

Relationship between ligand structure and electrochemical and relaxometric properties of acyclic poly(aminocarboxylate) complexes of Eu(II)†

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A detailed electrochemical study on a series of Eu(III) complexes with multidentate acyclic poly(aminocarboxylate) ligands is reported. For all Eu(III) complexes, a 1e *chemically* reversible and *electrochemically* irreversible or quasi-reversible process has been obtained. The electrode kinetics of the 1e reduction of Eu(III) aqua-ion is dependent on the supporting electrolyte as well as on the electrode surface. Pt and glassy carbon electrodes give quasi-reversible responses, whereas mercury shows the better-shaped curves, especially by using sodium *p*-toluenesulfonate as the supporting electrolyte. Chronoamperometric measurements have been carried out in the temperature range 1–35 °C and the diffusion coefficients of a few Eu(III)/Eu(II) complexes evaluated. The 1/T₁ ¹H nuclear magnetic relaxation dispersion (NMRD) curves have been measured at 25 °C in aqueous solution for selected Eu(II) complexes, analysed in terms of the standard theory of paramagnetic relaxation and compared with existing data for the isoelectronic Gd(III) derivatives.

Introduction

The electrochemical behaviour of europium complexes has been in the focus of interest for many years. The predominant stability of the +3 oxidation state for all lanthanide ions is well known, but much attention in their redox chemistry arises from unusual oxidation states. Indeed, the divalent state is readily accessible primarily for Eu, Yb, and Sm only. However, recent developments have shown that the reductive chemistry of the lanthanides can include several other elements.¹ The Eu(III)/Eu(II) reduction has been studied both by means of calorimetry and electrochemistry. A large amount of reports dealt with the redox kinetics of the europium aqua-ion at various electrode materials and with different supporting electrolytes.² As reported by Weaver *et al.*,³ the Eu(III)_{aq}/Eu(II)_{aq} couple shows a small heterogeneous electron transfer rate constant, which results in a 1e *chemically* reversible and *electrochemically* irreversible process. The data so far available for the electrochemical behaviour of europium complexes with poly(aminocarboxylate) ligands are less abundant and systematic.⁴

Recently, the interest in this class of compounds has been stimulated by the current research in contrast media for magnetic resonance imaging (MRI).⁵ New applications are under evaluation which requires paramagnetic probes whose response is a controlled function of a well defined biochemical parameter: pH, temperature, *p*O₂, metabolite concentration, enzymatic activity, *etc.*⁶ Particularly attractive is the possibility to design a probe responsive of the partial pressure of oxygen (*p*O₂), a parameter highly relevant in a number of pathological conditions. The availability of contrast agents (CA) whose relaxivity is dependent upon *p*O₂ would be useful to obtain a better separation of arterial and venous blood as well as to develop novel applications of functional MRI. The simplest design of a *p*O₂-responsive CA is based on a metal complex whose metal ions can switch between two redox states charac-

terized by different relaxation properties.⁷ A very efficient system could be provided by Eu(III)/Eu(II) complexes, for which relaxivities analogous to Gd(III), the typical metal used for traditional CA, would be expected for the lower oxidation state. However, a potential application of Eu(III)/Eu(II) complexes as redox responsive MRI probes requires the control of both the thermodynamic and kinetic stability of the complex in the lower oxidation state. Merbach and co-workers have pioneered the investigation of the relaxometric and structural properties of Eu(II) complexes in aqueous solution.⁸ Here, we report on a further study of the electrochemical behaviour and relaxometric properties of a series of complexes with acyclic poly(aminocarboxylate) ligands with the aim of improving our understanding of the general properties of this class of compounds in view of their potential future applications in biomedical studies.

Results and discussion

Electrochemical behaviour of Eu(III) aqua-ion (Eu(III)_{aq})

The cyclic voltammetric (CV) response of a 1 mM aqueous solution of Eu(III) (0.1 M NaClO₄, pH = 4) on a hanging mercury drop electrode (HMDE) reveals a 1e reduction process with the following electrochemical features in the scan rate (*v*) range 0.05–10.0 V s⁻¹:

$i_{p,a}/i_{p,c}$ ratio decreases from 0.74 to 0.52 by increasing *v*;

$\Delta E_p = E_{p,a} - E_{p,c}$ increases from 266 to 517 mV by increasing *v*;

$E^{of} = (E_{p,c} + E_{p,a})/2 = -0.62 \pm 0.01$ V vs. SCE over the entire scan rate interval;

E_p vs. $\log v$ plots are linear, with slope 40 mV for $E_{p,c}$ and 70 mV for $E_{p,a}$ (the theoretical values are 0 for an electrochemically reversible process, E_{rev} , and $30/an$ for an electrochemically irreversible process, E_{irr} , where *a* is the charge transfer coefficient, usually 0.5);

i_p vs. $v^{1/2}$ plots are linear through the origin, typical of a diffusion controlled process, for both $i_{p,a}$ and $i_{p,c}$; the slope is lower for $i_{p,a}$.

All these observations are consistent with a 1e *chemically* reversible and *electrochemically* quasi-reversible reduction process.⁹ The CVs, repeated several times, are superimposable,

† Electronic supplementary information (ESI) available: complete series of the plots reporting the diffusion coefficients *D* vs. temperature for Eu(III)_{aq} and [Eu(III)L] (L = edta, dtpa, bopta, ttha). See <http://www.rsc.org/suppdata/dt/b211533f/>

testifying the stability of $\text{Eu(II)}_{\text{aq}}$ in the CV time scale, and the absence of any poisoning processes at the mercury electrode.

