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# Including and Declaring Structural Fluctuations in the Study of Lanthanide(III) Coordination Chemistry in Solution

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#### Supporting Information

ABSTRACT: The physicochemical properties of lanthanide-(III) ions are directly linked to the structure of the surrounding ligands. Rapid ligand exchange prohibits direct structure-property relationships from being formed for simple complexes in solution because the property measured will be an average over several structures. For kinetically inert lanthanide(III) complexes, the simpler speciation may alleviate the problem, yet the archetypical complexes formed by ligands derived from cyclen are known to have at least four different forms in solution-each with a variation in the crystal field that gives rise to significantly different properties. Slow interchange between forms has been engineered, so that



a single complex geometry can be studied, but fast or intermediate interchange between forms is much more commonly observed. The rapid structural fluctuation can report on the changing chemical environment and can be disregarded if a specific property of a lanthanide(III) complex is exploited in an application. However, if we are to understand the chemistry of the lanthanide(III) ions in solution, we must include the structural fluctuation that takes place even in kinetically inert lanthanide(III) complexes in our studies. Here, we have scrutinized the processes that determine the speciation of lanthanide(III) complexes of 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetate (DOTA)-like ligands, in particular the processes that enable exchange between forms that have different physicochemical properties, exemplified by the exchange between the diastereomeric capped square-antiprismatic (cSAP) and capped twisted-square-antiprismatic (cTSAP) forms of DOTA-like lanthanide(III) complexes. In the characterization of a kinetically inert f-element complex, understanding the structural fluctuation in the system is critical because a single observed property can arise from a weighted average, from all forms present, or from a single form with a dominating contribution. Further, the experimental condition will influence both the distribution of lanthanide(III) species in solution and the rates of the processes that change the coordination sphere of the lanthanide(III) ions. This is highlighted using data from a series of cyclen-derived ligands with different pendant arms and different denticity. The data were obtained in experiments that take place on different time scales to show that the rate of the process that results in a structural change must be considered against the time of the experiment. We conclude that the structural fluctuations must be taken into account and that they cannot be predicted from the ligand structure. Thus, an estimate of the exchange rates between forms, the relative concentrations of the specific forms, and the effect of the specific structure of each form of the complex must be included in the description of the solution properties of f-element chelates.

# INTRODUCTION

The coordination chemistry of an f block is fascinating, and newer complexes include record-breaking single-molecule magnets,<sup>2-5</sup> responsive molecules for the detection of oxygen and cyanide,<sup>6,7</sup> and solution-based light upconverters.<sup>8,9</sup> The aqueous chemistry of 4f elements is often considered simple because a single redox state dominates; thus, all lanthanides are trivalent cations with no directional interactions.<sup>11,12</sup> While other oxidation states have been shown to be accessible,<sup>13–18</sup> the chemistry of lanthanides in aqueous solution is that of trivalent ions and is defined by rapid ligand exchange and structures that maximize the number of hard donors in the first coordination sphere.<sup>19–21</sup> In combination, the result is that, for 4f-element coordination chemistry in solution, we are missing

what we consider the foundation of chemistry: well-established structure-property relationships.

The solution chemistry of the f elements is of ever-increasing importance because lanthanides and actinides are found in all aspects of modern technology<sup>23-25</sup> and are critical in clean energy technology from windmill magnets over batteries to nuclear power. The primary area of concern is the separation and isolation of pure f elements, which requires understanding and control of the speciation in solvent extraction processes.<sup>26-30</sup> Investigation of the f-element speciation and structure in simple acids started with Choppin and Spedding

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and Habenschuss<sup>32,33</sup> and has continued with greater success for the 5f elements<sup>34–43</sup> rather than for the 4f elements,<sup>44–46</sup> although lanthanide luminescence is a strong tool that indirectly informs on the solution structure.<sup>47–51</sup> The main issue for the 4f elements is the purely electrostatic bonding and rapid ligand exchange that make most observed properties an average from several species in solution—an average that changes as a function of the concentration, pH, temperature, ionic strength, etc.<sup>52,53</sup> Further, if the time scale of the experiment is slow compared to the rate of ligand exchange, the possibility that an observation is a weighted average has to be considered. The number of possible structures in solution must be reduced and determined in order to build structure property relationships, and this can be done by using multidentate chelators that form kinetically inert complexes with trivalent lanthanide ions.<sup>55,56</sup>

