

Research into europium complexes as magnetic resonance imaging contrast agents (Review)

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Abstract. Europium (Eu) is a paramagnetic lanthanide element that possesses an outstanding luminescent property. Eu complexes are ideal fluorescence imaging (FI) agents. Eu²⁺ has satisfactory relaxivity and optical properties, and can realize magnetic resonance (MRI)-FI dual imaging applications when used with appropriate cryptands that render it oxidatively stable. By contrast, based on the chemical exchange saturation transfer (CEST) mechanism, Eu³⁺ complexes can provide enhanced MRI sensitivity when used with optimal cryptands, incorporated into polymeric CEST agents or blended with Gd³⁺. Eu complexes are promising in MRI-FI dual imaging applications and have a bright future.

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1. Introduction

Magnetic resonance imaging (MRI) is a useful medical imaging technique that utilizes the properties of nuclear magnetic resonance (NMR) to image the nuclei of atoms inside the body in detail and depth (1,2). With high resolution and good safety, MRI is widely used as an efficient information source in medical diagnosis of the whole body. Fluorescence

imaging (FI) provides better sensitivity than MRI, but cannot show tissues at different levels. The combination of MRI and FI, as a dual imaging application, should provide a balance between iconography and histology. In addition, diagnosis and treatment are likely to be more accurate and sensitive with an approach where tumors are positioned with MRI and completely removed under the guidance of FI.

The ability of contrast agents to alter the relaxivity of the protons of water molecules that are coordinated to tissue is the key of MRI (1). The trivalent gadolinium ion (Gd³⁺) has seven unpaired electrons in its outer electron shell, which makes it highly paramagnetic with a short spin-lattice relaxation time (longitudinal relaxation time, T₁), and complexes of Gd³⁺ have been widely used as MRI contrast agents (3). Gd³⁺ has a similar size to Ca²⁺ and so the former tends to interfere in the metabolism of Ca²⁺ in the human body. Therefore, ligands are necessary to reduce the toxicity. Functional groups on the ligands can also be designed to bond with nanoparticles (NPs), in order to extend the rotational correlation time and enhance relaxivity. Ligands that are frequently used include diethylene triamine pentacetic acid (DTPA), 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid (DOTA) and their derivatives (Fig. 1) (3,4).

Europium (Eu) is also lanthanide element, which is adjacent to gadolinium in the periodic table, and the application of its ions in MRI has also been the object of attention. Eu³⁺ has six unpaired electrons in the outer electron shell, which is indicative of good paramagnetism. It is photoluminescent, can emit strong fluorescence (585-630 nm, red) with a long life-time and is barely toxic. If the MRI and FI functions of complexed Eu are both achieved, and the complexes possess sensitivity and accuracy, a series of promising applications are predicted. Xu *et al* presented a variety of lanthanide oxide (Ln₂O₃) NPs and studied their water proton relaxivities (5). The authors coated Ln₂O₃ with D-glucuronic acid to prepare ultrasmall NPs (with diameters of ~2 nm), and measured their longitudinal relaxivity (r₁) and transverse relaxivity (spin-spin relaxivity; r₂). The results are listed in Table I (6), and show that the D-glucuronic acid-coated ultrasmall Eu₂O₃ NPs are not outstanding in r₁ or r₂. This may be attributed to the spin relaxation time of Eu³⁺ being too short to alter the relaxivity of protons. To achieve MRI-FI dual imaging, the optimal method is to blend Eu

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Key words: europium, magnetic resonance imaging, cryptand, longitudinal relaxivity, transverse relaxivity

