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Article

Structural Variations Across the Lanthanide Series of Macrocyclic DOTA Complexes: Insights into the Design of Contrast Agents for Magnetic Resonance Imaging

F. Benetollo,[†] G. Bombieri,*[‡] L. Calabi,[§] S. Aime,[||] and M. Botta[⊥]

ICIS-CNR, Corso Stati Uniti 4, 35127 Padova, Italy, Istituto di Chimica Farmaceutica, Università di Milano, Viale Abruzzi 42, 20131 Milano, Italy, Bracco Spa, Via Folli 50, 20131 Milano, Italy, IFM, Università di Torino, Via P. Giuria 8, 10125 Torino, Italy, and Dipartimento di Scienze e Tecnologie Avanzate, Università del Piemonte Orientale "Amedeo Avogadro", C.so Borsalino 54, 15100 Alessandria, Italy

It was early shown that the macrocyclic Ln(DOTA) complexes (DOTA = 1,4,7,10-tetra-azacyclododecane-N,N′,N″,N‴-tetraacetic acid) exists in solution as a mixture of two enantiomeric pairs of diastereoisomers differing in the ligand conformation, namely, square antiprismatic (SA) and twisted square antiprismatic (TSA) geometries, respectively. Later, extensive ^{1}H NMR investigations suggested that a coordination change may be superimposed on this conformational equilibrium involving two additional structures in which the metal ion possesses a coordination number of eight (CN 8). It was predicted that these two species, lacking the apical coordinated water molecule, would maintain the SA and TSA coordination geometries, and therefore, they have been labeled as SA′ and TSA′, respectively. In this work we report the X-ray solid-state crystal structure determination of six Ln(DOTA) complexes representative of all four coordination geometry typologies deduced from NMR solution studies. A distinctive structural feature that discriminates SA (and SA′) and TSA (and TSA′) structures is represented by the twist angle between the two square planes of the antiprism, the basal four nitrogen, and the apical four oxygen planes. [Ce(DOTA)(H$_2$O)]$^-$ displays a TSA structural typology with a twist angle of 25° and a Ce–O$_{water}$ distance of 2.59 Å. The SA-type structure has been found in the case of complexes with Pr(III), Nd(III), and Dy(III), where the twist angle is 39, 39, and 38°, respectively, and the metal–water oxygen distance varies significantly (Pr–O$_w$ 2.529 Å; Nd–O$_w$ 2.508 Å; and Dy–O$_w$ 2.474 Å). [Tm(DOTA)]$^-$ displays a TSA′-type structure with a twist angle of 24°. As compared with the TSA structure of the corresponding Ce(III) complex, the Tm(III) complex shows an overall marked shrinkage of all metal–nitrogen and metal–oxygen distances (ca. 0.2 Å), which reflects the contraction of the metal ionic radius across the series but also the effect associated with the decrease of the CN from 9 to 8. In [Sc(DOTA)]$^-$, the even smaller ionic radius of Sc(III) shifts the geometry of the coordination cage to the more compact SA′ typology with a twist angle of 41°, a value very similar to that found in the SA structures of lanthanide(III) ions with CN 9. Finally, an investigation was made into the hydration spheres of the complexes with SA and TSA geometries to account for the experimental evidence of a markedly different rate of water exchange for the two isomeric structures. This is of fundamental importance to the understanding of the corresponding Gd(III) complexes as MRI contrast agents.

Introduction

DOTA is an octacoordinating ligand based on the tetra-azacyclododecane ring in which each nitrogen atom bears an acetic substituent.[1] The set of coordinating donor atoms (four nitrogens and four oxygens) wraps around a lanthanide-(III) ion in a very efficient way to yield complexes endowed with a very high thermodynamic and kinetic stability. This property has been very important to draw the interest toward Gd(DOTA) that quickly became one of the reference compounds in the field of the contrast agents for MRI

* Author to whom correspondence should be addressed. E-mail: bombieri@mailserver.unimi.it.
† ICIS-CNR.
‡ Università di Milano.
§ Bracco Spa.
|| Università di Torino.
⊥ Università del Piemonte Orientale "Amedeo Avogadro".

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(Magnetic Resonance Imaging).[2] The X-ray solid-state structure of Gd(DOTA)[3] shows that the Gd(III) ion is at the center of a square antiprismatic (SA) cage, and its coordination sphere is completed by a water molecule in a capping position above the plane formed by the four carboxylate oxygens. Structures analogous to that found for Gd(DOTA) have been found for the related complexes with Eu(III),[4,5] Ho(III),[5] Lu(III),[6] and Y(III).[7]

As far as the solution state is concerned, it was shown that Ln(DOTA) complexes may adopt either the SA-type structure found in the solid state or an alternative twisted square antiprismatic (TSA) geometry.[8] From a quantitative analysis of the NMR dipolar shifts of the Yb(III) derivative, it was proposed that the TSA structure differs from the SA structure in the twist angle between the two square planes of the antiprism, and this may be envisaged as resulting from a different helicity of the four acetate arms by keeping fixed the conformation of the tetra-azacyclododecane ring. Furthermore, it was shown that the two isomers may interconvert on the NMR time scale either by rotation of the acetate arms or via the conformational interconversion of the ethylenic groups of the macrocyclic ring. The type of structural arrangement of DOTA around the lanthanide ion appears to be very important in determining the exchange rate of a water molecule from the inner coordination sphere to the bulk.

TSA structures exchange the coordinated water much faster than those of the SA type.[9–11] This finding has implications for the design of MRI contrast agents based on Gd(DOTA)-like complexes. Very high relaxivities can be obtained for slowly tumbling systems (a condition easily met when a complex is interacting with a macromolecular substrate) only if they are characterized by a fast exchange rate of their coordinated water molecule(s). Therefore, as Gd-DOTA-like complexes are considered, systems with a TSA-type structure are the candidates of choice for the attainment of very high relaxivities.

A thorough NMR study on the SA/TSA equilibrium for Ln(DOTA) chelates along the lanthanide series suggested that a coordination equilibrium has to be superimposed on the conformational equilibrium.[12] Two new species in which

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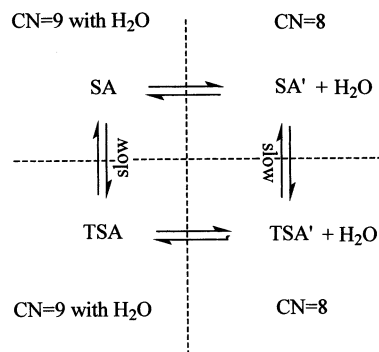
Figure 1. Equilibria between the isomeric forms of Ln(DOTA) complexes (the ′ indicates the absence of the water in the inner coordination sphere of the Ln(III) ion).

the Ln(III) ion has CN 8 have been proposed. These structures should be closely related to those discussed above except for the absence of the coordinated water molecule at the apical position above the four oxygen square plane. On this basis they have been labeled as SA′ and TSA′, respectively (Figure 1).

