

Crystal Structures of Lanthanide(III) Complexes with Cyclen Derivative Bearing Three Acetate and One Methylphosphonate Pendants

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A series of lanthanide(III) complexes formulated as $M[\text{Ln}(\text{Hdo3ap})] \cdot x\text{H}_2\text{O}$ ($M = \text{Li}$ or H and $\text{Ln} = \text{Tb}$, Dy , Er , Lu , and Y) with the monophosphonate analogue of H_4dota , 1,4,7,10-tetraazacyclododecane-1,4,7-triacetic-10-methylphosphonic acid ($\text{H}_5\text{do3ap}$), was prepared in the solid state and studied using X-ray crystallography. All of the structures show that the $(\text{Hdo3ap})^{4-}$ anion is octadentate coordinated to a lanthanide(III) ion similarly to the other H_4dota -like ligands, i.e., forming O_4 and N_4 planes that are parallel and have mutual angle smaller than 3° . The lanthanide(III) ions lie between these planes, closer to the O_4 base than to the N_4 plane. All of the structures present the lanthanide(III) complexes in their twisted-square-antiprismatic (TSA) configuration. Twist angles of the pendants vary in the range between -24 and -30° , and for each complex, they lie in a very narrow region of 1° . The coordinated phosphonate oxygen is located slightly above (0.02 – 0.19 \AA) the O_3 plane formed with the coordinated acetates. A water molecule was found to be coordinated only in the terbium(III) and neodymium(III) complexes. The bond distance $\text{Tb}-\text{O}_w$ is unusually long (2.678 \AA). The $\text{O}-\text{Ln}-\text{O}$ angles decrease from 140° [$\text{Nd}(\text{III})$] to 121° [$\text{Lu}(\text{III})$], thus confirming the increasing steric crowding around the water binding site. A comparison of a number of structures of $\text{Ln}(\text{III})$ complexes with DOTA-like ligands shows that the TSA arrangement is flexible. On the other hand, the SA arrangement is rigid, and the derived structural parameters are almost identical for different ligands and lanthanide(III) ions.

Introduction

Polyazamacrocycles with coordinating pendant arms form very stable complexes with a wide range of the transition metal ions and also with lanthanides. Ligands encapsulate metal ions in macrocyclic cavities, and the complexes often exhibit thermodynamic as well as kinetic stabilities that are essential for in vivo applications.¹ Convenient properties of these complexes have been explored in several areas, e.g., as contrast agents in magnetic resonance imaging (MRI),² in labeling of biomolecules with metal radioisotopes for both diagnostic and therapeutic purposes,³ or as luminescence

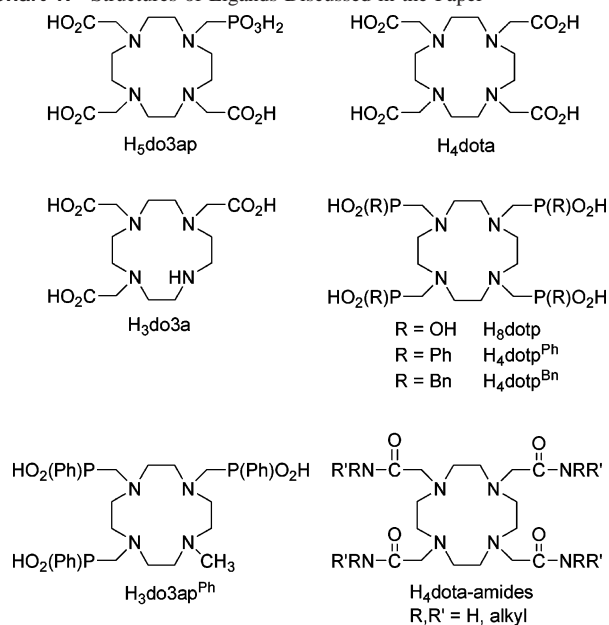
probes.⁴ The most widely studied, H_4dota ($\text{H}_4\text{dota} = 1,4,7,10$ -tetraazacyclododecane-1,4,7,10-tetraacetic acid, Chart 1), is a prototype ligand for the above applications. Therefore, a number of H_4dota derivatives and analogues have been synthesized and studied.^{1–4}

In this area of chemistry, the design of better MRI contrast agents is of high interest.^{2,5,6} Most currently approved MRI contrast agents are Gd^{3+} complexes with ligands derived

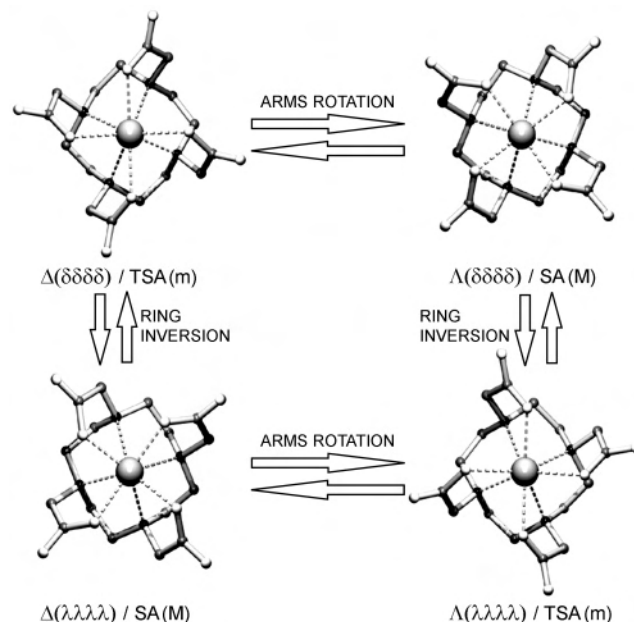
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Chart 1. Structures of Ligands Discussed in the Paper

