

Structural XAFS Investigation of Eu^{2+} and Sr^{2+} Poly(amino carboxylates): Consequences for Water Exchange Rates on MRI-Relevant Complexes

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The structure of the Eu^{2+} and Sr^{2+} DOTA^{4-} (1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetate), DTPA^{5-} (diethylenetriamine-*N,N,N',N'',N'''*-pentaacetate), and ODDA^{2-} (1,4,10,13-tetraoxa-7,16-diazacyclooctadecane-7,16-diacetate) complexes were characterized using XAFS in the solid state and in aqueous solution. The results show the structural similarity between the highly paramagnetic and MRI-relevant Eu^{2+} poly(amino carboxylate) complexes with their diamagnetic Sr^{2+} homologues in each state as well as the overall conservation of the solid-state structure in aqueous solution. The DOTA^{4-} ligand adopts a twisted-square antiprism conformation in aqueous solution to accommodate the large Eu^{2+} and Sr^{2+} ions, leading to metal ion-to-coordinated water distances 0.2 Å longer in the $[\text{M}^{\text{II}}(\text{DOTA})(\text{H}_2\text{O})]^{2-}$ complexes than in the $[\text{M}^{\text{II}}(\text{DTPA})(\text{H}_2\text{O})]^{3-}$ complexes ($\text{M}^{\text{II}} = \text{Eu}^{2+}, \text{Sr}^{2+}$). The different structures adopted by the complexes in aqueous solution were found to be responsible for their different water exchange mechanisms: changing from D ($\text{DTPA}^{5-}, \text{DOTA}^{4-}$) for Gd^{3+} to I_d (DTPA^{5-}), I (DOTA^{4-}), and I_a (ODDA^{2-}) for the Eu^{2+} complexes. Finally, a lower charge density and substantially longer $\text{M}-\text{O}_w$ distances for the Eu^{2+} ion explain the 3 orders of magnitude higher water exchange rates observed for the Eu^{2+} poly(amino carboxylates) over the corresponding Gd^{3+} complexes. Such high water exchange rates could be valuable in designing more efficient responsive contrast agents for magnetic resonance imaging.

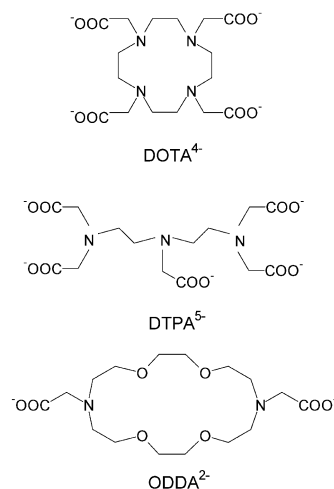
Introduction

Over the past two decades, Gd^{3+} poly(amino carboxylate) complexes have become widely used as contrast agents in medical diagnostics using magnetic resonance imaging (MRI).¹ Eu^{2+} (1.30 Å ionic radius² for nine coordination) is isoelectronic to Gd^{3+} (1.11 Å) and shows similar magnetic properties. The high magnetic moment of both ions ($S = 7/2$), associated with relatively slow electron-spin relaxation rates, makes them an ideal choice for nuclear magnetic relaxation enhancement,^{3,4} a highly regarded property in contrast agents for medical MRI.¹

The characterization of Eu^{2+} complexes has been hindered by their poor stability in aqueous solution⁵ because they react quickly with oxygen and more slowly with water.⁶ Moreover, Eu^{2+} is intermediate in size between the chemically stable and diamagnetic Ca^{2+} and Sr^{2+} (1.18 and 1.31 Å ionic radii,² respectively, for nine coordination) and exhibits similar coordination chemistry.⁷ Thus, the Sr^{2+} ion can be used as a chemically stable model for the Eu^{2+} complexes. Reciprocally, investigations of paramagnetic Eu^{2+} complexes using electron spin resonance (ESR) or nuclear magnetic resonance (NMR) relaxation give access to the water exchange rates and mechanism of the homologous Sr^{2+} complexes.

Recently it was demonstrated that careful preparation allows the production of samples that are stable for a few hours,⁸ which makes Eu^{2+} complexes of potential interest as MRI contrasting agents. Furthermore, the reaction of Eu^{2+} poly(amino carboxylate) complexes with oxygen or water could potentially be

SCHEME 1



exploited in the clinic to produce responsive or “smart” contrast agents.⁴ MRI research tends toward specific compounds that are able to produce an image depending on the physicochemical properties of their biological environment.

We recently studied the dynamic properties of the Eu^{2+} DOTA^{4-} , DTPA^{5-} , and ODDA^{2-} complexes (Scheme 1) in aqueous solution.^{9–11} DOTA^{4-} (1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetate) and DTPA^{5-} (diethylenetriamine-*N,N,N',N'',N'''*-pentaacetate) are among the most commonly used ligands for MRI contrast agents (Dotarem, Magnevist) and are used as building blocks in more specific contrast agents, and ODDA^{2-} (1,4,10,13-tetraoxa-7,16-diazacyclooctadecane-7,16-diacetate) forms the most redox-stable Eu^{2+} poly(amino carboxylate) complex studied so far. Until now, however, the only structural

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information available for these Eu²⁺ complexes was the crystal structure of [Eu(DTPA)(H₂O)][C(NH₂)₃]₃.¹⁰ Because this compound is quasi-isostructural with the corresponding Sr²⁺ complex, the isostructurality was presupposed for the other Eu²⁺ and Sr²⁺ poly(amino carboxylate) complexes, which have not been crystallized with the Eu²⁺ ion. Additionally, structural investigations have been performed on the Gd³⁺ DOTA⁴⁻ and DTPA⁵⁻ complexes using the X-ray absorption fine structure (XAFS) technique, which shows that the overall structure was retained in aqueous solution.¹² It was consequently supposed, given the high complexing properties of these poly(amino carboxylate) ligands, that the coordination polyhedron geometry of the Eu²⁺ ion was also retained in aqueous solution.

In the present work, the XAFS technique is used to characterize and compare the Eu²⁺ and Sr²⁺ DOTA⁴⁻, DTPA⁵⁻, and ODDA²⁻ complexes in the solid state and in solution. The experimental Eu²⁺ L₃-edge as well as the Sr²⁺ K-edge XAFS spectra have been measured, analyzed, and compared using a theoretical approach¹³ combined with efficient analysis techniques.^{14–16} Finally, the water exchange reaction rates and mechanisms of these Eu²⁺ and Sr²⁺ poly(amino carboxylate) complexes are discussed on a structural basis.

Experimental Section

Chemicals. H₄DOTA was purchased from Strem Chemicals, H₅DTPA and [C(NH₂)₃]₂CO₃ were purchased from Fluka, H₂ODDA was purchased from Acros Organics, and 98% CF₃SO₃H (triflic acid) was purchased from Aldrich Chemicals. All commercial compounds were used as received. [Eu(H₂O)₉](O₃SCF₃)₃ was prepared as described in the literature.¹⁷

The compounds [Eu(DOTA)(H₂O)][C(NH₂)₃]₂,¹¹ [Eu(DTPA)(H₂O)][C(NH₂)₃]₃,¹⁰ [Sr(DOTA)(H₂O)][C(NH₂)₃]₂,¹¹ [Sr(DTPA)(H₂O)][C(NH₂)₃]₃,¹⁰ and Sr(ODDA)¹⁰ were obtained from [Eu(H₂O)₉](O₃SCF₃)₃ and analytical grade SrCO₃ following literature procedures. The solid Eu(ODDA) was obtained by the evaporation of an electrochemically reduced solution of the corresponding Eu³⁺ complex.¹⁰ Crystals were not obtained by evaporation, and the resulting solid material contains about 10% NaO₃SCF₃.

Preparation of the Samples. Solutions of 0.2 M [Eu(DOTA)(H₂O)]Na₂, 0.1 M [Eu(DTPA)(H₂O)]Na₃, 0.1 M [Eu(ODDA)(H₂O)], 0.2 M [Sr(DOTA)(H₂O)]Na₂, 0.1 M [Sr(DTPA)(H₂O)]Na₃, and 0.1 M [Sr(ODDA)(H₂O)] were obtained by literature procedures.^{9–11} The solid guanidinium samples were finely ground and mechanically mixed with cellulose powder to give pressed pellets with a thickness chosen to obtain an absorption jump value of about 1. All of the Eu²⁺ solid compounds and solutions were prepared, handled, and stored under the oxygen-free nitrogen atmosphere of a glovebox to avoid oxidation.

Calculations of Surface Electrostatic Potentials. The electrostatic potentials on the Sr²⁺ and Gd³⁺ complexes with DOTA⁴⁻ and DTPA⁵⁻ ligands and on the Sr(ODDA) complex were described by calculations of their partial atomic charges using the Merz–Kollman method¹⁸ as implemented in the Gaussian 98 package¹⁹ and based on the X-ray crystal structures of the complexes.^{10,11,20,21} This method outputs atomic charges by fitting them to the electrostatic potential at a fixed distance through a dielectric medium, leading to a good representation of the electrostatic potential at the molecular surface. In the solid-state structure of the Sr²⁺ poly(amino carboxylate) complexes, the position of the protons of the coordinated water molecule is undetermined. Thus, for the calculations, the coordinated water molecule was replaced by an oxygen atom

in all Sr²⁺ and Gd³⁺ complexes. For the Sr²⁺ complexes, calculations were performed at the LANL2DZ level (Sr, H, C, N, O), and for the Gd³⁺ complexes, calculations were performed at the 6-31G** level (H, C, N, O), with pseudopotentials by Dolg and Stoll²² accounting for relativistic corrections in the treatment of the Gd³⁺ core electrons. The electrostatic potentials were plotted on the electronic density maps obtained from the Gaussian 98 outputs using Molekel software,²³ version 4.2, with a cutoff value of 0.012 that is identical for all complexes.

