

Unexpected Differences in the Dynamics and in the Nuclear and Electronic Relaxation Properties of the Isoelectronic $[\text{Eu}^{\text{II}}(\text{DTPA})(\text{H}_2\text{O})]^{3-}$ and $[\text{Gd}^{\text{III}}(\text{DTPA})(\text{H}_2\text{O})]^{2-}$ Complexes (DTPA = Diethylenetriamine Pentaacetate)¹

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Received October 21, 1999. Revised Manuscript Received March 10, 2000

Abstract: The $[\text{Eu}^{\text{II}}(\text{DTPA})(\text{H}_2\text{O})]^{3-}$ complex (DTPA = diethylenetriamine pentaacetate) has been prepared by controlled potential coulometry from $[\text{Eu}^{\text{III}}(\text{DTPA})(\text{H}_2\text{O})]^{2-}$. $[\text{Eu}^{\text{II}}(\text{DTPA})(\text{H}_2\text{O})]^{3-}$ is less stable toward oxidation than $\text{Eu}^{2+}_{(\text{aq})}$, as shown by its more negative redox potential ($E_{1/2} = -1.34$ V in comparison to $E_{1/2} = -0.61$ V vs calomel electrode, respectively). Nevertheless, the rate of oxidation was found to be reasonably slow in highly concentrated solutions. Variable-temperature and -pressure, multiple-field ¹⁷O NMR and nuclear magnetic relaxation dispersion (NMRD) measurements have been performed on $[\text{Eu}^{\text{II}}(\text{DTPA})(\text{H}_2\text{O})]^{3-}$ in aqueous solution. The water-exchange rate ($k_{\text{ex}}^{298} = 1.3 \times 10^9 \text{ s}^{-1}$) is 3 orders of magnitude higher than that on the corresponding Gd(III) complex, and it is only slightly smaller than that on the Eu(II) aqua ion. The positive activation volume ($\Delta V^\ddagger = +4.5 \text{ cm}^3 \text{ mol}^{-1}$) indicates a dissociatively activated water-exchange process. The rotational correlation time is slightly longer for $[\text{Eu}^{\text{II}}(\text{DTPA})(\text{H}_2\text{O})]^{3-}$ as compared to that for $[\text{Gd}^{\text{III}}(\text{DTPA})(\text{H}_2\text{O})]^{2-}$, which is explained by the higher number of water molecules hydrogen-bonded to the carboxylates of the ligand in the highly charged Eu(II) chelate. The electronic relaxation parameters obtained from NMRD and low-field transverse ¹⁷O relaxation rates indicate that electron spin relaxation is considerably faster on $[\text{Eu}^{\text{II}}(\text{DTPA})(\text{H}_2\text{O})]^{3-}$ than on $\text{Eu}^{2+}_{(\text{aq})}$ or on the isoelectronic $[\text{Gd}^{\text{III}}(\text{DTPA})(\text{H}_2\text{O})]^{2-}$. Possibilities to use Eu^{II} complexes as MRI contrast agents are discussed.

Introduction

The chemistry of Eu^{II} complexes, particularly their properties in aqueous medium, was not widely investigated during the past decades, although Eu(II) solutions and compounds had first been characterized a long time ago.^{2–5} Eu^{II} is the most easily accessible divalent lanthanide; nevertheless, it is very unstable toward oxidation.^{3,6–8} It reacts quickly with oxygen, and water can also slowly oxidize Eu^{II}.⁹ A large body of data is available in the literature on the electrochemical properties of Eu^{II} complexes, especially of the aqua and other solvate complexes.¹⁰ However, little is known about Eu^{II} poly(amino carboxylates),^{11–13}

besides some information on their thermodynamic and spectroscopic characteristics.^{14,15} Almost nothing has been reported on their kinetic behavior.^{16–18} We have recently investigated the water exchange of the Eu^{II} aqua complex, and it has been found to be the fastest water-exchange process ever measured by magnetic resonance ($k_{\text{ex}}^{298} = 3.5 \times 10^9 \text{ s}^{-1}$).^{17,18}

Eu^{II} is intermediate in size between Ca^{II} and Sr^{II} (ionic radii are 125, 112, and 126 pm for Eu^{II}, Ca^{II}, and Sr^{II}, respectively) and shows a comparable chemistry (except for the redox instability) with these two alkaline earth metals. It forms complexes with the same types of ligands and of similar stability constants as Ca^{II} and Sr^{II}.^{14,19} The water-exchange rates of these alkaline earth metal complexes cannot be determined directly (they were estimated by T-jump measurements on complex formation reactions);²⁰ thus, it can be of great interest to measure the water-exchange rate on the corresponding Eu^{II} complexes, which may

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(1) Part 93 of the series High-Pressure NMR Kinetics. For part 92, see: Monlien, F. J.; Abou-Hamdan, A.; Helm, L.; Merbach, A. E. *High Pressure*, in press.

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give insight into the chemistry and biochemistry of Ca^{II} and Sr^{II}.

Furthermore, Eu^{II} is isoelectronic with Gd^{III}. Over the past two decades metal complexes of Gd^{III} have become a powerful tool in medical diagnostics as MRI contrast agents.^{21,22} Water-exchange kinetics of these complexes have been intensively studied as one of the factors which influence their proton relaxivity, and thus their efficiency. Studying appropriate Eu^{II} complexes now could further illuminate the relaxation processes of ⁸S ions.

After a detailed study of the Eu^{II} aqua complex,^{17,18} our objective was to investigate how a poly(amino carboxylate) ligand influences the nuclear and electronic relaxation of a Eu^{II} system. The DTPA⁵⁻ (DTPA = diethylenetriamine pentaacetate) ligand has been chosen, since the appropriate Gd(III) complex is already successfully used as a commercial MRI contrast agent (Magnevist, Schering AG, Germany); thus, a direct comparison of the Eu(II) and Gd(III) complexes can be of great interest.

A recent approach in contrast agent development for MRI is oriented to provide agents which act as reporters of the local physicochemical conditions in the given tissue where they distribute. Consequently, these so-called "smart" contrast agents must have relaxivities that depend on the physicochemical parameter to be monitored, such as pH, temperature, or partial oxygen pressure.^{23–26} This latter factor is relevant in different pathologies (strokes, tumors). The simplest way to report on partial oxygen pressure could be through developing a contrast agent in which the metal may exist in two different redox states, depending on the oxidative or reductive character of the environment. If the oxidized and reduced forms have sufficiently different proton relaxivities, the switch between the two possible oxidation states will result in an observable relaxivity difference. Such a system can be provided by Eu^{III}/Eu^{II} chelates since the lower oxidation state, isoelectronic to Gd(III), is expected to have considerably higher relaxivities than the oxidized form.

This is the first attempt to provide a complete structural and kinetic investigation of a complex with such a negative redox potential in aqueous solution. We present here pH-dependent electrochemical data. A multiple-field, variable-temperature and -pressure ¹⁷O NMR study combined with variable-field ¹H NMR relaxivity measurements has been performed on [Eu^{II}(DTPA)(H₂O)]³⁻ and resulted in parameters characterizing water exchange, rotation, and electronic relaxation.

Experimental Section

Sample Preparation. The [Eu^{II}(DTPA)(H₂O)]³⁻ solutions were obtained electrochemically from [Eu^{III}(DTPA)(H₂O)]²⁻. [Eu^{III}(DTPA)(H₂O)]²⁻ stock solutions were prepared in situ by mixing Na₅DTPA and EuCl₃ (for the determination of the redox potentials) or Eu(O₃-SCF₃)₃ stock solution (for all other measurements) followed by pH adjustment. Na₅DTPA was obtained by adding NaOH to H₅DTPA (Fluka). EuCl₃ was prepared by dissolving Eu₂O₃ (99.9%, Fluka) in HCl, followed by the evaporation of the acid excess. The Eu(trif)₃ was purchased from Johnson & Mathey and used without further purification. The ligand was always added in a small excess (2–5%). The

concentrations of the [Eu^{II}(DTPA)(H₂O)]³⁻ sample solutions were 0.022–0.100 mol/kg (variable-temperature ¹⁷O NMR measurements), 0.0884 mol/kg (variable-pressure ¹⁷O NMR measurements), and 0.01 M (NMRD).