The results herein presented deal with the X-ray crystal structure determinations of six Ln(DOTA) chelates (M = Ce, Pr, Nd, Dy, Tm, and Sc) that, for the first time, provide structural evidence for the occurrence of SA′ (Sc) and TSA′ (Tm) typologies with a DOTA ligand. These results provide further support to the information gained by NMR solution studies on the structural changes occurring for Ln(DOTA) family as the lanthanide(III) ionic radius decreases. In summary, of all the X-ray data reported on the Ln(DOTA) family nowadays available, eight refer to structures of the SA type, two of the TSA type, and one each of the SA′ and TSA′ type, respectively.

Results

Solid-State Structures. Crystal Structure of Na[Ce-(DOTA)H$_2$O]·NaHCO$_3$]·7H$_2$O. The X-ray structure shows that the cerium derivative crystallizes with seven water molecules and one molecule of NaHCO$_3$. Therefore, the resulting formula is Na[Ce(DOTA)H$_2$O]·[NaHCO$_3$]·7H$_2$O. Figure 2 reports an ORTEP view of the [Ce(DOTA)H$_2$O]$^-$ moiety, and Figure 3 shows the unit cell content down the *b* axis. The asymmetric units are formed by the [Ce(DOTA)-H$_2$O]$^-$ anion, the [Na(H$_2$O)$_6$]$^+$ cation, the [NaHCO$_3$] salt, and the water of crystallization. In the [Ce(DOTA)H$_2$O]$^-$ unit, the four nitrogen and the four oxygen atoms form square planes that are nearly parallel each other. The cerium(III) ion is 0.7677(7) Å out of the oxygen plane and −1.7628(7) Å from the nitrogen plane. The twist angle between the two planes is 25° (i.e., similar to the value previously found in the X-ray structure determination of the La(DOTA)[13] complex). The structure of [Ce(DOTA)H$_2$O]$^-$ is then of the TSA type. As the compound crystallizes in a chiral space group, we can assign the absolute configuration also to the cyclododecane ring, which is (λλλλ) according to the IUPAC rules,[14] with averaged values of the torsion angles (C−C−

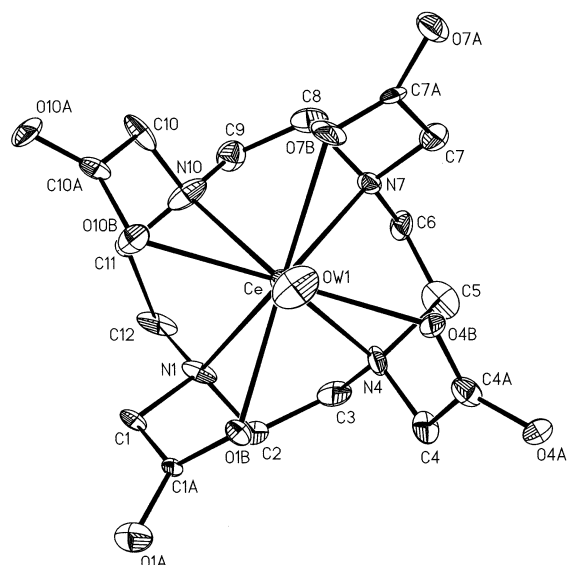(13) Aime, S.; Barge, A.; Benetollo, F.; Bombieri, G.; Botta, M.; Uggeri, F. *Inorg. Chem.* **1997**, *36*, 4287–4289.

Figure 2. TSA geometry in [Ce(DOTA)(H₂O)]⁻. ORTEP view down the Ce−O_W1 bond.

Figure 3. Unit cell content of Na[Ce(DOTA)(H₂O)]·NaHCO₃·7H₂O

N−C: 80(3); C−N−C−C: −160(3); N−C−C−N: 59(3); and C−C−N−C: 163(3)°).

The orientation of the acetate arms is rotated with respect to that found in the isostructural SA series, and the Ce(III) isomeric form can be identified as $\Lambda(\lambda\lambda\lambda\lambda)$.[15] The Ce−O_w bond distance is 2.59(1) Å. The Ce−N and Ce−O bond lengths within the DOTA chelate follow the trend expected for the decreased ionic radii (vide infra) when compared with
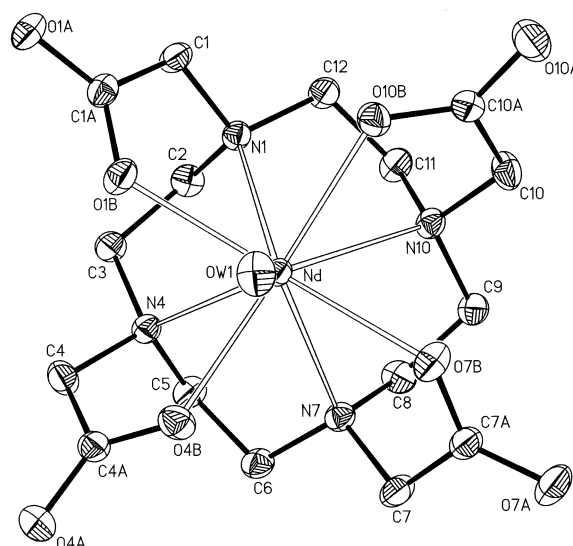
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Figure 4. SA geometry in [Nd(DOTA)(H₂O)]⁻, ORTEP view.

those found for the La(DOTA) complex. The two sodium cations play a different role, one being (Na1) octahedrally coordinated to six of the seven waters of crystallization with Na−water distances ranging from 2.36(2) to 2.53(2) Å and one (Na2) being part of the NaHCO₃ unit. The latter (Na2) is octahedrally coordinated to the seventh water molecule, to one oxygen of the HCO₃⁻ anion, and to the carboxylic oxygens of four different [Ce(DOTA)H₂O]⁻ units not involved in the coordination of the lanthanide ion (the range of the distances is from 2.32(2) to 2.41(2) Å) (Figure 3).

Crystal Structure of Na[Pr(DOTA)(H₂O)]·4H₂O and Na[Nd(DOTA)(H₂O)]·4H₂O. The crystal structures of Na-[Pr(DOTA)(H₂O)]·4H₂O and Na[Nd(DOTA)(H₂O)]·4H₂O (see Figure 4) do not deserve particular comments as they are isomorphous and isostructural to the other members of the series of Ln[(DOTA)(H₂O)]⁻ complexes endowed with SA-type structures (Ln = Y,[7] Eu,[4,5] Gd[3], Ho,[5] Lu[6]). ^{1}H NMR solution studies showed a higher amount of the TSA isomer for Pr derivatives and equal populations of the two isomeric forms for the Nd complexes.[12] However, our experimental protocol only yielded crystals containing SA-type structures. The respective Ln−N and Ln−O bond distances (either for the DOTA ligand or for the coordinated H₂O) are in agreement with the crystal radius trend (see Tables 1 and 2).