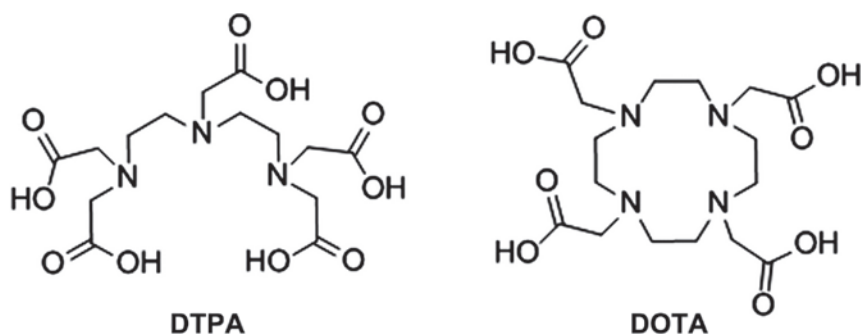


Figure 1. Frequently used ligands, diethylene triamine pentacetic acid (DTPA) and 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid (DOTA).

complexes with routine MRI contrast agents, for example, Gd^{3+} complexes (5,7) and Fe_3O_4 (8,9). Pinho *et al* studied the dual imaging capabilities of lanthanide-DTPA-grafted silica NPs, in which Eu^{3+} and Gd^{3+} complexes were blended together [$\text{SiO}_2@3\text{-aminopropyl-triethoxysilane}$ (APS)/DTPA: $\text{Gd}:\text{Eu}$] (7). The results revealed that the existence of Gd^{3+} did not disturb the photoluminescence of Eu^{3+} , while the addition of Eu^{3+} enhanced the relaxivity of Gd^{3+} .

However, in order to realize MRI-FI dual imaging with Eu complexes in the absence of highly paramagnetic ions, it is necessary to focus attention on improving the MRI properties of Eu complexes.

2. Studies of Eu^{2+} complexes as MRI contrast agents

Eu^{2+} has seven unpaired electrons in its outer electron shell, as does Gd^{3+} . However, Eu^{2+} has a larger ion size than Gd^{3+} and a lower charge, which gives Eu^{2+} a faster water-exchange rate and guarantees a relatively high relaxivity (10). Eu^{2+} is also photoluminescent; $f \rightarrow d$ transitions have been observed in Eu^{2+} , which have longer radiative emission lifetimes than $f \rightarrow f$ transitions in Eu^{3+} (11). However, the relaxivity of Eu^{2+} -containing DTPA chelates has been found to be 20% lower than that of Gd^{3+} -DTPA complexes at 20 MHz, which may be attributed to the fast ionic spin relaxation of Eu^{2+} (12). Not all Eu^{2+} complexes are restricted by ionic spin relaxation. The relaxivity of Eu^{2+} -DOTA complexes has been shown to reach $4.74 \text{ mM}^{-1}\text{sec}^{-1}$ at 20 MHz and 298K, much higher than that of Eu^{2+} -DTPA complexes (13). A fast water-exchange rate of Eu^{2+} is able to offset the disadvantage in ionic spin relaxation time.

The biggest obstacle in the development of MRI applications of Eu^{2+} complexes is the oxidative stability of the ion. Eu^{2+} has a propensity for being oxidized to Eu^{3+} , which possesses low relaxivity and relatively high toxicity. Coordination chemistry principles can be used to oxidatively stabilize Eu^{2+} without weakening the relaxivity and water-exchange rate. 4,7,13,16,21,24-Hexaoxa-1,10-diazabicyclo[8.8.8]hexacosane (crypt-222; ligand 1 in Fig. 2A) is known to have an appropriate cage size for Eu^{2+} , and the crypt-222 complex [$\text{Eu}(\text{crypt-222})(\text{H}_2\text{O})_2$] $^{2+}$ is one of the most redox-stable Eu^{2+} chelates (14). [$\text{Eu}(\text{crypt-222})$] $^{2+}$ coordinates immediately with two water molecules, and possesses an appropriate water-exchange rate and ionic spin relaxation time. However, [$\text{Eu}(\text{crypt-222})(\text{H}_2\text{O})_2$] $^{2+}$ is not sufficiently stable for the development of MRI applications in aqueous solution. However, it

is potentially useful as a pO_2 -responsive macromolecular MRI contrast agent (14).