Electrochemistry. The cyclovoltammograms, used for the determination of the redox potentials, were measured at 298 K with a Sycopel potentiostat at an HMD Metrohm electrode. The [Eu^{III}(DTPA)(H₂O)]²⁻ stock solutions were reduced by controlled potential (–1.6 V) coulometry in a homemade electrolysis cell (see Figure S1, Supporting Information) using an EG&G galvanostat/potentiostat 263 A equipped with a Ag/AgCl (3 M NaCl) standard electrode (EG&G). A silver wire, immersed in a NaCl solution, could not be used as a standard electrode, because it led to redox reactions at the junction which was in contact with the Eu^{II} solution. Furthermore, the compartments for the counter and reference electrodes were blocked with Agar–Agar gel (preparation 60 mg of Agar–Agar, 70 mg of KCl, 2 mL of H₂O) to avoid any contamination of the Eu^{II} solution with the electrolyte. After complete reduction, the sample was taken out with a syringe and filled into the tubes which had been previously sealed with a septum to avoid exposure to oxygen. Every manipulation was done under a nitrogen atmosphere.

Determination of the Eu^{II} Concentration. The exact concentration of the reduced [Eu^{II}(DTPA)(H₂O)]³⁻ sample was always determined by a Reinhardt–Zimmermann redox titration.^{4,27} Therefore, an excess of Fe₂(SO₄)₃ in 0.5 M H₂SO₄ was saturated with N₂ and then reacted with a known volume of the reduced [Eu^{II}(DTPA)(H₂O)]³⁻ solution. The produced Fe^{II}, corresponding to the amount of Eu^{II}, is stable in acidic medium and was titrated with a K₂Cr₂O₇ solution. The poly(amino carboxylate) ligand showed no interference with the K₂Cr₂O₇ solution. The progression of the titration was monitored by measuring the redox potentials of the solution using a combined Pt redox electrode (Ag/AgCl, 3 M KCl; Metrohm).

Preparation of [C(NH₂)₃]₂[Eu(HDTPA)(H₂O)]. We have successfully obtained the [C(NH₂)₃]₂[Eu(HDTPA)(H₂O)] complex as a solid, although only in low yield. The synthesis was performed in a glovebox under a nitrogen atmosphere. First, 370 mg (0.94 mmol) of H₅DTPA was added to a slurry solution of 200 mg (0.94 mmol) of EuCO₃²⁸ in 2 mL of water. When the production of CO₂ had finished, 169 mg (0.94 mmol) of [C(NH₂)₃]₂CO₃ was added. The pH of the mother liquor was around pH = 5. After the diffusion of ethanol into the solution (a few days), small, bright yellow crystals were obtained. These plates were not suitable for X-ray structure determination. The crystals were dried under vacuum at ambient temperature. The dried crystals were reasonably stable, even under aerobic conditions; they kept their yellow color for several days. However, after several weeks of storage in the glovebox, the crystals decomposed and a white solid was obtained. From the IR spectrum and the microanalysis of the dried Eu^{II} crystals, we concluded that the complex crystallized in the protonated form with one water molecule coordinated to the metal center; thus, the formula of the crystallized complex is (C₁₆O₁₁H₃₅N₉Eu); *M* = 679.5 g/mol. IR: ν = 1670 cm⁻¹ (COOH); ν = 1588 cm⁻¹ (COO coord.). Elemental analysis: C, 28.5 (calcd 28.3); H, 5.2 (calcd 4.6); N, 18.5 (calcd 18.5).

¹⁷O NMR Measurements. For the variable-field, variable-temperature studies, the samples were filled via a syringe into glass spheres which were fitted into 10-mm NMR tubes. Glass spheres are used in order to eliminate susceptibility effects.²⁹ The NMR tubes containing the spheres had been sealed prior to filling with a septum. Every step was done under rigorous exclusion of oxygen. The pH of the samples was between pH = 10 and 11 (5% ¹⁷O enrichment). The relaxation rates and chemical shifts were measured with respect to a NaOH solution (pH = 10, 5% ¹⁷O) as external reference. The measurements on the Eu²⁺ complex were performed at two different magnetic fields using a Bruker AM-400 spectrometer (9.4 T, 54.2 MHz) and an electromagnet which was connected to an AC-200 console (1.41 T, 8.13 MHz). Bulk water longitudinal relaxation rates, 1/*T*₁, were obtained

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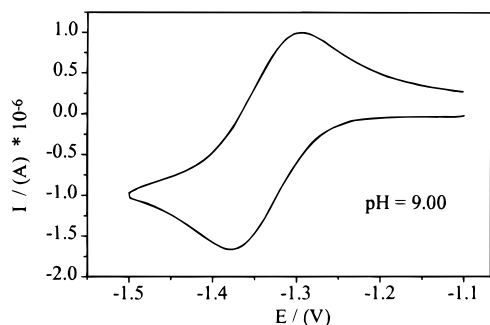


Figure 1. Cyclovoltammogram of the $[\text{Eu}^{\text{III}}(\text{DTPA})(\text{H}_2\text{O})]$ redox couple; pH = 9.0, $c_{\text{Eu}} = 1 \text{ mM}$, in excess of ligand as buffer, $I = 0.1 \text{ M NaNO}_3$.

by the inversion recovery method³⁰ and transverse relaxation rates, $1/T_2$, by the Carr–Purcell–Meiboom–Gill spin–echo technique.³¹

Variable-pressure NMR spectra were recorded up to a pressure of 200 MPa on a Bruker AMX-400 spectrometer equipped with a home-built high-pressure probe.³² The temperature was controlled by a circulating fluid from an external temperature bath and measured with a built-in Pt resistor.

NMRD. The $1/T_1$ nuclear magnetic relaxation dispersion (NMRD) profiles of the solvent protons at 5, 15, 25, and 45 °C were obtained on a Spinmaster FFC fast-field cycling NMR relaxometer (Stelar), covering a continuum of magnetic fields from 7×10^{-4} to 0.47 T (corresponding to a proton Larmor frequency range 0.03–20 MHz). High-field values were measured with a 60-MHz electromagnet, connected to an AC-200 console and on a Bruker AC-200 spectrometer.

UV–Vis Measurements. Electronic spectra were recorded on a Perkin-Elmer Lambda 5 UV–vis spectrometer. Solutions of Eu^{II} were filled under oxygen exclusion into special cuvettes suitable for use under anaerobic conditions.

EPR Measurements. The X-band (0.34 T) EPR spectra were recorded on a Bruker ESP 300E spectrometer. The samples were filled under nitrogen into quartz tubes, which were previously sealed with a septum.

Data Analysis. The simultaneous least-squares fit of ^{17}O NMR and NMRD data was performed with the program Scientist for Windows by Micromath, version 2.0. The reported errors correspond to one standard deviation obtained by statistical analysis.

Results and Discussion

Redox Potentials and Determination of the Stability Constant. The redox potential of the $[\text{Eu}^{\text{III}}(\text{DTPA})(\text{H}_2\text{O})]$ couple has been determined by cyclovoltammetry under ligand excess (see typical cyclovoltammogram in Figure 1). The potential of the DTPA complex ($E_{1/2} = -1.34 \text{ V}$ vs calomel, pH = 9, $c_{\text{Eu}} = 1 \text{ mM}$) is much more negative than that of the $\text{Eu}^{2+}_{(\text{aq})}$ ion ($E'_{1/2} = -0.61 \text{ V}$ vs calomel), clearly indicating that this poly(amino carboxylate) ligand destabilizes the divalent state of Eu.

