^{17}$O-NMR Shifts [ppm] of LnL Complexes at $\rho_L = 1$

<table>
<thead>
<tr>
<th>Ligand L</th>
<th>La$^{3+}$</th>
<th>Pr$^{3+}$</th>
<th>Nd$^{3+}$</th>
<th>Dy$^{3+}$</th>
<th>Tm$^{3+}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>dtpa$^a$</td>
<td>152</td>
<td>305</td>
<td>452</td>
<td>-1983</td>
<td>177</td>
</tr>
<tr>
<td>tth$^a$</td>
<td>0.60</td>
<td>8.26</td>
<td>13.05</td>
<td>-0.95</td>
<td>5</td>
</tr>
<tr>
<td>tth(NHEt$_2$)$_2$</td>
<td>0.44</td>
<td>0.32</td>
<td>-0.32</td>
<td>-0.04</td>
<td></td>
</tr>
<tr>
<td>tth(NHglu$_2$)$_2$</td>
<td>0.38</td>
<td>0.30</td>
<td>0.47</td>
<td>-0.10</td>
<td></td>
</tr>
</tbody>
</table>

$^a$[18]; $^b$[7]; $^c$This study, pH 6–6.5, $T = 75^\circ$. 

An excess of Dy$^{3+}$ ($\rho_L > 1$) is $-13408$, which corresponds to an average of 5.4 H$_2$O molecules ($-13408/(-2479)$) in the first coordination sphere of the Dy$^{3+}$ ion. If there would be free Dy$^{3+}$ present in solution, a slope corresponding to 8 H$_2$O molecules would be expected. Therefore, it may be concluded that the excess of Dy$^{3+}$ is bound to the [Dy(tth)]$^{3+}$ complex. In the crystal structure of the bis(guanidinium) salt of [Dy(tth)]$^{3+}$ reported by Ruoff et al. [7], the tth ligand is coordinated in a nine-fold coordination fashion through four N-atoms in the backbone and five of the carboxylate groups, whereas, one of the terminal acetate groups is not bound to the lanthanide ion. This uncoordinated carboxylate group might coordinate a second Dy$^{3+}$ ion in the solution, which could explain the evaluated $q$-value for $\rho_L > 1$.

Table 2. Complexometric $^{17}$O-NMR Titrations of LnL Complexes: Slopes of the Plots of $\delta$ [ppm] vs. $\rho_L$ at $\rho_L > 1$.

<table>
<thead>
<tr>
<th>pH 6–6.5, $T = 75^\circ$.</th>
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<tbody>
<tr>
<td></td>
</tr>
<tr>
<td>tth</td>
</tr>
<tr>
<td>tth(NHEt$_2$)$_2$</td>
</tr>
<tr>
<td>tth(NHglu$_2$)$_2$</td>
</tr>
</tbody>
</table>

2.2. Elucidation of the Coordination Mode of the tth and tth(NHR)$_2$ Ligands by Means of $^{13}$C-NMR. Upon stepwise addition of NdCl$_3$·6H$_2$O to a solution of 0.1M H$_2$tth in D$_2$O at pH 6–6.5, a second set of signals appears in the $^{13}$C-NMR spectrum, which indicates that the exchange between free and bound ligand is slow on the NMR time scale. Increase of the temperature to $80^\circ$ did not result in coalescence of the resonances for free and bound tth. Upon increase of $\rho_L$, the intensity of the new resonances increased at the expense of those of free tth until at $\rho_L (= [Nd^{3+}]/[L]) = 1$, where the NMR spectrum showed only one set of signals. This supports the 1:1 Ln$^{3+}$/tth stoichiometry already concluded from the $^{17}$O-NMR data. The number of signals that appeared in the spectrum at $\rho_L = 1$ indicates that several isomers of the lanthanide complex are formed in solution.

The $^{13}$C-NMR spectrum of [Dy(tth)]$^{3+}$ could not be observed, probably due to extensive line broadening, which is typical for the heavier lanthanide ions [10][18][19]. The $^{13}$C-NMR spectrum of the [Yb(tth)]$^{3+}$ complex was observable at $25^\circ$ but it was very crowded with 14 resonances between 7 and 300 ppm, and no unambiguous peak assignments could be made. Therefore, we focused our attention on the Nd$^{3+}$ complexes.
The $^{13}$C-NMR spectrum of the [Nd(ttha)]$^{3-}$ complex at 60° exhibited three sets of three signals for the carboxylate, acetate, and ethylene (=ethane-1,2-diyl) C-atoms, respectively (Fig. 2). This implies the presence of a ‘pseudo’ mirror plane in the complex that can be due to a rapid rearrangement of the ttha ligand. The integrals of the three carboxylate signals were comparable, which is consistent with the existence of such a ‘pseudo’ mirror plane. After addition of MeOH to the sample and cooling to −10°, the signals broadened. Further cooling to −30° led to splitting into at least six resonances in the carboxylate region (Fig. 2), indicating that the motion is frozen out at this temperature. From the coalescence temperature (−10°), the $\Delta G^*$ value for the exchange process was calculated to be 50 kJ·mol$^{-1}$. Referring to previous work on structure elucidation of analogous lanthanide complexes [19], an exchange process characterized by a $\Delta G^*$ value of this magnitude suggests that it is related to ‘wagging’ of the ethylenediamine backbone. This so-called ‘wagging motion’ involves the racemi-