XAFS Measurements. XAFS measurements were performed at the LURE synchrotron radiation facility (Orsay, France) on the DCI D21 (XAS 2) beam line. The positron-beam energy and average current were 1.85 GeV and 320 to 250 mA, respectively. The XAFS spectra of the Eu L₃-edge (6976 eV; 6900–7650 eV scans) and Sr K-edge (16105 eV; 16 000–17 000 eV scans) were measured in transmission mode. The synchrotron radiation was monochromatized using the Si(311) double-crystal monochromator, and in the case of the Eu L₃-edge, harmonic rejection was achieved using dedicated mirrors. The experimental spectra were measured using two ionization chambers (filled with air for Eu and with Ar for Sr measurements) with a count rate of 2 s per point, an energy resolution of 1 or 2 eV, a 0.5 or 1 eV step in the X-ray absorption near-edge structure (XANES) region, and a 1 or 2 eV step in the extended X-ray absorption fine structure (EXAFS) region for the Eu L₃-edge and the Sr K-edge, respectively. A multipurpose X-ray absorption cell²⁴ was used for the in situ XAFS measurements of sealed, oxygen, and water-free solutions. The measurements were carried out at optical lengths of 1–1.5 mm for Eu and 4–8 mm for Sr, resulting in values of the absorption jump of about 0.5 (white-line amplitude about 2) for Eu and about 1 for Sr. All samples were measured at room temperature (20–25 °C), and at least three complete and identical XAFS scans were collected for each.

Data Analysis. The experimental data were analyzed by implementing a simple constraints refinement based on the crystallographic data and lattice dynamics.²⁵ Because the coordination polyhedron in the characterized complexes is known (at least in the solid state), only integer values of the occupation numbers were considered, and all atoms of a similar type at similar distances (participating in the same subshell) were attributed the same DW factor, as described previously.^{12,26}

Low-symmetry crystalline complexes such as [Eu(DTPA)(H₂O)]³⁻ and [Eu(DOTA)(H₂O)]²⁻ contain many distances in one subshell, thus the fitted Debye–Waller (DW) factors (C_2) include both the static and the dynamic contributions. The experimental XAFS data were treated using the EDA software package,²⁷ as in the study of the Eu²⁺ and Sr²⁺ ions in water⁸ and in nonaqueous solutions.²⁸ The obtained XAFS spectra, $\chi(E)$, were converted to the k -space of the photoelectron wavevector, defined as $k = \sqrt{(2m/\hbar)(E - E_0)}$, where $(E - E_0)$ is the measured photoelectron kinetic energy. The experimental high-energy part of the XAFS spectra $\chi(k)$ (called EXAFS) of both the Eu²⁺ and Sr²⁺ complexes (Figures 1 and 2) was multiplied by a factor of k^3 or k^4 (see Table S1 in Supporting Information for experimental details) to compensate for the decrease in amplitude with increasing wavevector value. A k^4 instead of k^3 factor was occasionally needed (see Results section) to allow a precise single-out of the first shell of scatterers' contribution to the experimental EXAFS spectrum.

The experimental EXAFS spectra were Fourier transformed (FT) with a Kaiser–Bessel window in the 0–12 Å⁻¹ range for Eu and the 0–15 Å⁻¹ range for Sr (Figures 3 and 4). The first-shell EXAFS contributions were singled out by a back FT

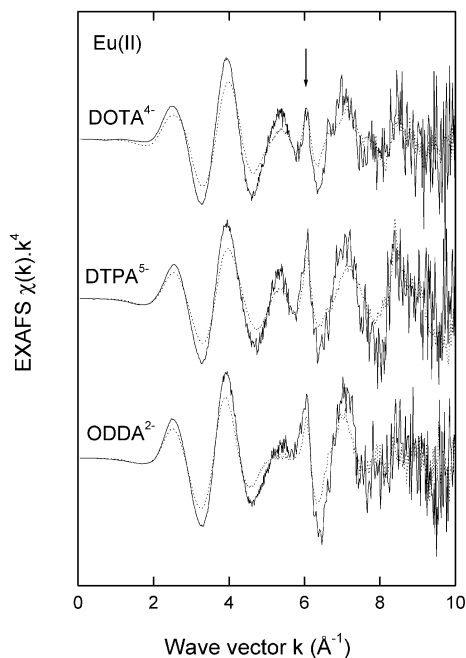


Figure 1. Experimental $\chi(k)k^4$ XAFS spectra of the Eu^{2+} DOTA^{4-} , DTPA^{5-} , and ODPA^{2-} complexes in the solid state (\cdots) and in solution ($-$).

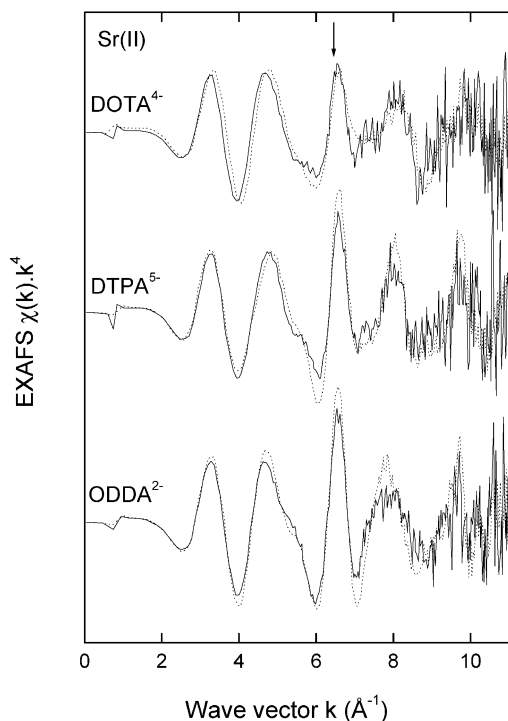


Figure 2. Experimental $\chi(k)k^4$ XAFS spectra of the Sr^{2+} DOTA^{4-} , DTPA^{5-} , and ODPA^{2-} complexes in the solid state (\cdots) and in solution ($-$).

procedure in the approximate 1.2–2.6 Å range (see Table S1 for experimental details) for both Eu^{2+} and Sr^{2+} . The FTs were not corrected for a photoelectron phase shift, as all peaks originate from different contributions with different photoelectron phase shifts. Therefore, the peak positions in Figures 3 and 4, as well as the back FT windows (Table S1), differ by about 0.5 Å from the true values obtained during the EXAFS fitting procedure.

The first-shell EXAFS spectra were fitted using standard harmonic two- or three-shell models²⁹ in which the distribution

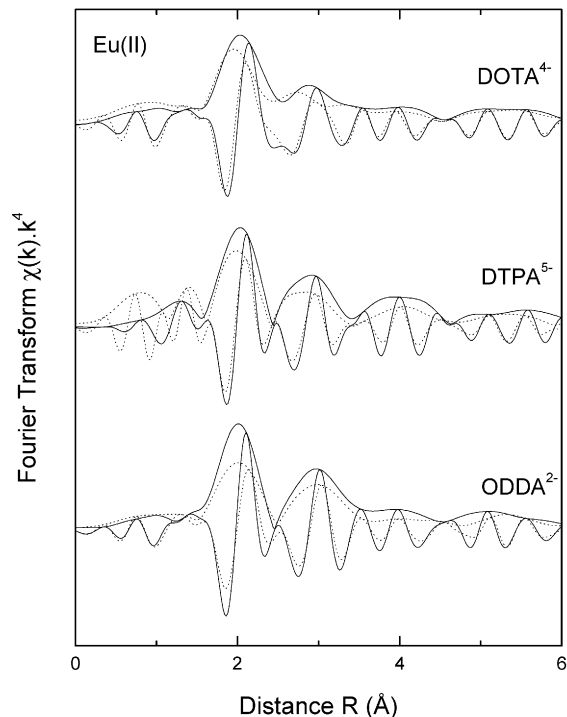


Figure 3. Fourier transforms (modulus and imaginary parts) of the experimental XAFS $\chi(k)k^4$ spectra of the Eu^{2+} DOTA^{4-} , DTPA^{5-} , and ODPA^{2-} complexes in the solid state (\cdots) and in solution ($-$).

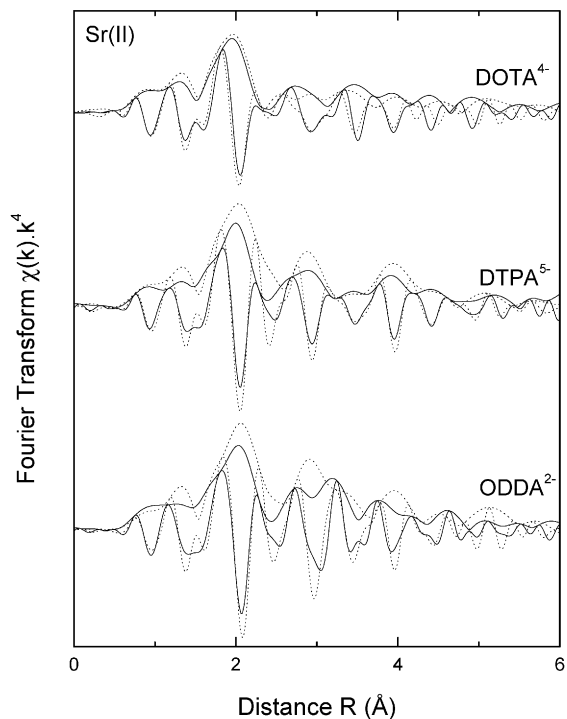


Figure 4. Fourier transforms (modulus and imaginary parts) of the experimental XAFS $\chi(k)k^4$ spectra of the Sr^{2+} DOTA^{4-} , DTPA^{5-} , and ODPA^{2-} complexes in the solid state (\cdots) and in solution ($-$).

of distances (RDF) is taken into account by a superposition of two or three Gaussian distributions:

$$\chi(k) = \sum_{i=1}^3 \frac{N_i}{k C_{1,i}^2} f(\pi, k) \exp\left(-\frac{2C_{1,i}}{\lambda(k)}\right) \exp(-2C_{2,i}k^2) \sin(2kC_{1,i} + \phi(\pi, k)) \quad (1)$$

N_i is the number of atoms in the i th scatterers' subshell; $C_{2,i} = \sigma^2$ is the subshell Debye–Waller (DW) factor, and $C_{1,i}$ is closely related to R_i , the interatomic distance averaged over the atoms composing the subshell.³⁰ $\lambda(k) = k/\Gamma$ is an adjustable function that models the low- k damping factors. As described previously,^{8,28} the Γ parameter was allowed to vary during the fitting procedure for fine adjustment between theoretical calculations and experimental data. This parameter also allows for the compensation of the FT boundary effects and was found within the classical range of 0 to 0.1.