Crystal Structure of Na[Dy(DOTA)(H₂O)]·Na(OH)·7H₂O. Crystals having the chemical composition Na[Dy-(DOTA)(H₂O)]·Na(OH)·7H₂O have been obtained. The coordination geometry around the metal ion is of the SA type. Again the coordination geometry involves four oxygen and four nitrogen atoms from the DOTA ligand with a water molecule in capping position. The twist angle is 38°, which is close to the value of 39° of the previously reported isomorphous series.[3,5,6,7] However, the crystal packing is different because of the different chemical composition, and it is controlled by the sodium coordination polyhedra and by the hydrogen bond network. The two unique sodium octahedra form a tetramer in the solid state through edge sharing, as shown in Figure 5. Around Na(1) five oxygens

Table 1. Bond Distances in the Metal Coordination Spheres

	Na[Ce(DOTA)(H$_2$O)]·NaHCO$_3$·7H$_2$O	Na[PrDOTA](H$_2$O)]·4H$_2$O	Na[NdDOTA](H$_2$O)]·4H$_2$O	Na[Dy(DOTA)(H$_2$O)]·NaOH·7H$_2$O	K[Tm(DOTA)]·6H$_2$O·0.5KCl	3(Na[Sc(DOTA)])·NaOH·18H$_2$O
M−N(1)	2.72(1)	2.711(3)	2.694(2)	2.614(8)	2.518(6)	2.441(3), 2.446(3), 2.450(2)
M−N(4)	2.77(1)	2.724(3)	2.704(2)	2.61(1)	2.532(6)	
M−N(7)	2.76(1)	2.703(3)	2.689(2)	2.63(1)	2.536(6)	
M−N(10)	2.70(1)	2.745(3)	2.727(2)	2.639(9)	2.531(5)	
M−O(1)	2.46(1)	2.439(3)	2.426(2)	2.329(7)	2.270(4)	2.151(2), 2.147(2), 2.163(2)
M−O(4)	2.44(1)	2.437(3)	2.420(2)	2.346(7)	2.288(4)	
M−O(7)	2.44(1)	2.418(3)	2.406(2)	2.326(7)	2.278(5)	
M−O(10)	2.47(1)	2.429(3)	2.413(2)	2.340(8)	2.283(4)	
M−O$_w$	2.59(1)	2.529(3)	2.508(2)	2.474(8)		

Table 2. Geometrical Parameters Involving the M(III)−Water Environment

	Ce	Pr	Nd	Eu[5]	Dy	Ho[5]	Tm	Lu[6]	Sc
M−O$_w$, Å	2.59(1)	2.529(3)	2.508(3)	2.483(3)	2.474(8)	2.444(2)		2.416(4)	
M−H$_w$		3.03(5)	2.94(4)	2.93(4)		2.97(5)		2.86(5)	
		2.96(6)	2.93(5)	2.90(4)		2.91(5)		2.81(5)	
H−O−H, deg		101(6)	105(5)					121(6)	
O(1B)−M−O(7B), deg	143.5(9)	146.83(9)	145.93(6)	144.13(6)	143.1(3)	142.60(7)	124.7(1)	141.7(1)	124.0(1)[b]
O(4B)−M−O(10B)	144.6(5)	149.09(9)	148.23(7)	146.33(6)	141.6(2)	144.58(7)	124.0(2)	143.3(1)	125.0(1)
									123.7(1)
twist angle, deg	25	39	39	39	38	39	24.5	39	40.99(8)[b]
									41.16
									40.15
isomer	TSA	SA	SA	SA	SA	SA	TSA′	SA	SA′
cryst radii	1.336	1.319	1.303	1.260	1.223	1.212	1.134[c]	1.172	1.010[c]

a For IX CN. (Shannon, R. D. *Acta Crystallogr.* **1976**, *A32*, 751). *b* For the three independent coordination spheres. *c* For VIII CN.
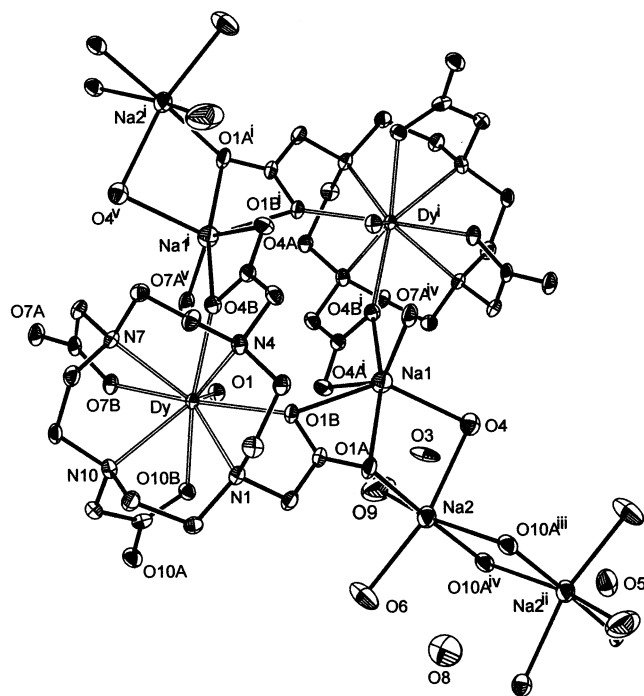

Figure 5. Na polyhedra interconnecting the [Dy(DOTA)(H$_2$O)]$^-$ moieties (ORTEP view). At (i) −x, −y, −z; (ii) 1 − x, −1 − y, −z; (iii) 1 − x, −y, −z; (iv) x, y − 1, z; and (v) −x, 1 − y, −z.

(O(4A)′, O(4B)′, O(7A) (iv), O(1B), and O(1A)) belonging to different [Dy(DOTA)H$_2$O]$^-$ moieties are coordinated. The sixth position is occupied by an oxygen O(4) (likely a hydroxide group) bridging, together with O(1A), the second Na(2) atom, which is also linked to two water molecules (O(6) and O(9)) and to two other carboxylic oxygens (O(10)-‴ and O(10) (iv)) bridging the next Na(2)″ position.
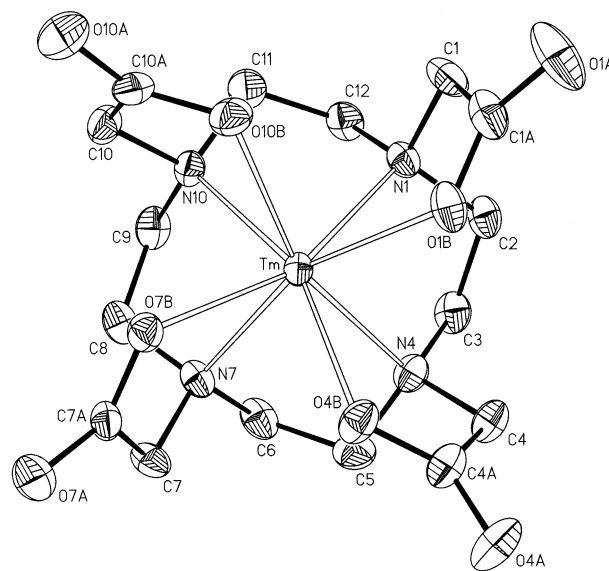

Figure 6. TSA′ geometry for [Tm(DOTA)]$^-$, ORTEP view.