Kinetically inert lanthanide(III) complexes have been explored for optical and magnetic bioimaging<sup>55,57</sup> and are dominated by octa- and nonadentate chelators made from macrocyclic 1,4,7,10-tetraazacyclododecane (cyclen) and 1,4,7triazacyclononane backbones.<sup>53,56</sup> In particular, cyclen with four carboxylate (1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid, DOTA) or carboxamide pendant arms has been studied in great detail.<sup>1,10,22,58-70</sup> The size match between these macrocyclic chelators and the lanthanide(III) ions results in the remarkable inertness of the DOTA-like complexes.<sup>22,55,56,71-73</sup> Because the structure is critical for the performance and properties of the molecule, the solution structure of the lanthanide complexes in use as magnetic resonance imaging (MRI) contrast agents has been described in detail.<sup>55,73-75</sup> Further, the structure of DOTA is one of the limiting forms that nine-coordinate complexes can have in solution. The solution to the Thompson problem for a coordination number (CN) of 9 is a tricapped trigonal prism, yet this structure and the capped square antiprism are both found as the limiting geometric structure of lanthanide complexes in the solid state and solution.<sup>74,76</sup> The DOTAlike ligands can further adopt a capped twisted square antiprism (cTSAP). In both the SAP and TSAP conformations, the structures of the DOTA-like complexes are defined by two planes of donor atoms, where the lanthanide(III) ion is coordinated in the cavity formed by the eight donor atoms (Figure 1). Although we refer to the structures as SAP and TSAP, it must be noted that the actual conformation of the complexes will not be the pure geometric form but can be assumed to be in a form that closely resembles one of the limiting forms, for DOTA-like complexes: TSAP and SAP.77,

The conformations of lanthanide(III) complexes of DOTA were first described by Desreux<sup>22,59</sup> and fully unraveled by



**Figure 1.** Schematic representation of the coordination sphere of DOTA with a lanthanide(III) ion illustrating the ligand geometry, cavity, and capping ligand position.

Aime and co-workers, and these supported the description of converting isomers in solution and added an equilibrium between the capped and noncapped forms, with and without an inner-sphere water molecule.<sup>1,60,62</sup> Thus, eight forms of DOTA-like complexes have been established, and the exchange processes between these have been scrutinized with particular goals in mind. In order to design lanthanide complexes with good relaxometric properties, high rates of water exchange, etc., both locked structures<sup>79,80</sup> and ligands that form complexes in a specific form have been made.<sup>55,65,69,81</sup>

While the use of a chelator that forms kinetically inert complexes leads to a simpler speciation<sup>56</sup> and dynamic fluctuations of lanthanide ions in solution have been reduced, at least eight interconverting forms still have to be considered in the building of structure—property relationships. The importance of linking a specific solution structure, e.g., a specific form of DOTA, to an observed property has been highlighted by the study and optimization of MRI contrast agents. The magnetic properties observed for a single form have been shown to vary greatly from the weighted average observed from the complex in solution.<sup>69</sup> This fact is highlighted by the values of the water exchange rate ( $k_{ex}$ ) shown in Chart 1.<sup>66,69,82</sup> At a higher level of detail, not only is

Chart 1. Differences in the Water Exchange Rates in SAP and TSAP Isomers  $^{66,82}$ 



the form of the complex important, but the orientation and interactions between the ligand scaffold and capping ligand have to be included to adequately describe the magnetic properties of some complexes.<sup>83</sup> Note that water exchange does not change the structure of the lanthanide(III) complex, and  $k_{\rm ex}$  here is used to illustrate a property that differs between two lanthanide(III) species in solution.

From the work on MRI contrast agents, it is evident that the structural fluctuation of kinetically inert lanthanide(III) complexes must be considered when the properties in solution are reported. Further, it has been shown that these will be perturbed by any change in ligand charge, solvent polarity, pH, temperature, or ionic strength.<sup>63,64,68,82</sup> Other examples that

illustrate the strong link between the observed properties and solution structure include the effect of changes in the capping ligand in kinetically inert complexes.<sup>67,84–87</sup> An additional support is found in studies of complexes in both the solid state and solution, where NMR and electron paramagnetic resonance spectroscopy show significant changes in observables with small structural perturbations.<sup>88–91</sup> Finally, it is worth noting that while the structural fluctuations are detrimental to linking observables to specific structures, they are instrumental in the design of next-generation luminescence probes, where small structural perturbations are used to make responsive optical probes. In these, the response arises with the weighted average and is changed by interactions between the lanthanide complex and an analyte.<sup>92–94</sup>

Here, we describe the structural fluctuations in kinetically inert lanthanide(III) complexes to highlight the effect of small changes in the solution structure on the solution properties of the 4f elements. We advocate that structural fluctuations of a lanthanide complex should be reported and contrasted to the time scale of the experiments performed, thereby allowing the reader to readily determine whether the reported property is due to a weighted average or arises from a single form of the studied compound.

#### RESULTS AND DISCUSSION

Weighted Average Issue. To create structure-property relationships, the two must be correlated. Figure 2 shows a



**Figure 2.** Top: Cartoon showing two lanthanide(III) species in solution and the process whereby the lanthanide(III) complex interconverts between the species. Bottom: Cartoon showing an observable from an experiment that is on a time scale much faster (A) or much slower (B) than the exchange process.

situation where a lanthanide complex is dissolved in a solution where there is a competing ligand. As a consequence, the solution will contain a mixture of two species. Assume that the two forms have different water exchange rates, luminescence quantum yields, chemical shifts, etc. Depending on the rates of the reaction and back-reaction, two different outcomes are possible from an experiment aimed at determining the property of the dissolved complex. If the process changing the speciation of the lanthanide(III) ion is slow on the time scale of the experiment, two properties will be determined (Figure 2A). If the process is fast, a single property will be determined (Figure 2B). In the case in Figure 2B, this may be erroneously attributed to structure 1, or it may be realized that it originates from a weighted average between 1 and 2. Because DOTA and DOTA-like ligands are the most widely explored, we choose to consider the structural fluctuations in solution of these complexes. We prepared europium(III) and ytterbium(III) complexes of the eight ligands shown in Chart 2. All of the compounds are known, but a collection of their <sup>1</sup>H

Chart 2. Ligands Used for the Illustration of Structural Fluctuations



NMR and luminescence spectra has not been reported from the same laboratory. The experimental details and synthetic procedures are included in the Supporting Information. The experimental data will be compared to the reported rates of conformational change, in order to contrast these with the time scales of commonly used experimental techniques.