Phases and Amplitudes. The Eu²⁺ and Sr²⁺ XAFS data were analyzed using only phases $\phi(\pi, k)$ and amplitudes $f(\pi, k)$ calculated theoretically using the FEFF6 code.¹³

To mimic the possible environment of the complexed Eu²⁺ and Sr²⁺ ions in solution, theoretical backscattering phases and amplitudes were calculated up to 4 Å for clusters on the basis of the [Sr(DOTA)(H₂O)][C(NH₂)₃]₂, [Sr(DTPA)(H₂O)][C(NH₂)₃]₃, and Sr(ODDA) crystal structures for the Sr²⁺ complexes and on the basis of the [Sr(DOTA)(H₂O)][C(NH₂)₃]₂, [Sr(DTPA)(H₂O)][C(NH₂)₃]₃, [Eu(DTPA)(H₂O)][C(NH₂)₃]₃, and Sr(ODDA) crystal structures for the Eu²⁺ complexes.

In [Sr(DOTA)(H₂O)][C(NH₂)₃]₂ (Figure 5),¹¹ the Sr²⁺ ion is nine-coordinated in a capped-square antiprism geometry formed by four carboxylate oxygen atoms at a distance M–O_{Ac} of 2.548 Å, four nitrogen atoms at a distance M–N of 2.731 Å, and one capping innersphere water molecule at a distance M–O_w of 2.85 Å. These three characteristic distances lead to three different contributions in the EXAFS spectrum that can theoretically be fitted simultaneously.

In the quasi-isostructural [Sr(DTPA)(H₂O)][C(NH₂)₃]₃ (Figure 5) and [Eu(DTPA)(H₂O)][C(NH₂)₃]₃ complexes,¹⁰ the metal ion is nine-coordinated in a distorted capped-square antiprism geometry formed by five carboxylate oxygen atoms at average distances M–O_{Ac} of 2.565 (2.556–2.589) and 2.574 (2.562–2.600) Å, one capping innersphere water molecule at distances M–O_w of 2.619 and 2.623 Å, and three nitrogen atoms at average distances M–N of 2.821 (2.769–2.910) and 2.808 (2.760–2.889) Å, respectively. Again, three characteristic sets of distances can be distinguished, leading to three different contributions in the EXAFS spectrum.

In the Sr(ODDA) solid compound (Figure 5),¹⁰ the metal ion is nine-coordinated, also in a distorted capped-square antiprism geometry, formed by two carboxylate oxygen atoms at 2.527 and 2.593 Å, one extramolecular carboxylate oxygen atom at 2.544 Å coming from a neighboring complex, four ring-oxygen atoms at an average distance M–O_{oxa} of 2.653 (2.626–2.702) Å, and two nitrogen atoms at an average distance M–N of 2.769 (2.762–2.776) Å. Because the two intramolecular, as well as the extramolecular, carboxylate oxygen atoms are located at very similar distances from the metal ion, their contributions cannot be distinguished. As a consequence, these atoms were fitted as a single contribution in the solid compound with an average distance of 2.555 Å. Finally, three characteristic sets of distances can once more be distinguished, corresponding to three different contributions in the EXAFS spectrum.

In each case, the first shell of scatterers can consequently be decomposed in three characteristic subshells, which can theoretically be fitted separately in the EXAFS spectrum. To allow for comparisons between the structural parameters fitted for the different compounds, the calculated backscattering phases and amplitudes were compared for similarity, within the precision limits, for similar atoms at similar distances in the different computed clusters.

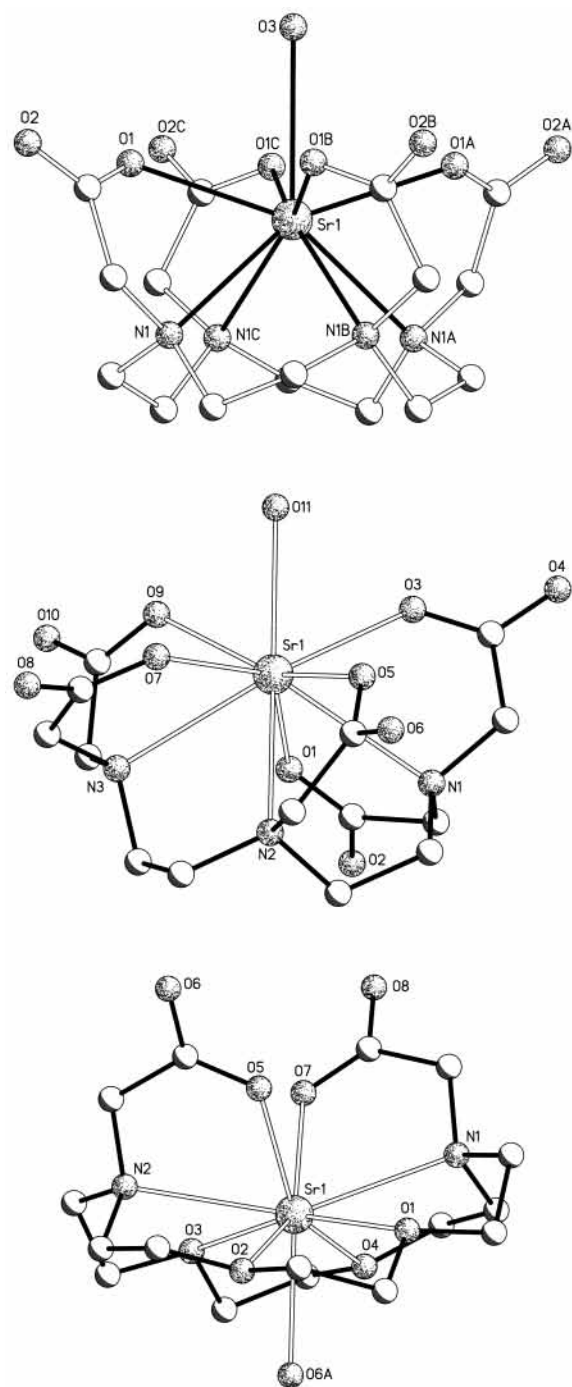


Figure 5. Ball-and-stick representation of the [Sr(DOTA)(H₂O)][C(NH₂)₃]₂, [Sr(DTPA)(H₂O)][C(NH₂)₃]₃, and Sr(ODDA) coordination polyhedra (from top to bottom).

Eu³⁺ Contamination. The low-energy part of the XAFS spectrum is called XANES and is very sensitive to both the valence and coordination polyhedron around the absorbing atom.³¹ Figure 6 presents the Eu L₃-edge XANES spectra of the [Eu(DOTA)(H₂O)]²⁻ complex in the solid state and in solution (see Figure S1 in Supporting Information for the DTPA⁵⁻ and ODDA²⁻ complexes). The spectra consist of a dominant white-line (WL) resonance (normalized amplitude 2.8–3.2 at 6974 eV) corresponding to the transition from the 2p_{3/2} level to the unoccupied 5d states, followed by important multiple-scattering contributions. In aqueous solution, the Eu²⁺ and Eu³⁺ valence states were easily distinguished because of the different threshold energies of their WLs ($\Delta E_0 \approx 8$ eV), and amounts of Eu³⁺ smaller than 1% could be detected by

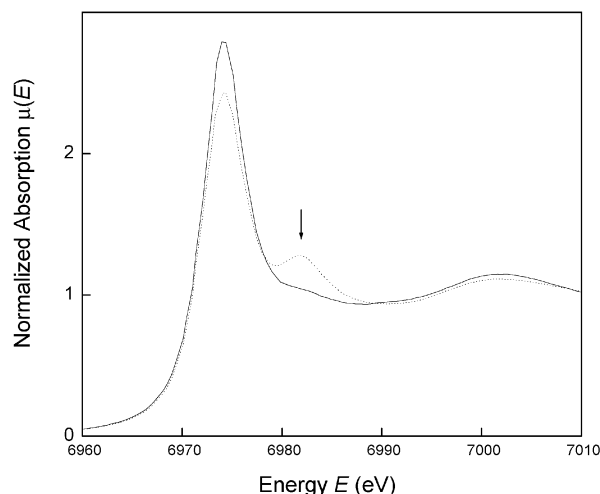


Figure 6. Eu L_3 -edge XANES spectra of the $[\text{Eu}(\text{DOTA})(\text{H}_2\text{O})]^{2-}$ complex in the solid state (\cdots) and in solution ($-$). The hump (see arrow) is due to Eu^{3+} contamination in the solid state.

XANES.⁸ The Eu^{2+} DOTA,⁴⁻ DTPA⁵⁻, and ODDA²⁻ complexes with redox potentials of -1.18 , -1.35 , and -0.82 V ($E_{1/2}$ vs Ag/AgCl), respectively, are expected to be even more reactive toward oxidation than the aqua ion (-0.63 V).