To obtain oxidatively stable aqueous Eu^{2+} complexes, Gamage *et al* carried out research and development based on the coordination of crypt-222 (15). The goals were: i) to increase the surrounding steric bulk to minimize interactions between Eu^{2+} and its environment; ii) to reduce the Lewis basicity of crypt-222 to favor Eu^{2+} over Eu^{3+} ; iii) to change the cavity size of the cryptand to match the size of the Eu^{2+} ion preferentially; and iv) to modify the hard-soft, acid-base (HSAB) properties of crypt-222 to coordinate Eu^{2+} in preference to Eu^{3+} . The authors presented five ligands (ligands 2-6 in Fig. 2) with crypt-222 as the prototype.

The steric bulk of ligand 2 was increased by the addition of methyl groups. Benzene rings were introduced to decrease the ion-donating ability of the adjacent oxygen atoms of ligands 3-5. The introduction of fluorine in ligand 4 and another benzene ring in ligand 5 modulated the extent of ion withdrawal. The existence of fused benzene moieties decreased the cavity size of the cryptand and provided a cavity size closer to that of Eu^{2+} . In ligand 6, relatively soft sulfur-atom donors were introduced to take the place of oxygen-atom donors, enabling the influence of HSAB properties to be explored. *In situ*, the authors mixed these ligands with $\text{Eu}(\text{NO}_3)_3 \cdot 5\text{H}_2\text{O}$ in aqueous solution. The mixture was placed in a standard three-electrode cell while the potential at the carbon electrode was held at -0.8 V to achieve metal complexation. Cyclic voltammograms were obtained following metallation for each complex in solution with ferrocene as an internal standard. Anodic peak potentials for each complex were obtained and are listed in Table II.

The results revealed that the new ligands all increased the oxidative stability of Eu^{2+} to a certain degree. There was almost no difference between the Eu complexes of ligands 5 and 3, indicating that the addition of one benzene ring was sufficient for stabilization. The Eu complex of ligand 6 had the highest anodic peak potential, higher than that of Fe^{2+} -hemoglobin, suggesting that it was an efficient ligand to prevent Eu^{2+} from oxidation. Garcia *et al* also reported the stability of Eu complexes with ligands 1 and 3 in the presence of Ca^{2+} , Mg^{2+} and Zn^{2+} (16), and the study indicated that the Eu^{2+} complexes remained stable in the presence of Ca^{2+} , Mg^{2+} and Zn^{2+} at concentrations 1.87-20-fold higher than biological concentrations. Eu^{2+} complexes have the potential to realize durable biological oxidative stability, and provide satisfactory magnetic and spectroscopic properties *in vivo*.

Table I. Average particle diameter (d_{avg}), r_1 , and r_2 of D-glucuronic acid-coated ultrasmall Ln_2O_3 nanoparticles and the M values of Ln(III) in ultrasmall Ln_2O_3 nanoparticles (6).

Ln_2O_3 nanoparticle	d_{avg} (nm)	M^a (μ_B)		r_1^b ($\text{mM}^{-1}\text{sec}^{-1}$)	r_2^b ($\text{mM}^{-1}\text{sec}^{-1}$)
		5K	300K		
Eu_2O_3	2.0	0.078	0.046	0.006	3.82
Gd_2O_3	2.4	6.42	0.24	4.25	27.11
Dy_2O_3	2.9	5.19	0.42	0.16	40.28
Ho_2O_3	2.4	4.66	0.39	0.13	31.24
Er_2O_3	2.9	4.52	0.34	0.06	14.74

^aMeasured with a magnetic field intensity of 5T. ^bMeasured at 22°C with a magnetic field intensity of 1.5T. r_1 , longitudinal relaxivity; r_2 , transverse relaxivity; Ln, lanthanide; Eu, europium, Gd, gadolinium; Dy, dysprosium; Ho, holmium; Er, erbium; M, magnetization.

Table II. Anodic peak potentials (Epa) of various samples with respect to ferrocene/ferrocenium (Fc/Fc^+).