Crystal Structure of K[Tm(DOTA)]·6H$_2$O. The chemical formula of the crystals subjected to the X-ray structure determination is K[Tm(DOTA)]·6H$_2$O. The crystal structure (Figure 6) shows that the Tm(III) ion is eight-coordinate through four nitrogen atoms (mean Tm−N: 2.530(5) Å) and four oxygens (mean Tm−O: 2.280(4) Å). The geometry of the coordination cage around the Tm ion corresponds to a TSA′ type. The four nitrogen atoms are planar as are the four oxygens with the two planes parallel to each other. The twist angle between the nitrogens and the oxygens is 24.5°. The thulium ion is closer to the oxygen plane (1.065(4) Å) than to the nitrogen plane (−1.466(4) Å) as in the analogous
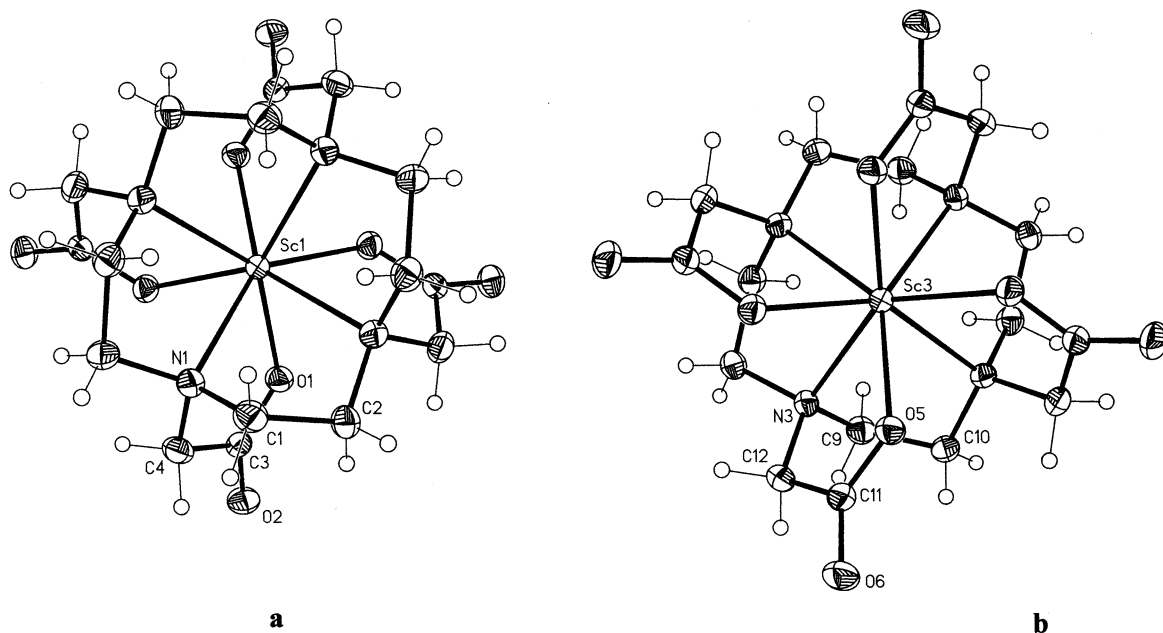
a

b

Figure 7. SA′ isomers of Sc(DOTA) with different torsion angles of the acetate arms: (a) N(1)−C(4)−C(3)−O(1) −15.8(4)° and (b) N(3)−C(12)−C(11)−O(5) 21.0(4)°.

compounds of monocapped SA geometries (water in capping position), and the Tm−N bonds (av: 2.535(6) Å) are larger than those of the Tm−O bonds (av: 2.280(5) Å).

It is worth noting that the Tm−O bond distances (2.270-(4) → 2.288(4) Å) in this derivative are similar to those found for Lu−O in Na[Lu(DOTA)(H$_2$O)]·4H$_2$O[6] (2.269(4) → 2.285(5) Å), while the Tm−N bond distances (2.518(6) → 2.536(6) Å) are significantly shorter than the corresponding Lu−N distances (range 2.597(4) → 2.640(4) Å). The ionic radius of the Tm(III) ion with CN 8 is 1.134 Å, whereas for the Lu(III) ion with CN 9 it is 1.172 Å.

The potassium ion is irregularly coordinated to two water molecules and to three carboxylate groups (one chelating and two monodentate) belonging to three different Tm-(DOTA) moieties. The remaining four water molecules in the asymmetric units are waters of crystallization. They form a network of hydrogen bond interactions as suggested from the contacts among them of ca. 2.8 Å (water hydrogens were poorly located and not included in the refinement).

Crystal Structure of 3{Na[Sc(DOTA)]}NaOH·18H$_2$O. The scandium derivative crystallizes as 3{Na[Sc(DOTA)]}·NaOH·18H$_2$O in a tetragonal cell with three independent scandium atoms lying on a 4-fold axis that is in the direction of the larger cell parameter c. Their distances are as follows: 6.510(2), (Sc(1)···Sc(1) (i)); 10.909(2), (Sc(1)···Sc(2)); 6.472(2), (Sc(2)···Sc(3)); and 6.741(2) Å, (Sc(3) ···Sc(3) (ii)) ((i) at 0, 0, −z; (ii) at 0, 0, 1 − z).

The coordination geometry around each scandium is SA. The torsion angle about the two squares of the oxygens and nitrogens is 40.99(8), 41.19(7), and 40.11(6)°, respectively, for the three Sc(1), Sc(2), and Sc(3) polyhedra. The lack of coordinated water molecules and the value of the torsion angle between the N$_4$/O$_4$ planes clearly suggest that the obtained structure can be classified as SA′ type. The three independent Sc−O bond lengths (2.152(2), 2.147(2), and

2.163(2) Å for Sc(1), Sc(2), and Sc(3), respectively) are comparable in the three polyhedra as are the Sc−N ones (2.441(3), 2.446(3), and 2.450(3) Å, respectively).

The main difference is in the geometry of the acetate arms of the DOTA ligand with torsion angles N−CH$_2$−C−O of −15.8(4), 21.8(4), and 21.0(4)° for Sc(1), Sc(2), and Sc(3), respectively, as shown in Figure 7. The whole structure consists of layers of Sc(1) and Sc(3) polyhedra connected by the Na polyhedra, where the sodium atoms have the usual distorted octahedral geometry (Figure 8). The coordinated oxygens belong either to the water molecules present in the structure or to the oxygens of the DOTA acetate arms not involved in the scandium coordination. The Sc(2) polyhedra are connected via a network of hydrogen bonds to the remaining water molecules, which allow the formation of independent layers parallel to those of Sc(1) and Sc(3) and perpendicularly to the c axis (Figure 9). A peculiarity of the structure is the high symmetry of the molecules not previously encountered in the series of the DOTA lanthanide derivatives.