The electrochemical behaviour is identical employing KNO_3 , K_2SO_4 and $[\text{CF}_3\text{SO}_3]\text{Na}$ as supporting electrolyte (0.1 M, pH = 4). Only in LiClO_4 , E° is 10 mV more cathodic. By increasing the supporting electrolyte concentration from 0.1 to 0.6 M, E° shifts *ca.* 50 mV more negative. These observations suggest that the cation of the supporting electrolyte plays some role in the reduction of Eu(III) .

The anodic and cathodic peak shape is different, with asymmetry due to an α value different from 0.5. In particular, as far as the anodic peak is broader, the α value should be >0.5 , in accord with the values previously obtained with different supporting electrolytes.¹⁰

On glassy carbon (GC) and Pt electrodes, the slowness of the electron transfer increases considerably, so that at $\nu > 1.50 \text{ V s}^{-1}$ no anodic peak could be observed at all.

Sampled-polarography corroborates the CV observations: a single, well-shaped reduction wave at $E^\circ = -0.65 \text{ V vs. SCE}$ (\log -plot slopes 71 mV) is observed. Polarography in the scan window 0 to -1.0 V perfectly overlaps that obtained with the reverse scan window -1.0 to 0 V. The i/i_d ratio at different drop times (1–5 s) is almost constant. Both these results confirm the absence of any chemical complication following the reduction on the polarographic time scale.

The polarograms are identical in the pH range 2–5. On the contrary, E° shifts 30 mV negative at pH < 1 , while at pH > 5 the reduction wave decreases in intensity and, in the meantime, a ill-defined wave at *ca.* -1.1 V begins to grow, probably due to the reduction of Eu -hydroxo-complexes.

As already reported by Weaver and co-workers,³ sodium *p*-toluenesulfonate (0.1 M NapTs, pH = 4) increases the heterogeneous electron transfer rate constant for the $\text{Eu(III)}/\text{Eu(II)}$ reduction. At a HMDE, the CV features in the scan rate range 0.05–10.0 V s^{-1} , are the following:

$i_{p,a}/i_{p,c}$ ratio is unity throughout;

ΔE_p grows from 78 to 181 mV by increasing ν ;

E_p vs. $\log \nu$ plots are linear with a slope of 0 mV up to 0.40 V s^{-1} and increase for higher sweep rates;

i_p vs. $\nu^{1/2}$ plots are linear through the origin and the slopes are equal for both processes.

All these data are consistent with a 1e *chemically* and *electrochemically* reversible redox step.⁹ Also using GC and Pt electrodes with NapTs salt, the electrochemical behaviour shows quasi-reversibility. The strong dependence of the electrode kinetics on the nature and concentration of the supporting electrolyte has been recently reported by Gritzner and co-workers in non-aqueous solvents.¹¹

Electrochemical behaviour of acyclic poly(aminocarboxylate) Eu(III) complexes $[\text{Eu(III)(L)}]^{3-n}$

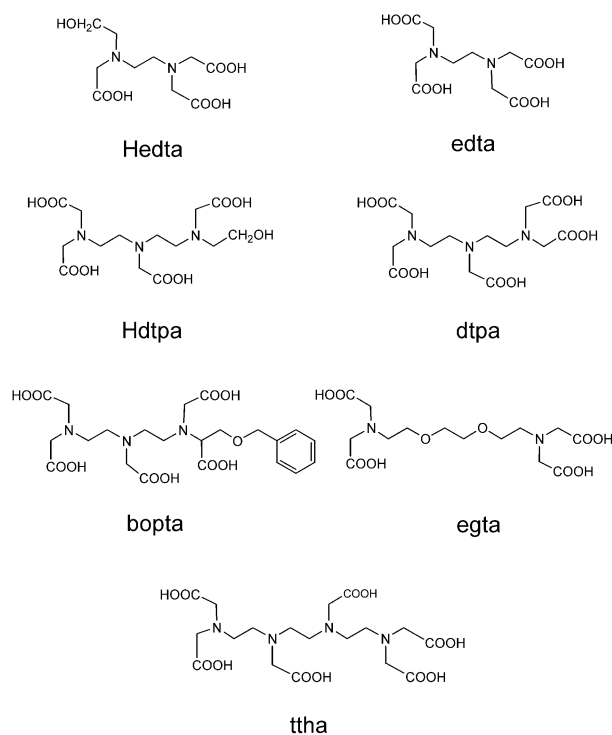
It is well known that Eu(III) cation forms in aqueous media complexes with poly(aminocarboxylic) acids endowed with high thermodynamic stability.¹² We have investigated the redox behaviour of the complexes $[\text{Eu(III)(L)}]^{3-n}$ ($\text{LH}_n = \text{Hedta}$, *N*-hydroxyethylethylenediaminetriacetic acid; edta, ethylenediaminetetraacetic acid; egta, ethylenedioxidiethylenedinitrilotetraacetic acid; Hdtpa, *N*-hydroxyethyldiethylenetriaminotriacetic acid; dtpa, diethylenetriaminopentaacetic acid; bopta, 4-carboxy-5,8,11-tris(carboxymethyl)-1-phenyl-2-oxa-5,8,11-triazatridecan-13-oic acid; ttha, triethylenetetraminehexaacetic acid, $n =$ number of carboxylic acid groups, Scheme 1) by a variety of electrochemical techniques.