from open-chain H_5dtpa (H_5dtpa = diethylenetriamine-pentaacetic acid) and macrocyclic H_4dota . The coordination environment of the central ion is formed by eight donor atoms coming from the ligand and one water molecule, which is responsible for transfer of magnetic information to the bulk water. The efficiency of such contrast agents is commonly expressed as *relaxivity*, r_1 (enhancement of the water proton relaxation rate). Relaxivity is governed by several parameters:⁵ the residence time of the coordinated water molecule τ_M , the rotational correlation time τ_R , and the electronic relaxation times $T_{1e,2e}$. These parameters are associated with the structure of the complexes, i.e., geometry and symmetry of the coordination polyhedron, size (molecular volume) of the complex, and distribution of electron density around the central ion. The relaxivity is also influenced by the Gd– O_w and Gd– H_w distances between the central ion and the atoms of the coordinated water molecule. The prototype dota^{4-} anion is coordinated to a lanthanide(III) ion by four ring nitrogen atoms and four carboxylate groups. The nitrogen and oxygen atoms form N_4 and O_4 bases that are planar and virtually parallel. The O_4 plane is capped with a water molecule. The ethylene groups of the macrocycle adopt a gauche conformation forming a five-membered coordination metallacycle with either δ or λ configuration. This results in two possible macrocycle square [3,3,3,3] conformations: $\delta\delta\delta\delta$ and $\lambda\lambda\lambda\lambda$.⁷ The pendant acetate arms can occupy two orientations: Δ or Λ . In solution, the ring interconversion $\delta \leftrightarrow \lambda$ and acetate rotation $\Delta \leftrightarrow \Lambda$ lead to four stereoisomers (two racemic diastereoisomers $\Delta\delta\delta\delta/\Lambda\lambda\lambda\lambda$ and $\Delta\lambda\lambda\lambda/\Lambda\delta\delta\delta$, respectively; Scheme 1). In addition, the two diastereoisomers differ in the angle ω formed by the mutual rotation of the O_4 and N_4 planes (Chart 2). In the isomers $\Delta\lambda\lambda\lambda/\Lambda\delta\delta\delta$, rotation of about 40° leads to the square-antiprismatic (SA) isomer (ideal angle of 45°). This diastereoisomer is also traditionally

Scheme 1. Possible Isomers for Lanthanide(III) Complexes with H_4dota -like Ligands

termed “major” (M) because of its higher abundance in solutions of the $[\text{Gd}(\text{dota})(\text{H}_2\text{O})]^-$ complex.⁸ In the pair of enantiomers $\Lambda\lambda\lambda\lambda/\Delta\delta\delta\delta$, rotation of about -24° corresponds to the twisted-square-antiprismatic isomer TSA (ideal angle of -22.5°) or “minor” (m) isomer. The signs \pm are commonly used for the SA/TSA isomers of the prototype dota^{4-} complexes and will also be used in this paper.

The two diastereoisomers play a key role in MRI applications. It was found that the lanthanide(III) complexes of H_4dota -like ligands (with one water molecule in the first coordination sphere) show different residence times, τ_M , of the coordinated water for SA and TSA isomers.^{9,10} The water molecule is exchanged 10–100 times faster in the TSA isomer than in the SA one. An explanation for the difference follows from the assumed sterically crowded environment of the coordinated water molecule in the TSA isomer. The water exchange rate in the TSA isomers of gadolinium(III) complexes of the carboxylate ligands approaches the optimal range of τ_M (10–30 ns).⁹ Thus, gadolinium(III) complexes with a higher content of the desired TSA isomer should exhibit a higher relaxivity, especially in high-molecular-weight molecules with very long τ_R values. It was also shown that lanthanide(III) complexes of H_4dota analogues with four phosphonic or phosphinic acid pendant arms are found in solution exclusively as TSA isomers as a consequence of

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the steric requirements of phosphorus atoms.^{11–13} However, in these complexes, no water is directly coordinated to lanthanide(III) ions. If water molecules were coordinated in similar complexes containing phosphorus pendant arm(s), a faster water exchange would occur. This effect was observed in gadolinium(III) complexes of pyridine-containing macrocycles with phosphonic acid pendant arms¹⁴ as well as upon coordination of a HPO_4^{2-} anion to gadolinium(III) complexes of $\text{H}_3\text{do3a}$ amides ($\text{H}_3\text{do3a} = 1,4,7,10$ -tetraazacyclododecane-1,4,7-triacetic acid, Chart 1).¹⁵ Moreover, it is well-known that complexes of ligands with phosphonate/phosphinate pendants exhibit a rather ordered second hydration sphere that also enhances the overall relaxivity of the complexes.^{11–14,16}

In the solid state, lanthanide(III) complexes of H_4dota form mostly SA isomers.^{17–23} TSA isomers were observed in structures of large ions such as lanthanum(III)²⁴ or cerium(III)¹⁷ or for small thulium(III),¹⁷ but without a coordinated water molecule in the case of Tm(III) (such an arrangement with no bound water molecule is often denoted TSA' or m'). On the other hand, complexes of the tetrakis(methylene-phosphinic) acid analogues of H_4dota form exclusively TSA [(La(III), Ce(III))^{12b,13a} or TSA' isomers [other Ln(III)]].¹³

Therefore, we intended to combine the convenient properties of H_4dota complexes (one coordinated water molecule, high kinetic inertness, high thermodynamic stability) with

the properties of complexes of tetraphosphonic/tetraphosphonic acid analogues of H_4dota (bulkiness of the phosphorus atom, only TSA isomer formation, ordering of the outer hydration sphere). The monophosphonate analogue of H_4dota ($\text{H}_5\text{do3ap}$, Chart 1) can be considered as a model compound for other H_4dota -like ligands with one pendant arm containing a phosphorus acid group. In this work, the preparation and X-ray structures of a series of lanthanide(III) complexes are described. We recently published a complementary studies dealing with solution properties of lanthanide(III) complexes of $\text{H}_5\text{do3ap}$,²⁵ its aminobenzylphosphinate analogue,²⁶ and H_5dtpa ²⁷ analogues with one phosphonic/phosphinic acid pendant arm on the central nitrogen atom. In these papers,^{25–27} it was shown that the presence of phosphorus acid moieties does indeed lead to the faster water exchange and enhanced relaxivity for their gadolinium(III) complexes.