Whereas the Eu^{2+} solution samples are practically Eu^{3+} -free, completely pure Eu^{2+} solid samples could not be obtained. From the XANES analysis (Figures 6 and S1), we estimated the Eu^{3+} contamination to be up to 10% in the case of the $[\text{Eu}(\text{DOTA})(\text{H}_2\text{O})][\text{C}(\text{NH}_2)_3]_2$ complex (6% for $[\text{Eu}(\text{DTPA})(\text{H}_2\text{O})][\text{C}(\text{NH}_2)_3]_3$ and 4% for $\text{Eu}(\text{ODDA})$). The rough EXAFS spectrum of the $[\text{Eu}(\text{DOTA})(\text{H}_2\text{O})][\text{C}(\text{NH}_2)_3]_2$ complex was fitted to evaluate the uncertainties due to Eu^{3+} contamination on the fitted structural parameters. The distances obtained were quite reasonable, but the DW factors were far too large (0.019, 0.018, and 0.013 \AA^2 for M–O_{Ac}, M–N, and M–O_w, respectively) essentially because of the error introduced by the Eu^{3+} atomlike contribution μ_o ^{27,32} in the normalization process. Moreover, for Eu^{2+} poly(amino carboxylate), as for other Eu^{2+} compounds,⁸ the experimental XAFS spectra $\chi(E)$ of the Eu^{2+} and Eu^{3+} complexes show destructive interference due to their different E_0 energies. Since the Eu^{3+} EXAFS spectrum is about twice as high as that of Eu^{2+} , even small amounts of Eu^{3+} in solution can interfere with the analysis of Eu^{2+} XAFS spectra and could lead to a misinterpretation of the data.

To correct the XAFS spectra from the Eu^{3+} contamination, experimental XAFS spectra of the Eu^{3+} DOTA⁴⁻, DTPA⁵⁻, and ODDA²⁻ solid complexes were measured under identical conditions to those for the Eu^{2+} and Sr^{2+} solid compounds. The spectra were corrected for the background contribution μ_b ^{27,32} before the corresponding Eu^{3+} complex contributions were subtracted from the contaminated Eu^{2+} spectra. The corrected spectra were then analyzed as described in the Data Analysis section.

Multielectron Transition Effect. As in the case of the aqua ion⁸ and in the case of the free Eu^{2+} ion in nonaqueous solvents,²⁸ a sharp contribution due to a 2p4d double-electron transition (indicated by arrows in Figure 1) is observed around 6.2 \AA^{-1} in the EXAFS spectrum of the Eu^{2+} complexes with DOTA,⁴⁻ DTPA⁵⁻, and ODDA²⁻ ligands. Such an anomalous contribution is not distinctively visible in the EXAFS spectrum of the supposedly isostructural Sr^{2+} complexes (see arrows in Figure 2) whereas a sharp contribution due to the simultaneous excitation of 1s3d electrons was clearly observed around 6.4 \AA^{-1} for Sr^{2+} in aqueous and nonaqueous solutions. The presence

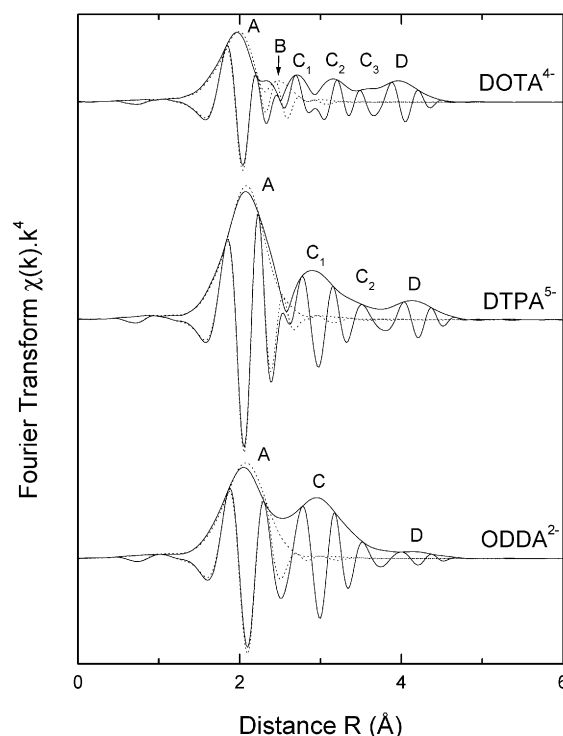


Figure 7. Fourier transforms (modulus and imaginary parts) of the theoretical XAFS $\chi(k)k^4$ spectra of the Sr^{2+} DOTA⁴⁻, DTPA⁵⁻, and ODDA²⁻ complexes ($-$) with their respective first shell of scatterers' contributions (\cdots) based on crystallographic coordinates.

of a structural peak in the EXAFS spectrum of the Sr^{2+} poly(amino carboxylates) could, for instance, mask such a low-intensity contribution.

Finally, even if these multielectron transition (MET) effects slightly distort the base of the first peak at small distances,^{8,28} the use of the 2001 EDA software package²⁷ combined with the use of the k^3 and k^4 compensation factors prevents any additional MET removal after the Fourier filtering process.

Results

In the EXAFS study of the Eu^{2+} and Sr^{2+} aqua ions in aqueous solution,⁸ only one type of scatterer was present. As a consequence, the single scattering from the first shell of scatterers was analyzed quantitatively without difficulty. In the dimethyl sulfoxide (DMSO) solution, the sulfur atoms of the coordinated solvent molecules formed a second shell of scatterers, leading to additional single-scattering (SS) and multiple-scattering (MS) contributions.²⁸ In the poly(amino carboxylate) complexes, different types of atoms constitute the first shell of scatterers. Additionally, the rigidity of the complex cages leads to significant SS and MS contributions of the outer shells of scatterers, further complicating the experimental XAFS spectrum.^{12,26}

Theoretical calculations based on the crystallographic structures of the $[\text{Sr}(\text{DOTA})(\text{H}_2\text{O})][\text{C}(\text{NH}_2)_3]_2$, $[\text{Sr}(\text{DTPA})(\text{H}_2\text{O})][\text{C}(\text{NH}_2)_3]_3$, and $\text{Sr}(\text{ODDA})$ complexes using the FEFF6 code¹³ were performed to understand the Eu^{2+} and Sr^{2+} experimental XAFS spectra. Figure 7 shows that for both DTPA⁵⁻ and ODDA²⁻ complexes the first shell of scatterers is well defined and well separated from the outer contributions. The calculated spectrum is more complicated for the DOTA⁴⁻ complex; the first sphere contribution (Figure 7) does not consist of only one dominant peak but of one major peak A (half as intense as that for the DTPA⁵⁻ complex) followed by a smaller peak B due to

destructive interference between the M–O_{Ac}, M–N, and M–O_w contributions. The calculations also show that peak B cannot be singled out precisely from the experimental spectrum, leading to uncertainties in the determination of the M–O_w distance.

For the three DOTA⁴⁻, DTPA⁵⁻, and ODDA²⁻ complexes, peak A corresponds to the first peak of scatterers, as already described in the Experimental Section. The following peaks labeled C correspond to the carbon atoms of the carboxylate function of the acetate arms and of the ethylenic groups, but the peaks cannot be assigned individually (with and without taking into account MS contributions). Finally, peak D corresponds to the uncoordinated carboxylate oxygen atoms. Calculations also show that a number of low-amplitude MS contributions that could give significant contributions to the C and D peaks occur in the poly(amino carboxylate) EXAFS spectra starting around 3.5 Å.

The general patterns predicted by the theoretical calculations are effectively observed on the experimental FT spectra, with a somewhat lower resolution on the Eu²⁺ L₃-edges (Figure 3) than on the Sr²⁺ K-edges (Figure 4). Deviations from the calculated spectrum do occur, as the DW factors characterizing the outer spheres of scatterers and the MS contributions could not be predicted accurately and are subjected to thermal vibrations. In all cases, the FT imaginary part shows more specifically that the structure observed in the solid state is globally retained in solution. That peak D is so intense in the experimental spectrum is quite remarkable, as it corresponds to atoms located quite far from the metal ion. In the solid-state structures of [Sr(DTPA)(H₂O)][C(NH₂)₃]₃, [Eu(DTPA)(H₂O)][C(NH₂)₃]₃, and Sr(ODDA), noncoordinated crystallized water molecules are located at a similar distance (but were omitted from the theoretical calculations and Figure 7). In the structures of [Sr(DOTA)(H₂O)][C(NH₂)₃]₂, [Sr(DTPA)(H₂O)][C(NH₂)₃]₃, and [Eu(DTPA)(H₂O)][C(NH₂)₃]₃, nitrogen atoms from the guanidinium counterions (again omitted from the theoretical calculations and Figure 7) are also found at the same distance. This explains the high intensity of the D peak in the solid state. The experimental spectra moreover suggest that these spaces are accessible in solution to second-sphere water molecules.

As discussed, the contributions of the outer shells of scatterers are numerous and cannot be easily gathered into coherent and distinct subgroups. With two fitting parameters per contribution (i.e., distance and DW factor), the maximum number of fitting parameters would be easily reached, leading to strongly enhanced correlation among parameters. Thus, the first shell of scatterers was singled out and fitted separately.

The number of fitting parameters is limited by the number of independent data points $N_{\text{ind}} \cong 2\Delta k\Delta R/\pi + 2$, where Δk and ΔR are the k and the R ranges used.³³ For the study of the first shell of scatterers of the poly(amino carboxylates), three-contribution models (as described in the Experimental Section) were considered. Each contribution was characterized by two fitting parameters (i.e., distance and DW factor (N_{ind} , Δk , and ΔR values are detailed in Table S1)). In addition, two contribution models were considered to check the physical significance of the proposed models.