The addition of the ligands L to Eu(III) water solutions (pH = 7) causes the decrease of the peak/wave reduction current. This is due to the lower diffusion coefficient, D , of the *in situ* assembled $[\text{Eu(III)L}]^{3-n}$ complex with respect to that of free $\text{Eu(III)}_{\text{aq}}$. The appearance of a new redox couple at more negative potentials (Table 1), assigned to $[\text{Eu(III)L}]/[\text{Eu(II)L}]$, is

Table 1

	$E^\circ/\text{V vs. SCE}$	$\Delta E^\circ/\text{mV}$	$\log \beta_{\text{ox}}^a$	$\log \beta_{\text{red}}$
$(\text{Eu}^{3+})_{\text{aq}}$	-0.624	—	—	—
$[\text{Eu}(\text{Hedta})]$	-1.081	0.457	15.45	7.73
$[\text{Eu}(\text{edta})]^-$	-1.109	0.485	17.32	9.11
$[\text{Eu}(\text{egta})]^-$	-1.120	0.496	17.77	9.38
$[\text{Eu}(\text{Hdtpa})]^-$	-1.312	0.688	—	—
$[\text{Eu}(\text{bopta})]^{2-}$	-1.331	0.707	22.6 ^b	13.3
$[\text{Eu}(\text{dtpa})]^{2-}$	-1.342	0.718	22.39	10.24
$[\text{Eu}(\text{ttha})]^{3-}$	-1.373	0.724	$\approx 23^c$	≈ 11

^a $\log \beta_{\text{ox}}$ from ref. 15. ^b Ref. 16. ^c Taken as the mean of $\log \beta$ for Nd- and Sm-ttha complexes.



Scheme 1 Sketch of the ligands

observed up to 1 : 1 metal to ligand ratio. No shifts in potential are observed by increasing the ligand concentration, except for edta and Hedta. This behaviour is typical of kinetically inert complexes, generally corresponding to ions of high charge density (*e.g.* Bi(III)).¹³

For all complexes studied, the nature of the supporting electrolyte has no longer an effect on the CV/polarography shape; a single *chemically* reversible and *electrochemically* quasi-reversible couple has been obtained, even in the presence of perchlorate ion as supporting electrolyte. However, the nature of the electrode material still affects the electron transfer rate.

Determination of $[\text{Eu(II)(L)}]^{2-n}$ formation constants

Electrochemistry is a tool to gauge the stabilization of the lanthanide metal ions provided by organic ligands. When a metal complex ML_p is reversibly reduced:



its potential (E°_{complex}) is different from that of the free metal ion (E°_{free}). The variation of the formal standard potential (ΔE°) depends on the ligand concentration and the stability of the complexes in the two oxidation forms, according to the following equation:¹⁴

$$\Delta E^{\circ'} = E_{\text{complex}}^{\circ'} - E_{\text{free}}^{\circ'} = -\frac{RT}{(n-m)F} \ln\left(\frac{\beta_{\text{ox}}}{\beta_{\text{red}}}\right) - (p-q)\frac{RT}{(n-m)F} \ln[L] \quad (2)$$

where β_{ox} and β_{red} are the stability constants of the oxidised and reduced forms, respectively. Since in our case $n - m = 1$ and $p - q = 0$, the equation assumes the simplified form:

$$\Delta E^{\circ'} = E_{\text{complex}}^{\circ'} - E_{\text{free}}^{\circ'} = -0.059 \log\left(\frac{\beta_{\text{ox}}}{\beta_{\text{red}}}\right) \quad (3)$$

(at 25 °C).

In Table 1 are reported the $\log\beta_{\text{red}}$ values, calculated from the experimental $\Delta E^{\circ'}$ and tabulated β_{ox} values.¹⁵

The calculated $\log\beta_{\text{red}}$ values clearly show that [Eu(III)L] complexes are much more stable than the corresponding [Eu(II)L] complexes indicating that these poly(aminocarboxylates) are not well suited for the stabilisation of the +2 oxidation state. As expected, by increasing the number of chelating atoms (O, N) of the ligand, $\log\beta_{\text{red}}$ increases.

Determination of diffusion coefficients, D

As reported above, peak currents are proportional to $v^{1/2}$ and concentration, confirming the diffusion-controlled character of the Eu(III)/Eu(II) reduction in H₂O/NapTs. This was also confirmed by chronoamperometric (CA) experiments. The Cottrell plots between the current decay and the inverse of the square root of time (i vs. $t^{-1/2}$), after application of a potential step beyond the formal standard potential, are linear. The diffusion coefficients of the different Eu complexes were computed using Randles–Sevcik (CV) and Cottrell (CA) equations.⁹

From the different chronoamperograms we extracted ten data points in the range 100 ms to 5 s which were analysed in terms of a linear least squares plot. The slope of the straight line obtained was used to determine D values of the Eu(III) species. The resulting values for D values obtained from CV and CA experiments are similar. Fig. 1 shows their temperature dependence in the range 1–35 °C. As expected, D values decrease as the molecular weight increases.

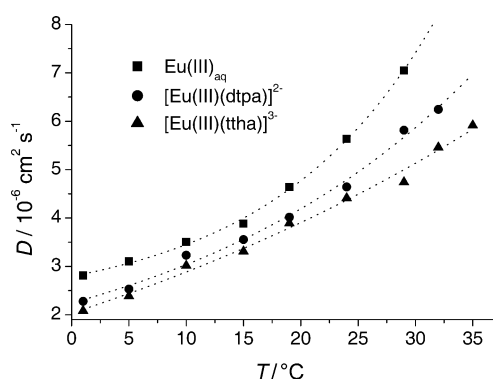


Fig. 1 Temperature dependence of the diffusion coefficients D for Eu(III)_{aq} and [Eu(III)L] (L = dtpa, ttha). Data for L = edta and bopta are nearly identical to those of the dtpa complex and are not shown for clarity reasons (ESI†).