Results

Synthesis. The complexes were prepared from the corresponding metal chlorides as it is described in the Experimental Section. The very slow vapor or liquid diffusion of an organic solvent (EtOH, *i*PrOH) into the aqueous solution was necessary to obtain crystals suitable for X-ray analysis. Single crystals of the salts were obtained only in the presence of lithium(I) as a counterion.

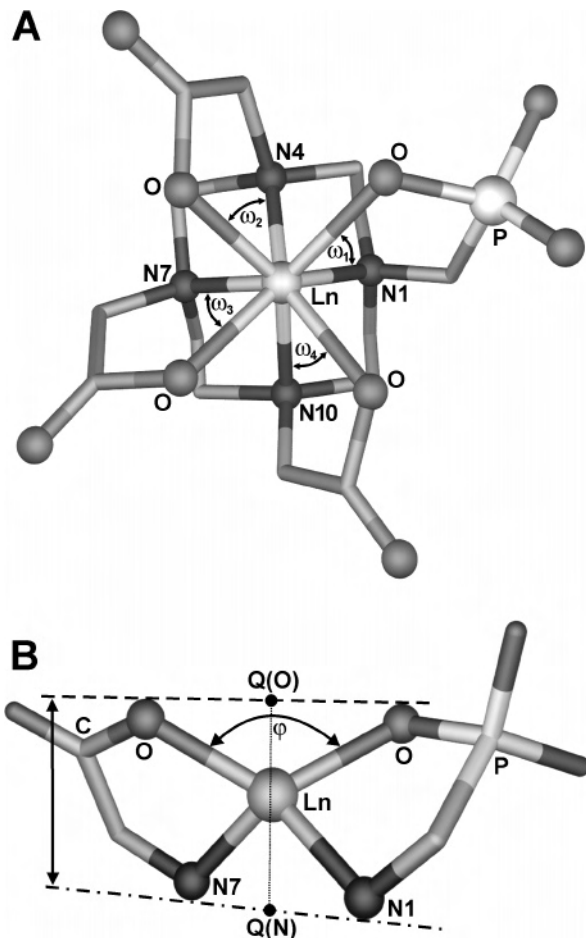
Crystal Structure of $\text{Li}[\text{Tb}(\text{Hdo3ap})(\text{H}_2\text{O})]\cdot 0.5\text{HCl}\cdot 5\text{H}_2\text{O}$. Aside from the $[\text{Nd}(\text{Hdo3ap})(\text{H}_2\text{O})]^-$ ion found in the structure of $\text{Li}[\text{Nd}(\text{Hdo3ap})(\text{H}_2\text{O})]\cdot 11.5\text{H}_2\text{O}$ published recently,²⁵ only the $[\text{Tb}(\text{Hdo3ap})(\text{H}_2\text{O})]^-$ species present in $\text{Li}[\text{Tb}(\text{Hdo3ap})(\text{H}_2\text{O})]\cdot 0.5\text{HCl}\cdot 5\text{H}_2\text{O}$ contains directly coordinated water molecule. The structure is shown in Figure 1; Tables 1 and 2 list the selected bond distances and angles. The $(\text{Hdo3ap})^{4-}$ anion is coordinated to the terbium(III) ion by four nitrogen atoms and four oxygen atoms, three from acetates and one from phosphonate. The nitrogen atoms form the N_4 plane. The three acetates and one phosphonate form a similar O_4 base that is virtually planar. Deviations of the atoms from planarity for both the planes are listed in Table 2. The O_4 and N_4 planes are parallel and have a mutual angle of about 2.6° . The terbium(III) ion lies between these planes, closer to the O_4 base (Table 2).

The mean twist angle ω of the planes around the local 4-fold axis is about -27.2° (see Chart 2 and Table 2). Thus, the arrangement should be termed a twisted-square antiprism (TSA). The configuration of pendant arms and conformation of ethylenediamine bridges give the enantiomeric pair $\Lambda\lambda\lambda\lambda/\Delta\delta\delta\delta$, which also corresponds to the TSA isomer. A molecule of water capping the O_4 plane completes the coordination sphere of the lanthanide. The deviation of the

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Chart 2. Schematic Drawing of the Complexes with the Depicted Structural Parameters: (A) Twist Angles ω and (B) Opening Angle φ and Centroids Q of O₄ and N₄ Planes



Tb—O_w bond vector from the local 4-fold axis is only 3.6°. The Tb—O_w bond length [2.678(8) Å] is significantly longer than that observed in the complexes [Tb(dota-tetraamide)-(H₂O)]⁻ (2.461 Å),²⁸ [Tb(dota-propionate)₄](H₂O)]⁻ (2.427 Å),^{9c} and [Nd(Hdo3ap)(H₂O)]⁻ (2.499 and 2.591 Å).²⁵ This corresponds to the value 135.9° observed for the O—Tb—O angle (opening angle φ , Chart 2), which is close to the limiting value of 135° for water coordination/noncoordination documented in a series of lanthanide(III) complexes with H₄dota and its phosphorus acid derivatives.⁶ The average bond distances of the terbium(III) ion and the donor atoms of the ligand lie in the range expected for complexes with similar type of ligands. Although low-quality diffraction data did not allow the hydrogen atoms bound to the oxygen atoms to be located, the coordinated phosphonate moiety is probably monoprotonated on oxygen atom O13, as can be seen from differences of phosphorus—oxygen bond connections [O11 is coordinated to terbium(III) and O12 and O13 to lithium] and distances [P1—O12 1.508(7) Å and P1—O13 1.522(8) Å]. As mentioned, the lithium(I) ion is coordinated to the oxygen atoms O12 and O13 of two neighboring phosphonates, carboxylate, and two water molecules. Its coord-