In the solid state, the coordinated water molecule of the [Sr(DOTA)(H₂O)][C(NH₂)₃]₂ complex seems to be loosely bound to the metal ion. The [M^{II}(DOTA)(H₂O)]²⁻ complexes (M^{II} = Eu²⁺, Sr²⁺) in solution with 4 × O_{Ac} and 4 × N subshell models were analyzed for the presence of an innersphere water molecule. Similarly to the [Gd(DOTA)(H₂O)]⁻ and [Gd(DTPA)(H₂O)]²⁻ complexes,¹² a two-subshells model including one innershell water molecule was sufficient to fit the EXAFS

spectra of the [M^{II}(DOTA)(H₂O)]²⁻ complexes (M^{II} = Eu²⁺, Sr²⁺). For the DOTA⁴⁻ complexes, however, the use of 5 × O_{Ac} and 4 × N subshell models led to unrealistic DW factor and distance values, confirming that the innersphere water molecule has to be fitted separately. The presence of the water molecule was then tested at different distances from the metal ion, and the only feasible results were obtained with M–O_w > M–N. Table 1 shows that the fitted M–O_w distances for the DOTA⁴⁻ complexes are slightly larger than the crystallographic distances. The fitted distance that is excessively large is due to partial overlap between the first-shell B peak and the outer shells' contribution (Figure 7), which prevents the first shell of scatterers from being precisely singled out. For the same reasons, the corresponding DW factor values are smaller than their true values, which cannot be measured from experimental data. Nevertheless, fitting gave very close distances and DW factor values for both Eu²⁺ and Sr²⁺ complexes in both the solid state and in solution, indicating the consistency of the analyses. This consistency allows the M–O_w distance in the [M^{II}(DOTA)(H₂O)]²⁻ complexes (M^{II} = Eu²⁺, Sr²⁺) to be estimated as 2.85(5) Å. The reliability of the M–O_w distance in the [M^{II}(DTPA)(H₂O)]³⁻ complexes was similarly checked. Estimated from the EXAFS fitting results as 2.62(5) Å, the M–O_w distance is slightly increased in solution, but the overall structure remains the same, albeit slightly swelled.

The ¹⁷O NMR chemical shift measurements on the Eu(ODDA) complex¹⁰ show that the extramolecular carboxylate oxygen atom coordinating the metal ion in the solid state is replaced by a water molecule in aqueous solution. The presence of this water molecule was verified using XAFS data in solution with 2 × O_{Ac}, 4 × O_{oxa}, and 2 × N subshell models. The distances and DW factors of the (2 × O_{Ac} + 1 × O_{ax}) subshell are very similar in the solid state and in solution, indicating that even if the water molecule cannot be located precisely it clearly stands inside the first subshell. Consequently, the M–O_{ax} distance is virtually unchanged in the solid state and in solution. A swelling tendency was observed within the DTPA⁵⁻ complexes, whereas the ODDA²⁻ complexes seem to undergo more subtle changes: In the solid state, one carboxylate group bridges two Sr²⁺ ions (Figure 5), leading to a slightly longer M–O_{Ac} distance than observed for the other carboxylate arm.¹⁰ In solution, the two acetate arms are equivalent, leading to a slight shortening of the M–O_{Ac} average distance and consequently to a subtle reorganization of the overall structure. Therefore, in the [M^{II}(ODDA)(H₂O)] complexes, the M–O_w distance in aqueous solution can be estimated from the EXAFS fitting results to be 2.54(5) Å.

Table 1 summarizes the characteristic distances and DW factors obtained for the metal ion first shell of scatterers in the different complexes. In multishell systems, systematic errors are predominant and were accounted for in the table, together with statistical errors. Statistical errors (Table S1) were estimated by extensive fitting of the experimental first-shell XAFS spectra, and outside the fitting intervals indicated, the fitting errors were at least doubled. The distances obtained for the first shell of scatterers (Table 1) in the Eu²⁺ and Sr²⁺ complexes in the solid state and in solution are in good agreement with the distances observed by XRD with respect to the experimental errors. Therefore, the overall structure of the different complexes is globally conserved from the solid state to the solution and from the Sr²⁺ ion to the Eu²⁺ ion.

The XAFS experimental spectra after the first-shell filtering of the [M^{II}(DOTA)(H₂O)]²⁻, [M^{II}(DTPA)(H₂O)]³⁻, and M^{II}(ODDA) complexes (M^{II} = Eu²⁺, Sr²⁺) in the solid state

TABLE 1: First Shell of Scatterers Structural Data Obtained from XAFS Analysis with Theoretical Phase and Amplitude at Room Temperature and Comparison with X-ray Diffraction Data^a

DOTA ⁴⁻ Ligand						
sample	4 × M–O _{Ac}		4 × M–N		1 × M–O _w	
	<i>R</i> (Å)	<i>C</i> ₂ (Å ²)	<i>R</i> (Å)	<i>C</i> ₂ (Å ²)	<i>R</i> (Å)	<i>C</i> ₂ (Å ²)
[Eu(DOTA)(H ₂ O)][C(NH ₂) ₃] ₂	2.57(2)	0.011(1)	2.78(2)	0.008(1)	2.94(2)	0.004(1)
[Eu(DOTA)(H ₂ O)] ²⁻ 0.2 M	2.59(2)	0.011(1)	2.79(2)	0.009(2)	2.94(3)	0.006(2)
[Sr(DOTA)(H ₂ O)][C(NH ₂) ₃] ₂ ^b	2.548		2.731		2.85	
[Sr(DOTA)(H ₂ O)][C(NH ₂) ₃] ₂	2.56(2)	0.009(1)	2.78(2)	0.008(1)	2.94(3)	0.004(1)
[Sr(DOTA)(H ₂ O)] ²⁻ 0.2 M	2.58(2)	0.009(1)	2.77(2)	0.007(1)	2.92(3)	0.004(1)
DTPA ⁵⁻ Ligand						
sample	5 × M–O _{Ac}		1 × M–O _w		3 × M–N	
	<i>R</i> (Å)	<i>C</i> ₂ (Å ²)	<i>R</i> (Å)	<i>C</i> ₂ (Å ²)	<i>R</i> (Å)	<i>C</i> ₂ (Å ²)
[Eu(DTPA)(H ₂ O)][C(NH ₂) ₃] ₃ ^b	2.574		2.623		2.808	
[Eu(DTPA)(H ₂ O)][C(NH ₂) ₃] ₃	2.56(2)	0.011(2)	2.58(3)	0.009(3)	2.77(2)	0.008(3)
[Eu(DTPA)(H ₂ O)] ³⁻ 0.1 M	2.58(2)	0.012(2)	2.62(3)	0.008(2)	2.80(2)	0.010(2)
[Sr(DTPA)(H ₂ O)][C(NH ₂) ₃] ₃ ^b	2.565		2.619		2.821	
[Sr(DTPA)(H ₂ O)][C(NH ₂) ₃] ₃	2.55(2)	0.011(1)	2.58(2)	0.005(1)	2.76(2)	0.014(1)
[Sr(DTPA)(H ₂ O)] ³⁻ 0.1 M	2.56(2)	0.012(1)	2.64(4)	0.009(2)	2.79(3)	0.013(2)
ODDA ²⁻ Ligand						
sample	2 × M–O _{Ac} + 1 × M–O _{ax} ^c		4 × M–O _{oxa}		2 × M–N	
	<i>R</i> (Å)	<i>C</i> ₂ (Å ²)	<i>R</i> (Å)	<i>C</i> ₂ (Å ²)	<i>R</i> (Å)	<i>C</i> ₂ (Å ²)
[Eu(ODDA)]	2.55(2)	0.010(1)	2.70(2)	0.010(1)	2.83(2)	0.009(1)
[Eu(ODDA)(H ₂ O)] 0.1 M	2.54(2)	0.007(1)	2.66(2)	0.010(1)	2.90(3)	0.009(1)
[Sr(ODDA)] ^b	2.555		2.653		2.769	
[Sr(ODDA)]	2.52(2)	0.010(1)	2.62(2)	0.006(1)	2.80(2)	0.007(1)
[Sr(ODDA)(H ₂ O)] 0.1 M	2.53(2)	0.012(1)	2.63(2)	0.010(1)	2.84(3)	0.012(1)

^a For each subshell of scatterers at an average distance *R* from the metal, *C*₂ = *σ*² is the DW factor. Estimated errors (both statistical and systematic) are presented within parentheses. ^b Average crystallographic data (see text). ^c O_{ax} comes from a carboxylate group in the solid state and from a coordinated water molecule in solution.

and in aqueous solution are presented in Figure S1 together with the fitted spectra with theoretical phases and amplitudes. The low residual intensities (dotted lines) demonstrate the quality of these fits.

Discussion

Structural Comparison between Eu²⁺ and Sr²⁺ Complexes. Our EXAFS study of the Eu²⁺ and Sr²⁺ solvation in aqueous and nonaqueous solvents²⁸ showed that the Eu²⁺ and Sr²⁺ ionic radii should be considered to be equivalent for the same coordination number. Furthermore, Eu²⁺ seems to be a slightly softer ion than Sr²⁺, leading to shorter M–N and longer M–O bonds and to smaller coordination numbers in O-coordinating solvents. For instance, in aqueous solution, the [Eu(H₂O)₇]²⁺ and [Sr(H₂O)₈]²⁺ ions feature a 1-unit solvation number difference as well as a 0.016 Å M–O bond length difference. These differences are directly visible (differences in amplitude and in periodicity) when comparing the corresponding crude experimental EXAFS spectra (Figure 8a).