Discussion

In all DOTA complexes the tetra-azacyclododecane ring adopts a square [3333] conformation and forms the basal plane of a square antiprismatic cage of donor atoms. The N$_4$ and O$_4$ square planes are parallel, and the metal ions are shifted toward the O$_4$ face. When the M−N/M−O distance ratios are compared, it appears that the metal ions are less shifted toward the O$_4$ face in the TSA-type structures. In general, the SA-type structures appear more compact and the TSA more expanded, and this is clearly reflected in the solution ¹H NMR spectra of the two isomeric forms.[8,12,16] In fact, when the complexes of the paramagnetic metal ions

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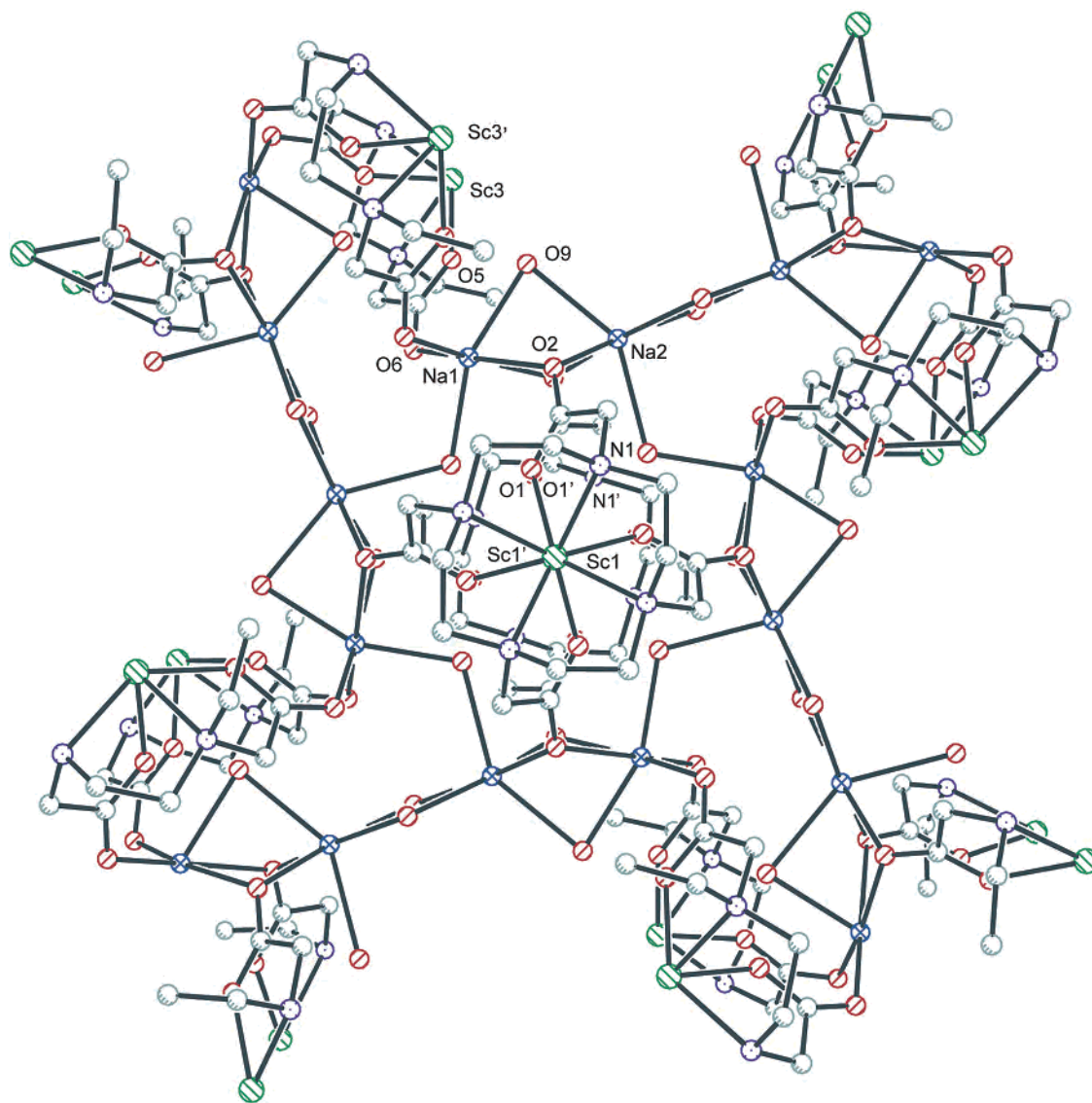(16) Hoeft, S.; Roth, K. *Chem. Ber.* **1993**, *126*, 869−873.

Figure 8. View down *c* of the Sc(1) and Sc(3) polyhedra in Sc(DOTA) (′ at 0, 0, −*z*).

(except Gd) are considered, SA structures invariably display an isotropic shift range larger than the TSA ones. The results obtained in this work are in general consistent with the expectations foreseen from the solution work (i.e., the size of the metal ion determines the structural arrangement of the DOTA ligand in the complex). This implies that the cavity size is decreasing in the order TSA > SA > TSA′ > SA′. The case of Lu(III) is an exception, as it crystallizes as an SA-type structure. Because of the dominant electrostatic nature of the lanthanide bonds, the crystal packing forces seem to be prevalent to induce a particular structure in the solid state. Furthermore, it has been confirmed from the result of the NMR solution studies that the peculiar structural feature that discriminates between TSA/TSA′ and SA/SA′ classes is represented by the twist angle between the basal N_4 and the apical O_4 planes. From the new data reported in this work, it is definitively established that in SA-type structures the twist angle is approximatively 39°. Only in the case of the smallest Sc(III) ion (in the absence of coordinated water) it further shifts toward the ideal value of 45°.

In Ce(DOTA) (TSA structure) and in Tm(DOTA) (TSA′ structure) the twist angle is ca. 25°. This value is slightly higher than that found in the polymeric structure[13] of La-(DOTA) (22°), but in that case the asymmetric unit contained two lanthanide chelates with capping positions occupied by bridging carboxylates. Other TSA structures with twist angles of 29.7, 26, and 28° have been seen for Gd(III) complexes made with the DOTA derivatives DO3MA (DO3MA = (1*R*,4*R*,7*R*)-α,α′,α″-trimethyl-1,4,7,10-tetra-azacyclododecane-1,4,7-tetra-acetic acid),[17] HPDO3A (HPDO3A = 10-(2-hydroxypropyl)-1,4,7,10-tetra-azacyclododecane-1,4,7-tri-acetic acid),[18] and DO3A (DO3A = 1,4,7,10-tetraaza-cyclododecane-1,4,7-triacetic acid),[3] respectively. TSA′ co-ordination geometries have been seen in the Y(III),[19] Eu-