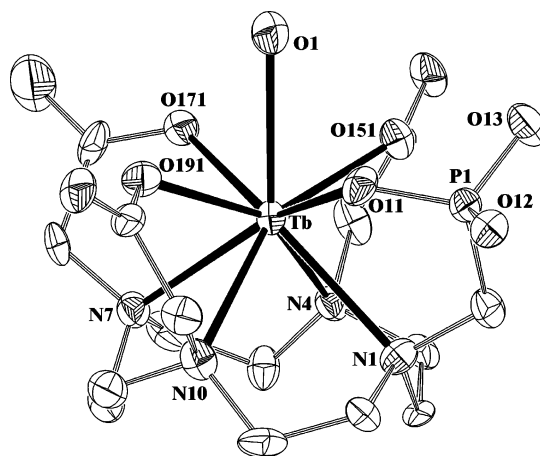


Figure 1. Molecular structure of [Tb(Hdo3ap)(H₂O)]⁻ anion with atom labeling scheme.

dination number is 5, and the lithium subunits connect terbium polyhedrons into an infinite zigzag chain, as shown in Figure 2. The Cl⁻ ion is disordered, and the corresponding proton is probably present as an oxonium cation in the water of hydration.

Crystal Structures of Isostructural Li[Dy(Hdo3ap)]·5H₂O, Li[Lu(Hdo3ap)]·5H₂O and Li[Y(Hdo3ap)]·5H₂O Complexes. The high quality of the crystals of all of the complexes enable us to refine the positions of the hydrogen atoms attached to the oxygen atoms. The [Dy(Hdo3ap)]⁻ anion in the Li[Dy(Hdo3ap)]·5H₂O structure is shown in Figure 3; Table 1 lists selected bond distances and angles. The Hdo3ap⁴⁻ anion is coordinated to the lanthanide(III) ion in a manner similar to that found in the terbium(III) complex, i.e., by four nitrogen atoms and four oxygen atoms, three from acetates and one from phosphonate. The nitrogen and oxygen atoms form N₄ and O₄ bases that are planar and parallel. Deviations of the atoms from planarity are listed in Table 2, and the mutual angles of these planes vary in the range 2.7–2.8°. The lanthanide(III) ions lie between these planes, closer to the O₄ base, as shown in Table 2. The twist angles ω between the O₄ and N₄ planes around the local 4-fold axis are about -25°, and this corresponds to the TSA (*m*) arrangement. No water molecule is coordinated to the central ions; their coordination number is 8. The bond lengths between the central ions and the donor atoms of the ligands are in the range expected for this type of compound. The O12 atom of the phosphonic acid group was found to be protonated. As is also shown in Figure 3, the lithium(I) ion is coordinated to the oxygen atoms of one carboxylate (O172) and three water molecules (O97, O98, and O99), forming an almost-regular tetrahedron. Crystal packing with the hydrogen-bond network shown in Figure 5 is discussed later.

Crystal Structures of Isostructural H[Er(Hdo3ap)]·5H₂O and H[Lu(Hdo3ap)]·6H₂O Complexes. Their coordination number of 8 and their molecular structures are analogous to those found for Li[Dy(Hdo3ap)]·5H₂O as shown in Figure 3. Selected bond distances are listed in Table 1. Hydrogen atoms were not found; nevertheless, in addition to phosphonate protonation, we assume that the additional

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Table 1. Selected Bond Lengths (Å) in Solid Lanthanide(III) Complexes of H₅do3ap (H₅L)

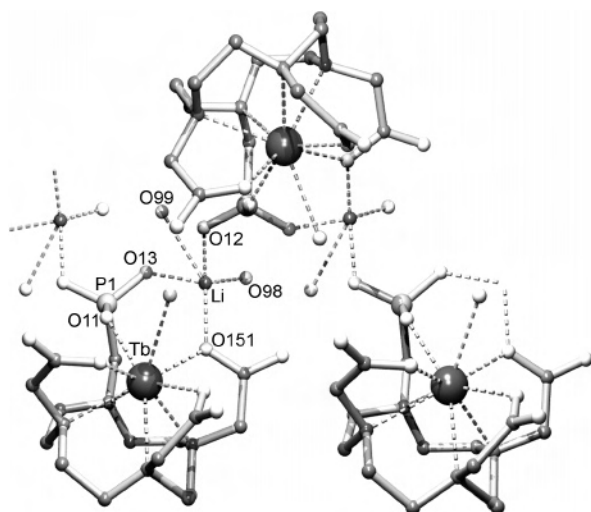
bond	Li[Dy(HL)]· 5H ₂ O	Li[Lu(HL)]· 5H ₂ O	Li[Y(HL)]· 5H ₂ O	Li[Tb(HL)(H ₂ O)]· 0.5HCl·5H ₂ O	H[Lu(HL)]· 6H ₂ O	H[Er(HL)]· 5H ₂ O	Li[Nd(HL)(H ₂ O)]· 11.5H ₂ O ^{25 b}
Ln—O1	—	—	—	2.678(8)	—	—	2.499(4) 2.591(4)
Ln—O(11)	2.267(2)	2.225(2)	2.261(1)	2.275(6)	2.221(5)	2.257(5)	2.431(4) 2.403(4)
Ln—O(151)	2.341(2)	2.298(2)	2.331(1)	2.373(7)	2.291(5)	2.336(6)	2.457(4) 2.438(4)
Ln—O(171)	2.323(2)	2.277(2)	2.310(1)	2.350(5)	2.271(5)	2.283(5)	2.435(4) 2.431(4)
Ln—O(191)	2.313(2)	2.271(2)	2.304(1)	2.369(8)	2.279(5)	2.309(5)	2.449(4) 2.430(4)
Ln—Q(O) ^a	1.035	1.065	1.043	0.853	1.068	1.054	0.783 0.792
Ln—N(1)	2.596(2)	2.559(3)	2.594(2)	2.708(10)	2.552(5)	2.576(5)	2.699(5) 2.696(5)
Ln—N(4)	2.557(2)	2.521(3)	2.555(2)	2.643(12)	2.505(6)	2.533(5)	2.736(5) 2.682(5)
Ln—N(7)	2.578(2)	2.538(3)	2.573(2)	2.662(11)	2.508(6)	2.552(5)	2.750(5) 2.771(5)
Ln—N(10)	2.575(2)	2.526(3)	2.565(2)	2.637(10)	2.534(5)	2.553(6)	2.676(5) 2.733(5)
Ln—Q(N) ^a	1.531	1.483	1.525	1.663	1.472	1.472	1.738 1.746
Q(O)—Q(N) ^a	2.564	2.547	2.566	2.514	2.489	2.525	2.519 2.536