Sample	Epa vs. Fc/Fc^+ (V)	Sample	Epa vs. Fc/Fc^+ (V)
1. $\text{Eu}(\text{NO}_3)_3$	-0.701±0.030	5. Eu-2	-0.169±0.006
2. Eu-1	-0.336±0.016	6. Eu-4	-0.079±0.007
3. Eu-5	-0.211±0.004	7. hemoglobin	-0.070±0.003
4. Eu-3	-0.208±0.009	8. Eu-6	-0.035±0.010

Eu-n (n=1-6) is a complex of europium (Eu^{2+}) with ligand n; ligand 1 is 4,7,13,16,21,24-hexaoxa-1,10-diazabicyclo[8.8.8]hexacosane (crypt-222); ligands 2-6 are crypt-222 derivatives as shown in Fig. 2.

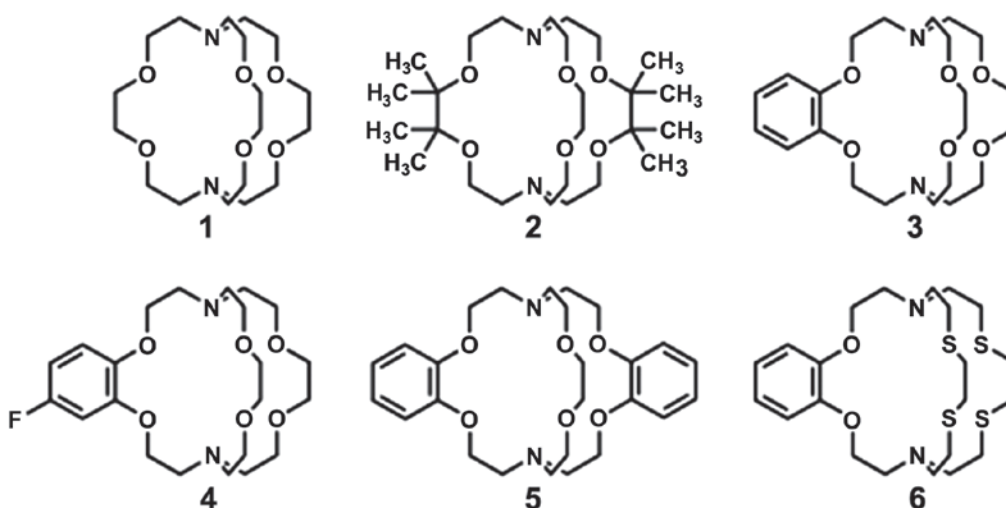


Figure 2. 4,7,13,16,21,24-Hexaoxa-1,10-diazabicyclo[8.8.8]hexacosane (crypt-222; ligand 1) and its derivatives (ligands 2-6).

3. MRI of Eu^{3+} complexes based on CEST

Chemical exchange saturation transfer (CEST) is a novel mechanism for generating image contrast in MRI (1). Protons on ligands or water molecules coordinated with a metal ion are saturated by a radiofrequency pulse and then exchanged with bulk water molecules, presenting a negative image. Imaging can be made more efficient by the utilization of paramagnetic nuclei. The effects of these agents,

referred to as PARACEST agents, can be switched on and off depending on the application of radiofrequency radiation. Theoretically, with an optimal water-exchange rate, chemical shift and relaxation properties, the detection limit of a single PARACEST exchanging species is comparable to that of a single Gd^{3+} -based T1 imaging agent (17). The applications of CEST include the visualization of living tissue structure, the imaging of metabolic processes, the marking of cells and pH measurements (18).