Polydentate ligands are usually more structuring than monodentate ligands and frequently dictate the coordination geometry around the metal center. The poly(amino carboxylate) ligands can therefore force the Eu²⁺ and Sr²⁺ ions into very close coordination polyhedrons that are hardly distinguishable in their crude experimental EXAFS spectra (Figure 8b). In the [M^{II}(DOTA)(H₂O)]²⁻, [M^{II}(DTPA)(H₂O)]³⁻, and [M^{II}(ODDA)(H₂O)] (M^{II} = Eu²⁺ or Sr²⁺) complexes, the first shell of scatterers can be split into three characteristic subshells that can be fitted separately in the EXAFS spectrum (see Experimental Section). Because of the large number of contributions needed for the analysis of the first shell of scatterers of the poly(amino carboxylate) complexes (Table 1), the fitting errors are 1 order

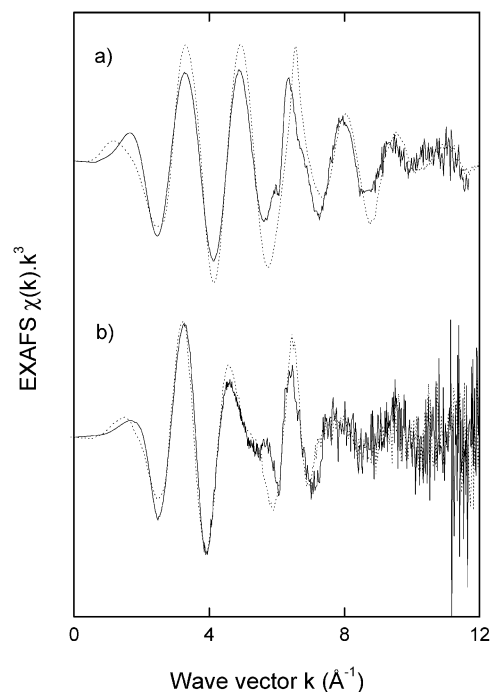


Figure 8. Correction-free experimental $\chi(k)k^3$ XAFS spectra of (a) 0.15 M [Eu(H₂O)₇]²⁺ (—) and 0.14 M [Sr(H₂O)₈]²⁺ (··) ions in aqueous solution and (b) 0.1 M [Eu(ODDA)(H₂O)] (—) and [Sr(ODDA)(H₂O)] (··) complexes in aqueous solution. The phases of the Eu²⁺ spectra were inverted for clarity.

of magnitude higher than in the case of the solvates. Hence, within the XAFS fitting errors, the distances obtained for the first shell of scatterers of both Eu²⁺ and Sr²⁺ ions (Table 1) in the DOTA⁴⁻, DTPA⁵⁻, and ODDA²⁻ complexes are very

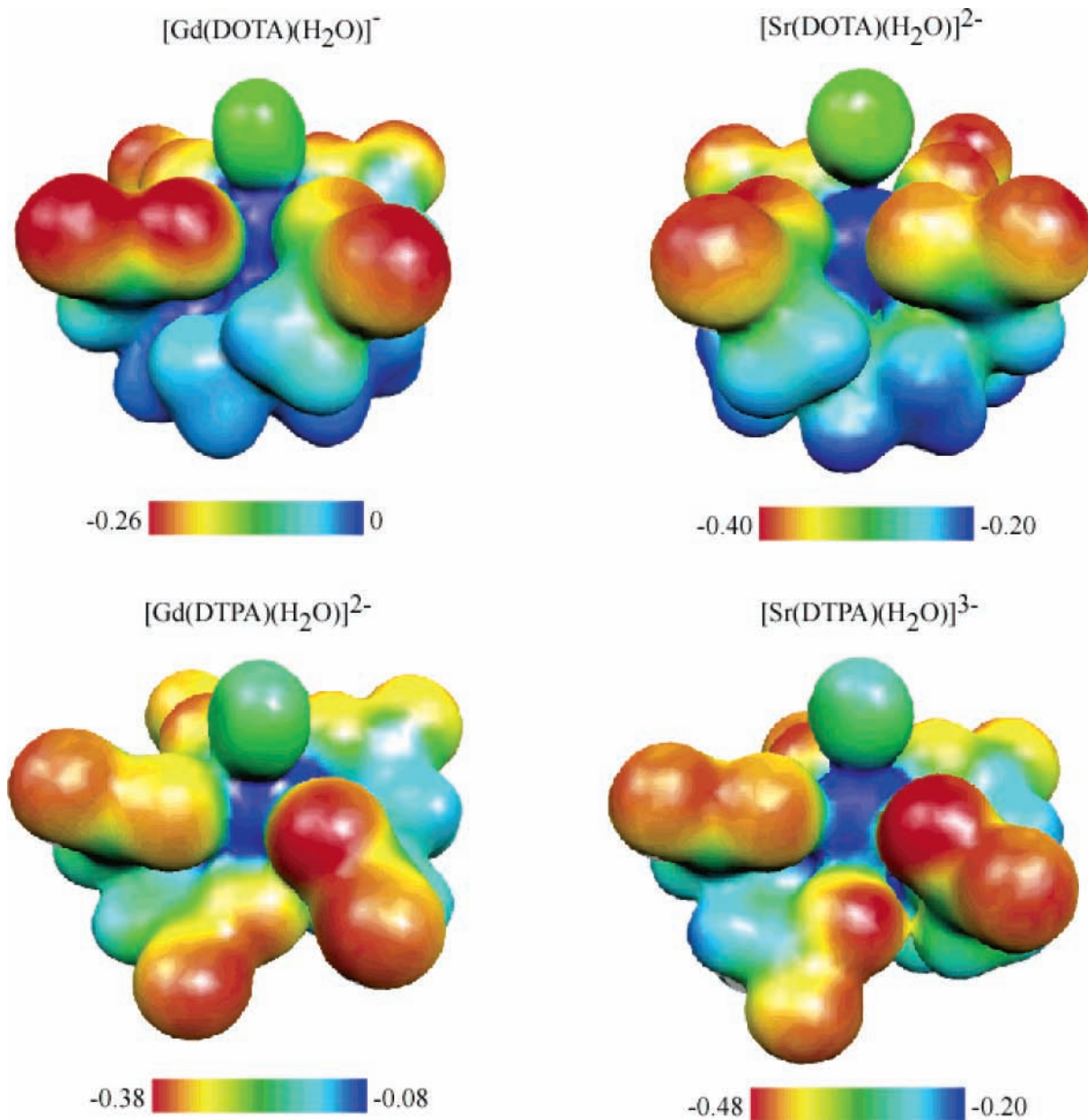
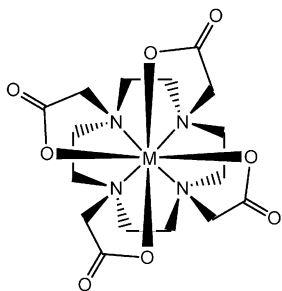
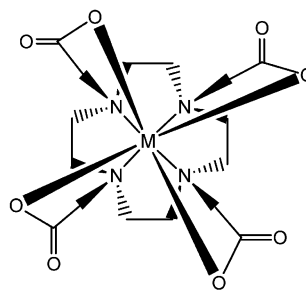


Figure 9. Electrostatic potential (au) plotted on the electronic density maps of the Sr²⁺ and Gd³⁺ DOTA⁴⁻ and DTPA⁵⁻ complexes. Only the oxygen atom of the water molecule has been represented.

SCHEME 2: Schematic Structure of the Two Diastereoisomers of the DOTA⁴⁻ Complexes^a



Square Antiprism (SA or M) Isomer

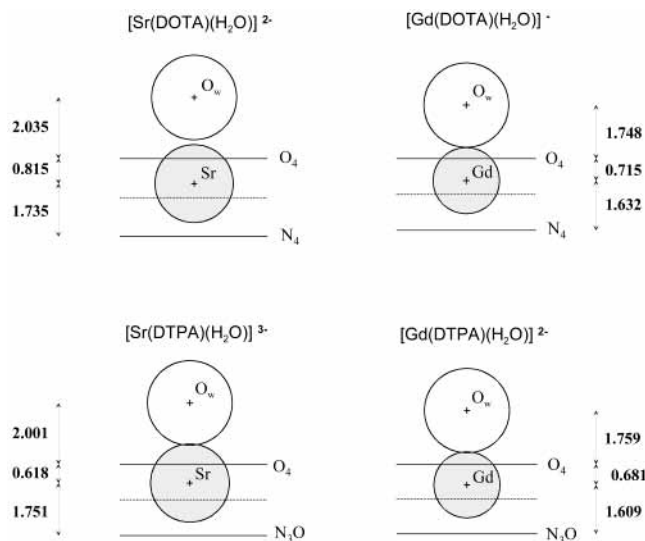


Twisted Square Antiprism (TSA or m) Isomer

^a Coordinated water molecule has been omitted for clarity.

similar for the same subshell in both the solid state and in solution and are in good agreement with the distances observed by X-ray diffraction (XRD). This latter method gives access to more precise distances for the solid-state complexes and indicates that the Eu–O bond lengths are 0.015 Å longer in

the XRD structures of isomorphous acetates^{34,35} than in their Sr²⁺ homologues. In the [Eu(DTPA)(H₂O)][C(NH₂)₃]₃ and [Sr(DTPA)(H₂O)][C(NH₂)₃]₃ XRD structures,¹⁰ the M–N bond lengths are shorter on average by 0.013 Å, and M–O bond lengths are 0.011 Å longer for the Eu²⁺ than for the Sr²⁺ ion.

SCHEME 3: Scaled Schematic Description of the Metal Position in the Sr^{2+} and Gd^{3+} DOTA $^{4-}$ and DTPA $^{5-}$ Complexes^a


^a Basal and apical planes are represented by a solid line, and the midplane is represented by a dotted line. The radii used to represent the Sr^{2+} and Gd^{3+} metal ions and the coordinated water oxygen atom correspond to the ionic radii determined by Shannon² for nine coordination (1.31, 1.107, and 1.40 Å, respectively). Distances between the basal plane, the metal ion, the apical plane, and the coordinated water oxygen atom are given in angstroms.