Double-step chronoamperometry was used to obtain in the same experiment both D_{ox} and D_{red} . The first Cottrell experiment is performed at a potential where the reduction of Eu(III) species occurs; after a time interval τ the potential is set to a value that ensure the reoxidation of the Eu(II) species. From the two i vs. $t^{-1/2}$ plots, both D_{ox} and D_{red} are obtained. Within experimental error, the calculated D values are identical.¹⁷

Electrochemical parameters by simulation

In order to estimate the heterogeneous rate constant (k_{h}) and the electron transfer coefficient (a), digital simulation analysis

Table 2 Heterogeneous rate constant (k_{h}) and electron transfer coefficient (a) from digital simulation analysis of the experimental CVs of selected complexes

	$k_{\text{h}}/\text{cm s}^{-1}$	a
(Eu ³⁺) _{aq}	1.9×10^{-2}	0.65
[Eu(edta)] ⁻	0.9×10^{-2}	0.60
[Eu(dtpa)] ²⁻	1.2×10^{-2}	0.70
[Eu(ttha)] ³⁻	1.0×10^{-2}	0.65

of the CVs has been performed using the ESP program,¹⁸ based on the finite difference algorithm developed by Gosser and Zhang.¹⁹ The heterogeneous electron transfer reactions are assumed to be moderately fast with k_{h} ranging between 10^{-2} and 10^{-3} cm s⁻¹ and the diffusion coefficients (D_{red} and D_{ox}) used as determined from the CA experiments. A number of simulations were performed on several CVs (in the scan rate range 0.1–1.0 V s⁻¹) by varying the input parameters, the rate of heterogeneous reaction and the charge transfer coefficient until a good visual (manual single-fit) and a quantitative comparison (automatic best-fitting routine) between the experimental and simulated CVs is obtained. The experimental and simulated CVs are reported in Fig. 2. The parameters obtained for the different complexes are shown in Table 2.

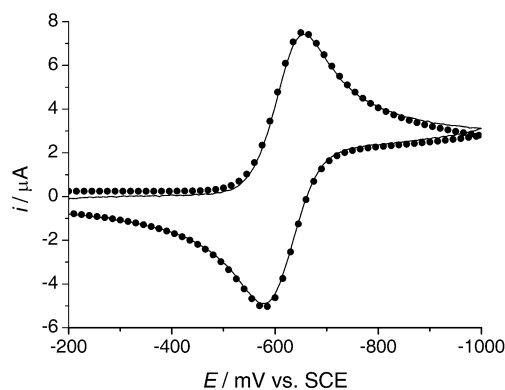


Fig. 2 Experimental (solid line) and simulated (dotted line) CVs of a 1 mM solution of Eu(III)_{aq} in 0.1 M NapTs, working electrode HMDE, scan rate = 0.2 V s⁻¹.

As a rule of thumb, all complexes show similar electrochemical parameters (k_{h} and a), the aqua-ion showing the highest k_{h} value. The heterogeneous rate constants obtained here are compatible with reversible charge transfer, by calculating the dimensionless parameter ψ proposed by Nicholson²⁰ ($\psi \approx 30$ at 0.2 V s⁻¹).

Electrochemical parameters for Eu(III)_{aq} in perchlorate solution data are quite different: k_{h} value is one order of magnitude lower with respect to that observed in NapTs solution ($k_{\text{h}} = 1.0 \times 10^{-3}$ cm s⁻¹) and a is 0.8 (Fig. 3).

The value of ψ ($\psi \approx 3$ at 0.2 V s⁻¹) allocates the redox process in the quasi-reversible charge transfer region.

The electron transfer coefficient a is a measure of the symmetry of the energy barrier to the reaction under study (*i.e.* Eu(III) + e⁻ → Eu(II)). Physically, it provides an insight into the way the rate constants for the forward and reverse reactions are altered by the applied voltage. In most systems one uses 0.5 in the absence of real measurements. A value of 0.5 means that forward and backward reactions are equally influenced by the applied voltage, while for $a > 0.5$ the forward reaction is faster than the backward reaction and the cathodic peak appears sharper and higher than the anodic counterpart.

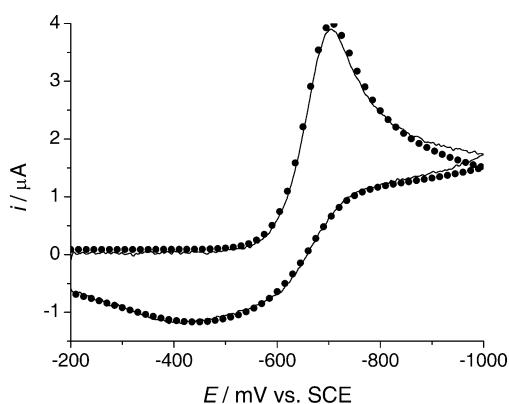


Fig. 3 Experimental (solid line) and simulated (dotted line) CVs of a 1 mM solution of $\text{Eu(III)}_{\text{aq}}$ in 0.1 M NaClO_4 , working electrode HMDE, scan rate = 0.2 V s^{-1} .