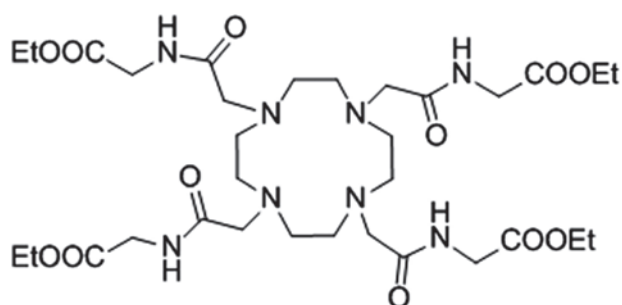


Figure 3. 1,4,7,10-Tetraazacyclododecane tetrakis(ethyl-acetamidoacetate), ligand 7. Et, ethyl.

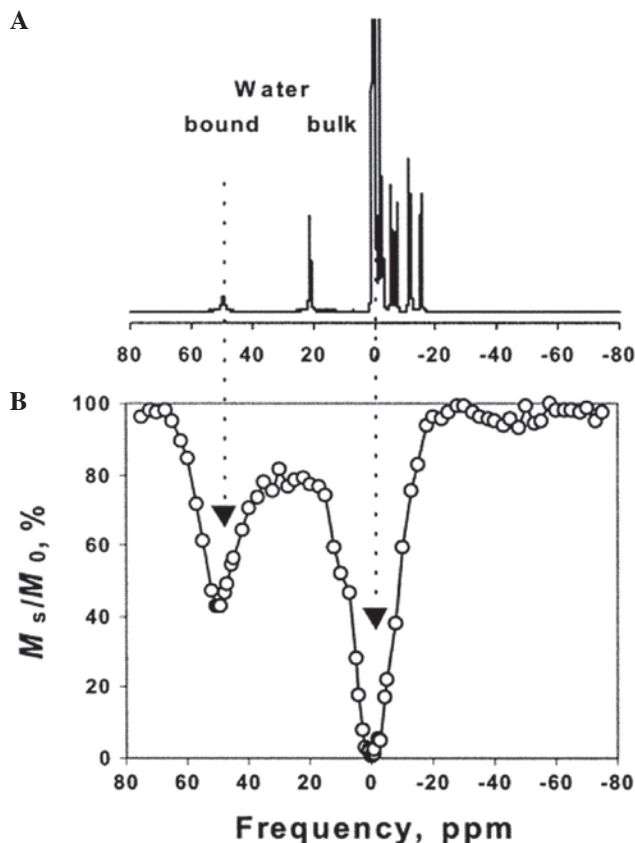


Figure 4. (A) ^1H nuclear magnetic resonance spectrum and (B) chemical exchange saturation transfer curve of Eu-7 in aqueous solution. Eu-7 is a complex of europium (Eu^{3+}) with 1,4,7,10-tetraazacyclododecane tetrakis(ethyl-acetamidoacetate). M_s/M_0 , ratio of saturated protons; M_s , water proton signal in the presence of saturation; M_0 , signal under control conditions; ppm, parts per million.

Zhang *et al* studied the CEST properties of a complex of Eu^{3+} with a DOTA-tetraamide derivative (ligand 7 in Fig. 3) (19). ^1H NMR spectroscopy was used to examine an aqueous solution of the Eu complex of ligand 7 (Fig. 4A). The peak corresponding to complexed water shifted to ~ 50 ppm. If protons were exchanged between the complexed water and bulk water following the application of radiofrequency energy, the signal intensities of would change, revealing directly the ratio of saturated protons. The ratio of saturated protons is defined as M_s/M_0 , where M_s is the water proton signal in the presence of saturation and M_0 is the signal under control conditions. CEST curves were drawn based on the aforementioned