Within the XAFS fitting errors, the distances obtained for the first shell of scatterers (Table 1) of the DOTA $^{4-}$ and DTPA $^{5-}$ complexes in both the solid state and in solution are very similar for both the Eu^{2+} and Sr^{2+} ions. In the ODDA $^{2-}$ complexes, the overall complex structure is rearranged slightly from the solid state to the solution (see Results section), with the bridging carboxylate group being replaced by a coordinating water molecule. In summary, the overall structure of these poly(amino carboxylate) complexes is globally conserved from the solid state to solution. Thus, the structure of the Eu^{2+} and Sr^{2+} poly(amino carboxylate) complexes in solution can be discussed on the basis of the XRD structure of the isostructural solid-state Sr^{2+} complexes.

Solution and Solid-State Structures of the M^{II} ($\text{M}^{\text{II}} = \text{Eu}^{2+}$, Sr^{2+}) and Gd^{3+} Poly(amino carboxylates). In the nine-coordinated DOTA $^{4-}$ complexes, the metal ion coordination polyhedron consists of capped-square antiprisms. The two square planes are formed by the four ring nitrogen atoms (N_4 basal plane) and the four coordinated carboxylate oxygen atoms (O_4 apical plane). The water molecule caps the apical plane. In the DTPA $^{5-}$ complexes, the metal ion is coordinated in distorted capped-square antiprisms. The three nitrogen atoms and a terminal carboxylate oxygen atom form the basal plane (N_3O), and the four other coordinated carboxylate oxygen atoms form the apical plane (O_4), where the water molecule is coordinated. In all of the Gd^{3+} DOTA $^{4-}$ and DTPA $^{5-}$ derivatives, for which XRD structures are known,^{20,21,36–38} both Gd^{3+} ion positions inside the ligand cavity (with respect to the basal and apical planes) and the $\text{Gd}-\text{O}_w$ distances (from 2.43 to 2.46 Å) are very close.

In the $[\text{M}^{\text{II}}(\text{DOTA})(\text{H}_2\text{O})]^{2-}$ ($\text{M}^{\text{II}} = \text{Eu}^{2+}$, Sr^{2+}) complexes studied here, the DOTA $^{4-}$ ligand is structurally reorganized around the metal ion to accommodate these larger ions (Figure 9). All of the solid-state X-ray structures of Gd^{3+} DOTA $^{4-}$ derivatives exhibit a square antiprismatic (SA) conformation (Scheme 2) characterized by a twist angle between the O_4 and

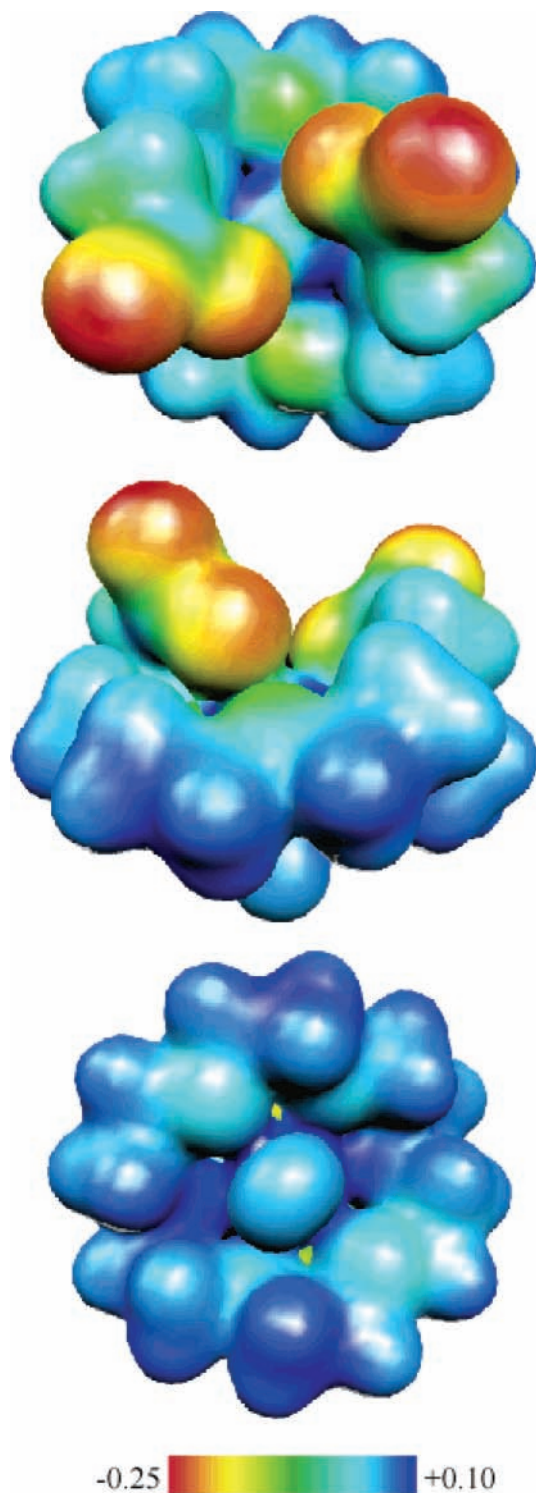


Figure 10. Electrostatic potential (au) plotted on the electronic density map of the $[\text{Sr}(\text{ODDA})(\text{H}_2\text{O})]$ complex (from top to bottom: carboxylate coordinating site, side view, and water-coordinating site). Only the oxygen atom of the water molecule has been represented.

N_4 planes close to 39° (39.3° in the $[\text{Gd}(\text{DOTA})(\text{H}_2\text{O})]^{-}$ complex). In the $[\text{M}^{\text{II}}(\text{DOTA})(\text{H}_2\text{O})]^{2-}$ complexes, the twist angle is -24.8° , characteristic of a twisted-square antiprismatic (TSA) conformation (Scheme 2).^{20,39–41} The change of conformation of the carboxylate arms leads to an increase in the cavity size of 0.2 Å (an increase in the distance between the basal and apical planes; see Scheme 3). Consequently, despite their larger ionic radii, the Eu^{2+} and Sr^{2+} ions are located slightly deeper inside the DOTA $^{4-}$ cavity than the Gd^{3+} ion (the position of

TABLE 2: Selected Constants Characterizing the Solution Structure and Water Exchange of the Eu²⁺ and Gd³⁺ Poly(amino carboxylate) Complexes^a

complex	[Eu(H ₂ O) ₇] ²⁺	[Eu(DOTA)(H ₂ O)] ²⁻	[Eu(DTPA)(H ₂ O)] ³⁻	[Eu(ODDA)(H ₂ O)]	[Gd(H ₂ O) ₈] ³⁺	[Gd(DOTA)(H ₂ O)] ⁻	[Gd(DTPA)(H ₂ O)] ²⁻
M–O _w (Å)	2.584(5) ^b	2.85(5) ^{c,d}	2.62(5) ^d	2.54(5) ^d	2.41(1) ^g	2.46(5) ^g	2.47(5) ^g
ΔV [‡] (cm ³ mol ⁻¹)	-11.3 ^b	+0.1 ^e	+4.5 ^f	-3.9 ^f	-3.3 ^h	+10.5 ⁱ	+12.5 ⁱ
mechanism	A ^b	I ^e	I _d ^f	I _d ^f	A ^h	D ⁱ	D ⁱ
K _{ex} ²⁹⁸ (s ⁻¹)	5 × 10 ⁹ ^b	2.46 × 10 ⁹ ^e	1.3 × 10 ⁹ ^f	0.43 × 10 ⁹ ^f	0.8 × 10 ⁹ ^h	4.1 × 10 ⁶ ⁱ	3.3 × 10 ⁶ ⁱ

^a M–O_w distances are obtained from XAFS analysis; ΔV[‡] and K_{ex}²⁹⁸ are respectively the activation volume and the rate constant at 25 °C of the water-exchange reaction. ^b Reference 8. ^c X-ray value (see text). ^d This study. ^e Reference 11. ^f Reference 10. ^g Reference 12. ^h Reference 48. ⁱ Reference 46.

the metal ion inside the cavity is characterized by the ratio between the M–O₄ and O₄–N₄ distances to account for the different cavity sizes).

The conformational reorganization occurring from the Gd³⁺ to the [M^{II}(DTPA)(H₂O)]³⁻ complexes is much smaller (Figure 9). The DTPA⁵⁻ ligand has no opportunity to reorganize itself to generate a larger cavity, and the larger Eu²⁺ and Sr²⁺ ions are, on the contrary, shifted from the center of the cavity toward the O₄ plane (Scheme 3). Thus, the Eu²⁺ and Sr²⁺ ions lie about 0.2 Å closer to the O₄ plane in the DTPA⁵⁻ complexes than in the DOTA⁴⁻ complexes.