^a Q(O) is the centroid of the O₄ plane; Q(N) is the centroid of the N₄ plane. ^b Two independent molecules in the unit.

Table 2. Distances (Å) and Angles (deg) in Solid Lanthanide(III) Complexes of H₅do3aP (H₅L)

	Li[Dy(HL)]· 5H ₂ O	Li[Lu(HL)]· 5H ₂ O	Li[Y(HL)]· 5H ₂ O	Li[Tb(HL)(H ₂ O)]· 0.5HCl·5H ₂ O	H[Lu(HL)]· 6H ₂ O	H[Er(HL)]· 5H ₂ O	Li[Nd(HL)(H ₂ O)]· 11.5H ₂ O ^{25 c}	
Distances								
O1 from O3	0.189(3)	0.192(4)	0.191(3)	0.034(14)	0.190(10)	0.162(11)	0.022(8) 0.111(8)	
O from O4 ^a	0.047	0.048	0.048	0.016	0.047	0.041	0.006 0.028	
N from N4 ^a	0.001	0.001	0.001	0.010	0.006	0.003	0.004 0.002	
Ln—(plane O4)	1.039(1)	1.064(1)	1.043(1)	0.852(4)	1.067(2)	1.054(2)	0.782(2) 0.792(2)	
Ln—(plane N4)	1.530(1)	1.483(1)	1.524(1)	1.663(4)	1.468(3)	1.506(3)	1.739(2) 1.744(2)	
Angles								
O4—N4 angle	2.77(6)	2.72(7)	2.78(5)	2.6(3)	1.9(2)	1.6(3)	1.8(2) 2.1(2)	
twist angle ω of								
pendant 1 (N1)	−25.53(7)	−26.7(1)	−25.82(6)	−26.9(3)	−26.6(2)	−26.4(2)	−30.0(2) −28.9(2)	
pendant 2 (N4)	−24.72(8)	−26.0(1)	−24.95(6)	−27.2(3)	−25.9(2)	−24.2(2)	−23.3(2) −23.3(2)	
pendant 3 (N7)	−25.74(7)	−26.4(1)	−25.39(6)	−27.4(3)	−25.9(3)	−24.0(3)	−28.6(2) −28.1(2)	
pendant 4 (N10)	−25.17(8)	−26.3(1)	−25.25(6)	−27.1(3)	−25.5(2)	−25.0(3)	−24.0(2) −23.5(2)	
mean twist angle ω	−25.3	−26.4	−25.4	−27.2	−26.0	−24.9	−26.5 −26.0	
opening angle φ^b	123.5(5)	120.77(6)	123.01(5)	135.9(2)	126.9(2)	122.2(2)	142.2(1) 140.3(1)	

^a Mean deviations of the atom from the plane. ^b Smaller value from O11—Ln—O171 and O151—Ln—O191 angles. ^c Two independent molecules in the unit.

**Figure 2.** Infinite chain in the structure of Li[Tb(Hdo3ap)(H₂O)]·0.5HCl·5H₂O with additional numbering scheme.

proton is bound to the water molecules of hydration. The structural motif of the acids is shown for H[Lu(Hdo3ap)]·5H₂O in Figure 4 as an example. In the crystal packing, two molecules of the complex are very close and oriented with their O₄ planes to each other. Four water molecules are placed between these O₄ planes, and they probably connect the oxygen parts of the two molecules through a hydrogen-bond

network. This motif offers the possibility of localization of the acid protons between these two molecules. Unfortunately, some molecules of solvate water are disordered, and thus, the numbers of water molecules in the two formulas are not the same.

Discussion

Complexes of H₅do3ap. The molecular structures of the studied H₅do3ap complexes are very similar. In all of the complexes, the tetraazacyclododecane ring forms the [3,3,3,3] conformation with nitrogen atoms lying in the planes with deviations mostly less than 0.01 Å. The four coordinate oxygen atoms (three from acetate and one from phosphonate) also form a plane, but with higher deviations from planarity (0.01–0.05 Å) than those found for the N₄ plane (<0.01 Å), as is documented in Table 2. In an alternative view, considering only O₃ planes formed with three acetates oxygen atoms, the coordinated phosphonate oxygen atoms are located slightly above these O₃ planes (0.02–0.19 Å), and the angles between the O₃ and O₄ planes are smaller than 3°. Thus, the positions of the two alternative oxygen planes with respect to the N₄ planes are virtually the same. The distances between the N₄ and O₄ planes are about 2.5 Å, and the values are similar in all structures. Lanthanide(III) ions are located between these planes, closer to the oxygen planes (see Table 2). The relative position of the