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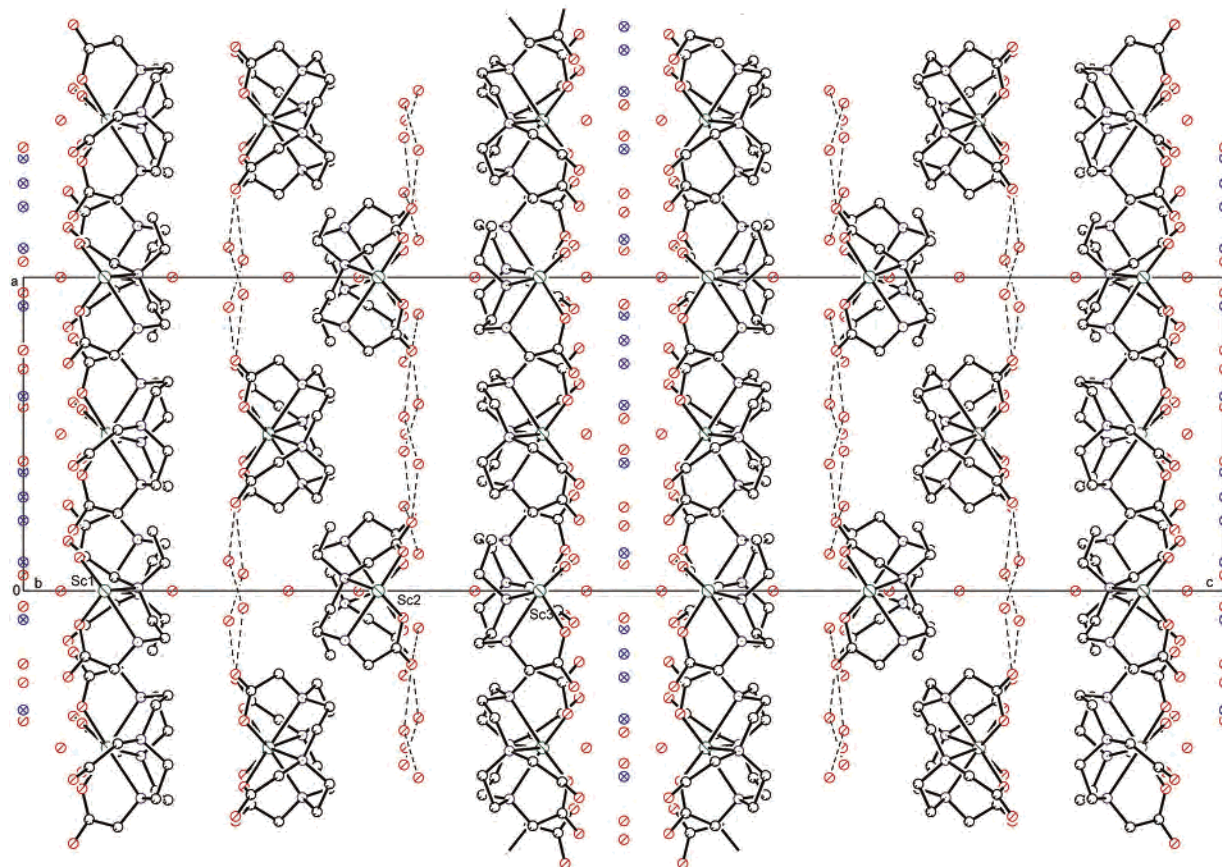
Figure 9. Unit cell content of Sc(DOTA) down *b*. ⊕ (blue) circles indicate the Na position and ◯ (red) the water positions. The interconnection of Sc(2) polyhedra via hydrogen bonds with water molecules is shown with dotted lines.

(III),[20] and Yb(III)[20] (twist angle 29°) complexes of DOTPBz (DOTPBz = 1,4,7,10-tetra-azacyclododecane-tetrakis(methylenebenzylphophinato)), while the La(III) derivative formed a TSA structure.[20] The largest angle seen was 30.7° for the Gd(III) complex with ODOTRA,[21] a ligand related to DO3A in which the secondary amine nitrogen is replaced by an oxygen atom. All these data point to indicate that other complexes based on the TAZA ring show analogous trends with regard to Ln size and type of coordination geometry; thus, because of the close relationship between structural features and relaxometric properties, the results of the present work can be of help for the design of optimized MRI contrast agents.

On the basis of the above considerations it seems that a rather large modulation of the twist angle appears possible in TSA- and TSA′-type structures, whereas a much more defined angle has been found for SA-type structures. As far as the metal water distances are concerned, an almost linear relationship with the lanthanide ionic radii has been found among the homogeneous series of the DOTA complexes endowed with a SA-type structure (Table 4). Only Dy-(DOTA) does not fit this relationship as the bond length

appears longer than expected. This might be due to the fact that it crystallizes with a unit cell different from those of all other SA-type Ln(DOTA) complexes.

Structural Features of the Hydration Sphere. As recalled above, an important difference between SA- and TSA-type structures is the difference in the exchange rate of the coordinated water molecule. This finding is highly relevant for the design of efficient Gd(III)-based contrast agents for MRI applications. We now consider whether the structural characteristics of the hydration sphere for the two typologies of complexes can account for their different behavior.

In the isostructural series of Na[Ln(DOTA)H$_2$O]·4H$_2$O complexes (Ln = Pr, Nd, Eu, Gd, Ho, Lu) (SA isomer), the four uncoordinated water molecules lie in a plane with deviations in the range of −0.008(3)−0.040(4) Å. The coordinated water is 0.335(2) Å apart from this plane and does not interact with the other water molecules present in the structure but with two uncoordinated oxygens of the ligand of adjacent molecules (Table 3). The structure of the Nd derivative is reported as a representative example (Figure 10). Also in the dysprosium derivative (SA isomer), the coordinated water does not form hydrogen bonds with the numerous water molecules present in the cell (seven per asymmetric unit). Conversely, in the cerium derivative (TSA isomer), the coordinated water interacts with a water present in the crystal cell. Of the seven water molecules present per

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Table 3. Hydrogen Bonds Involving Water Molecules in the Isomorphous Na[Ln(DOTA)(H$_2$O)]·4H$_2$O Complexes[a]

D−H···X	D−H (Å)	H···X (Å)	D−H···X (deg)	D···X (Å)	equiv position of X
			Nd		
O$_w$1−H102···O1A	0.71	2.08	174	2.790	−x + 1, −y, −z + 1
O$_w$1−H103···O4	0.74	2.04	176	2.773	−x + 1, −y + 1, −z + 1
O$_w$2−H200···O4B	0.74	2.16	165	2.882	
O$_w$3−H300···O10A	0.85	1.99	171	2.842	
O$_w$3−H301···OW5	0.63	2.12	171	2.746	
O$_w$5−H500···O7A	1.01	1.77	164	2.756	
O$_w$4−H400···OW3	0.75	1.98	167	2.718	−x, −y + 1, −z
O$_w$4−H401···O7A	0.76	2.02	172	2.767	
			Pr		
O$_w$1−H102···O1A	0.76	2.03	169	2.785	−x + 1, −y, −z + 1
O$_w$1−H103···O4A	0.75	2.02	176	2.769	−x + 1, −y + 1, −z + 1
O$_w$2−H200···O4B	0.80	2.10	165	2.888	
O$_w$3−H301···O10A	0.80	2.05	169	2.839	
O$_w$3−H300···OW5	0.67	2.08	178	2.756	
O$_w$5−H501···OW4	0.94	1.90	146	2.733	−x, −y + 1, −z
O$_w$4−H401···OW3	0.70	2.05	164	2.731	x, y + 1, z
O$_w$4−H401···O7A	0.76	2.02	170	2.767	