**Example of Structural Fluctuation.** As an illustration as to why the fluxional nature of lanthanide(III) complexes must be reported, we use the SAP/TSAP equilibrium. This structural fluctuation in DOTA-like ligands has been extensively studied.<sup>59,60,62</sup> Figure 3 shows four forms of the complex that are two interconverting sets of diaster-eomers.<sup>22,60,62</sup> There are two different helicities in complexes from DOTA-like ligands. One is formed by the four five-membered rings,  $\delta\delta\delta\delta$  or  $\lambda\lambda\lambda\lambda$ , between the nitrogen atoms, the lanthanide, and the ethylene bridge, indicated with blue in Figure 3. The second helicity is formed by the layout of the



Figure 3. Schematic representation of the dynamic exchange processes between isomers in solution. The blue circle represents the chirality associated with the cyclen ring  $(\delta\delta\delta\delta/\lambda\lambda\lambda\lambda)$ . The red circle shows the helicity formed by the layout of the acetate arms  $(\Delta/\Lambda)$ .

acetate arms  $\Delta$  or  $\Lambda$ , indicated with red in Figure 3. The difference between the two diastereomers is seen as the angle between the two donor-atom planes. This gives rise to two forms: a square-antiprismatic form [SAP;  $\Lambda(\delta\delta\delta\delta)$  and  $\Delta(\lambda\lambda\lambda\lambda)$ ] with opposite helicities in the two chiral elements and a twisted square-antiprismatic form [TSAP;  $\Delta(\delta\delta\delta\delta)$  and  $\Lambda(\lambda\lambda\lambda\lambda)$ ]. The four forms interconvert in solution by arm rotation ( $\Delta \leftrightarrow \Lambda$ ) or ring inversion ( $\delta\delta\delta\delta \leftrightarrow \lambda\lambda\lambda\lambda$ ).

Through this relatively minor change in the conformation, it is apparent how fluctuations in speciation affect the solution properties. The SAP/TSAP is reported to change important properties like relaxivity (through the water exchange rates; Chart 1) and the chemical shift observed from ligand resonances in NMR. Thus, the SAP and TSAP conformations are possible to distinguish in <sup>1</sup>H NMR spectra. Note that any chiral asymmetric substitution on the ligand will make all four enantiomers shown in Figure 3 different, and all four forms will give rise to distinct physicochemical properties.

The interchange of isomers has been probed using NMR spectroscopy; in particular, exchange spectroscopy (EXSY) spectra, variable-temperature NMR, and <sup>17</sup>O NMR have been used.<sup>10,60,64,70,98,99</sup>

In addition to the diastereomeric form of the complex, the nature of the capping ligand has to be considered.<sup>62</sup> If two capping ligands are found in the solution, a minimum of eight forms must be considered. However, it is important to emphasize that the SAP/TSAP structural variation and exchange between different capping ligands are not the only equilibria of importance for the solution structure but are just examples of these. In contrast to complexes with labile ligands, where the nature of the ligands at all eight or nine positions available in the complex must be considered, the kinetically inert complexes are found in a highly limited number of forms because the ligand takes up seven or eight positions, thus leaving only one or two exchanging ligands and leading to smaller structural fluctuations.<sup>56</sup> Even so, we have to address the fact that the properties observed from kinetically inert lanthanide(III) complexes are still a weighted average of all possible forms.

One option is to make tailored ligands that adopt a preferred form. To optimize the performance of MRI contrast agents, complexes have been made that favor the TSAP form. This was done by introducing a chiral center in the ligand backbone, thus limiting the number of forms found in solution.<sup>100</sup> Alternatively, it is possible to limit the number of isomers in solution by adding chiral centers to the macrocycle, to the pendant arms, or to both.<sup>54,64,65,67,79–81,101</sup> The structures of the ligands influence the ratio of isomers and thus the properties observed.

To simplify this picture, "locked" structures have been synthesized, where the SAP/TSAP isomerization has been frozen out. This has allowed for one isomer to be isolated, thus limiting the number of possible conformations in solution.<sup>80,79</sup> However, ternary complexes and capping solvent molecules will still give rise to changes in the constitution of the complexes. Further, the time scales of the experiment must be considered to determine how "locked" the structures are, and the exchange between different forms of the investigated complex must be considered in relation to the time scale of the experiment used to determine a given property.