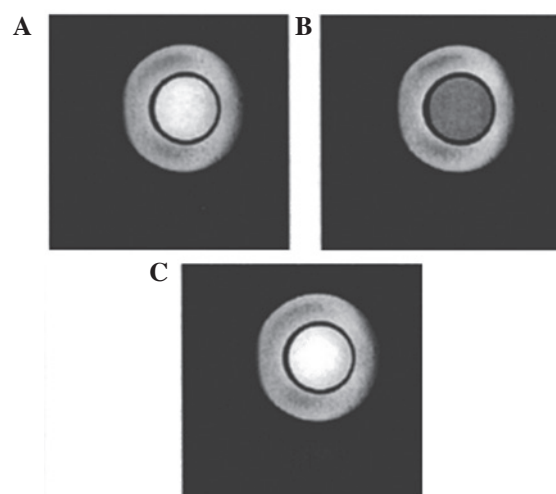


Figure 5. Magnetization transfer T1-weighted spin-echo images of a phantom. The outer vial contained deionized water, while inner vial contained 63 mM Eu-7 dissolved in pure water. (A) No saturation, (B) saturation at +9,800 Hz and (C) saturation at -9,800 Hz. Eu-7 is a complex of europium (Eu^{3+}) with 1,4,7,10-tetraazacyclododecane tetrakis(ethyl-acetamidoacetate).

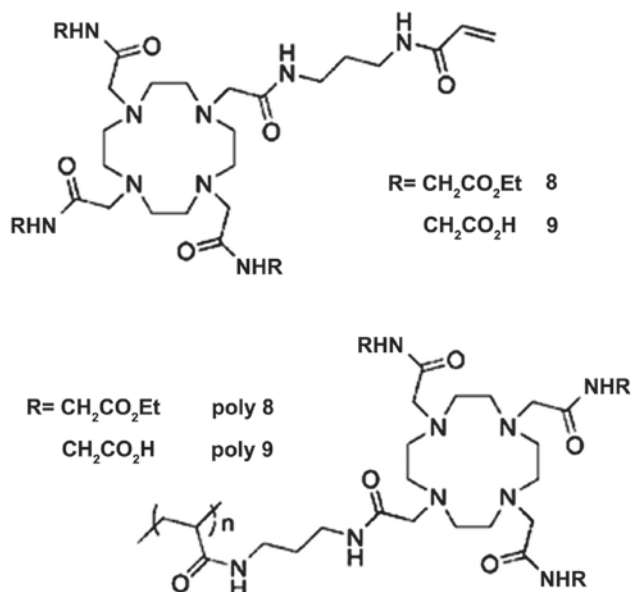


Figure 6. 1,4,7,10-Tetraazacyclododecane-1,4,7,10-tetraacetic acid derivatives with acrylamide substituents (ligands 8 and 9) and their polymers (poly 8 and poly 9, respectively). Et, ethyl.

method (Fig. 4B). Lower M_s/M_0 values indicated higher CEST effects. Magnetization transfer T1-weighted spin-echo images for a phantom were obtained with no saturation (Fig. 5A), saturation at +9,800 Hz (Fig. 5B) and saturation at -9,800 Hz (Fig. 5C). The image at +9,800 Hz was dimmer than the others, demonstrating the weakening effect of CEST on the magnetic resonance signals of protons, and the ability to be switched on and off at will was achieved.

To lower the detection limit of PARACEST agents, Wu *et al* reported the polymerization of PARACEST agents in order to enhance MRI contrast sensitivity (17). The authors presented two kinds of DOTA ligands with acrylamide substituents to coordinate with Eu^{3+} (ligands 8 and 9 in Fig. 6), and synthesized