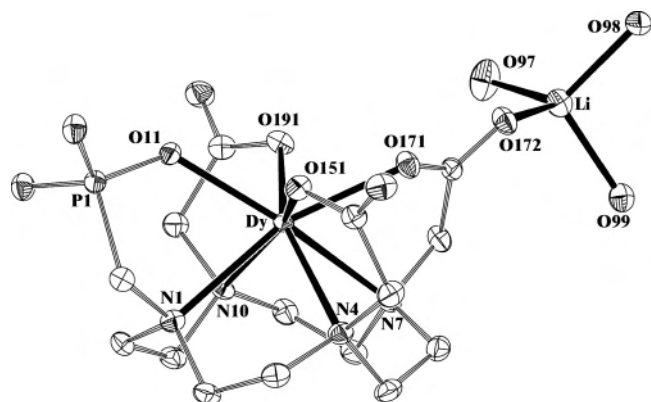


Figure 3. Molecular structure of $\{[Li(H_2O)_3][Dy(Hdo3ap)]\}$ fragment with atom numbering scheme.

lanthanide(III) ion shifted toward the N_4 plane is dependent on the size of the ion, and it is deeper along the series from neodymium(III) to lutetium(III).

The average values of the twist angles ω of the pendants and their orientation with respect to the five-membered coordination rings of cycle skeleton point to the TSA (m) conformation in all of the complexes studied. The twist angles ω for each complex fall into a very narrow region within 1° (see Table 2). In contrast, in the structure of $Li[Nd(Hdo3ap)(H_2O)] \cdot 11H_2O$ published previously,²⁵ the ω value is in the range between -23 and -30° for two independent molecules.

The influence of the external counterion, lithium(I) or proton, on the crystal packing is variable. The frequently observed formation of infinite chains [here, through lithium(I) ions] connecting the coordination polyhedrons was found in $Li[Tb(Hdo3ap)(H_2O)] \cdot 0.5HCl \cdot 5H_2O$ (Figure 2) and also in $Li[Nd(Hdo3ap)(H_2O)] \cdot 11.5H_2O$ (ref 25). On the other hand, in the isostructural $Li[Ln(Hdo3ap)] \cdot 5H_2O$ ($Ln = Dy, Y, Lu$) complexes, the lithium(I) ion is bonded only to one carboxylate group and does not form any chain. In the $H[Lu(Hdo3ap)] \cdot 6H_2O$ and $H[Er(Hdo3ap)] \cdot 5H_2O$ acids, the O_4 planes of two molecules face each other. Thus, in both of these structures, the building motif seems to be a hydrogen-bond network between the water molecules themselves and water molecules linked with carboxylate and phosphonate groups. Hydrogen atoms attached to oxygen atoms were found in the isostructural series $Li[Ln(Hdo3ap)] \cdot 5H_2O$ ($Ln = Dy, Y, Lu$); the packing found in $Li[Dy(Hdo3ap)] \cdot 5H_2O$ is shown in Figure 5. From this picture, it is clear that the water molecules form layers and mostly link to each other and also to the acetates. In the direction of the c axis, water molecules connect the protonated phosphonate and acetate groups and also show additional contacts to other water molecules (Figure 5). Unfortunately, the hydrogen-bond network arrangement in the other structures can only be estimated from the distances between the oxygen atoms. Their positions indicate variations in organization of the hydration. In the $Li[Tb(Hdo3ap)(H_2O)] \cdot 0.5HCl \cdot 5H_2O$ structure, a single water molecule is coordinated, and the $O \cdots O$ distances indicate hydrogen bonds to the free water molecule above the O_4 plane. However, the main water layer is on the opposite side of the complex. This organization of the

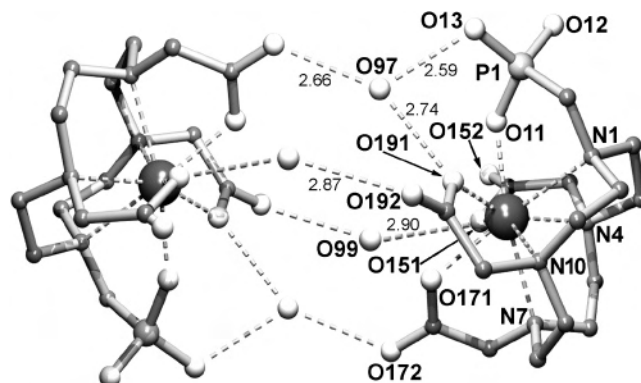


Figure 4. Arrangement of a "dimer" in the $H[Lu(Hdo3ap)] \cdot 5H_2O$ structure with atom numbering scheme and $O \cdots O$ distances (Å).

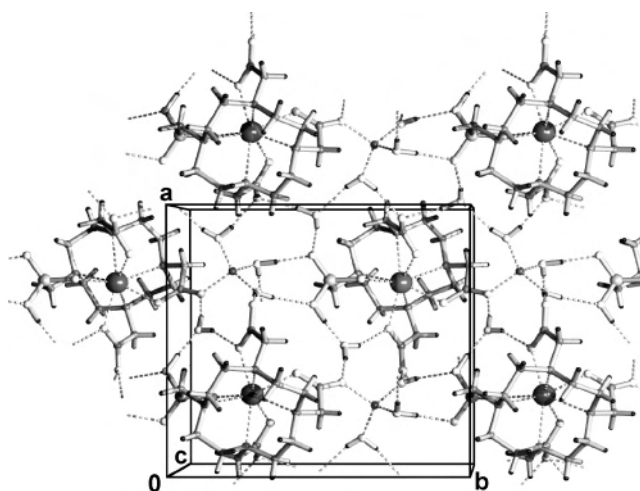


Figure 5. Crystal packing in the $Li[Dy(Hdo3ap)] \cdot 5H_2O$ structure. Hydrogen bonds are shown as dashed lines.

hydrogen-bond network is different from that found in $Li[Nd(Hdo3ap)(H_2O)] \cdot 11.5H_2O$ (ref 25). In the structure of the Nd(III) complex, two independent Nd—O bond lengths, were observed in the two molecules [2.499(4) and 2.591(4) Å] with different hydrogen-bond contacts to water molecules of hydration; however, both of the molecules involve hydrogen-bond contacts to the phosphonate of the neighboring molecule.