^1H Relaxometric properties of selected complexes

The ion Eu(II) has seven unpaired f electrons and therefore it presents the same ^8S electronic configuration of the iso-electronic Gd(III) . As a consequence, the aqueous solution of the Eu(II) complexes are well suitable to relaxometric NMR investigations. Relaxometry is the study of the dependence of the longitudinal (T_1) and transverse (T_2) water proton relaxation times from pH, temperature and magnetic field strength in the solution of a paramagnetic solute and provides a set of important structural and dynamic parameters characterizing the inner and outer coordination shells of the metal ion.²¹ In the last few years Merbach and Toth have pioneered the ^1H and ^{17}O relaxometric studies of Eu(II) chelates and assessed several general characteristics, thus establishing a firm basis for further investigations.^{8,22}

We have measured the NMRD (nuclear magnetic relaxation dispersion) profiles of two new complexes, $[\text{Eu}(\text{bopta})]^{3-}$ and $[\text{Eu}(\text{ttha})]^{4-}$, and compared the results with those of the aqua-ion and of $[\text{Eu}(\text{dtpa})]^{3-}$ as well as with the corresponding isoelectronic Gd(III) derivatives. The measure of the NMRD profiles for the latter two species, already reported by Merbach and co-workers, was carried out also as a way of checking the reliability of the procedure for transferring the solution from the electrochemical cell to the NMR tube.

$[\text{Eu}(\text{H}_2\text{O})_7]^{2+}$. The aqua-ion is the first lanthanide complex in the oxidation state +2 whose relaxometric properties have been investigated.^{22a,b} A variable temperature ^{17}O study indicated an extremely fast water exchange rate k_{ex} and a smaller hyperfine coupling constant A/\hbar , as compared to $[\text{Gd}(\text{H}_2\text{O})_8]^{3+}$, in accord with the weaker metal–oxygen interaction due to the decreased charge density of the Eu(II) cation. The hydration number q of the metal ion was assumed to be 8 on the basis of comparison with structural data for Sr(II) , a cation of very similar ionic radius. Very recently, structural parameters of the Eu(II) ion were determined by the XAFS technique and the analysis of the data indicated that in aqueous solution the first coordination shell of the cation is occupied by seven water molecules with an Eu–O distance of $2.584(5) \text{ \AA}$.²³ Thus, unlike $[\text{Eu}(\text{H}_2\text{O})_8]^{3+}$ the predominant species for Eu(II) is $[\text{Eu}(\text{H}_2\text{O})_7]^{2+}$. On the other hand, partial coordination of the chloride ions present in the solution could result in a lower apparent hydration number. However, this possibility can be ruled out since no changes in relaxivity are observed for the corresponding $[\text{Gd}(\text{H}_2\text{O})_8]^{3+}$ species following the addition of NaCl up to a 0.15 M concentration. Merbach and co-workers have calculated that this new estimation of the hydration number involves an increase of the water exchange rate to $5 \times 10^9 \text{ s}^{-1}$ and of the reorientational correlation time τ_R to 20.5 ps.²³ We have remeasured the NMRD profile of the aqua-ion, at 25°C and $\text{pH} = 3.5$. The new values of q and τ_M ($\tau_M = 1/k_{\text{ex}}$) were used as fixed parameters in

Table 3 Best-fit parameters obtained from the analysis of the $1/T_1$ NMRD profiles of $[\text{Eu}(\text{H}_2\text{O})_7]^{2+}$ and its complexes with the ligands dtpa, bopta and ttha at 25°C .

	Aqua-ion	dtpa	bopta	ttha
$10^{20} \Delta^2/\text{s}^{-2}$	1.20	1.17	1.03	0.91
τ_V/ps	1.8	16.3	15.3	11.5
τ_M/ns	0.2	0.8	0.8	–
τ_R/ps	20	56	59	–
$r/\text{\AA}$	3.27	3.21	3.21	–
q	7	1	1	0
$a/\text{\AA}$	4.4	3.8	3.8	3.8
$10^5 D/\text{cm}^2 \text{ s}^{-1}$	2.80	2.70	2.69	2.67

our fitting procedure. Furthermore, the relative diffusion constant D between the complex and the proton nuclei of the outer coordination sphere water molecules was taken as the sum of the self-diffusion coefficients of the free water ($2.24 \times 10^{-5} \text{ cm}^2 \text{ s}^{-1}$) and that of the aqua-ion, deduced by electrochemical data ($5.63 \times 10^{-6} \text{ cm}^2 \text{ s}^{-1}$). The best fit parameters, reported in Table 3, are quite similar to those originally derived by Merbach and coworkers and represent a convincing proof that our procedure for transferring the Eu(II) solution from the electrochemical cell to the NMR tube preserves the integrity of the complex.

$[\text{Eu}(\text{bopta})(\text{H}_2\text{O})]^{3-}$. The ligand bopta differs from dtpa by the presence of a benzyloxymethylenic residue on a terminal acetic group.¹⁶ The related Gd(III) complexes, $[\text{Gd}(\text{dtpa})(\text{H}_2\text{O})]^{2-}$ (Magnevist®, Schering AG, Germany) and $[\text{Gd}(\text{bopta})(\text{H}_2\text{O})]^{2-}$ (MULTI-HANCE®, Bracco S.p.A., Italy), are particularly used in the imaging of the lesions in the blood–brain barrier and of the liver, respectively. Both complexes present one coordinated water molecule and have very similar structures in solution and in the solid state.^{16,24} The relaxivity, r_{1p} (*i.e.* the increase of the water proton relaxation rate induced by one millimolar concentration of the paramagnetic solute), of $\text{Gd}(\text{bopta})$ is greater than that of $\text{Gd}(\text{dtpa})$ over a wide range of proton Larmor frequencies (0.01–60 MHz) as a result of a longer reorientational correlation time τ_R (about 20%) and a slightly shorter Gd–O_w distance ($\sim 4\%$). The relaxivity difference is somehow attenuated at low fields because of the shorter values of the electronic relaxation times (expressed in terms of the parameters Δ^2 and τ_V) of $\text{Gd}(\text{bopta})$.¹⁶