Types of Structural Fluctuations in DOTA-like Ligands. There are multiple forms of structural fluctuations to consider for lanthanide(III) complexes of DOTA-like ligands in solution. The best described is the conformational equilibrium between diastereomers, which has been explained in detail vide supra. The SAP/TSAP equilibrium will act as an illustration here, but as pointed out by Aime,<sup>62</sup> the capping position must also be considered. In fact, there are a minimum of five processes that must be considered in the description of the form of a complex in aqueous solution, and these are shown in Figure 4. The first process is decomplexation  $(K_1)$ , which is expected to be irrelevant in kinetically inert complexes but relevant for linear ligands and some DO3A complexes.<sup>5</sup> The second process is often ignored and involves the nature of the capping ligands. Because the constitution of the lanthanide(III) complexes changes according to the medium composition, the process leading to the formation of ternary complexes must be included  $(K_2)$ , that is, each individual process where the solvent is displaced by anions like fluoride, carbonate, or hydroxide (e.g., by deprotonation).<sup>87,102</sup> Partial decomplexation by reorientation of the coordinating arms or simply ligand reorientation that allows for additional capping ligands  $(K_5)$  is a third process that, like the first two, causes a change in both the constitution and structure of the complex.<sup>52,102–105</sup> Finally, the equilibrium between solvated and solvent-free complexes (K<sub>6</sub>) has to be included before considering that each of the different lanthanide(III)containing species are present in up to four interconverting conformations  $(K_3/K_4)$ . Figure 4 includes an estimate of the forms that are relevant for complexes of DOTA and substituted DO3A ligands when dissolved in a buffer at constant ionic strength. This illustration shows the vast complexity of the speciation of kinetically inert lanthanide (III) complexes in, e.g., biological media. Note that all of the different forms of the kinetically inert lanthanide(III) complex are influenced by the medium, and drastic changes have been observed when parameters such as the pH, solvent or ionic strength are varied.<sup>68,106</sup> Thus, all of the processes in Figure 4 lead to solution structures, where the lanthanide(III) ions will give rise to different observable properties. Accordingly, the time scale of each process must be contrasted to that of the experiment. In a kinetically inert lanthanide (III) complex, the



**Figure 4.** Different forms of equilibria when both the constitution and conformation that is the solution structure of lanthanide(III) complexes in solution are changed.  $K_1$  is dissociation.  $K_2$  shows the exchange of a solvent molecule with a competitive monodentate ligand.  $K_3$  and  $K_4$  are the conformational changes in the ligand from the SAP to TSAP form by either ring inversion ( $k_3$ ) or arm rotation ( $k_4$ ).  $K_5$  is the equilibrium between one and two solvent molecules in the inner sphere due to a reorientation/decomplexation of one coordinating arm.  $K_6$  is the loss of a capping water ligand moving between CN = 8 and 9. On the sides, the number of possible species of the europium(III) complex of DOTA and a lanthanide(III) complex of a DO3A-type ligand are shown.

first process  $(k_1)$  occurs with a time constant that is  $10^{-3} \text{ s}^{-1}$  or slower<sup>56</sup> and can be ignored in all laboratory experiments. Similarly, the rate of the process exchanging axial fluoride with water  $(k_2)$  has been calculated to approximately 1 s<sup>-1</sup>, which is slow in most experimental techniques.<sup>87</sup> In contrast, the solvent-exchange process  $(k_5/k_6)$  can occur with a time constant of ~ $10^6-10^9 \text{ s}^{-1}$ , which is fast compared to most experimental time scales (Figure 5).

If the medium is not changed and the constitution of the lanthanide complex is maintained like for complexes of DOTA, the problem is reduced to a level where only the interconverting diastereomers SAP and TSAP have to be considered. This simpler case is what we use as an example to highlight the issue of the weighted average. Using the data from the europium(III) and ytterbium(III) complexes made from the ligands shown in Chart 2, we compare situations where a weighted average is observed (Figure 2B) to situations where observables for each form in solution are determined (Figure 2A).

Before considering the experimental data, we consider the literature data. The exchange rates of inversion between stereoisomers SAP and TSAP ( $k_3$  and  $k_4$ ) have been determined for several DOTA-like systems. We have compiled these in Table 1, and all ligands are shown in the Supporting

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**Figure 5.** Time scale of different experimental techniques against rate constants for some processes. For MRI, the time scale is from milliseconds to seconds, as indicated by the purple region.  $k_1$  is metal dissociation for  $[Gd(DOTA)]^-$ ,  $k_2$  is fluoride exchange in the axial position,  $k_1'$  is dissociation in [Gd(NOTA)],  $k_3$  is the exchange rate of ring inversion for  $[Eu(DOTA)]^-$ ,  $k_4$  is the rate of arm rotation in  $[Eu(DOTA)]^-$ ,  $k_4'$  is the rate of arm rotation in  $[Eu(DOTA)]^-$ ,  $k_4'$  is the rate of  $[Gd(DOTA)]^-$ , and  $k_6$  is the rate of water exchange on  $[Gd(DOTA)(H_2O)]^-$ .