In the acids $H[Lu(Hdo3ap)] \cdot 6H_2O$ and $H[Er(Hdo3ap)] \cdot 5H_2O$, two molecules of the complexes are probably connected by a hydrogen-bond network through four hydrate water molecules. The found $O \cdots O$ distances between oxygen atoms from phosphonate or carboxylate groups on one side and water oxygen atoms on the other side are in the wide range 2.59–3.30 Å. The contacts of about 2.6 Å are shorter than those observed in complexes with coordinated water molecules such as those involving neodymium(III)²⁵ and terbium(III) (> 2.7 Å). This arrangement, with short (P)O \cdots O(water) contacts, indicates a stronger interaction between ligand oxygens and close water molecules in acid solution than in the neutral one. The enhanced interactions toward the close water molecules would decrease the water exchange and, thus, increase the water residence time τ_M . It was really observed at pH lower than 5.²⁵

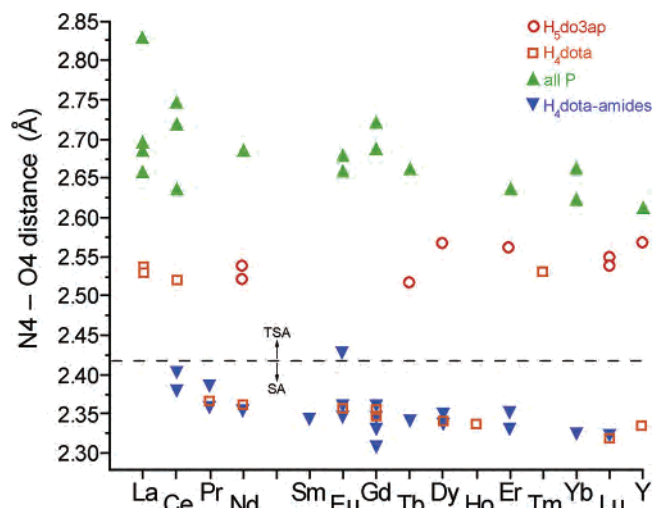


Figure 6. Dependence of distance between the O_4 and N_4 planes in complexes of H_4dota -like ligands on the lanthanide: H_5do3ap (open red circles), H_4dota (open orange squares), ligands with four phosphorus atoms (full green triangles), and H_4dota -amides (full blue triangles).

Comparison of Structures of Complexes of H_4dota -like Ligands. A comparison of the structures of the lanthanide(III) complexes with H_4dota , H_4dota -amides, H_8dotp [$H_8dotp = 1,4,7,10$ -tetraazacyclododecane-1,4,7,10-tetrakis(methylphosphonic acid), Chart 1], H_3do3p^{Ph} [$H_3do3p^{Ph} = 10$ -methyl-1,4,7,10-tetraazacyclododecane-1,4,7-tris(methyl(phenyl)phosphinic acid), Chart 1], H_4dotp^R [$H_4dotp^R = 1,4,7,10$ -tetraazacyclododecane-1,4,7,10-tetrakis(methylphosphonic acid), $R = Ph, Bn$; Chart 1], and H_5do3ap based on the geometry of the cyclen skeleton and on the distances and twist angles of O_4 and N_4 planes (see Table S1) points to some general remarks.

The conformation of the cyclen ring follows from the signs of its torsion angles. The values found for the H_5do3ap complexes are virtually the same as those observed in the series of H_4dota complexes.¹⁷ The twist angle ω between the O_4 and N_4 planes (ca. -25°) observed in the H_5do3ap complexes for lanthanide(III) complexes from neodymium(III)²⁵ to lutetium(III) confirmed the expected influence of the bulky phosphonic acid moiety and, therefore, the formation of isomers with the TSA or TSA' geometry in the solid state. In solution {pH = 2.5–3.5, the monoprotonated complex $[Ln(Hdo3ap)(H_2O)]^-$ is the main species (>90%)}, the abundance of the TSA isomer ranges from 100% [Nd(III) complex], through approximately 50% [Tb(III) complex], to ca. 20% [lutetium(III) complex].²⁵ In comparison with the H_4dota complexes, the proportion of the TSA form in solution is higher for H_5do3ap complexes through the lanthanide series. Probably because of a lower solubility, crystallization of the TSA form is preferred for complexes of the phosphonic acid derivative. A comparison of these structures with those found for complexes with H_4dota , its tetraamides, and tri- and tetra(phosphorus) analogues is shown on the plot of the distances between the O_4 and N_4 planes for the various lanthanides (Figure 6, Table S1). From the figure, it is clear that the distances found for the H_8dotp^R and H_3do3p^{Ph} complexes are in the range 2.63–2.82 Å, and they increase slightly with increasing size of the

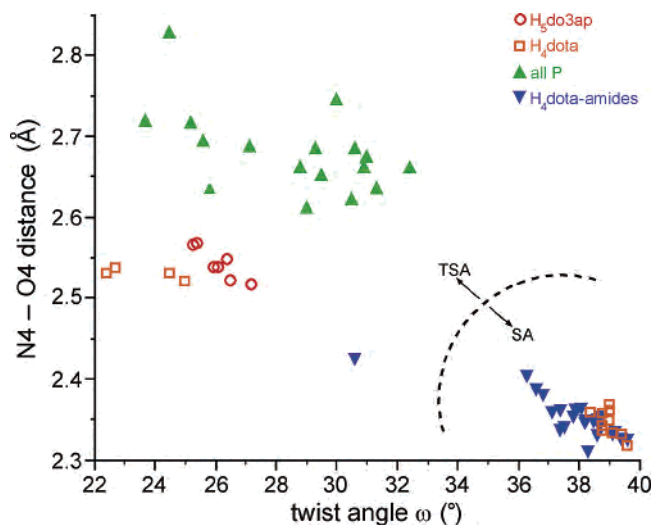


Figure 7. Dependence of the distance between the O_4 and N_4 planes on twist angle ω for lanthanide(III) complexes with H_4dota -like ligands: H_5do3ap (open red circles), H_4dota (open orange squares), ligands with four phosphorus atoms (full green triangles), and H_4dota -amides (full blue triangles).