![NMR Spectra of the carboxylate region of [Nd(ttha)]$^{3-}$ at 60° (top), −10° (middle), and −30° (bottom)]
zation of the two gauche conformations (λ and δ) of Ln^{3+}-bound ethylenediamine bridges.

The 13C-NMR spectra of [Nd([thta(NHEt)_2])] and [Nd([thta(NHgluca)_2])] at pH 6–6.5 are much more complex. The carboxylate region of the thta(NHEt)<sub>2</sub> complex exhibits at least 16 resonances. As a consequence, a detailed peak assignment is impossible, and only groups of signals (e.g., carboxylate, acetate, or ethylene C-signals) were identified. These 13C-NMR spectra indicate that the [Nd([thta(NHR)_2])] complexes occur in several isomeric forms. An analysis of the possible isomers that can be formed in solution and the dynamic processes that can occur between these isomers is given below.

To determine the distances between the various C-atoms in the ligand and the lanthanide ion, 13C longitudinal relaxation time (T<sub>1</sub>) measurements were performed. Among the lighter Ln<sup>3+</sup> ions, Nd<sup>3+</sup> has the longest electronic relaxation times, so this ion is favorable for these studies. The 13C longitudinal relaxation rates for the [Nd([thta])] complex were determined at 60°. At this temperature, the species in solution are in the fast-exchange regime on the NMR time scale, which resulted in relatively simple spectra (see above). For [Nd([thta(NHEt)_2])] the longitudinal relaxation times were determined at 25° and at a relatively high concentration (0.4M). As was mentioned in the previous paragraph, the 13C-NMR spectrum of this complex is rather crowded due to the presence of various isomers in solution. The longitudinal relaxation rates of the various 13C nuclei in the Nd<sup>3+</sup> complex were corrected for the diamagnetic contribution by subtraction of their respective relaxation rates in the La<sup>3+</sup> complex at the same temperature. The data obtained are compiled in Table 3.

Table 3. 13C-NMR 1/T<sub>1</sub> Relaxation Rates [s<sup>-1</sup>] of LnL Complexes (at 75.5 MHz)

<table>
<thead>
<tr>
<th>Ligand L</th>
<th>C-Atom</th>
<th>Nd&lt;sup&gt;3+&lt;/sup&gt; complex</th>
<th>La&lt;sup&gt;3+&lt;/sup&gt; complex</th>
</tr>
</thead>
<tbody>
<tr>
<td>thta&lt;sup&gt;a)&lt;/sup&gt;</td>
<td>CO</td>
<td>7.01 – 8.03</td>
<td>0.14 – 0.16</td>
</tr>
<tr>
<td></td>
<td>CH&lt;sub&gt;2&lt;/sub&gt;CO</td>
<td>7.38 – 10.22</td>
<td>2.19 – 2.43</td>
</tr>
<tr>
<td></td>
<td>CH&lt;sub&gt;2&lt;/sub&gt;CH&lt;sub&gt;2&lt;/sub&gt;</td>
<td>7.54 – 9.63</td>
<td>2.63 – 2.89</td>
</tr>
<tr>
<td>thta(NHEt)&lt;sub&gt;2&lt;/sub&gt;&lt;sup&gt;b)&lt;/sup&gt;</td>
<td>CO</td>
<td>9.25 – 14.98</td>
<td>0.70 – 0.92</td>
</tr>
</tbody>
</table>

<sup>a)</sup> 0.1M, 60°.  <sup>b)</sup> 0.4M, 25°.

Since various isomers exist in solution, the relaxation rates obtained are weighted averages for the individual isomers. Two relaxation mechanisms are of importance in this case: the ‘classical’ dipolar relaxation (1/T<sub>1, dip</sub>) [13 – 15] and the Curie relaxation (1/T<sub>1, Curie</sub>) [20] [21]. Eqs. 1 and 2 give the contributions of these mechanisms, respectively, where μ<sub>0</sub>/4π is the magnetic permeability of a vacuum, γ<sub>1</sub> is the magnetogyric ratio of 13C, μ<sub>eff</sub> is the effective moment of Nd<sup>3+</sup>, β is the Bohr magneton, r is the distance between the nucleus under study and Nd<sup>3+</sup>, H<sub>r</sub> is the magnetic field strength, and τ<sub>R</sub> is the rotational correlation time of the Nd<sup>3+</sup> complex. If it is assumed that the magnitude of the rotational correlation time (τ<sub>R</sub>) of the compounds under study is between 60 and 300 ps, then it can be calculated via Eqs. 1 and 2 that the Curie contribution to the total relaxation is between 8 and 30%, under the conditions applied. We decided to neglect this contribution for the calculation of Nd – C distances, since, as
a result of the $r^{-6}$ relationship, this leads to an error in the distances of less than 4%.