[a] Ln = Nd, Pr.
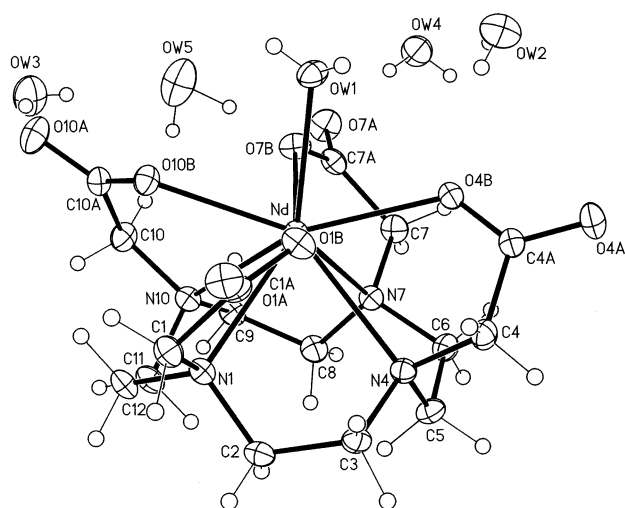
Figure 10. Orientation of the four water molecules in Na[Nd(DOTA)]·4H$_2$O.

asymmetric unit, four of them (O$_w$2, O$_w$3, O$_w$4, and O$_w$5) are arranged in a plane as in the isomorphous series, and again, none of them is in contact with the coordinated water. The interaction involves O$_w$(8) (O$_w$1···O$_w$8 = 2.85(4) Å), one of the adjacent water molecules out of the plane of the four (Figure 3).

This finding may account for the higher water exchange rate in the TSA isomer; that is, in the latter isomer the coordinated water is facilitated to leave the lanthanide(III) ion because of the hydrogen bond interaction with a water molecule in the second coordination sphere. Another interesting clue comes from the lanthanide−water distances.

While the Ln−O$_{DOTA}$ bond distances follow the decrease of the crystal radii, the Ln−water distance seems to be influenced by the O$_{DOTA}$−Ln−O$_{DOTA}$ angle that does not allow, on steric hindrance ground, the same level of bond contraction, as the Ln−water distance decreases less than expected by the crystal radii (Table 2). On comparing the value of this angle in the Ce derivative (TSA structure) with that of Pr (SA structure) next in the series, we find an opening of about 4°. Apparently, the less prismatic arrangement of

the coordinated atoms in Ce causes a restriction of the angle with a consequent lengthening of the Ce−O$_w$ bond distance, which is greater than the difference of the crystal radii (Table 3). Again, this could effect a preferred loss of the coordinated water from the TSA isomer than from the SA one.

Support to the view that TSA-type structure has a longer water distance than the SA isomer has been gained also from previously reported observations on Gd(DO3MA).[17] The X-ray solid-state structure of the latter complex showed the simultaneous presence of TSA and SA conformations whose Gd−H$_2$O distances are 2.53(1) and 2.42(1) Å, respectively. In summary, it appears that the higher exchange rate of the coordinated water in the TSA isomer could receive a substantial contribution from the lower bond enthalphy of the Ln−O bond. However, it does not seem to be the only reason. In fact, if the exchange rate is determined by an assisted dissociative mechanism, the aqueous microenvironment around the coordinated water would have a role in stabilizing the intermediate state. Finally, it must be noted that whereas a direct use of solid-state data to discuss solution observation is in general questionable, the close correspondence found between the structural features of the complexes in solution (high-resolution NMR and relaxometric data) and in the solid state (X-ray determination) makes in the present case this comparison useful and justified.

Conclusion

The crystallographic data reported and discussed in this work represent a complete and detailed study of the influence of the Ln(III) size on the structure of their DOTA complexes. Moreover, for the first time the crystal structures of Ln-(DOTA) complexes are shown in the previously predicted TSA′ and SA′ coordination geometries. The coordination of lanthanide ions to the DOTA ligand has been shown to yield complexes endowed with quite different crystal structures. The more striking example is the polymeric structure of the lanthanum derivative. A possible role of the cation, generally sodium, on the type of isomer present in the crystal cell was also considered. In fact, each SA isomer of the isostructural

Table 4. Selected Structural Parameters for (DOTA) Derivatives[a]

	M–N	M–O	M–O_w	isomer
Na[La(HDOTA)La(DOTA)]·10H_2O[13]	2.784(6) → 2.810(6)	2.473(6) → 2.506(6)	2.571(5)[b]	TSA
	2.747(6) → 2.786(6)	2.481(6) → 2.508(6)	2.536(5)[b]	
Na[Ce(DOTA)(H_2O)]·NaHCO_3·7H_2O	2.70(1) → 2.77(1)	2.44(1) → 2.47(1)	2.59(1)	TSA
Na[PrDOTA(H_2O)]·4H_2O	2.703(3) → 2.745(3)	2.418(3) → 2.439(3)	2.529(3)	SA
Na[NdDOTA(H_2O)]·4H_2O	2.689(3) → 2.728(3)	2.405(3) → 2.424(3)	2.508(2)	SA
Na[Eu(DOTA)(H_2O)]·4H_2O[5]	2.602(2) → 2.772(2)	2.362(3) → 2.389(2)	2.483(3)	SA
Na[Gd(DOTA)(H_2O)]·4H_2O	2.645(3) → 2.688(3)	2.359(3) → 2.379(3)	2.463(3)	SA
Na[Dy(DOTA)(H_2O)]·NaOH·7H_2O	2.61(1) → 2.64(1)	2.326(7) → 2.346(7)	2.474(8)	SA
Na[Ho(DOTA)(H_2O)]·4H_2O[5]	2.628(2) → 2.665(3)	2.323(2) → 2.336(2)	2.444(2)	SA
K[Tm(DOTA)]·6H_2O·0.5KCl	2.518(6) → 2.536(6)	2.270(4) → 2.2884		TSA′
Na[Lu(DOTA)(H_2O)]·4H_2O[6]	2.597(4) → 2.640(4)	2.269(4) → 2.285(3)	2.416(4)	SA
3{Na[Sc(DOTA)]}·NaOH·18H_2O	2.441(3)	2.151(2)		SA′
	2446(3)	2.147(2)		
	2.450(2)	2.163(2)		
Na[Y(DOTA)(H_2O)]·4H_2O[7]	2.625(4) → 2.666(4)	2.316(3) → 2.327(3)	2.453(3)	SA

[a] Distances in Å. [b] Oxygens of the bridging carboxylic groups.

series crystallizes with a Ln/Na ratio of 1:1, while this ratio is 2:1 for the La derivative, (polymeric TSA isomer) and 1:2 for Ce (TSA isomer) and for Dy (SA isomer), respectively. Clearly, no relationship can be drawn between the amount of Na$^+$ in the crystal unit and the observed structure. Then the role of the water content in the crystal cell has been considered. It ranges from 10 molecules for the La complex to seven for Ce and four for each complex of the isostructural and isomorphous series (Pr, Nd, Eu, Gd, Dy, Ho, and Lu complexes), but it is seven in the isostructural Dy cation. No correlation can be drawn between the type of isomer present and the amount of water in the crystal cell.