The potentials measured for the $[\text{Eu}^{\text{III}}(\text{DTPA})(\text{H}_2\text{O})]$ system (see Table 1) show a strong pH dependence in the pH range 3–6, whereas at higher pH values they are constant (below pH = 3 even $[\text{Eu}^{\text{III}}(\text{DTPA})(\text{H}_2\text{O})]^{2-}$ dissociates, whereas $[\text{Eu}^{\text{II}}(\text{DTPA})(\text{H}_2\text{O})]^{3-}$ is certainly even less stable). From the electrode potentials obtained above pH = 6 for the $[\text{Eu}^{\text{II}}(\text{DTPA})(\text{H}_2\text{O})]^{3-}/[\text{Eu}^{\text{III}}(\text{DTPA})(\text{H}_2\text{O})]^{2-}$ system, $E_{1/2}$, one can calculate the stability constant of the $[\text{Eu}^{\text{II}}(\text{DTPA})(\text{H}_2\text{O})]^{3-}$ complex by using the known stability constant of $[\text{Eu}^{\text{III}}(\text{DTPA})(\text{H}_2\text{O})]^{2-}$ ($\log K^{\text{III}} = 22.39$)¹⁹ and the potential of the $\text{Eu}^{2+}_{(\text{aq})}/\text{Eu}^{3+}_{(\text{aq})}$ redox

Table 1. Redox Potentials of $[\text{Eu}(\text{DTPA})^{3-}/[\text{Eu}(\text{DTPA})]^{2-}$ as a Function of pH

pH	$E_{1/2}$ (V) vs calomel	Δ (mV)
2.99	−1.035	209
3.80	−1.171	136
5.10	−1.321	149
5.99	−1.335	14
7.09	−1.339	
8.08	−1.338	
9.00	−1.336	

couple, $E'_{1/2}$, and considering eqs 1–6.^{33,34} The Nernst equations for the redox couple $\text{Eu}^{2+}_{(\text{aq})}/\text{Eu}^{3+}_{(\text{aq})}$ and $[\text{Eu}^{\text{II}}(\text{DTPA})(\text{H}_2\text{O})]^{3-}/[\text{Eu}^{\text{III}}(\text{DTPA})(\text{H}_2\text{O})]^{2-}$ are given in eqs 1 and 2, respectively:

$$E'_{1/2} = E^0_{1/2} + \frac{RT}{F} \ln \frac{[\text{Eu}^{3+}_{(\text{aq})}]}{[\text{Eu}^{2+}_{(\text{aq})}]} \quad (1)$$

$$E_{1/2} = E^0_{1/2} + \frac{RT}{F} \ln \frac{[\text{Eu}^{\text{III}}(\text{DTPA})(\text{H}_2\text{O})]^{2-}}{[\text{Eu}^{\text{II}}(\text{DTPA})(\text{H}_2\text{O})]^{3-}} \quad (2)$$

The stability constants of the two complexes are expressed by eqs 3 and 4:

$$K^{\text{III}} = \frac{[\text{Eu}^{\text{III}}(\text{DTPA})(\text{H}_2\text{O})]^{2-}}{[\text{Eu}^{3+}_{(\text{aq})}][\text{DTPA}^{5-}]} \quad (3)$$

$$K^{\text{II}} = \frac{[\text{Eu}^{\text{II}}(\text{DTPA})(\text{H}_2\text{O})]^{3-}}{[\text{Eu}^{2+}_{(\text{aq})}][\text{DTPA}^{5-}]} \quad (4)$$

Insertion of eqs 3 and 4 into eq 2 yields

$$E_{1/2} = E^0_{1/2} + \frac{RT}{F} \ln \frac{[\text{Eu}^{3+}_{(\text{aq})}]}{[\text{Eu}^{2+}_{(\text{aq})}]} + \frac{RT}{F} \ln \frac{K^{\text{III}}}{K^{\text{II}}} \quad (5)$$

After making the general assumption of $E^0_{1/2} = E^0_{1/2}$,^{33,34} we obtain

$$E_{1/2} - E'_{1/2} = \frac{RT}{F} \ln \frac{K^{\text{III}}}{K^{\text{II}}} \quad (6)$$

The stability constant obtained in this way is $\log K^{\text{II}} = 9.94$ (25 °C; $I = 0.5 \text{ M}$), which corresponds well to the value previously determined by pH potentiometry, $\log K^{\text{II}} = 10.08$ (25 °C; $I = 1 \text{ M KCl}$).¹⁴ The electrochemical data also confirm that at higher pH only the nonprotonated species is present in solution, which is in accordance with the $\text{p}K_{\text{a}} = 5.45$ value published in the literature (see Figure S2, Supporting Information).¹⁴

The pH dependence of the potentials in the pH range 3–6 can be accounted for by the higher stability of $[\text{Eu}^{\text{III}}(\text{DTPA})(\text{H}_2\text{O})]^{2-}$ as compared to that of $[\text{Eu}^{\text{II}}(\text{DTPA})(\text{H}_2\text{O})]^{3-}$. Under these conditions (pH = 3–6, $c_{\text{Eu}} = 1 \text{ mM}$, 10-fold excess of ligand as buffer), the Eu^{III} complex is completely formed, whereas the Eu^{II} complex is only partially formed. Therefore, immediately after the reduction on the electrode, the freshly formed $[\text{Eu}^{\text{II}}(\text{DTPA})(\text{H}_2\text{O})]^{3-}$ complex will partly dissociate to free $\text{Eu}^{2+}_{(\text{aq})}$ and DTPA^{5-} . Thus, in the Nernst equation describing the electrode reaction (eq 2), the concentration of

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[Eu^{II}(DTPA)(H₂O)]³⁻ can be expressed with the stability constant using eq 4, which leads to eq 7:

$$E_{1/2} = E_0 + \frac{RT}{F} \ln \frac{[\text{Eu}^{\text{III}}(\text{DTPA})(\text{H}_2\text{O})^{2-}]}{K^{\text{II}}[\text{Eu}^{2+}_{(\text{aq})}][\text{DTPA}^{5-}]} \quad (7)$$

The liberated DTPA⁵⁻ ligand will protonate as determined by its protonation constant, K_n:



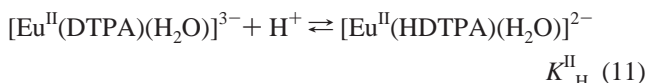
$$K_n = \frac{[\text{H}_n\text{DTPA}^{(5-n)-}]}{[\text{DTPA}^{5-}][\text{H}^+]^n} \quad (9)$$

The substitution of eq 9 into eq 7 clearly shows that the potential depends on the hydrogen ion concentration:

$$E_{1/2} = E^0_{1/2} + \frac{RT}{F} \ln \frac{[\text{Eu}^{\text{III}}(\text{DTPA})(\text{H}_2\text{O})^{2-}]K_n[\text{H}^+]^n}{K^{\text{II}}[\text{Eu}^{2+}_{(\text{aq})}][\text{H}_n\text{DTPA}^{(5-n)-}]} \quad (10)$$

Equation 10 therefore predicts that in the pH range where the Eu^{III} complex is stable, but the Eu^{II} complex is only partially formed, the potential is increasing with increasing acidity, as it is experimentally observed.