$$\frac{1}{T_{1,\text{dup}}} = \frac{4}{3} \left( \frac{\mu_0}{4\pi} \right)^2 \frac{\gamma^2_1 H_{\text{eff}}^2}{r^6} T_{1e}$$

(1)

$$\frac{1}{T_{1,\text{Curie}}} = \frac{6}{5} \left( \frac{\gamma^2_1 H_{\text{eff}}^2}{(3kT)^2} \right)^{\frac{1}{2}} \frac{x_R}{1 + q^2 r^2}$$

(2)

By use of the data reported by Alsaadi et al., the longitudinal electronic relaxation time, $T_{1e}$, for Nd$^{3+}$ complexes at 60° is estimated to be $1.74 \cdot 10^{-13}$ s [22][23]. The distances as determined with Eqn. 1 are summarized in Table 4. A comparison is made with the average distances in the crystal structures of [Nd(thta)]$^{3+}$ and [Dy(thta)]$^{3+}$ described respectively by Mondry et al. [5] and Rufolff et al. [7]. In the crystals of the Nd complex [5], the ligand is coordinated to the metal ion in a decadenate fashion via the four N-atoms of the ethylenetriamine backbone and six carboxylate O-atoms, whereas the corresponding Dy$^{3+}$ complex [7] has one of the acetate groups uncoordinated. Since the average distances of the three carboxylate resonances as determined from the relaxation rates are about the same and in good agreement with those in the crystal structure of [Nd(thta)]$^{3+}$, it can be concluded that the solution-state structure of [Nd(thta)]$^{3+}$ is comparable to that in the solid state. If one of the carboxylate groups would not have been bound to the Nd$^{3+}$ ion (as in the structure of [Dy(thta)]$^{3+}$ in the solid state), its distance to the Nd$^{3+}$ ion would have been ca. 4.9 Å rather than ca. 3.4 Å. A significantly larger relaxation rate would have been obtained for the concerning resonance, even if it is taken into account that exchange of unbound and bound carboxylates may occur.

Table 4. Ln–C Distances [Å] in [Nd(thta)]$^{3+}$ and [Nd(thta(NHEt)2)]$^{3+}$ from $^{13}$C-NMR $T_1$ Analysis and Comparison with Crystal Structure Data and NMR Data of a dtpa Analogue

<table>
<thead>
<tr>
<th></th>
<th>CO</th>
<th>CH$_2$CO</th>
<th>CH$_3$CH$_2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>[Nd(thta)]$^{3+}$ (NMR) $^a$</td>
<td>3.48, 3.48, 3.40</td>
<td>3.40, 3.68, 3.47</td>
<td>3.63, 3.50, 3.72</td>
</tr>
<tr>
<td>[Nd(thta)]$^{3+}$ (X-ray) $^b$</td>
<td>3.36 ± 0.06</td>
<td>3.51 ± 0.05</td>
<td>3.55 ± 0.07</td>
</tr>
<tr>
<td>[Dy(thta)]$^{3+}$ (X-ray) $^c$</td>
<td>3.25 ± 0.03, 4.90</td>
<td>3.40 ± 0.07</td>
<td>3.47 ± 0.07</td>
</tr>
<tr>
<td>[Nd(thta(NHEt)2)]$^{3+}$ (NMR) $^a$</td>
<td>3.00 – 3.26</td>
<td></td>
<td></td>
</tr>
<tr>
<td>[Nd(dtpa(NHPr$_2$)$_3$)]$^{3+}$ (NMR) $^a$</td>
<td>3.08 – 3.19</td>
<td>3.25 – 3.37</td>
<td>3.36 – 3.43</td>
</tr>
</tbody>
</table>

$^a$ This work. $^b$ Measured from model based on crystal coordinates reported by Mondry et al. [5]. $^c$ Measured from model based on crystal coordinates reported by Rufolff et al. [7]. $^*$ [18]; H$_2$dtpa(NHPr)$_2$: N,N′-bis[2-oxo-2-propylamino]ethyl]diethylenetriamine-N,N′,N′′-triacetic acid.

The distances that were obtained for carbonyl C-atoms in the [Nd(thta(NHEt)2)]$^{3+}$ complex were similar to those reported previously for [Nd(dtpa(NHPr)$_2$)$_3$] complexes [19], suggesting that the coordination mode is similar (binding of the Nd$^{3+}$ ion via four N atoms of the thta backbone, four carboxylate O-atoms, and two amide O-atoms). Unfortunately, the crowding in the $^{13}$C-NMR spectra of [Nd(thta(NHEt)2)]$^{3+}$ did not allow the determination of the $T_1$ values for the other resonances.