The comparison of the NMRD profiles of the Eu(II) complexes of dtpa and bopta (measured at 25°C , Fig. 4) shows an analogous trend. The r_{1p} value of the bopta complex is only about 10% higher than that of the dtpa complex over the entire range of magnetic fields and this can be well accounted for by the presence of one, fast-exchanging coordinated water molecule on both complexes and a slower tumbling rate ($1/\tau_M$) for the larger Eu(II) chelate bearing the benzyloxymethyl residue. The

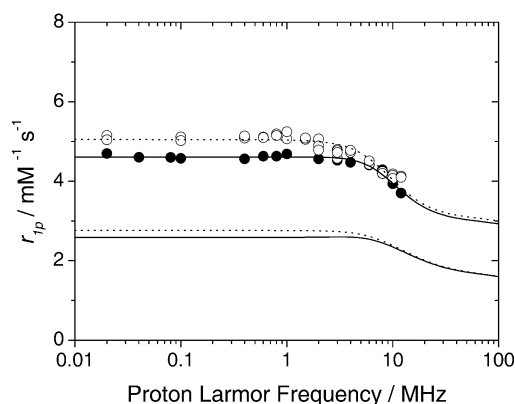


Fig. 4 $1/T_1$ NMRD profiles of aqueous solutions of $[\text{Eu}(\text{dtpa})]^{3-}$ (● and solid lines) and $[\text{Eu}(\text{bopta})]^{3-}$ (○ and dotted lines) measured at 25°C and $\text{pH} 7$. The lower curves represent the outer-sphere contribution to proton relaxivity.

analysis of the data was performed by fixing the value of q (1), D (2.70×10^{-5} and 2.69×10^{-5} $\text{cm}^2 \text{s}^{-1}$ for dtpa and bopta, respectively), τ_M (for both complexes the value of 0.77 ns found for $[\text{Eu}(\text{dtpa})(\text{H}_2\text{O})]^{3-}$ was used)^{21c} and a (3.8 Å; a is the distance of closest approach between the water molecules in the outer coordination sphere and the metal centre) and by using for the other parameters as initial values those reported by Merbach and co-workers.⁸ The best-fit parameters are reported in Table 3 and confirm the above qualitative analysis.

In analogy to the related Gd(III) complexes, $[\text{Eu}(\text{dtpa})(\text{H}_2\text{O})]^{3-}$ and $[\text{Eu}(\text{bopta})(\text{H}_2\text{O})]^{3-}$ present rather similar relaxometric properties, and minor differences are only found in the rotational correlation times. Unlike the Gd(III) analogs the electronic relaxation times of the Eu(II) complexes of dtpa and bopta are quite similar, as can be also seen by comparing the calculated profiles of the outer-sphere relaxivity (lower curves in Fig. 4).

$[\text{Eu}(\text{ttha})]^{4-}$. This ligand is potentially decadentate and thus able to fully occupy the coordination sites of Gd(III) and Eu(II). The NMRD profile of $[\text{Eu}(\text{ttha})]^{4-}$ has been recorded at 25 °C and pH = 7.2 and is shown in Fig. 5. The low relaxivity values over the entire frequency range is a clear indication of the lack of water molecules in the inner coordination sphere of Eu(II). Thus, Eu(II) is only dipolarly coupled with the water molecules in its outer coordination sphere and its NMRD profile can be compared with the calculated outer-sphere r_{1p} of Eu(II)-complexes endowed with $q \neq 0$. In Fig. 5 the experimental data of $[\text{Eu}(\text{ttha})]^{4-}$ are compared with computed curve of $[\text{Eu}(\text{dtpa})]^{3-}$: at high field the two profiles converge to indicate similar values of D and a , whereas they diverge at low field as a result of small differences in their electron relaxation time. However, the similarity of the two curves represents a good support to the validity of the analysis of the relaxation properties of the available Eu(II) discussed previously and in the present work.

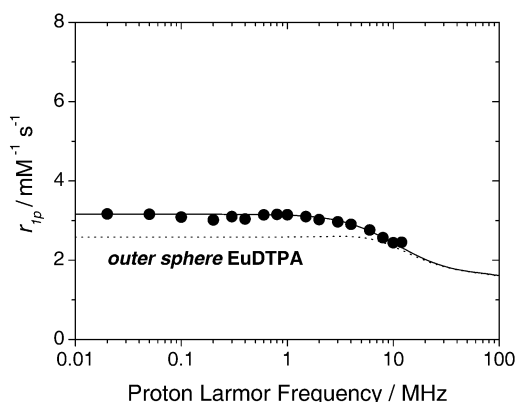


Fig. 5 $1/T_1$ NMRD profiles of an aqueous solution of $[\text{Eu}(\text{ttha})]^{4-}$ measured at 25 °C and pH 7. The solid line represents the calculated profile with parameters of Table 3. The lower dotted curve shows the calculated outer sphere contribution to the relaxivity of $[\text{Eu}(\text{dtpa})]^{3-}$.

Conclusions

The Eu(II) complexes with acyclic poly(aminocarboxylic) ligands are characterised by lower stability constants than the corresponding Eu(III) complexes. The $\log \beta$ values increase with denticity but the relative stability of Eu(II) vs. Eu(III) complexes decreases, probably as a consequence of the increase of the overall negative charge that stabilises preferentially the harder metal ion.