A further complication may arise from the fact that [Eu^{II}(DTPA)(H₂O)]³⁻ can protonate above pH = 4 (protonated [Eu^{III}(DTPA)(H₂O)]²⁻ complexes do not exist above pH = 4):



As there is no experimental evidence for the number of inner-sphere water molecules in the protonated complex in solution, on the basis of the elementary analysis of solid [C(NH₂)₃]₂[Eu(HDTPA)(H₂O)] we suppose that it equals 1. Although for transition metal complexes the protonation of the complex is often accompanied by the entering of a second water molecule into the inner sphere, for lanthanide chelates a protonated carboxylate group can remain coordinated, as proved for [Gd^{III}(HDTPA)(H₂O)]⁻³⁵ and for different Ln(III) DOTA-type complexes in the solid state^{36,37} or for [Gd^{III}(HDOTA)(H₂O)] in solution.³⁸

The pH dependence of the potential induced by the protonation of the Eu^{II} complex is expressed by eq 12, obtained by introducing the protonation constant, K^{II}_H into the Nernst equation eq 2:

$$E_{1/2} = E^0_{1/2} + \frac{RT}{F} \ln \frac{[\text{Eu}^{\text{III}}(\text{DTPA})(\text{H}_2\text{O})^{2-}]K^{\text{II}}_{\text{H}}[\text{H}^+]}{[\text{Eu}^{\text{II}}(\text{HDTPA})(\text{H}_2\text{O})^{2-}]} \quad (12)$$

According to eq 12, this protonation reaction leads to the same pH dependence as the dissociation of [Eu^{II}(DTPA)(H₂O)]³⁻; the measured potential is increasing with increasing H⁺ ion concentration.

It has to be noted that the dissociation of the protonated Eu^{II} complex to Eu²⁺_(aq) and HDTPA⁴⁻ has the same pH effect as

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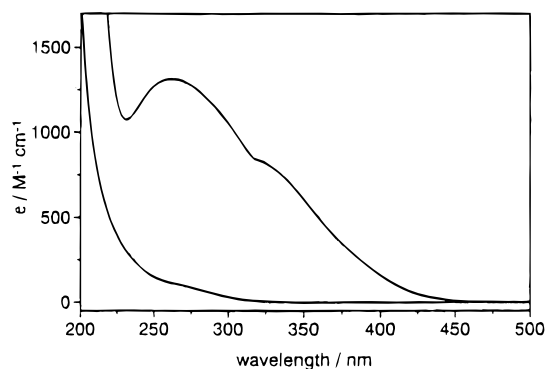
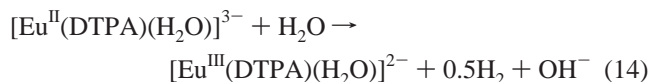
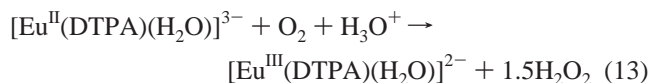


Figure 2. Electronic spectra of [Eu^{II}(DTPA)(H₂O)]³⁻ and [Eu^{III}(DTPA)(H₂O)]²⁻, c = 10 mM, pH = 10.3, l = 0.1 cm.

that described for the nonprotonated complex (see eq 10). The liberated HDTPA⁴⁻ will always immediately take further protons and, consequently, the H⁺ ion concentration always appears in the numerator of eq 10.

Between pH 3 and 4, [Eu^{III}(DTPA)(H₂O)]²⁻ starts to protonate as well, which, if it were the single pH-dependent procedure, would lead to an opposite pH dependence of the potential. This opposite pH dependence is not observed since it is compensated by the dissociation of [Eu^{II}(DTPA)(H₂O)]³⁻ and [Eu^{II}(HDTPA)(H₂O)]²⁻ and the consequent protonation of the liberated DTPA⁵⁻ ligand.

Redox Stability of the [Eu^{II}(DTPA)(H₂O)]³⁻ Complex. The large negative redox potential of [Eu^{II}(DTPA)(H₂O)]³⁻ implies that it reacts easily with oxygen and also with water⁹ which is used as solvent, pursuant to the following reactions:



We have investigated the oxidation of [Eu^{II}(DTPA)(H₂O)]³⁻ by UV/vis spectroscopy. The UV/vis spectrum shows two maxima at 257 and 320 nm at basic pH (Figure 2) with the extinction coefficients of ε₂₅₇ ≈ 1300 M⁻¹ cm⁻¹ and ε₃₂₀ ≈ 850 M⁻¹ cm⁻¹. The redox stability is strongly concentration dependent; the higher the Eu^{II} concentration, the more stable the solution. The oxidation reaction shows a rather complicated, however reproducible, kinetic behavior as it is not possible to satisfactorily fit the experimental data with normal exponential functions. Nevertheless, we have tried to get an impression of the stability of the complex by fitting the data to one exponential which led to a half-life of 1 h for c = 1 mM. At higher (19 mM) concentration, the oxidation was monitored by the Reinhardt–Zimmermann-type titration, and a half-life of 40 h could be estimated. A 500 mM solution maintains its bright yellow color, corresponding to Eu^{II}, for several weeks. The observation of higher stability for higher concentrations has also already been observed for the aqua complex³⁹ and seems to be a general trend in Eu^{II} chemistry. The fact that the redox stability of [Eu^{II}(DTPA)(H₂O)]³⁻ is strongly concentration dependent may suggest that the process observed is the scavenging of a trace impurity (maybe residual O₂) rather than the thermodynamically anticipated oxidation of water. The phenomenon of concentra-

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tion dependence is not limited to Eu^{II} chemistry; many strongly reducing or oxidizing solutes show it, despite one's best efforts to eliminate redox-active impurities.

These results gave indications on the optimal conditions for the ¹⁷O NMR and NMRD measurements. Correspondingly, we used relatively high concentrations. However, to avoid the effect of any oxidation, ¹⁷O NMR data points at each temperature were obtained with freshly prepared samples. These samples were stable during the manipulation time.

¹⁷O NMR and NMRD Measurements. The variable-temperature, multiple-field reduced ¹⁷O relaxation rates (T_{1r} and T_{2r}) and chemical shifts ($\Delta\omega_r$) and the proton relaxivities (r_1) measured on $[\text{Eu}^{\text{II}}(\text{DTPA})(\text{H}_2\text{O})]^{3-}$ solutions have been analyzed simultaneously using the approach that has already been successfully applied for several Gd(III) complexes as well as for the Eu^{II}_(aq).^{18,40} All formulas used in the data treatment are described in the Appendix. The experimental data and the fits are presented in Figure 3, and the parameters obtained are given in Table 2. The fit to the data is remarkably good, given the large magnetic field range covered in this study (5×10^{-4} –9.4 T).

For the analysis of both ¹H and ¹⁷O NMR data, it is necessary to know the number of inner-sphere water molecules. As there is no easy and trivial means to assess the hydration number in solution for a Eu(II) complex, the value of 1, obtained from the elemental analysis of dried $[\text{C}(\text{NH}_2)_3]_2[\text{Eu}(\text{HDTPA})(\text{H}_2\text{O})]$ crystals, was used in the calculations. This assumption of $q = 1$ is also supported by the ¹⁷O scalar coupling constant determined from the ¹⁷O chemical shifts and transverse relaxation rates. The hyperfine coupling constant is a measure of electron delocalization from the ion onto the ligand nucleus; thus, its value has to be similar for similar complexes. Indeed, a value of $A/\hbar = -3.5 \times 10^6 \text{ rad s}^{-1}$ is calculated with $q = 1$ for the $[\text{Eu}^{\text{II}}(\text{DTPA})(\text{H}_2\text{O})]^{3-}$ complex, which corresponds well to that reported for the $[\text{Eu}(\text{H}_2\text{O})_8]^{2+}$ ion ($-3.7 \times 10^6 \text{ rad s}^{-1}$).¹⁸ It should be noted, however, that in the case of Gd(III) there is a significant difference between the hyperfine coupling constants determined for the aqua ion and for the DTPA complex (Table 2).⁴⁰ The assumption of a similar tendency for Eu(II) would mean that the real hydration number for the DTPA complex is higher than 1, and thus a hydration equilibrium between mono- and bishydrated species cannot be excluded.⁴¹

Water Exchange. The water-exchange rate of the complex is determined from the transverse ¹⁷O relaxation rates (see Figure 3b). As the system is in the fast exchange limit throughout the whole temperature range studied, the measured reduced transverse relaxation rates, $1/T_{2r}$, are given by the relaxation rates of the coordinated inner-sphere water molecule, $1/T_{2m}$, itself determined by the water residence time, $\tau_m = 1/k_{\text{ex}}$, the longitudinal electronic relaxation time, T_{1e} , and the nuclear hyperfine coupling constant, A/\hbar (eq 20 in the Appendix). The water-exchange rate, k_{ex} , on $[\text{Eu}^{\text{II}}(\text{DTPA})(\text{H}_2\text{O})]^{3-}$ is 3 orders of magnitude higher than that on the corresponding Gd(III) complex, and it is only slightly smaller than that on the Eu(II) aqua ion (see Table 2). As the Eu²⁺ ion has a larger ionic radius and a smaller charge compared to those of Gd³⁺, the bonding between the metal center and the water molecule is supposed to be more labile, which facilitates the release of the bound water and thus results in a faster exchange.