2.3. Isomers of the Ln$^{3+}$ Complexes of thta and thta(NHR)$_2$. The results of the $^{13}$C relaxation rate measurements (see above) indicate decadenate coordination of the
ttha ligand with Nd\(^{3+}\) through the four N-atoms of the ethylenediamine backbone and six O-atoms of the carboxylate groups. We assume that, also in solution, the complexes with the heavier Ln\(^{3+}\) ions will have nonadentate coordination, with one of the acetate groups not bound to the Ln\(^{3+}\) ion. This would be in line with previous \(^1\)H- and \(^{13}\)C-NMR studies of Holz and Horrocks [3] on the diamagnetic La\(^{3+}\), Lu\(^{3+}\), and Y\(^{3+}\) complexes of ttha. Assignments could not be made due to fluxional processes. The spectra of the Lu\(^{3+}\) and Y\(^{3+}\) complexes showed nine and ten resonances, respectively, in the carboxylate C-region. The NMR spectrum of the La\(^{3+}\) complex was similar to the spectra of the Nd\(^{3+}\) complex at high temperature (>60\(^\circ\)) described above and consisted of three carboxylate, three acetate and three ethylene signals.

Upon binding in either a nine- or a ten-coordinate fashion, the inversion of the N-atoms is precluded and, therefore, N(2) and N(3) (for labeling of atoms, see Fig. 3) are chiral. Furthermore, it is remarkable that in crystal structures of the [Ln(ttha)]\(^{3+}\) complexes, the ethylene units in the triethylenetetramine backbone occur exclusively in the \(\lambda\lambda\delta\) or \(\lambda\delta\lambda\) conformation. The ethylenediamine bridge that has a opposing conformation is in all cases carrying the carboxylate group that is characterized by a longer binding distance towards the lanthanide ion (ten-fold coordination) or that is not bound at all (nine-fold coordination). For the complexes with the ttha ligand bound in a 9-coordinate fashion, the N-atom carrying the uncoordinated acetate function is chiral as well. We assume, however, that a rapid coordination-decoordination process effectively produces a racemization with respect to this N-atom. If we furthermore assume that the ethylene bridges can occur in \(\lambda\lambda\delta\) or \(\lambda\delta\lambda\) conformations, at most eight enantiomeric forms can be expected for a [Ln(ttha)]\(^{3+}\) complex. However, an inspection of Dreiding models shows that the ttha ligand can be wrapped around a Ln\(^{3+}\) ion in only six different ways, one of the diastereomeric pairs is impossible to form for steric reasons. In Fig. 3, the possible isomers are depicted schematically, assuming nine-coordination in a tricapped trigonal prism. Similar structures can be envisaged for ten-coordination. The labels in Fig. 3, (S,S), (R,R), (S,R), and (R,S), describe the arrangement of the substituents on N(2) and N(3).

The six isomers are three pairs of mirror images, 1 and 1', 2 and 2', and 3 and 3'. Only the latter pair of isomers, 3 and 3' i.e., (S,R) and (R,S) can interconvert without decoordination. The interconversion from (R,R) to (S,S) always requires decoordination of N(2) or N(3). For dtpa (and dtpa(NHR)\(_2\)), this (R,S)/(S,R) interconversion is possible via the so-called ‘wagging motion’ that results in the racemization of the central N-atom. Inspection of molecular models indicates that the wagging motion as such is not possible for the ttha ligand. The \(^{13}\)C-NMR spectrum of [Nd(ttha)]\(^{3+}\) described above suggests that one of the three possible diastereoisomeric pairs is predominant, since the spectrum at low temperature shows only one set of signals for each C-atom in the complex. The exchange process observed between these isomers with a \(\Delta G^+\) value of 50 kJ·mol\(^{-1}\) (see above) indicates that these isomers can be assigned to (R,S) and (S,R), i.e., to 3 and 3'. Exchange between isomers involving decoordination of terminal N-atoms and the adjacent acetate groups would have a \(\Delta G^+\) value of ca. 70 kJ·mol\(^{-1}\) [19].

A variable-temperature \(^{13}\)C-NMR study on the [Nd([ttha(NHe\(_2\)])\(_2\)]\(^{3+}\) complex provided more-complicated spectra. The situation in case of the ttha(NHe\(_2\)])\(_2\) complexes is much more complicated because the terminal N-atoms are also chiral.
upon coordination, so four times as many isomers (8·4 = 32, or 16 diastereomeric pairs) can be formed in solution. The occurrence of various isomers is confirmed by the $^{13}$C-NMR spectrum at 25°, which showed at least 16 signals in the carboxylate region. At 80°, some of these signals remained sharp while others had broadened and almost disappeared in the base line. So probably two dynamic processes occur between the isomers, one is relatively fast and the other is much slower, and most likely involves partial decoordination of the ligand. Previously, similar exchange processes have been observed in the [Ln[dtpa(NHR)$_2$]] complexes [12][19]. However, the number of different species of Ln$^{3+}$ complexes of ttha or its derivatives that can be formed in aqueous solution has strongly increased with respect to the corresponding dtpa derivatives [12][19].