Information. The exchange rates are defined for both arm rotation and ring inversion (Figure 3) and vary from 17 to 7650 s<sup>-1</sup>. This range of time constants overlaps with typical experiments such as luminescence and NMR spectroscopy, and the SAP/TSAP equilibrium must thus be considered when properties derived from these experiments are reported. Note that the structural fluctuations are all in equilibrium and that all are characterized by a medium- and temperature-dependent time constant. The observable solution properties of a lanthanide(III) complex in solution are defined by all of the processes—and indeed rates thereof—influencing the speciation of the lanthanide(III) ion in the sample.

**Contrasting Structural Fluctuation and Experimental Time Scales.** As emphasized, it is essential to consider structural fluctuations against the related time scale of an experiment. The properties observed are evaluated by the rate of fluctuations ( $k_{\text{process}}$ ) against the rate of experiment ( $k_{\text{exp}}$ ). See Figures 2 and 4. The most common techniques for studying f-element chelates are paramagnetic NMR spectroscopy, luminescence measurements, and various bioimaging techniques.

The time scale in NMR spectroscopy is determined by the difference in the chemical shift between different exchanging conformations and the field strength of the instrument.<sup>107</sup> Multiple protons exchange in the studied complexes by either arm rotation or ring inversion. However, the largest difference between exchanging signals is between the axial proton in SAP and an equatorial proton in TSAP, with a difference in chemical shift of ~35 ppm. Hence, the shortest time scale for a europium(III) complex studied using <sup>1</sup>H NMR spectroscopy is ~26  $\mu s/k_{exp} \sim 3.9 \times 10^4 \text{ s}^{-1}$  on a 500 MHz instrument. A ytterbium(III) spectrum, where the signals are shifted by up to 140 ppm, would have a significantly shorter time constant of ~6  $\mu s/k_{exp} - 1.5 \times 10^5 \text{ s}^{-1}$ .

The time constant of luminescence spectroscopy is determined by the excited state lifetime of the emitter which varies between solvents, ligand structures, and lanthanide ions, but ranges from 100 ns/ $k_{\rm exp} \sim 1 \times 10^7$  s<sup>-1</sup> to 4 ms/ $k_{\rm exp} \sim 250$  s<sup>-1</sup>.

Table	e 1.	Kinetic	Data	from	the	Literature	for	DOTA-like	Complexes"
									1

complex	$\Delta G^{\ddagger}$ (kJ mol <sup>-1</sup> )	$\Delta H^{\ddagger}$ (kJ mol <sup>-1</sup> )	$\Delta S^{\ddagger}$ (J mol <sup>-1</sup> K <sup>-1</sup> )	$k_{\rm ex}  ({\rm s}^{-1})$	process	ref
Lu(DOTA)	62.7(2.0)	69.3(1.0)	22.02(3.4)	64 <sup>b</sup>	$SAP \rightarrow TSAP$	1
Lu(DOTA)	58.7(2.0)	54.4(1.0)	-14.1(3.5)	319 <sup>b</sup>	$TSAP \rightarrow SAP$	1
Yb(DOTA)	61.2(0.6)	64(8)	9(27)	116 <sup>b</sup>	ring inversion	10
La(DOTA)	60.7(1.2)	59.4(0.8)	-4.6(3.3)	23 (278 K)	ring inversion	22
La(DOTP)	101(11)			$12 \times 10^{-6}$	ring inversion	31
Lu(DO3A-Bz)	23.4 <sup>c</sup>			$4.9 \times 10^{8}$	arm rotation	54
Lu(DO3A-Bz)	61.1 <sup>c</sup>			122	ring inversion	54
Eu(DOTA)	62.2 <sup>d</sup>			78	arm rotation	61, 76
Eu(DOTA)	64.2 <sup>d</sup>			35	ring inversion	61
Eu(4-RRRR)	63.6 <sup>d</sup>			45(15)	ring Inversion (SAP $\rightarrow$ TSAP)	65, 79
Eu(4-RRRS)	63.8 <sup>d</sup>			40(15)	ring Inversion (SAP $\rightarrow$ TSAP)	65, 79
Eu(DOTAM)	54.6 <sup>d</sup>	39.1(2)	-52.1(7)	1700(200)	$SAP \rightarrow TSAP$ arm rotation	66, 80
Eu(DOTAM)	50.8 <sup>d</sup>	39.1(2)	-39.4(7)	7650(200)	$TSAP \rightarrow SAP$ arm rotation	66
Eu(DTMA)	56.9 <sup>d</sup>	62.5(2)	18.7(6)	671(43)	$SAP \rightarrow TSAP$ arm rotation	66
Eu(DTMA)	53.0 <sup>d</sup>	58.8(3)	19.4(10)	<b>3192</b> (330)	$TSAP \rightarrow SAP$ arm rotation	66
Eu(DTMA)	62.1 <sup>d</sup>	55.9(1)	-21.1(5)	<b>79.5</b> (5)	$SAP \rightarrow TSAP$ ring inversion	66
Eu(DTMA)	58.0 <sup>d</sup>	61.0(3)	10.1(10)	430 (53)	$TSAP \rightarrow SAP$ ring inversion	66
Eu(DOTMAM)	59.5 <sup>d</sup>	60.2(3)	2.3(11)	<b>232.9</b> (25)	$SAP \rightarrow TSAP$ ring inversion	66
Eu(DOTMAM)	62.4 <sup>d</sup>	63.9(3)	4.8(11)	7 <b>0.8</b> (8)	$TSAP \rightarrow SAP$ ring inversion	66
Eu(DOTA-2dma)	66			17 <sup>b</sup>	arm rotation	60, 82
La(DO2A2P)	64.9(0.8)	109.2(0.8)	145.2(17.6)	18.7(1)	arm rotation	95
La(DO2A2P)	65.7(12)	38.9(2.9)	-89.5(10.0)	19.7(1)	ring inversion	62, 95
Lu(DO2A2P)	65.8(10.0)	127.2(10.46)	205.9(33.9)	20.1(1)	arm rotation	95
Lu(DO2A2P)	64.4(3.8)	60.5(3.8)	-14.2(12.1)	31.3(1)	ring inversion	96
Lu(DTMA)	62.2			77 <sup>6</sup>	ring inversion	79, 95
Lu(DTMA)	56.9			660 <sup>b</sup>	arm rotation	95
Lu(DO3A-PIC)	65(5)	119(2)	181(2)	25 <sup>b</sup>	ring inversion	10, 70, 97