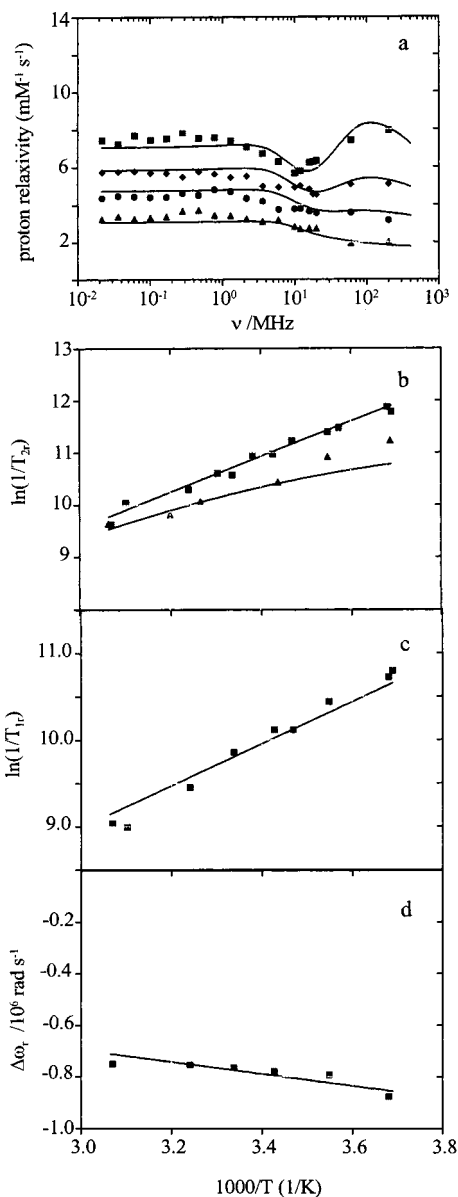


Figure 3. (a) NMRD profiles of $[\text{Eu}^{\text{II}}(\text{DTPA})(\text{H}_2\text{O})]^{3-}$ at 5 (■), 15 (◆), 25 (●), and 45 °C (▲). Temperature dependence of (b) reduced transverse and (c) longitudinal ¹⁷O relaxation rates and (d) chemical shifts for $[\text{Eu}^{\text{II}}(\text{DTPA})(\text{H}_2\text{O})]^{3-}$ at $B = 9.4$ (■) and 1.41 T (▲). The lines represent the simultaneous least-squares fit to all data points as described in the text.

The pressure dependence of the reduced transverse relaxation rates, $1/T_{2r}$, for $[\text{Eu}^{\text{II}}(\text{DTPA})(\text{H}_2\text{O})]^{3-}$ at 286 K and 9.4 T is shown in Figure 4. At this temperature and magnetic field, $1/T_{2r}$ is in the fast exchange limit and is dominated by the scalar interaction. The increase of $1/T_{2r}$ with pressure is, therefore, due to a slowing of the water-exchange process and suggests a dissociatively activated interchange (I_d) mechanism.⁴² The scalar coupling constant (A/\hbar) was previously found to be independent of pressure,⁴³ so we assume that it is constant and equal to the value in Table 2. τ_v was also assumed to be pressure independent. In fact, ascribing a pressure dependence equivalent to activation volumes between -4 and $+4 \text{ cm}^3 \text{ mol}^{-1}$ to τ_v had a negligible effect on both fitted parameters ($<5\%$). The result of the least-squares fit is shown in Figure 4; the fitted parameters are $(k_{\text{ex}})_0^{286} = (8.7 \pm 0.1) \times 10^8 \text{ s}^{-1}$ and $\Delta V^\ddagger = (+4.5 \pm 0.2)$

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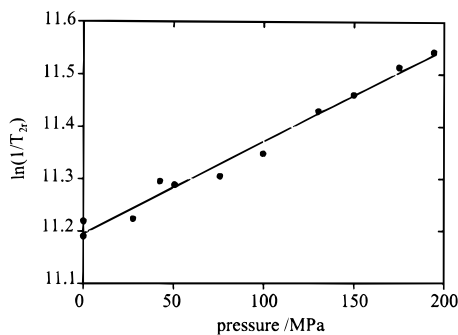
(41) Since the submission of the present paper, we have managed to obtain the solid-state X-ray structure of $[\text{C}(\text{NH}_2)_3]_3[\text{Eu}(\text{DTPA})(\text{H}_2\text{O})]$ crystals, and they contain one inner-sphere water molecule. These results will be published elsewhere.

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Table 2. Parameters Obtained from the Simultaneous Fit of ¹⁷O NMR and NMRD Data

	[Gd(H ₂ O) ₈] ³⁺ ^a	[Gd ^{III} (DTPA)(H ₂ O)] ²⁻ ^a	[Eu(H ₂ O) ₈] ²⁺ ^a	[Eu ^{II} (DTPA)(H ₂ O)] ³⁻
$k_{\text{ex}}/10^9 \text{ s}^{-1}$	0.8	0.0033	4.4	1.3 ± 0.1
$\Delta H^\ddagger/\text{kJ mol}^{-1}$	15.3	51.6	15.7	26.3 ± 0.3
$\Delta S^\ddagger/\text{J mol}^{-1} \text{ K}^{-1}$	-23.1	+53	-7.0	+18.4 ± 1.0
$\Delta V^\ddagger/\text{cm}^3 \text{ mol}^{-1}$	-3.3	+12.5	-11.3	+4.5 ± 0.2
$A/\hbar/10^6 \text{ rad s}^{-1}$	-5.3	-3.8	-3.7	-3.5 ± 0.2
$\tau_{\text{R}}/298/\text{ps}$	41	58	16.3	74 ± 1
$E_{\text{R}}/\text{kJ mol}^{-1}$	15.0	17.3	21.3	18.9 ± 1.0
$\tau_{\text{v}}/298/\text{ps}$	7.3	25	1.0	13.6 ± 3
$E_{\text{v}}/\text{kJ mol}^{-1}$	18.4	1.6	12.5	1
$\Delta^2/10^{20} \text{ s}^{-2}$	1.19	0.46	1.13	1.7 ± 0.2
$D_{\text{LNH}}/10^{-10} \text{ m}^2 \text{ s}^{-1}$	23	20	22.9	23 ± 2
$E_{D_{\text{LNH}}}/\text{kJ mol}^{-1}$	22	19.4	20.1	29 ± 1

^a From ¹⁷O NMR, NMRD, and EPR data.**Figure 4.** Pressure dependence of the reduced transverse ¹⁷O relaxation rates for [Eu^{II}(DTPA)(H₂O)]³⁻ at 9.4 T and 288 K. The line represents the least-squares fit as explained in the text.

cm³ mol⁻¹. The positive activation entropy, $\Delta S^\ddagger = 18.4 \pm 0.3$ kJ mol⁻¹, is also consistent with a dissociatively activated water-exchange mechanism.