2.4. Determination of the Location of Counter-Ions. Because of its very small quadrupolar moment, $^4$Li has a slow quadrupolar relaxation and, therefore, is a very
suitable probe for studying the location of counter-ions of negatively charged \(\text{Ln}^{3+}\) complexes [24]. The longitudinal relaxation rate \((1/T_1)\) was measured in a solution of 0.1M \(\text{Li}_2(\text{tha})\) and \(\text{Nd}^{3+}\) at \(\rho = 0.95\) in \(\text{D}_2\text{O}\) at pH 6.5 and at 60°. For the calculation of the longitudinal relaxation rate, it was assumed that all \(\text{Nd}^{3+}\) was present as \(\text{Li}_2[\text{Nd(tha)}]\). This implies that half of the \(\text{Li}^+\) ions are bound to the \([\text{Nd(tha)}]^{3-}\) complex. The ‘bound’ counter-ions are in fast exchange on the NMR timescale with the ‘free’ \(\text{Li}^+\) ions. If it is assumed that the relaxation rate of free \(\text{Li}^+\) is negligible [24], the longitudinal relaxation rate of the \(\text{Li}^+\) ions in the \([\text{Li}_2[\text{Nd(tha)}]\) is calculated to be 0.085 s\(^{-1}\).

By using Eqn. 1 and the estimated value for \(T_{1\text{e}} = 1.74 \cdot 10^{-11}\) at 60°, a \(\text{Nd}^{3+} - \text{Li}^+\) distance of 6.8 Å was calculated. This \(\text{Nd}^{3+} - \text{Li}^+\) distance is slightly larger than the value determined for the analogous dtpa complex \(t_{\text{Nd-Li}} = 5.6\) Å [18], which can be explained by the larger radius of the \(\text{Li}_2[\text{Nd(tha)}]\) complex.

2.5. NMRD Profiles. The NMRD profiles of the \([\text{Gd(tha)}]^{3-}\), \([\text{Gd(tha(NHglucose))}^2\] complexes were recorded at different temperatures (5, 15, 25, 37, and 45°). The profiles show significant differences (see Fig. 4), indicating that the profile of \([\text{Gd(tha)}]^{3-}\) cannot be used as a general model for the outer-sphere contribution to the relaxivity of \(\text{Gd}^{3+}\) complexes of acyclic polyaminocarboxylates.

From the magnetic-field dependence of the \(\text{H}_2\text{O}\) proton \(1/T_1\) longitudinal relaxation times, induced by the paramagnetic \(\text{Gd}^{3+}\) ion, several parameters that govern the relaxivity were evaluated by fitting the experimental data to the outer-sphere relaxation model as described by Freed (Eqns. 3 and 4) [25], where \(N_\Lambda\) is Avogadro’s number, \(a_{\text{GdH}}\) is the distance of closest approach of the \(\text{H}_2\text{O}\) molecule to \(\text{Gd}^{3+}\), and \(\tau_{\text{GdH}}\) is the correlation time corresponding with \(a_{\text{GdH}}^{2/3}D_{\text{GdH}}\). \(D_{\text{GdH}}\) stands for the diffusion coefficient. The spectral density functions, \(J_{\text{OS}}(\omega, T_{\text{e}})\) \((j = 1, 2)\) in Eqn. 4, express the electronic-relaxation dependence, \(\omega_s\) is the nuclear Larmor frequency, and \(T_{\text{e}}\) is the electronic relaxation times, which are described by the Solomon–Bloembergen–Morgan theory [13 – 15]. In this case, the semi-empirical equations proposed by Merbach and co-workers were applied (Eqns. 5 – 8) [26]. Here, \(\tau_s\) is the correlation time of the modulation of the zero-field splitting, \(1/T_{\text{sh}}\) is a correction for the so-called spin-rotation mechanism, and \(\tau_{\text{e}}\) is the rotation correlation time. Although the Solomon–Bloembergen–Morgan theory is oversimplified [27][28], it generally adequately describes NMRD profiles, and it has the advantage of its simplicity.

\[
\begin{align*}
J_{\text{OS}}(\omega, T_{\text{e}}) = & \left. \frac{1 + \frac{1}{4} \left[ i \omega \frac{T_{\text{GdH}}}{T_{\text{e}}} + \frac{T_{\text{GdH}}}{T_{\text{e}}} \right] \right]^{\frac{1}{2}} \\
& \left. \frac{1 + \frac{1}{9} \left[ i \omega \frac{T_{\text{GdH}}}{T_{\text{e}}} + \frac{T_{\text{GdH}}}{T_{\text{e}}} \right] \right]^{\frac{1}{2}} \\
\end{align*}
\]