The M^{II}–O_w distance is more than 0.2 Å longer in the [M^{II}(DOTA)(H₂O)]²⁻ (M^{II} = Eu²⁺ or Sr²⁺) complexes than in the [M^{II}(DTPA)(H₂O)]³⁻ complexes whereas the Gd–O_w distance is approximately the same in the [Gd(DOTA)(H₂O)]⁻ and [Gd(DTPA)(H₂O)]²⁻ complexes.^{20,21} In these latter complexes, the position of the water molecule results from the attraction of the metal cation and from the repulsion of the coordinating carboxylates that define the capping site. In both the [M^{II}(DOTA)(H₂O)]²⁻ and [M^{II}(DTPA)(H₂O)]³⁻ (M^{II} = Eu²⁺ or Sr²⁺) complexes, the water molecule is located at a distance of *R* = 2.0 Å from the O₄ apical plane (Scheme 3). In the [Gd(DOTA)(H₂O)]⁻ and [Gd(DTPA)(H₂O)]²⁻ complexes,^{20,21} this distance *R* is shortened to 1.75–1.76 Å and is practically identical for the two complexes. Among the Gd³⁺ DOTA⁴⁻ and DTPA⁵⁻ derivatives, *R* ranges from 1.71 to 1.76 Å.^{36–38} Therefore, for the same metal ion, *R* appears to be only slightly dependent on the charge and ligand substituents. The repulsive effect of the carboxylate functions is responsible for this *R* distance, but the 0.25 Å shortening observed from the M²⁺ to the Gd³⁺ ions can be explained only by the higher charge density on the trivalent Gd³⁺ ion (higher charge and smaller ionic radius). Thus, the difference in the M^{II}–O_w distance between the [M^{II}(DOTA)(H₂O)]²⁻ and [M^{II}(DTPA)(H₂O)]³⁻ (M^{II} = Eu²⁺ or Sr²⁺) complexes is completely explained by the difference in the M–O₄ distance resulting from the various positions of the metal ion in the ligand cavity. The position of the Gd³⁺ ion inside the complex cavities is very similar in the DOTA⁴⁻ and DTPA⁵⁻ derivatives; therefore, it could be predicted that the 0.2 Å M^{II}–O_w difference also occurs between the M^{II} DOTA⁴⁻ and DTPA⁵⁻ derivatives.

In the solid-state complex Sr(ODDA),¹⁰ the metal ion is coordinated by an extramolecular carboxylate oxygen atom (Figure 5). The ¹⁷O NMR chemical shifts measured on Eu(ODDA) solutions¹⁰ clearly indicate the presence of an innersphere water molecule replacing the extramolecular carboxylate in solution, as confirmed by our XAFS measurements. The innersphere water molecule and the intramolecular carboxylates coordinate the metal ion from opposite sides of the macrocyclic plane (Figure 5). The water molecule coordinating site is far less crowded and less electrostatically constrained in the ODDA²⁻ complexes than in the DOTA⁴⁻ or DTPA⁵⁻ complexes (Figures 9 and 10). It could be speculated that a second water molecule coordinates the metal ion in solution,

but both the XAFS and the ¹⁷O NMR chemical shift measurements¹⁰ show that the Eu(ODDA) complex occurs in aqueous solution as a monohydrated species.

The unique design of the ODDA²⁻ complex makes it hardly comparable with the DOTA⁴⁻ and DTPA⁵⁻ complexes, except for the M–O_w distance. Our XAFS study of the Eu²⁺ and Sr²⁺ aqua ions in aqueous solution⁸ led to M^{II}–O_w distances of 2.584(5) and 2.600(3) Å. In the DTPA⁵⁻ complex, this distance is slightly increased by about 0.04 Å. In the DOTA⁴⁻ complex, this distance increases to 2.85 Å for structural reasons. The M^{II}–O_w distance in the [M^{II}(ODDA)(H₂O)] complexes was estimated in aqueous solution to be low, 2.54(5) Å. In the ODDA²⁻ complexes, the water-coordinating site is very open, and the coordinated water molecule does not suffer any carboxylate electrostatic repulsion. The M^{II}–O_w distances in the [M^{II}(ODDA)(H₂O)] complexes are therefore very close to the ones observed for the [Eu(H₂O)₇]²⁺ and [Sr(H₂O)₈]²⁺ ions (Table 2).

Structural Consequences for the Water Exchange Reaction on Eu²⁺ and Gd³⁺ Poly(amino carboxylates). The DOTA⁴⁻ derivative complexes of the trivalent lanthanide ions occur in aqueous solution as an equilibrium between SA and TSA isomers (also called M and m isomers), the m/M ratio being very low for the smaller ions and very close to 1 for the La³⁺ and Ce³⁺ ions.⁴² It has been shown that the exchange of the coordinated water molecule is much faster in TSA than in SA isomers.^{43,44} The water exchange reaction (both the rate and mechanism) is then greatly influenced by the structure adopted by the complex in solution. The water exchange rate constant is strongly dependent on the M–O_w bond properties and can therefore be related to the M–O_w distance. Table 2 presents selected constants characterizing the structure and dynamics of the Eu²⁺ and Gd³⁺ aqua ions and poly(amino carboxylate) complexes in aqueous solution.

In the [Gd(DOTA)(H₂O)]⁻ and [Gd(DTPA)(H₂O)]²⁻ complexes, the entering water molecule can be coordinated only to the site of the leaving water molecule (Figure 9) and cannot participate in the bond-breaking process, leading to limiting dissociative (D) reaction mechanisms and a relatively slow exchange rate compared with that of the [Gd(H₂O)₈]³⁺ ion, which features a limiting associative (A) mechanism (Table 2).^{45,46} In these two complexes, all of the characteristic distances of the Gd³⁺ coordination polyhedron including the Gd–O_w distance are approximately the same (Table 2). The water exchange rates are also similar for the two complexes, with a slight 20% increase from the [Gd(DTPA)(H₂O)]²⁻ to the [Gd(DOTA)(H₂O)]⁻ complex.

The mechanism of the [Gd(DTPA)(H₂O)]²⁻ complex is limiting dissociative (D) whereas the [Eu(DTPA)(H₂O)]³⁻ complex features a dissociative interchange (I_d) mechanism,⁹ where the approach of another water molecule helps the departure of the coordinated water molecule. This difference in mechanism could be explained by the substantially longer M–O_w distances as well as the lower charge density on the

metal ion (lower charge and larger ionic radius), both inducing weaker interactions between the metal center and the coordinated water molecule and a greater ability to break the M–O_w bond. In addition, this weaker interaction is explicitly shown by the difference in electronic density between the metal ion and the water oxygen atom.

In the [Eu(DOTA)(H₂O)]²⁻ complex, the Eu–O_w distance is even longer (Table 2). The water molecule is very loosely coordinated and markedly less bound to the metal center than in the [Eu(DTPA)(H₂O)]³⁻ complex. Once again, the weaker interaction is clearly seen in Figure 9 by the differences in the electronic density between the metal ion and the water oxygen atom. An entering water molecule can participate in the bond-breaking process, leading to an interchange (I) mechanism.¹¹ This shift in mechanism is associated with a large 0.2 Å increase in M–O_w distance and leads, for the Eu²⁺ ion, to an increase in the water exchange rate from the [Eu(DTPA)(H₂O)]³⁻ to the [Eu(DOTA)(H₂O)]²⁻ complex (Table 2) by a factor of 2.

The [Eu(ODDA)(H₂O)] complex features an associative interchange (I_a) water exchange mechanism.¹⁰ In the transition state, the water-coordinating site accommodates a second water molecule, leading to the concerted departure of the previously coordinated molecule. A limiting associative (A) mechanism involving the coordination of a second inner-sphere water molecule prior to the departure of the leaving molecule is barely conceivable, the potential binding site not being large enough to accommodate two water molecules simultaneously (Figure 10 bottom). A dissociative activation mode is highly disfavored because of the very short M–O_w distance (Table 2); therefore, an I_a mechanism is privileged. Note that a progressive change in the water exchange mechanism from D to I_d to I with increasing ionic radius has already been observed in the case of the [Ln(DTPA–BMA)(H₂O)] complexes along the lanthanide series.⁴⁷

Conclusions

This XAFS study establishes the similarity of the Eu²⁺ and Sr²⁺ poly(amino carboxylates) structures in the solid state and in solution. In addition, the overall solid-state structure is conserved in solution. We showed that the DOTA⁴⁻ ligand adopts a twisted-square antiprismatic conformation in aqueous solution to accommodate the large Eu²⁺ and Sr²⁺ ions, leading to a metal ion-to-coordinated water distance in the [M^{II}(DOTA)(H₂O)]²⁻ complexes that is 0.2 Å longer than in the [M^{II}(DTPA)(H₂O)]³⁻ (M^{II} = Eu²⁺, Sr²⁺) complexes. The study of the solid-state structures of the Gd³⁺ DOTA⁴⁻ and DTPA⁵⁻ derivatives shows that this 0.2 Å difference should occur in the M^{II} DOTA⁴⁻ and DTPA⁵⁻ derivatives and that a similar lengthening might even exist between the M^{III} (M^{III} = La³⁺, Ce³⁺) DOTA⁴⁻ and DTPA⁵⁻ derivatives in aqueous solution.

The different structures adopted in aqueous solution by the [Gd(DOTA)(H₂O)]⁻, [Eu(DTPA)(H₂O)]³⁻, [Eu(DOTA)(H₂O)]²⁻, and [Eu(ODDA)(H₂O)] complexes were found to be responsible for the shift in the water exchange mechanism from D to I_d, I, and I_a, respectively. Three reasons are proposed to explain why the Eu²⁺ poly(amino carboxylate) complexes feature water exchange rates 3 orders of magnitude higher than those of the corresponding Gd³⁺ complexes: first, a lower charge density on the Eu²⁺ metal ion; second, substantially longer M–O_w distances for the Eu²⁺ ion; and third, a change in the water exchange mechanism from D (DTPA⁵⁻, DOTA⁴⁻) for Gd³⁺ to I_d (DTPA⁵⁻), I (DOTA⁴⁻), and I_a (ODDA²⁻) for the Eu²⁺ complexes.

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Supporting Information Available: Results from the analyses with theoretical phases and amplitudes with all of the experimental details. XAFS experimental spectra after first-shell filtering of the Sr²⁺ and Eu²⁺ DOTA,⁴⁻ DTPA⁵⁻, and ODDA²⁻ complexes in the solid state and in aqueous solution, together with the fitted spectra with theoretical phases and amplitudes. A comparison of the Eu L₃-edge XANES spectra of the Eu²⁺ DOTA,⁴⁻ DTPA⁵⁻, and ODDA²⁻ complexes in the solid state and in solution and a comparison of the Sr K-edge XANES spectra of the Sr²⁺ DOTA,⁴⁻ DTPA⁵⁻, and ODDA²⁻ complexes in the solid state and in solution. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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