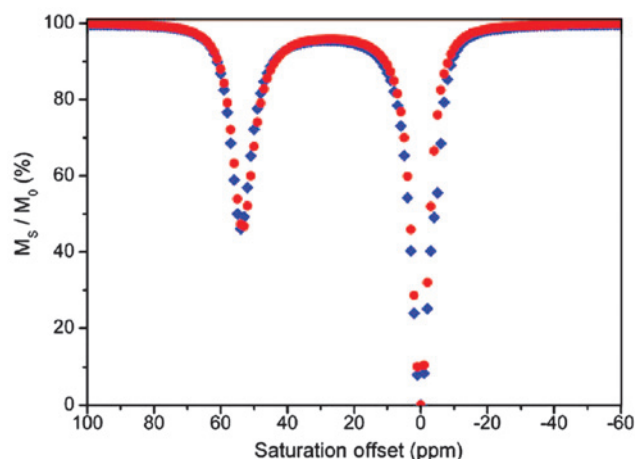


Figure 7. Chemical exchange saturation transfer spectra of Eu-9 (red) and Eu-poly 9 (2%; blue); concentration of Eu^{3+} , 30 mM. Eu-9 is a complex of europium (Eu^{3+}) with an acrylamide-substituted derivative of 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid (ligand 9), and Eu-poly 9 is a complex of Eu^{3+} with a polymer of ligand 9. M_s/M_0 , ratio of saturated protons; M_s , water proton signal in the presence of saturation; M_0 , signal under control conditions; ppm, parts per million.

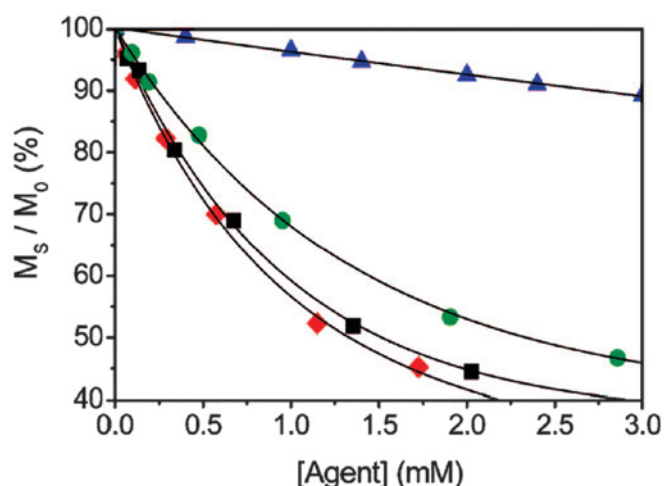


Figure 8. Maximum chemical exchange saturation transfer per concentration of agent [agent] for Eu-9 (▲) and Eu-poly 9 (●, 2%; ■, 5%; ◆, 10%). Eu-9 is a complex of europium (Eu^{3+}) with an acrylamide-substituted derivative of 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid (ligand 9), and Eu-poly 9 is a complex of Eu^{3+} with a polymer of ligand 9. M_s/M_0 , ratio of saturated protons; M_s , water proton signal in the presence of saturation; M_0 , signal under control conditions.

polymeric ligands by the respective radical polymerization of ligands 8 and 9 (poly 8 and poly 9 in Fig. 6). The CEST spectra of Eu complexes of ligands 9 and poly 9 were almost identical at equal Eu^{3+} concentrations (Fig. 7), suggesting that the polymerization had no impact of the exchange of protons. A comparison among the maximum CEST for each concentration of the Eu complexes of ligand 9 and poly 9 with different initiator ratios (Fig. 8) revealed that polymerization efficiently lowered the detection limit.

In another article from these authors, 2-methylacrylic acid (MAA), 2-(acryloylamino)-2-methyl-1-propanesulfonic acid (AMPS) and N-isopropylacrylamide (NIPAM) were respectively used to copolymerize with ligand 9, to form the polymers