<sup>*a*</sup>Ligands in boldface are revisited here. <sup>*b*</sup>Calculated values from reported  $\Delta G^{\ddagger}$ . <sup>*c*</sup>Computed values from density functional theory calculations. <sup>*d*</sup>Calculated values from reported rate constants.

Absorption is an instantaneous process with a time constant of femtoseconds, in contrast to MRI scans, where a time scale in the range of milliseconds to multiple seconds has to be considered. Figure 5 compares the time constants of relevant experimental techniques to those of processes that change the speciation of lanthanide(III) complexes in solution (Table 1 and Figure 4). Note that only absorption spectroscopy gives data that are unaffected by structural changes and that even decomplexation—often the slowest process—must be considered for some complexes.

Structural Fluctuation on the Microsecond Time Scale: <sup>1</sup>H NMR. Complexes of europium(III) and ytterbium-(III) were made and purified from the ligands in Chart 2, following a literature procedure.<sup>52</sup> <sup>1</sup>H NMR spectra were recorded in D<sub>2</sub>O, and the spectra are plotted in Figure 6 (see the Supporting Information for details). The time scale of the experiments depends on the lanthanide(III) ion, the field strength of the spectrometer, and the chemical shift of the resonances under consideration. For the axial protons,  $k_{exp}$  is  $3.8\times10^4~s^{-1}$  for europium(III) complexes and  $1.5\times10^5~s^{-1}$ for ytterbium(III) complexes. The spectra from the complexes of DOTA ( $k_1 \approx 10^{-8} \text{ s}^{-1}$ ,  $k_3 = 35 \text{ s}^{-1}$ , and  $k_4 = 78 \text{ s}^{-1}$ ) were used as references.<sup>60,61</sup> The structure of DOTA is considered to be frozen on the NMR time scale because both ring inversion ( $k_{exp} = 3 \times 10^4 \text{ s}^{-1} \gg k_3 = 35 \text{ s}^{-1}$ ) and arm rotation ( $k_{exp} = 3 \times 10^4 \text{ s}^{-1} \gg k_3 = 78 \text{ s}^{-1}$ ) are slower than the time frame of the experiment. The resonances used in the analysis of the NMR spectra are the axial ring protons that are observed in specific regions of the spectra indicated in Figure 6. Because the DOTA complexes are frozen, we can report observables

from both the SAP and TSAP conformers with  $\delta_{\text{SAP}} = 34$  ppm and  $\delta_{\text{TSAP}} = 14$  ppm for  $[\text{Eu}(\text{DOTA})(\text{D}_2\text{O})]^-$ , values that we can relate to a specific structure. This is equivalent to case A illustrated in Figure 2, where the time scale of the experiment is faster than the change in speciation and two properties can be determined. In contrast, the DOTAM complexes have an arm rotation process ( $k_{\text{exp}} = 3 \times 10^4 \text{ s}^{-1}$  to  $k_4 = 1 \times 10^4 \text{ s}^{-1}$ ) that appears fast compared to the NMR time scale; here the observable cannot be related to a specific structure and must be reported as  $\delta_{\text{average}} = 26$  for  $[\text{Eu}(\text{DOTAM})(\text{D}_2\text{O})]^{3+}$ originating from a weighted average between different forms (Figure 2B).<sup>63,64</sup>

The <sup>1</sup>H NMR spectra in Figure 6 can be used to group the complexes according to the observed rate constants for the processes interconverting the SAP and TSAP forms of the complexes. Ring inversion  $(k_3)$  and arm rotation  $(k_4)$  are both slow on the NMR time scale for complexes of DOTA and the DOTA-monoamides DOTA-methylamide and DOTA-pentylamide. Thus, the observable from the NMR spectra and all experiments with a similar time constant can be used in structure-property relationships to determine different properties (Figure 2A). The DOTA-tetraamides DOTAM and DTMA  $(k_3 = 430 \text{ s}^{-1} \text{ and } k_4 = 3192 \text{ s}^{-1})$ , and to a lesser extent DOTA-dipentylamide, have fast arm rotation  $(k_4)$  on the NMR time scale. As a result, we do not know if the resonance is shifted from the expected value (DOTA) because of ligand-field effects or the observation is due to exchange between forms (Figure 2B). Because we cannot relate the property directly to the structure, we cannot use the observable to build structure-property relationships. Finally, the