The dissociative character of the water exchange is also an indication that the assumption of a total coordination number of 9 with one inner-sphere water molecule is correct according to the following consideration. The eight-coordinate Eu(II) aqua ion has a large negative activation volume; thus it undergoes an associatively activated water exchange, proceeding through a nine-coordinate transition state. The exchange on the DTPA complex is dissociatively activated and occurs via an eight-coordinate transition state. Therefore, it is very probable that, analogously to Gd(III), Eu(II) may have coordination numbers of 8 or 9 in solution, notably 8 for the aqua complex and 9 for the octadentate poly(amino carboxylates) with one inner-sphere water molecule.

The water exchange on both Eu(II) and Gd(III) aqua ions is very fast, which can be accounted for in terms of structural factors. It is known that the [Gd(H₂O)₈]³⁺ is close to an equilibrium state between eight- and nine-coordinate species,⁴⁴ which is probably true for [Eu(H₂O)₈]²⁺ as well. This implies that, in an associatively activated water-exchange process, little activation energy is required for the complex to pass from the eight-coordinate ground state to the nine-coordinate transition state, which explains the lability of these aqua ions.

The coordination of octadentate poly(amino carboxylate) ligands to both Gd(III) and Eu(II) results in a change in the water-exchange mechanism from an associative character for the aqua ions to a dissociatively activated process for the metal chelates. In the case of Gd(III) complexes, this change in the mechanism is accompanied by a considerable decrease (several orders of magnitude) in the water-exchange rate. Contrary to

this, the water exchange on [Eu^{II}(DTPA)(H₂O)]³⁻ is only slightly slowed as compared to that on Eu²⁺_(aq). Due to the lower charge and larger ionic radius, the charge density is significantly smaller on the Eu^{II} ion as compared to that on Gd^{III}. In a dissociatively activated exchange, the rate-determining dissociation of the metal–water O bond will be much easier for a metal with low charge density, such as Eu^{II}. The longer metal–coordinated water distance is also favorable for the fast water exchange. On the other hand, the water exchange has a definitely less dissociative character for [Eu^{II}(DTPA)(H₂O)]³⁻ ($\Delta V^\ddagger = +4.5$ cm³ mol⁻¹; thus rather I_{d}) as compared to that for [Gd^{III}(DTPA)(H₂O)]²⁻ ($\Delta V^\ddagger = +12.5$ cm³ mol⁻¹; limiting D), indicating less steric crowding around the Eu^{II}, which is evidently a consequence of its larger size. The lower ΔH^\ddagger and the less positive ΔS^\ddagger values obtained for the Eu(II) complex (Table 2) are also consistent with a less dissociative water-exchange mechanism. Consequently, in the case of [Eu^{II}(DTPA)(H₂O)]³⁻, there is a much stronger participation of the incoming water molecule, which is another factor that facilitates the water exchange, and thus increases the rate.

Rotation. Information on rotation can be obtained from longitudinal water ¹H and ¹⁷O relaxation rates. The rotational correlation times are associated with the Eu–water H and Eu–water O distances (see eqs 19 and 28 in the Appendix). Since no structural information is available for [Eu^{II}(DTPA)(H₂O)]³⁻ in solution nor in solid, we used the same metal–proton and metal–oxygen distances as those assumed previously for the aqua ion ($r_{\text{EuO}} = 2.63$ Å and $r_{\text{EuH}} = 3.23$ Å).¹⁸ These assumptions were based on comparison with the available data for Sr(II),^{45–47} whose ionic radius is very similar to that of Eu(II).

The simultaneous fit of both ¹H and ¹⁷O NMR data gave a rotational correlation time, $\tau_{\text{R}}/298$, for [Eu^{II}(DTPA)(H₂O)]³⁻ which is about 25% higher than that obtained for the corresponding Gd(III) chelate. The larger ionic size of Eu(II) leads to a larger size of the complex; however, this results only in a negligible increase in the rotational correlation time. The higher negative charge on [Eu^{II}(DTPA)(H₂O)]³⁻ has more influence: it is likely that there are stronger interactions between the water molecules and the carboxylates of the ligand than in the less negatively charged Gd(III) analogue; hence, the whole tumbling entity becomes larger in size.

Electronic Relaxation. The parameters characterizing electronic relaxation are the trace of the square of the transient zero-field-splitting tensor, Δ^2 , and the correlation time for the

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modulation of the ZFS, τ_v . In the simultaneous fit, they are mainly determined from NMRD data and from the low-field ^{17}O transverse relaxation rates (for the 9.4 T ^{17}O relaxation rates there is less than 5% contribution from electronic relaxation). The electronic relaxation is found to be very fast for $[\text{Eu}^{\text{II}}(\text{DTPA})(\text{H}_2\text{O})]^{3-}$, mainly shown by the high value of Δ^2 ($1.7 \times 10^{20} \text{ s}^{-2}$ versus $1.13 \times 10^{20} \text{ s}^{-2}$ and $1.19 \times 10^{20} \text{ s}^{-2}$ for $\text{Eu}^{2+}_{(\text{aq})}$ and $\text{Gd}^{3+}_{(\text{aq})}$, respectively). As a consequence of this fast electron spin relaxation, the EPR spectra recorded at the X-band showed extremely broad lines, which gave an experimental hint for a fast transverse electron spin relaxation, though they could not be analyzed to provide the relaxation rates. Certainly, the situation is more complicated for Eu(II) than it is for Gd(III), since the Eu(II) EPR spectra need to be interpreted as superimposed isotropic hyperfine structures of naturally abundant ^{151}Eu and ^{153}Eu isotopes. Both nuclei have a nuclear spin of $5/2$ and a similar natural abundance (47.82% and 52.18%, respectively); thus, the spectra are the superposition of 12 lines.¹⁸ It has to be noted that for the $\text{Eu}^{2+}_{(\text{aq})}$ ion X-band EPR bands were not so broad and could be analyzed without any problem. For the isoelectronic $\text{Gd}^{3+}_{(\text{aq})}$ and $\text{Eu}^{2+}_{(\text{aq})}$ ions, the Δ^2 values are quite similar; however, the modulation of the transient zero-field splitting distortions is faster for $\text{Eu}^{2+}_{(\text{aq})}$, shown by the lower τ_v , and this results in longer electronic relaxation times, $1/T_{1e}$ and $1/T_{2e}$. When poly(amino carboxylate) complexes form, electronic relaxation, in general, becomes slower for Gd(III) and faster for Eu(II), as illustrated by the $1/T_{2e}$ values calculated for 20-MHz proton Larmor frequency (0.47 T) and 25 °C for the four different complexes: $7.6 \times 10^9 \text{ s}^{-1}$ ($\text{Gd}^{3+}_{(\text{aq})}$), $4.6 \times 10^9 \text{ s}^{-1}$ ($[\text{Gd}^{\text{III}}(\text{DTPA})(\text{H}_2\text{O})]^{2-}$), $1.4 \times 10^9 \text{ s}^{-1}$ ($\text{Eu}^{2+}_{(\text{aq})}$), and $16 \times 10^9 \text{ s}^{-1}$ ($[\text{Eu}^{\text{II}}(\text{DTPA})(\text{H}_2\text{O})]^{3-}$).^{18,40} However, this trend has to be confirmed in the future by other examples of Eu(II) complexes.