The K[Tm(DOTA)] complex, displaying six water molecules, has the coordination geometry of a twisted square antiprism (TSA′ isomer) with no water coordinated, while Lu[6] at the end of the series shows the monocapped prismatic geometry (SA isomer). On the basis of the isomeric ratio detected in the solution for the Tm and Lu complexes, these are not the structures one would have predicted. However, besides crystal packing effects, the intimate mechanism that leads to the formation of a particular structural entity could be also influenced by the presence of inorganic salts that with their coordination requirements may favor a particular geometry of the Ln(DOTA) derivative.

The smaller Sc(III) ion has been investigated to assess the effect of the reduced coordination number on the preferred isomeric type. It shows a regular square antiprismatic geometry (SA′ isomer) in a very complicated context where the different Sc(DOTA) units, connected either through hydrogen bond interactions and/or by sodium polyhedra, differ only for the torsion of the acetate arms.

Finally, consideration of the water molecules in the outer coordination sphere of the Ln(III) ions revealed that in the TSA structure the coordinated water molecule is hydrogen bonded to water in the lattice. This suggests a possible assistance in the departure of the coordinated water that could account for the faster rate of exchange k_{ex} observed in this type of structure. Furthermore, a longer Ln–O_w bond distance, as a consequence of a restriction of the O_DOTA–Ln–O_DOTA angle, is found for the complexes with the TSA-type structure that again is consistent with a faster rate of water exchange. As k_{ex} represents a key parameter in determining the relaxivity of macromolecular Gd-based contrast agents, the results of this work may contribute to the design and the development of suitable macrocyclic complexes of optimized efficacy.

Experimental Section

Synthesis. The ligand DOTA was synthesized as described previously.[1] The Ce, Pr, Nd, and Dy complexes were prepared as sodium salts by mixing stoichiometric amounts of H_4DOTA, the given LnCl_3 salt (Aldrich Chemical Co.) and NaOH. Typically, to a suspension of H_4DOTA (20 mmol) in water (20 mL), NaOH (1 mol) was added until pH 5 for complete dissolution. LnCl_3 (20 mmol) was then added, and the reaction mixture was heated at 60 °C for 12 h at pH 7.0 by addition of NaOH (1 mol) and subsequently loaded onto a column of Amberlite XAD 16-00 polystyrene resin (1.0 L), which was eluted with water (5.0 L). Complexes were obtained as white solids. Yield: 90–95%. The thulium complex was prepared in the same way except for the use of KOH instead of NaOH.

The scandium complex was prepared from Sc(acetate)_3, instead of ScCl_3, at pH 4 as previously described except for the concentration of the reaction mixture to eliminate the acetic acid. The residue was then dissolved in water (20 mL), basified with NaOH (1 mol) at pH 7.0, and evaporated to dryness under reduced pressure obtaining the desired complex as a white solid. Yield: 95%.

X-ray Structure. Single crystals suitable for X-ray analysis were obtained by vapor diffusion of acetone into the corresponding water solution (room temperature) for Ce, Pr, Nd, Dy, Tm, and Sc derivatives.

Crystals were lodged in Lindemann glass capillaries and centered on a four circle Philips PW1100 diffractometer using graphite monochromated Mo Kα radiation (0.71073 Å). Unit cell parameters were obtained by a least squares refinement of 25 strong reflections in the 2θ range of 20–28°. The diffraction data were corrected for Lorentz polarization effects and for absorption, as described by North et al.[22]

The structures of the Ce, Dy, and Tm derivatives were solved by standard Patterson methods and subsequently completed by Fourier syntheses. The structure of Sc(I) was solved by direct methods,[23] and those of the Pr and Nd derivatives were refined from the atomic coordinates of the isomorphous holmium.[5] Non-

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Table 5. Crystal Data

	Na[Ce(DOTA)(H$_2$O)]·NaHCO$_3$·7H$_2$O	Na[PrDOTA)(H$_2$O)]·4H$_2$O	Na[NdDOTA)(H$_2$O)]·4H$_2$O	Na[Dy(DOTA)(H$_2$O)]·NaOH·7H$_2$O	K[Tm(DOTA)]·6H$_2$O·0.5KCl	3(Na[Sc(DOTA)])·NaOH·18H$_2$O
space group	monoclinic	triclinic	triclinic	monoclinic	monoclinic	tetragonal
	$P2_1$ (No. 4)	$P\bar{1}$ (No. 2)	$P\bar{1}$ (No. 2)	$P2/c$ (No. 13)	$C2/c$ (No. 15)	$I4/m$ (No. 87)
a, Å	9.040(3)	8.715(2)	8.705(2)	12.170(4)	37.550(6)	12.517(2)
b, Å	9.024(2)	9.188(2)	9.160(2)	8.977(2)	8.981(3)	12.517(2)
c, Å	18.266(3)	15.880(5)	15.840(4)	27.891(6)	16.783(5)	48.015(9)
α, deg	90	82.74(3)	82.77(3)	90	90	90
β, deg	92.00(3)	84.93(3)	85.05(3)	99.88	111.09(3)	90
γ, deg	90	80.98(2)	81.09(3)	90	90	90
Z	2	2	2	4	8	4
μ(Mo Kα)	1.631	2.047	2.190	2.593	3.715	0.393
ρ_{calcd}, g cm^{-3}	1.643	1.749	1.769	1.704	1.7501	1.558
V, Å^3	1489.2(6)	1242.7(7)	1235.0(6)	3002(1)	5280(2)	7523(2)
R (F_o) ($I \geq 2\sigma I$)^a	0.071	0.025	0.017	0.064	0.035	0.055
R_w (F_o)^2 ($I \geq 2\sigma I$)^a	0.185	0.062	0.045	0.167	0.088	0.144

^{a} $R = \sum|F_o| - |F_c|/\sum|F_o|$. $R_w = \{\sum[w(F_o^2 - F_c^2)^2]/\sum[w(F_o^2)^2]\}^{1/2}$.

hydrogen atoms were refined anisotropically in all the structures. The hydrogen atoms of the DOTA ligand were introduced at the calculated positions with fixed isotropic thermal parameters (1.2 U$_{equiv}$ of the parent carbon atom) for the Ce, Dy, and Sc compounds except those of the noncoordinated water molecule that were ignored. In the Pr and Nd compounds all the hydrogen atom positions were located on difference Fourier maps and refined isotropically. In Tm only those belonging to the DOTA ligand were located on a difference Fourier map and included in the refinement with isotropically thermal parameters; those of the water molecules were not introduced.

Structure refinement and final geometrical calculations were carried out with the SHELXL-97[23] program, and drawings were produced using ORTEP II.[24] Experimental data and selected bond distances are listed in Tables 5 and 1.

Supporting Information Available: X-ray crystallographic file in CIF format for the reported structures. This material is available free of charge via the Internet at http://pubs.acs.org.

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