Eqn. 4
\[ \frac{1}{T_{1e}} = \frac{1}{2S} A^2 \tau_e \left[ 4S(S + 1) - 3 \right] \left( \frac{1}{1 + \omega_e^2 \tau_e^2} + \frac{4}{1 + 4\omega_e^2 \tau_e^2} \right) + \frac{1}{T_{1e}} \]  

(5)

\[ \frac{1}{T_{2e}} = A^2 \tau_e \left( \frac{5.26}{1 + 0.372\omega_e^2 \tau_e^2} + \frac{7.18}{1 + 1.24\omega_e^2 \tau_e^2} \right) + \frac{1}{T_{2e}} \]  

(6)

\[ \frac{1}{T_{cse}} = \frac{\delta g^2}{g \tau_R} \]  

(7)

To limit the number of variables in the fitting procedure, diffusion coefficients of the different Ln\(^{3+}\) complexes were estimated by the recently derived semi-empirical Eqn. 8 [29]. Here \(M_1\) is the molecular weight (= relative molar mass) of the complex under study. The value of the distance of closest approach of H\(_2\)O protons to Gd\(^{3+}\) (\(d_{GdH}\)) was fixed at 3.5 Å, the same value as applied in previous studies on dtpa derivatives [12][30]. Good fits were obtained by using this model (see Fig. 4). In Table 5, the best-fit parameters are compared with reported values for corresponding dtpa compounds. The values of \(\tau_e\), the correlation time for modulation of the zero-field splitting that were found for the Gd\(^{3+}\) complexes of the ttha type of ligands are significantly smaller than those of corresponding dtpa ligands [11][26] (see Table 5). The zero-field limiting values of the electronic relaxation times, \(\tau_{\text{so}}\), were calculated from \(\tau_e\), and the mean-square of the zero-field splitting interaction, \(A^2\), by using the relation \(\tau_{\text{so}} = (12A^2\tau_e)\). The electronic relaxation time of \([\text{Gd(ttha)}]^+\) is significantly larger than that of \([\text{Gd(dtpa)}]^+\), which may be ascribed to the relative rigidity of the ttha complex as a result of the complete encapsulation of the paramagnetic center by the ligand molecule.

\[ D_{\text{GdTH}} = 2.17 \cdot 10^{-9} + \frac{3.97 \cdot 10^{-8}}{M_1} + \frac{1.01 \cdot 10^{-4}}{M_1^2} \]  

(8)

Fig. 4. NMRD Profiles of \([\text{Gd(ttha)}]^+\), \([\text{Gd(ttha(NHEt)}]^+\), and \([\text{Gd(ttha(NHgluca)}]^+\) with best fit curves (see text) at 5 (○), 15 (●), 25 (▲), 37 (▼), and 45° (●).

A second set of fittings of the NMRD profiles was performed with a model in which a second-sphere contribution was included. This contribution was calculated analogously to the well-known procedures for the calculation of the inner-sphere
contribution [1]. It is difficult to evaluate the second-sphere parameters because a strong correlation exists among various parameters. The distance of the second-sphere H$_2$O molecules was fixed at 4.1 Å and their residence time in the second coordination sphere at 25 ps [31]. The rotational correlation time $\tau_R$ was estimated from that of [Gd(dtpa)]$^{3-}$ [30] by using a correction for the difference in molecular volume as determined from molecular models. Furthermore, the parameter $\delta_{i2}$ was fixed at 0.021. Keeping $\alpha_{GH}$ fixed at 3.5 Å resulted in optimal fits for the number of second-sphere H$_2$O molecules, $q_{ss}$, close to zero. Only upon treating $\alpha_{GH}$ as an adjustable parameter optimal fits with non-zero $q_{ss}$ values ($q_{ss} = 1-2$ see Table 5) and somewhat higher $\alpha_{GH}$ values (3.7-4.1 Å) were obtained. However, the goodness-of-fit did not improve upon inclusion of the second-sphere contribution to the relaxivity.

2.6. EPR Measurements. The X-band (0.34 T) EPR spectra of [Gd(dtpa)]$^{3-}$, [Gd[dtpa(NHMe)$_2$]], [Gd[dtpa(NHCH$_2$Ph)]], [Gd(tha)]$^{3-}$, and [Gd(tha(NHCH$_2$Ph))] showed approximately Lorentzian lines of g \approx 2. The EPR spectra of [Gd(dtpa)]$^{3-}$, [Gd[dtpa(NHMe)$_2$]] were in good agreement with those reported by Merbach and co-workers [30]. The transverse electronic relaxation times were calculated from the peak-to-peak line widths, $\Delta H_{pp}$, with Eqn. 9, where $g_L$ is the Landé $g$ factor. The results obtained are compiled in Table 6 and compared with the $T_{2e}$ values evaluated from the fittings of the NMRD profiles. The line width of resonance of [Gd(tha)]$^{3-}$ was remarkably narrow indicating a relatively long relaxation time for this complex, which is in good values obtained from the fitting of the NMRD profile with the model without second-sphere H$_2$O molecules. However, the EPR data of the diamide derivatives agree slightly better with the NMRD parameters for a model that includes one to two second-sphere H$_2$O molecules.