Figure 6. <sup>1</sup>H NMR spectra of ytterbium(III) (left) and europium(III) (right) complexes with resonances from axial ring protons in the SAP and TSAP forms observed in  $[Ln(DOTA)]^-$ , as indicated by the gray regions.

heptadentate DO3A-benzyl and DO3A-propargyl ligands show fast or intermediate exchange between isomers on the NMR time scale.<sup>54,70</sup> Calculations of the activation barrier for DO3A-

benzyl have shown arm rotation to be much faster than ring inversion and were thereby assumed to be the process responsible for the fast interconversion between isomers observed in the experimental data.<sup>54</sup> Experimentally, arm rotation and ring inversion can be distinguished because the former results in exchange between the resonances indicated as SAP and TSAP in Figure 6, while the latter results in exchange between protons at positive and negative chemical shifts.<sup>10,61,82</sup>

Structural Fluctuation on the Millisecond Time Scale: Europium(III)-Centered Luminescence. Europium(III)centered emission has been reported as a tool to determine the conformational changes in solution,  ${}^{58,59,65,74,103,108}$  and according to crystal-field splitting, it is possible to deduce the number of species in solution by counting the number of peaks observed in specific transitions. The transitions originate in the nondegenerate  ${}^{5}D_{0}$  state, and a number of emission lines must reflect the degeneracy of the lower-energy *J* state. Hence, it should be possible to compare the number of observed lines in a band to the maximum possible degeneracy of this *J* state in a specific coordination symmetry.<sup>109,110</sup> For example, if [Eu-(DOTA)(H<sub>2</sub>O)]<sup>-</sup> is assumed to have  $C_4$  symmetry, only one line is possible in the  ${}^{5}D_0 \rightarrow {}^{7}F_0$  transition and seven lines should be seen in the  ${}^{5}D_0 \rightarrow {}^{7}F_4$  band.<sup>108</sup>

Complexes with frozen structures are expected to show sharp defined lines in the europium(III) emission spectra with a number of peaks equal to or less the degeneracy. Complexes with intermediate or fast exchange between forms compared to the excited state lifetime of the complex will show broader and less defined peaks due to the presence of multiple forms, all with different ligand fields resulting in broad ill-defined emission bands. Note that the emission spectrum from each species will always be a series of narrow emission lines, and that broad emission bands in lanthanide luminescence itself is an indication that the sample is a mixture of species.

The excited state lifetime of a lanthanide complex depends on the surrounding medium and they have been determined for the europium(III) complexes in both  $H_2O$  and  $D_2O$ . The result are compiled in Table 2 along with the calculated

Table 2. Luminescence Lifetimes of Europium(III) Complexes Measured in  $H_2O$  and  $D_2O^a$ 

complex	$ au_{ m H_2O}/ m ms$	$ au_{\mathrm{D_2O}}/\mathrm{ms}$	9			
[Eu(DOTA)] <sup>-</sup>	0.65	2.44	1.2			
[Eu(DOTAM)] <sup>3+</sup>	0.51	1.90	0.9			
[Eu(DTMA)] <sup>3+</sup>	0.57	2.10	1.0			
[Eu(DOTA-dipentylamide)] <sup>+</sup>	0.46	1.64	1.5			
[Eu(DOTA-methylamide)]	0.61	2.35	1.2			
[Eu(DOTA-pentylamide)]	0.64	2.38	1.0			
[Eu(DO3A-propargyl)]	0.46	1.73	1.7			
[Eu(DO3A-benzyl)]	0.39	1.72	2.1			
<sup><i>a</i></sup> The modified Horrocks' equation was used to determine $q$ . <sup>111</sup> $q = A$ ( $\tau_{\rm H,O}^{-1} - \tau_{\rm D,O}^{-1} - B - C$ ).						

number of inner sphere solvent molcules q.<sup>50,111,112</sup> The time scale of the luminescence experiments are fairly similar across the complexes around 0.5 ms/ $k_{exp} \sim 2000 \text{ s}^{-1}$  in H<sub>2</sub>O and  $\sim 2 \text{ ms}/k_{exp} \sim 500 \text{ s}^{-1}$  in D<sub>2</sub>O, which in these complexes does not constitute a major difference. This is borne out in the spectra in Figure 7, where no major difference is observed between H<sub>2</sub>O and D<sub>2</sub>O. This is partly due to the fact that changes in the luminescence spectra requires a significant change in ligand field, partly due to the similar time scales of the two



Figure 7. Emission spectra of europium(III) complexes measured in  $H_2O$  (red) and  $D_2O$  (black) following excitation at 393 nm.

experiments, and partly because the bands from each form overlap. This implies that even though the structural fluctuations are slow, we cannot resolve the luminescence lifetime or the luminescence quantum yield inherent to any form. It is only possible to report the excited state properties of the distribution of different forms in solution i.e. the pie chart in Figure 4.