In the analysis of the NMRD and ^{17}O NMR data, we have considered the modulation of the zero-field splitting as the only mechanism to result in electron spin relaxation. It has been shown previously for Gd(III) complexes that spin–spin dipolar interactions can also strongly contribute to the electronic relaxation, which is manifested in the concentration dependence of the measured electronic relaxation rates.⁴⁰ This relaxation mechanism becomes important, and thus observable, only at relatively high magnetic fields ($B > 2$ T) and relatively high concentrations. Similar spin–spin coupling must be expected in Eu^{II} systems as well. However, the magnetic field range covered by NMRD (> 1.4 T, corresponding to 60-MHz proton Larmor frequency) is below this limit; moreover, the NMRD profiles have been recorded at relatively low Eu^{II} concentration (0.01 M), and therefore the contribution of spin–spin interactions to the overall electronic relaxation can be neglected. The ^{17}O NMR measurements have been performed at much higher fields (up to 9.4 T) as well as at higher concentrations (0.02–0.10 mol/kg). However, the water-exchange rate is very high, and the system is in the fast exchange regime; thus, the electronic relaxation rate ($1/T_{1e}$) contributes only a few percent to the measured transverse ^{17}O relaxation rates. Consequently, though in principle spin–spin interactions should be also considered in electronic relaxation under the conditions of the ^{17}O NMR measurements, neglecting them has no influence on the calculated water-exchange parameters. This is also evidenced by the fact that no concentration effects (in the range 0.02–0.10 mol/kg) have been observed on the transverse ^{17}O relaxation rates.

For a modulated transient zero-field splitting (ZFS) relaxation mechanism, which operates for Eu(II), the line widths decrease

dramatically with increasing frequency.⁴⁸ Consequently, high-field EPR measurements would be useful for obtaining direct experimental information on the electron spin relaxation rates of a series of Eu(II) complexes. This problem is currently being addressed in this laboratory.

Proton Relaxivity. The proton relaxivity, r_1 , of $[\text{Eu}^{\text{II}}(\text{DTPA})(\text{H}_2\text{O})]^{3-}$ measured at 20 MHz and 25 °C is lower than that of $[\text{Gd}^{\text{III}}(\text{DTPA})(\text{H}_2\text{O})]^{2-}$ ($3.57 \text{ mM}^{-1} \text{ s}^{-1}$ and $4.30 \text{ mM}^{-1} \text{ s}^{-1}$, respectively).²² Although the water-exchange rates differ by 3 orders of magnitude for the two complexes, this parameter has, in general, no (or very little) influence on the proton relaxivity of small molecular weight complexes. The rotation is somewhat faster for the Gd(III) analogue, which, as the usual limiting parameter for the monomeric agents, would result in a smaller relaxivity for this compound, contrary to what is observed. The shorter metal–proton distance of $[\text{Gd}^{\text{III}}(\text{DTPA})(\text{H}_2\text{O})]^{2-}$ as compared to that of $[\text{Eu}^{\text{II}}(\text{DTPA})(\text{H}_2\text{O})]^{3-}$ is favorable for proton relaxivity; however, this would not be enough to compensate for the fast rotation. Therefore, the major factor that accounts for the 20% difference in proton relaxivity between $[\text{Gd}^{\text{III}}(\text{DTPA})(\text{H}_2\text{O})]^{2-}$ and $[\text{Eu}^{\text{II}}(\text{DTPA})(\text{H}_2\text{O})]^{3-}$ is their different electron spin relaxation, which, being faster, is clearly an unfavorable parameter for the Eu(II) chelate.

Another interesting feature of the NMRD profiles is that at low temperatures (5 and 15 °C) they show a clear high-field peak between 60- and 200-MHz proton Larmor frequency. So far, high-field peaks have only been observed for slowly rotating, macromolecular Gd(III) complexes.²² Certainly, slow rotation cannot only be evoked in this case; the high-field peaks are again the consequence of the interplay between the faster electronic relaxation and the somewhat slightly slower rotation for the Eu(II) chelate in comparison with that for the Gd(III) analogue.

The analysis of the NMRD profiles lets us conclude that the proton relaxivities of $[\text{Eu}^{\text{II}}(\text{DTPA})(\text{H}_2\text{O})]^{3-}$ at imaging fields 20–60 MHz are mainly limited by fast rotation, as expected for a small molecular weight chelate. However, besides rotation, fast electronic relaxation also has some limiting effect. In the case of Gd(III) complexes, it has been proposed only for compounds with long (at least nanosecond) rotational correlation times that electronic relaxation can limit proton relaxivity at medium fields (20 MHz), though no example has been reported so far. This is mainly because electronic relaxation is relatively slow for Gd(III) complexes (which is a great advantage of this paramagnetic metal ion over others in MRI applications); hence, slow water exchange starts to limit the relaxivity of these slowly rotating agents before one can see the effect of the electronic relaxation. This Eu(II) chelate is the first case where the limitation of electron spin relaxation is observed even at fast rotation. By increasing the rotational correlation time, the limiting effect of electronic relaxation would evidently become much more accentuated. Under such conditions (long τ_R), water exchange could also limit proton relaxivity for a $\text{Eu}^{\text{II}}(\text{DTPA})$ macromolecular derivative; however, in contrast to the case of Gd(III) complexes, for the Eu^{II} agent the rate of water exchange could be too fast to attain optimal relaxivities.

Conclusion

Although the $[\text{Eu}^{\text{II}}(\text{DTPA})(\text{H}_2\text{O})]^{3-}$ complex is less stable toward oxidation than the $\text{Eu}^{2+}_{(\text{aq})}$ ion, it is stable enough to be studied by ^{17}O and ^1H NMR. The water exchange on the poly(amino carboxylate) complex is remarkably fast and proceeds

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via a dissociatively activated mechanism. The rotational correlation time is slightly longer for [Eu^{II}(DTPA)(H₂O)]³⁻ as compared to that for [Gd^{III}(DTPA)(H₂O)]²⁻, which can be explained by the stronger interactions between the water molecules and the carboxylates of the highly charged Eu(II) chelate. Electronic relaxation is considerably faster on [Eu^{II}(DTPA)(H₂O)]³⁻ than that on the aqua ion, which is an unfavorable aspect for proton relaxivities. This trend is opposite to that observed for the isoelectronic Gd(III).

Acknowledgment. We thank Prof. H. Girault and Dr. R. Ferrigno for the kind assistance with the measurements with their Sycopel Potentiostat. We appreciate the Swiss National Science Foundation and the Office for Education and Science (OFES) for financial support. We thank the reviewers for their constructive comments. This research was carried out in the frame of the EC COST Action D8.

Appendix

Oxygen-17 NMR. From the measured ¹⁷O NMR relaxation rates and angular frequencies of the paramagnetic solutions, 1/T₁, 1/T₂, and ω, and of the water reference, 1/T_{1A}, 1/T_{2A}, and ω_A, one can calculate the reduced relaxation rates and chemical shift, 1/T_{1r}, 1/T_{2r}, and ω_r, which may be written as in eqs 15–17, where 1/T_{1m} and 1/T_{2m} are the relaxation rates of the bound water, Δω_m is the chemical shift difference between bound and bulk water, and P_m is the molal fraction of bound water.

$$\frac{1}{T_{1r}} = \frac{1}{P_m} \left[\frac{1}{T_1} - \frac{1}{T_{1A}} \right] = \frac{1}{T_{1m} + \tau_m} \quad (15)$$

$$\frac{1}{T_{2r}} = \frac{1}{P_m} \left[\frac{1}{T_2} - \frac{1}{T_{2A}} \right] = \frac{1}{\tau_m} \frac{T_{2m}^{-2} + \tau_m^{-1} T_{2m}^{-1} + \Delta\omega_m^2}{(\tau_m^{-1} + T_{2m}^{-1})^2 + \Delta\omega_m^2} \quad (16)$$

$$\Delta\omega_r = \frac{1}{P_m} (\omega - \omega_A) = \frac{\Delta\omega_m}{(1 + \tau_m T_{2m}^{-1})^2 + \tau_m^2 \Delta\omega_m^2} \quad (17)$$

Δω_m is determined by the hyperfine or scalar coupling constant, A/ħ, according to eq 18, where B represents the magnetic field, S is the electron spin, and g_L is the isotropic Landé g factor.

$$\Delta\omega_m = \frac{g_L \mu_B S(S+1) B A}{3 k_B T \hbar} \quad (18)$$

We assume that outer-sphere contributions are negligible.