\[
T_{2e} = \frac{2h}{g_L \beta \Delta H_{pp} \sqrt{3}}
\]  

It may be concluded that the parameters governing the electronic relaxation of Gd$^{3+}$ complexes are too sensitive to structural changes to allow use of the NMRD profile of [Gd(tha)]$^{3-}$ (or other complexes that have no inner-sphere H$_2$O molecules)

| Table 5. Results of NMRD Fittings, Comparison with Parameters Reported for Gd$^{3+}$ Complexes of dtpa Derivatives *) |
|-----------------|-----------------|-----------------|-----------------|-----------------|
| q_{ss} [ps]     | $\tau_R$ [ps]   | $\tau_\alpha$ [ps] | $D_{cut}$ [ps$^{-1}$] | $E_{GH}$ [kcal/mol] |
| 25 ± 1          | 25 ± 1          | 14 ± 1         | 9 ± 1          | 1.6 ± 1.8     |
| $\alpha_{GH}$ [Å] | 3.5            | 3.5            | 3.5            | 3.5           |

*) The values in italics were fixed during the fitting procedure. $E_c$ and $E_{GH}$ are the activation energies for $\tau_c$ and $D_{cut}$, respectively. *) [30], *) [12]. *) This work. *) Estimated with Eqn. 8.
Table 6. Linewidths in X-Band EPR Spectra of Gd\(^{3+}\) Complexes of dtpa, ttha, and Some of Their Diamides at 25° and pH 7

<table>
<thead>
<tr>
<th></th>
<th>(\Delta H_p) [G]</th>
<th>(T_2) (exp) [ps]</th>
<th>(T_2) (calc) [ps](^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>[Gd(dtpa)](^{3+})</td>
<td>560 ± 50</td>
<td>117 ± 10</td>
<td></td>
</tr>
<tr>
<td>[Gd(dtpa)(NHMe)$_2$]</td>
<td>420 ± 50</td>
<td>156 ± 19</td>
<td></td>
</tr>
<tr>
<td>[Gd(dtpa)(NHBu)$_2$]</td>
<td>415 ± 50</td>
<td>158 ± 19</td>
<td></td>
</tr>
<tr>
<td>[Gd(ttha)](^{3+})</td>
<td>280 ± 50</td>
<td>234 ± 42</td>
<td>211 ((q_s = 0)); 157 ((q_s = 1.6))</td>
</tr>
<tr>
<td>[Gd[ttha(NHBu)$_2$)]</td>
<td>350 ± 50</td>
<td>187 ± 27</td>
<td>104 ((q_s = 0)); 130 ((q_s = 0.9))(^b)</td>
</tr>
</tbody>
</table>

\(^a\) Calculated with the best-fit parameters given in Table 5. \(^b\) Values for [Gd[ttha(NHEt)$_2$)]\(^{3+}\).

as a general model for the outer- and second-sphere contributions. The present study also shows that the NMRD profiles can be adequately fit with a model that does not take into account a second-sphere contribution. However, a small contribution of a few second-sphere H$_2$O molecules cannot be excluded on the basis of the present results.

Previously, Chen et al. have suggested that the second-sphere contributes more than 30% of the relaxivity of [Gd(ttha)]\(^{3+}\) [32]. These authors have fit their data with the value of \(d_{G_\text{sat}}\) fixed at 4.4 Å, which results in a considerably lower calculated outer-sphere contribution than in the present study, where we used \(d_{G_\text{sat}} = 3.5 - 3.7\) Å. This is compensated by a large second-sphere contribution and by a relatively low best-fit value of \(T_2\) of 81.5 ps. The latter value does not agree with that obtained in the present study (126 – 141 ps), which is supported by the EPR data.

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**Experimental Part**

General. All chemicals used were purchased from Acros or Aldrich and were used without further purification. A color test reaction for free lanthanides was performed with Arsenazo III as the indicator [33]. pH Measurements were made at r.t. with a Corning 125 pH meter and a calibrated micro-combination probe purchased from Aldrich Chemical Co. The pH values given are direct meter readings; no correction was made for the deuterium isotope effect. Membrane filtrations were performed at neutral pH under 20 bar N$_2$ pressure over a Toray Romembra\(^a\)-UTC-60 membrane, Toray Industries Inc., Tokyo, Japan.