The relaxometric data are in full agreement with previous studies and indicate that, with exception of the aqua-ion, the Eu(III) and Eu(II) complexes are characterized by identical hydration and coordination number.

Taken together, the data here reported indicate that a potential use of the Eu(III)/Eu(II) redox couple as a diagnostic probe in living systems requires different type of ligands, able to stabilise the lower oxidation state.

Experimental

The ligands Hedta, edta, egta, dtpa, ttha and $\text{EuCl}_3 \cdot 6 \text{H}_2\text{O}$ were purchased from Aldrich, Hdtpa and bopta were kindly provided by Bracco S.p.A. (Milan, Italy)

The solution of the Eu(III) aqua-ion was prepared by dissolving $\text{EuCl}_3 \cdot 6 \text{H}_2\text{O}$ in distilled water and by adjusting the pH to the desired value with *p*-toluenesulfonic or perchloric acid. The complexes have been prepared by mixing equimolar amounts of the aqua-ion and of the ligand, at pH = 7, and by stirring the resulting aqueous solution for about 1 h to ensure complete complexation.

Electrochemical measurements

Electrochemical experiments were performed using an EG&G PAR 273 electrochemical analyser interfaced to a micro-computer, employing PAR M270 electrochemical software. A standard three-electrode cell was designed to allow the tip of the reference electrode (saturated calomel electrode, SCE) to closely approach the working electrode. Positive-feedback iR compensation was applied routinely. All measurements were carried out under argon or nitrogen in water; solutions were 1 mM with respect to the compounds under study and 0.1 M with respect to the supporting electrolyte. The temperature of the solution was kept constant within ± 1 °C. For cyclic voltammetry (CV), the working electrodes were a hanging mercury drop electrode (HMDE, Metrohm) and a platinum or glassy carbon disk (diameter 0.1 cm) sealed in Teflon. The solid electrodes were polished with alumina followed by diamond paste, then washed with distilled water and dried. This process yielded a reproducible surface for all experiments. For polarography, a dropping mercury electrode (DME) was employed. The drop time (typically 1 s) was controlled by an electromechanical hammer.

The divalent species were produced in quantitative yield by bulk electrolysis. This was carried out in a conventional two-compartment glass cell with sintered glass separation. A Hg pool was used as the cathode at a potential *ca.* 150 mV more negative of the formal potential $E^{\circ'}$, a Pt wire was used as the anode, and SCE was the reference electrode. Argon was continuously bubbled through the solution during electrolysis. In all cases, the complete transformation of Eu(III) to Eu(II) was checked by *in situ* polarography.

Relaxometric measurements

The Eu(II) solution was transferred into a 10 mm NMR tube, under argon atmosphere, through a glass tube with a Rotaflo valve. The NMR tube was sealed *in situ*. Relaxometric experiments were performed by using a Stellar (Mede, Pavia, Italy) Fast Field Cycling Relaxometer installed at the Bioindustry Park of Canavese, Ivrea (Torino, Italy). The instrument operates in a continuous of magnetic field strength from 0.00024 to 0.28 T (corresponding to 0.01–12 MHz proton Larmor frequency). The temperature was regulated by a VTC 91 temperature controller based on circulation of air. The temperature of the sample was checked using a thermometer directly inserted into the probe. The non prepolarized field cycling sequence was used for all the T_1 determinations in the field strength range of 4–12 MHz (proton Larmor frequency), whereas the prepolarized field cycling sequence was used for the T_1 measurements at lower magnetic field strength. The concentration of the Eu(II) complexes were about 3 mM and the exact value was determined by a potentiometric titration of the oxidised Eu(III) solution, carried out at 25.0 ± 0.1 °C and $\mu = 0.1$ M

(KCl). A known amounts of standard solid edta was added to the Eu(III) solution that was titrated with a CO₂ free standard solution (0.1 M) of KOH by using a Crison microbu 2030 equipped with 2.500 ml syringe, in a thermostated cell under a stream of nitrogen. Potentiometric data were recorded by a Crison microPH 2002, equipped with a Metrohm combined glass electrode and interfaced with a PC (NEWPASAT 2.00 software). The combined glass electrode was calibrate as a hydrogen concentration probe by titrating a known amount of HCl with 0.1 M KOH and determining the equivalent point by Gran's method which allows the determination of the standard potential E° and of the ionic product of water K_w .²⁵ The cell temperature was controlled with a ISCO Crioterm GTR 190. At least three measurements (about 100 data points) were obtained for each sample and were fitted by the computer program SUPERQUAD 3.2,²⁶ using the tabulated values of the protonation and complexation constants for edta and [Eu(III)(edta)].¹⁵