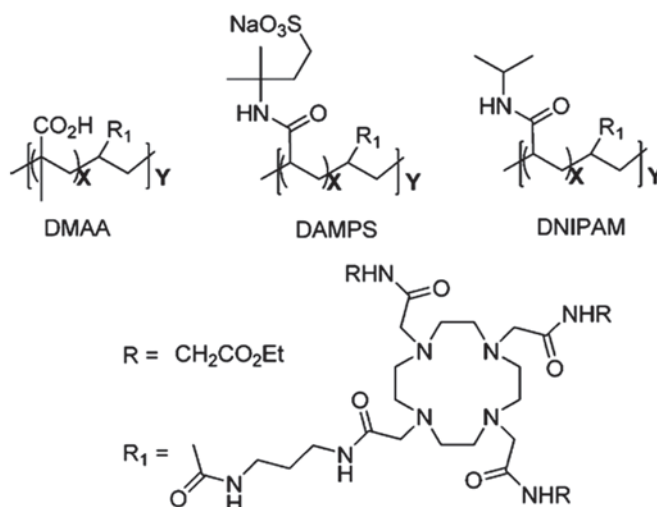


Figure 9. Copolymers of an acrylamide-substituted derivative of 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid (ligand 9) with 2-methylacrylic acid (MAA), 2-(acryloylamino)-2-methyl-1-propanesulfonic acid (AMPS) and N-isopropylacrylamide (NIPAM). Et, ethyl; D, ligand 9.

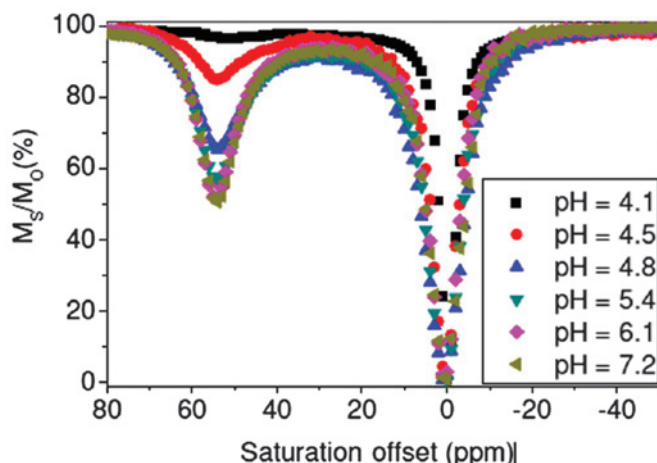


Figure 10. Chemical exchange saturation transfer curves of Eu-DMAA at different pH values. Eu-DMAA is a complex of europium (Eu^{3+}) with a copolymer of an acrylamide-substituted derivative of 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid (ligand 9) and 2-methylacrylic acid (MAA). M_s/M_0 , ratio of saturated protons; M_s , water proton signal in the presence of saturation; M_0 , signal under control conditions; ppm, parts per million.

DMAA, DAMPS and DNIPAM (D: ligand 9), respectively (Fig. 9), in order to investigate the effect of water-exchange rate on the CEST properties of Eu^{3+} complexes (20).

Unlike Gd^{3+} -based T1 imaging agents that rely on rapid water exchange between metal ion-bound water and bulk solvent, the signals of PARACEST agents become quenched as the bound protons on the agent are not readily saturated at a rapid water-exchange rate; they require moderate-to-slow water exchange rates for optimal performance. From the CEST results of an Eu complex of DMAA at different pH values (Fig. 10), the signals were attenuated as the pH was reduced from 8 to 4. The carboxyl group was stable enough to bond with water at lower pH and water exchange between water and the complexes was promoted. Copolymerization also rendered the

complexes responsive to temperature. The water-exchange rate increased as the temperature rose. However, unlike DMAA, which is hydrophilic along the full length of the polymer, the interaction between water and the side groups of DNIPAM was attenuated when the temperature rose, and the side groups tended to aggregate against water, which avoided an unfavorably rapid exchange rate. The aforementioned factors explain why changes in the signals generated by the Eu-DNIPAM complex were more moderate than those generated by Eu-DMAA as the temperature changed. The results of these studies indicate that Eu³⁺-based CEST agents are promising for use in pH- and temperature-responsive MRI applications.

4. Conclusion and prospects

Eu³⁺ and Eu²⁺ possesses six and seven unpaired electrons in the 4f orbital, respectively, which is indicative of paramagnetism. However, the short ionic spin relaxation time of Eu³⁺ and the propensity of Eu²⁺ to be oxidized result in the MRI properties of Eu complexes being inferior to those of Gd complexes. The design of ligands and enhancement by CEST are the main approaches at present to compensate for the deficiencies of Eu ions, enhance their properties as MRI contrast agents and eventually realize MRI-FI dual imaging with further efforts.

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