\(\text{NN-}
\text{Ethane}-1,2-diylbis[\text{N}-(2,6-dioxoethan-4-yl)glycine (H$_2$ ttha-dianhydride). A suspension of H$_2$ttha (25 g, 50 mmol) in Ac$_2$O (19 ml, 200 mmol) and pyridine (24 ml) was stirred for 24 h at 65°. The brownish solid obtained was filtered and washed with dry Et$_2$O and then dried overnight under vacuum: 176.6 g, 76.6%) H$_2$ttha-dianhydride.\)

\(^{13}\)CNMR (100.6 MHz, (D$_2$)DMSO): 172.3; 170.4; 55.0; 54.6; 51.4; 50.4.

\(^{6,9}\)-Bis(2-carboxymethyl)-6,9,12-tetraazatetradecanedioic acid (H$_2$ttha(NH$\text{Et}_2$)$_2$). A mixture of DBN (=1.5 diazabicyclo[4.3.0]non-5-ene; 2 ml), DMSO (200 ml), and ethanamine (70% in H$_2$O; 3.1 g, 68 mmol) was heated at 50°. Then, H$_2$ttha-dianhydride (6.5 g, 14.2 mmol) was added in small portions within 30 min. The mixture was stirred for 4 h and subsequently evaporated. The brownish oil obtained was diluted with H$_2$O (15 ml) and brought to pH 10.5 with 4M NaOH. This soln. was purified by ion-exchange chromatography (Dowex-OAc\(^-$, O = 3m AcOH gradient). The fractions were analyzed by \(^{13}\)CNMR. The combined aq. fractions containing pure product were neutralized (pH 7) and then desalted via membrane filtration. Lyophilization gave H$_2$ttha(NH$\text{Et}_2$)$_2$ (1.78 g, 22.5%). Yellow-brownish solid.

\(^{13}\)CNMR (100.6 MHz, D$_2$O, pH 1.5): 174.0; 173.4; 169.8; 58.5; 57.9; 56.5; 53.4; 53.0; 52.4; 36.0; 15.0.

\(^{3,12}\)-Bis[2-\(\alpha\)-gluco-2,3,4,5,6-pentahydroxysulfamino-2-oxoethyl]-6,9-bis(carboxymethyl)-6,9,12-tetraazatetradecanedioic Acid (H$_2$ttha(NHglu$_2$)$_2$). To a soln. of (+)-\(\alpha\)-glucamine (12.8 g, 70.7 mmol) in DMSO
(175 ml) containing DBN (1 ml). H₂thta-dianhydride (6.5 g, 14.2 mmol) was added in small portions, and the red-brown mixture was stirred overnight at 50°. After concentration, a dark oil was obtained that was diluted with H₂O (15 ml). The pH was brought to 2.5 with 2 M HCl soln., and the soln. obtained purified by ion-exchange chromatography (Dowex-H⁺, 0 → 2 M HCl gradient). After ¹³C-NMR analysis, the pH of the combined aq. fractions containing pure product was adjusted to 8, and then the salts were removed via membrane filtration. Lyophilization gave H₂thta(NH₂gluca), (76 g, 55%). Pale yellow solid. ¹³C-NMR (100.6 MHz, D₂O, pH 12): 181.0; 180.6; 180.4; 175.9; 175.7; 73.3; 72.7; 72.6; 71.6; 64.3; 60.5; 59.7; 53.7; 53.1; 52.8; 43.6; 43.2; 23.4.

NMR Measurements. ¹H, ¹³Li, ¹³C-, and ¹⁷O-NMR Spectra: Varian Unity-300 or Varian VXR-400-S spectrometer, ¹H and ¹³Cspectra, r-BuOH as internal standard (¹H signal at 1.2 ppm, Me ¹³C signal at 31.2 ppm); ¹⁷O spectra, D₂O as external reference and determination of δ by fitting the observed signal with a Lorentzian line function; ¹Li spectra were recorded without lock to prevent interference with the lock frequency.

NMRD Measurements. The 1/T₁ NMR dispersion (NMRD) profiles of the H₂O protons were recorded at several temperatures on an IBM Research Relaxometer at the University of Mons-Hainaut (Belgium), by using the field-cycling method and covering a continuum of magnetic fields from 2.5 · 10⁻⁴ T to 1.2 T (corresponding to a Larmor-frequency range of 0.01 – 50 MHz). The absolute uncertainty in the measured 1/T₁ for the NMRD measurements was ±3%. The longitudinal ¹H relaxation rates at 20 MHz were also measured on a Minispec Bruker PC-20.

EPR Measurements. EPR Spectra: Bruker ESP-300E spectrometer, operating at 9.43 GHz (0.34 T, X-band). The 5 mm aq. solns. of the complexes were measured at 298 K in a quartz flat cell. Typical parameters used were: sweep width 40 mT, microwave power 20 mW, modulation amplitude 0.32 mT, and time constant 0.02 s. The frequency was calibrated with diphenylpicrylhydrazyl (dpph) and the magnetic field by using Mn²⁺ in MgO.

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