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References

- 1 W. J. Evans, *Coord. Chem. Rev.*, 2000, **206–207**, 263.
- 2 (a) W. D. Shults, *Anal. Chem.*, 1959, **6**, 1095; (b) I. M. Kolthoff and J. Coetzee, *J. Am. Chem. Soc.*, 1957, **79**, 1852; (c) J. F. Coetzee and W.-S. Siao, *Inorg. Chem.*, 1963, **2**, 14; (d) J. F. Coetzee, D. K. McGuire and C. Hedrick, *J. Phys. Chem.*, 1963, **67**, 1814; (e) J. N. Gaur and K. Zutshi, *J. Electroanal. Chem.*, 1966, **11**, 390; (f) G. Gritzner, V. Gutmann and G. Schöber, *Monatsh. Chem.*, 1965, **96**, 1956; (g) J. Chlistunoff and Z. Galus, *J. Electroanal. Chem.*, 1985, **193**, 175; (h) N. S. Hush and J. M. Dyke, *J. Electroanal. Chem.*, 1974, **53**, 253.
- 3 E. L. Yee, R. J. Cave, K. L. Guyer, P. D. Tyma and M. J. Weaver, *J. Am. Chem. Soc.*, 1979, **101**, 1131.
- 4 (a) E. J. Onstott, *J. Am. Chem. Soc.*, 1952, **74**, 3773; (b) L. Kisova, M. Sluyters-Rehbach and J. H. Sluyters, *J. Electroanal. Chem.*, 1972, **40**, 29; (c) X.-T. Fu, C.-M. Wang and Y.-X. Zhang, *Anal. Chim. Acta*, 1993, **272**, 221.
- 5 *The Chemistry of Contrast Agents in Medical Magnetic Resonance Imaging*, ed. A. E. Merbach, and É. Tóth, J. Wiley, New York, 2001.
- 6 D. Parker, R. S. Dickins, H. Puschmann, C. Crossland and J. A. K. Howard, *Chem. Rev.*, 2002, **102**, 1977.

- 7 S. Aime, M. Botta and E. Gianolio, *Angew. Chem., Int. Ed.*, 2000, **39**, 747.
- 8 E. Toth, L. Burai and A. E. Merbach, *Coord. Chem. Rev.*, 2001, **216–217**, 363.
- 9 A. J. Bard and L. R. Faulkner, in *Electrochemical Methods. Fundamentals, and Applications*, J. Wiley, New York, 2nd edn., 2001.
- 10 J. Němec and T. Loučka, *Collect. Czech. Chem. Commun.*, 1990, **55**, 1666 and references therein.
- 11 F. Marauer, L. Kišová, J. Komenda and G. Gritzner, *J. Electroanal. Chem.*, 1999, **470**, 1.
- 12 G. R. Choppin, in *Lanthanide Probes in Life, Chemical, and Earth Sciences. Theory and Practices*, ed. J.-C. G. Bunzli and G. R. Choppin, Elsevier, Amsterdam, 1989, ch. 1.
- 13 A. E. Martell and R. D. Hancock, in *Metal Complexes in Aqueous Solution*, Plenum Press, New York, 1966, p. 235.
- 14 (a) M. v. Stackelberg and H. v. Freyhold, *Z. Electrochem.*, 1940, **46**, 120; (b) J. Lingane, *Chem. Rev.*, 1941, **29**, 1; (c) J. Bjerrum, *Chem. Rev.*, 1950, **46**, 381; (d) D. D. De Ford and D. N. Hume, *J. Am. Chem. Soc.*, 1951, **73**, 5321; (e) A. A. Vlček, *Collect. Czech. Chem. Commun.*, 1955, **20**, 400; (f) J. Koryta, *Electrochim. Acta*, 1965, **1**, 26.
- 15 A. E. Martell and R. M. Smith, *Critical Stability Constants*, Plenum Press, New York, 1974, vol. 1.
- 16 F. Uggeri, S. Aime, P. L. Anelli, M. Botta, M. Brocchetta, C. de Haën, G. Ermondi, M. Grandi and P. Paoli, *Inorg. Chem.*, 1995, **34**, 633.
- 17 C. W. De Kreuk, M. Sluyters-Rehbach and J. H. Sluyters, *J. Electroanal. Chem.*, 1970, **28**, 391.
- 18 C. Nervi, ESP (Electrochemical Simulations Package), Version 2.4. The program is free of charge at <http://lem.ch.unito.it/chemistry/esp24b.zip>.
- 19 (a) D. K. Gosser and F. Zhang, *Talanta*, 1991, **38**, 715; (b) D. Britz, *Digital Simulation in Electrochemistry*, Springer, Berlin, 1988.
- 20 R. S. Nicholson, *Anal. Chem.*, 1965, **37**, 1351.
- 21 (a) S. H. Koenig and R. D. Brown III, *Prog. Nucl. Magn. Reson. Spectrosc.*, 1990, **22**, 487; (b) S. Aime, M. Botta, M. Fasano and E. Terreno, *Chem. Soc. Rev.*, 1998, **27**, 19; (c) P. Caravan, J. J. Ellison, T. J. McMurry and R. B. Lauffer, *Chem. Rev.*, 1999, **99**, 2293; (d) É. Tóth, L. Helm and A. E. Merbach, in *The Chemistry of Contrast Agents in Medical Magnetic Resonance Imaging*, ed. A. E. Merbach and É. Tóth, J. Wiley, New York, 2001.
- 22 (a) P. Caravan and A. E. Merbach, *Chem. Commun.*, 1997, 2147; (b) P. Caravan, É. Tóth, A. Rockenbauer and A. E. Merbach, *J. Am. Chem. Soc.*, 1999, **121**, 10403; (c) S. Seibig, É. Tóth and A. E. Merbach, *J. Am. Chem. Soc.*, 2000, **122**, 5822; (d) L. Burai, É. Tóth, S. Seibig, R. Scopelliti and A. E. Merbach, *Chem. Eur. J.*, 2000, **6**, 3761.
- 23 G. Moreau, L. Helm, J. Purans and A. E. Merbach, *J. Phys. Chem. A*, 2002, **106**, 3034.
- 24 H. Gries and H. Miklautz, *Physiol. Chem. Phys. Med. NMR*, 1984, **16**, 105.
- 25 G. Gran, *Analyst*, 1952, **77**, 661.
- 26 L. D. Pettit, Academic Software, UK.