As above, DOTA is used as internal reference first for contrasting the numbers in Table 2. Remembering that the error on q is  $\pm 0.5$ ,<sup>111</sup> it would appear that the complexes fall into three groups: DOTA, DOTA-tetraamide, and DOTA-monoamide complexes that, as expected, have a single capping water molecule, DO3A complexes with two coordinating water molecules, and the DOTA-diamide that is assumed to be present in a form with one water molecule and in a form where one carboxamide arm is replaced with water. Because the emission spectrum of DOTA-dipentylamide is similar to that of the DOTA complex, slow exchange between the q = 1 and 2 forms must be assumed. Thus, the octadentate ligands lead to nine-coordinate complexes with one capping water molecule, and the heptadentate DO3A complexes result in complexes with two additional ligands.

Closer inspection of the spectra in Figure 7 reveals that there are complexes that show differences between  $H_2O$  and  $D_2O$ . The europium(III) complexes of DOTAM, DO3A-propargyl, and, to a lesser extent, DO3A-benzyl give rise to different spectra in  $H_2O$  and  $D_2O$ . This implies that structural fluctuations occur on a time scale equal or faster than that of the experiment and that the structural fluctuations give rise to species with significantly different properties, as illustrated in Figure 2. Because the spectra were not recorded using controlled conditions, e.g., with known pH, ionic strength, and temperature, a detailed analysis was not performed.

Media Effects on Speciation and Structural Fluctuation. The media effects in lanthanide luminescence have been investigated for DOTA-like complexes, and drastic fluctuations in speciation and solution structure can be ascribed to what in other subfields of chemistry would be described as innocent media changes.<sup>106,112,113</sup> To highlight the importance of absolute control of the solvent parameters, DO3A-propargyl was investigated at pH 6 and 10 using NMR spectroscopy, where the structural fluctuations are directly observed.

Figure 8 shows the <sup>1</sup>H NMR spectra of europium(III) and ytterbium(III) complexes of DO3A-propargyl at pD = 6 and



**Figure 8.** <sup>1</sup>H NMR spectra of [Yb(DO3A-propagyl)] (top) and [Eu(DO3A-Propargyl)] (bottom) measured at pD 6 and 10 to show the structural variations with varying pD. The resonances from the axial ring protons in the SAP and TSAP forms observed in the [Ln(DOTA)]<sup>-</sup> indicated by the gray regions.

10. The spectra are evidently different; e.g., as seen in the spectrum of the europium(III) complex, at pD = 10 only one resonance corresponding to the axial protons is observed. This indicates a fast exchange between multiple forms in solution. At pD = 6, where very broad resonances are observed in a limited number, the exchange process appears to be on an intermediate time scale. A similar observation is made for the ytterbium(III) complex, which at pD = 6 appears to be in slow exchange because resonances from all of the axial protons in the unsymmetrical complex are observed from the SAP form of the complex. At pD = 10, these collapse to just a single, less shifted resonance, indicating that the forms are in fast exchange. While the change in pD is dramatic in this example, so is the accompanying change in the solution structure, serving as a good example of why both the solution structure and medium composition must be reported in complete detail in the creation of structure-property relationships in lanthanide(III) coordination chemistry.

# CONCLUSIONS

The allure of f-element coordination chemistry in solution is strong. On the fundamental level, there is a plethora of areas where it is possible to contribute significantly to our understanding of these elements, and the ever-increasing demand for these elements in their pure form provides amble motivation for the work. The challenge is that the f elements, in stark contrast to organic molecules, exhibit rapidly fluctuating structures in solutions. Both the constitution and conformation changes not only with the medium composition but also in time. Here, we have shown that these fluctuations have to be taken into account in the building of structureproperty relationships and explored the time scales of the structural fluctuations that occur in DOTA-like kinetically inert lanthanide(III) complexes. In these, dissociation can be ignored in all experiments, a fact that is true only for complexes with documented kinetic inertness. This leaves changes in the constitution associated with the capping ligand that can be present where the CN is 9 and absent if steric hindrance of the ligand favors a CN of 8. Using Horrocks' equation to determine q or relaxometric studies will often allow the importance of this equilibrium to be determined. If capping ligands are present, the composition of the media used to study the properties of the complex becomes important. Competing ligands from adventitious bicarbonate to coordinating buffers and changes due to the pH must be taken into account, and the constitution of the complex(es) in the sample studied must be determined. This can be extremely challenging. Finally, when the constitution of the complexes studied has been determined, the different conformations of each constitution must be considered, here illustrated with the equilibrium between the SAP and TSAP forms of DOTA-like complexes. This is important because each individual form of the complex will have unique properties that are directly related to the actual structure surrounding the lanthanide(III) center.

While the challenge may seem exceedingly complicated, we are able to determine the solution structure of lanthanide(III) complexes with DOTA and DOTA-like ligands. In turn, this allows us to build structure—property relationships, but only if we as a field are completely transparent regarding the experimental conditions and declare when an observed property is from a specific structure and when it is the result of a weighted average.

# ASSOCIATED CONTENT

#### **Supporting Information**

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Experimental conditions and compound characterization (PDF)

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# Notes

The authors declare no competing financial interest.

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