The ¹⁷O longitudinal relaxation rates are given by eq 19, where γ_S is the electron and γ_I is the nuclear gyromagnetic ratio (γ_S = 1.76 × 10¹¹ rad s⁻¹ T⁻¹, γ_I = -3.626 × 10⁷ rad s⁻¹ T⁻¹), r is the effective distance between the electron charge and the ¹⁷O nucleus, I is the nuclear spin (5/2 for ¹⁷O), χ is the quadrupolar coupling constant, and η is an asymmetry parameter.

$$\frac{1}{T_{1m}} = \left[\frac{1}{15(4\pi)} \frac{2\hbar^2 \gamma_I^2 \gamma_S^2}{r_{EuO}^6} S(S+1) \right] \left[6\tau_{dl} + 14 \frac{\tau_{d2}}{1 + \omega_S^2 \tau_{d2}^2} \right] + \frac{3\pi^2}{10} \frac{2I+3}{I^2(2I-1)} \chi^2 (1 + \eta^2/3) \tau_R \quad (19)$$

In the transverse relaxation the scalar contribution, 1/T_{2sc}, is

the most important one (eq 20). In eq 20, 1/τ_{s1} is the sum of the exchange rate constant and the electron spin relaxation rate.

$$\frac{1}{T_{2m}} \cong \frac{1}{T_{2sc}} = \frac{S(S+1)}{3} \left(\frac{A}{\hbar} \right)^2 \tau_{s1} \quad (20)$$

$$\frac{1}{\tau_{s1}} = \frac{1}{\tau_m} + \frac{1}{T_{1e}}$$

The binding time (or exchange rate, k_{ex}) of water molecules in the inner sphere is assumed to obey the Eyring equation (eq 21), where ΔS[‡] and ΔH[‡] are the entropy and enthalpy of activation for the exchange process, and k_{ex}²⁹⁸ is the exchange rate at 298.15 K.

$$\frac{1}{\tau_m} = k_{ex} = \frac{k_B T}{h} \exp \left\{ \frac{\Delta S^\ddagger}{R} - \frac{\Delta H^\ddagger}{RT} \right\}$$

$$= \frac{k_{ex}^{298} T}{298.15} \exp \left\{ \frac{\Delta H^\ddagger}{R} \left(\frac{1}{298.15} - \frac{1}{T} \right) \right\} \quad (21)$$

The electron spin relaxation rates, 1/T_{1e} and 1/T_{2e}, for metal ions in solution with S > 1/2 are mainly governed by a transient zero-field-splitting mechanism (ZFS). The ZFS terms can be expressed by eqs 22 and 23,^{49,50} where Δ² is the trace of the square of the transient zero-field-splitting tensor, τ_v is the correlation time for the modulation of the ZFS with the activation energy E_v, and ω_s is the Larmor frequency of the electron spin.

$$\left(\frac{1}{T_{1e}} \right)^{ZFS} = \frac{1}{25} \Delta^2 \tau_v \{ 4S(S+1) - 3 \} \left(\frac{1}{1 + \omega_S^2 \tau_v^2} + \frac{4}{1 + 4\omega_S^2 \tau_v^2} \right) \quad (22)$$

$$\left(\frac{1}{T_{2e}} \right)^{ZFS} = \Delta^2 \tau_v \left(\frac{5.26}{1 + 0.372\omega_S^2 \tau_v^2} + \frac{7.18}{1 + 1.24\omega_S^2 \tau_v^2} \right) \quad (23)$$

$$\tau_v = \tau_v^{298} \exp \left\{ \frac{E_v}{R} \left(\frac{1}{T} - \frac{1}{298.15} \right) \right\} \quad (24)$$

The pressure dependence of ln(k_{ex}) is linear (eq 25), where ΔV[‡] is the activation volume and (k_{ex})₀^T is the water-exchange rate at zero pressure and temperature T.

$$\frac{1}{\tau_m} = k_{ex} = (k_{ex})_0^T \exp \left\{ -\frac{\Delta V^\ddagger}{RT} P \right\} \quad (25)$$

NMRD. The measured proton relaxivities (normalized to 1 mM Eu²⁺ concentration) contain both inner-sphere and outer-sphere contributions:

$$r_1 = r_{1is} + r_{1os} \quad (26)$$

The inner-sphere term is given by eq 27, where q is the number of inner-sphere water molecules.

$$r_{1is} = \frac{1}{1000} \frac{q}{55.55} \frac{1}{T_{1m}^H + \tau_m} \quad (27)$$

(49) McLachlan, A. D. *Proc. R. Soc. London, A* **1964**, 280, 271.

(50) Powell, D. H.; Merbach, A. E.; González, G.; Brücher, E.; Micskei, K.; Ottaviani, M. F.; Köhler, K.; von Zelewsky, A.; Grinberg, O. Y.; Lebedev, Y. S. *Helv. Chim. Acta* **1993**, 76, 2129.

The longitudinal relaxation rate of inner-sphere protons, $1/T_{1m}^H$, can be expressed as in eq 28:

$$\frac{1}{T_{1m}^H} = \frac{2}{15} \left(\frac{\mu_o}{4\pi} \right)^2 \frac{\hbar^2 \gamma_S^2 \gamma_I^2}{r_{EuH}^6} S(S+1) \left[\frac{3\tau_{dl}}{1 + \omega_I^2 \tau_{dl}^2} + \frac{7\tau_{d2}}{1 + \omega_S^2 \tau_{d2}^2} \right] \quad (28)$$

In eq 28, r_{EuH} is the effective distance between the Eu(II) electron spin and the water protons, ω_I is the proton resonance frequency, and τ_{di} is given by eq 29:

$$\frac{1}{\tau_{di}} = \frac{1}{\tau_m} + \frac{1}{\tau_R} + \frac{1}{T_{ie}} \quad i = 1, 2 \quad (29)$$

The outer-sphere contribution can be described by eq 30, where N_A is the Avogadro constant, and J_{os} is a spectral density function.

$$r_{1os} = \frac{32N_A\pi}{405} \left(\frac{\mu_o}{4\pi} \right)^2 \frac{\hbar^2 \gamma_S^2 \gamma_I^2}{a_{EuH} D_{EuH}} S(S+1) [3J_{os}(\omega_p, T_{1e}) + 7J_{os}(\omega_s, T_{2e})] \quad (30)$$

$$J_{os}(\omega, T_{je}) = Re \times \left[\frac{1 + 1/4(i\omega\tau_{EuH} + \tau_{EuH}/T_{je})^{1/2}}{1 + (i\omega\tau_{EuH} + \tau_{EuH}/T_{je})^{1/2} + 1/9(i\omega\tau_{EuH} + \tau_{EuH}/T_{je}) + 1/9(i\omega\tau_{EuH} + \tau_{EuH}/T_{je})^{3/2}} \right] \quad j = 1, 2 \quad (31)$$

For the temperature dependence of the diffusion coefficient for the diffusion of a water proton away from a Eu(II) complex, D_{EuH} , we assume an exponential temperature dependence, with an activation energy E_{DEuH} :

$$D_{EuH} = D_{EuH}^{298} \exp \left\{ \frac{E_{DEuH}}{R} \left(\frac{1}{T} - \frac{1}{298.15} \right) \right\} \quad (32)$$

Supporting Information Available: Scheme showing the electrolysis cell (Figure S1), species distribution diagram of the $[Eu^{II}(DTPA)(H_2O)]^{3-}$ complex (Figure S2), variable-temperature reduced transverse and longitudinal ^{17}O relaxation rates and chemical shifts (Tables S1 and S2), reduced transverse ^{17}O relaxation rates as a function of pressure (Table S3), and proton relaxivities as a function of the magnetic field (Table S4) (PDF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

JA9937829