lanthanide(III) ion. The distances observed for the H_4dota and H_4dota -tetraamide complexes are split into two groups. The H_4dota complexes of lanthanum(III), cerium(III), and thulium(III) with the value of ca. 2.5 Å correspond to the TSA (La, Ce) or TSA' (Tm) geometry, and the other lanthanide(III) complexes with the value of ca. 2.3 Å conform to the SA arrangement. As mentioned above and shown in the plot, H_5do3ap complexes exhibit the distance of ca. 2.5 Å and, thus, follow the range of H_4dota complexes with the TSA and TSA' arrangements (with and without a coordinated water molecule, respectively).

In solution, the H_4dota complexes with trivalent lanthanides from Nd to Lu are partly present as the TSA isomer. Therefore, the structures determined for the H_5do3ap complexes can be used for estimating the structural parameters of the corresponding TSA isomers of the H_4dota complexes. From this point of view, the structure of the TSA isomer of $[Gd(dota)(H_2O)]^-$ species can be estimated from the structure of $Li[Tb(Hdo3ap)(H_2O)] \cdot 0.5HCl \cdot 5H_2O$. The O–Gd–O angle (φ) in the TSA isomer of $[Gd(dota)(H_2O)]^-$ would be lower than those found in the solid state for the SA isomer of this complex (143.6°)^{20,21} but close to those found for the $[Tb(Hdo3ap)(H_2O)]^-$ species (135.9°). The Gd– O_w distance should also be similar to that found in the Tb(III) structure (2.678 Å). To the best of our knowledge, the Tb– O_w bond length of 2.678 Å is the longest distance between the lanthanide(III) ion and the coordinated water found in complexes of H_4dota -like ligands. In addition, the value 135.9° observed for the O–Tb–O angle (angle φ , see Scheme 1) is the lowest value found in a series of lanthanide(III) complexes with H_4dota -like ligands and coordinated water.⁶ Thus, these values would confirm the expected steric strain above the oxygen plane of the TSA isomer of $[Gd(dota)(H_2O)]^-$, which results in the observed high rate of water exchange for such TSA isomers.⁹

A plot of the distance between the O_4 and N_4 planes as a function of twist angle ω is shown in Figure 7. We can

distinguish two main point clusters: a compact high-density cluster corresponding to the SA isomers and a scattered cluster containing two groups belonging to the TSA isomers. It is clear that, for the SA isomers, the distances and angles fall into a very narrow range and, thus, their structures are very rigid and tight. The range of the TSA isomers is rather spread, and one can observe a group corresponding to H₄dota and H₅do3ap complexes and another belonging to complexes of H₈dotp, H₄dotp^R, and H₃do3p^{Ph}. The arrangement of the points indicates that the structure of the TSA isomers is not as rigid as that of the SA isomers, being much more influenced by some other interactions.

The comparison indicates that the TSA vs SA isomer preference is based on the geometry of the donor atom cavity, which is defined by the ligand, and the size of a lanthanide(III) ion. The geometry and resulting size of the cavity in complexes of H₄dota-like ligands can be governed only by rotation of the pendants. As was shown, this rotation leads to the different distances between the N₄ and O₄ planes. The SA arrangement should be preferred because of the lower repulsion of the donor atoms. Large lanthanide ions such as La(III) and Ce(III) enforce a larger cavity and thus the N₄–O₄ distance of 2.5 Å or higher and the formation of the TSA isomer are mostly required for their complexes. As the radius of the lanthanide decreases, the ion moves to the N₄ plane, as was documented in ref 6 and is shown for [Ln(Hdo3ap)(H₂O)_n][−] (*n* = 0, 1) complexes in Table 1. For complexes with non-phosphorus H₄dota-like ligands, the shorter distance between the planes is adequate for the lanthanide ions after Ce(III), and thus, the formation of the SA isomer is preferred. In phosphonic and phosphinic acid derivatives, the pendants show a different geometry resulting from the tetrahedral arrangement of the donor groups, and in addition, the C–P and O–P bonds are longer than the C–C and O–C in the acetate pendant. Therefore, the H₄dota-like ligands even with only one phosphonic acid group prefer longer distances from the N₄ plane and the formation of TSA isomer. The ligand cavity in TSA isomers of the small lanthanides is not rigid, as demonstrated above and in Figure 7.

The results and their discussion point to the possibility of the increasing abundance of TSA (*m*) isomer in complexes of H₄dota-like ligands by modification of one of the pendants. A higher abundance of the TSA isomer was observed for complexes of H₄dota-like ligands where acetate methylene hydrogen atoms were substituted by an alkyl group.^{9a,9c,29} On the other hand, the fast exchange of water can be governed only by strain of the O₄ plane, and a high abundance of the TSA isomer is desired exclusively for the H₄dota complexes. Then, modification of the H₄dota-like ligands could also be directed to the ligands forming only SA (*M*) complexes with the strain on the O₄ plane and, consequently, with the fast exchange of water molecules. We have confirmed the existence in lanthanide(III) complexes of H₄dota derivatives with one pyridine oxide pendant arm that are present in solution exclusively as SA isomers

and that the Gd(III) complex exhibits a short water residence time ($\tau_M = 39$ ns).³⁰

Conclusion

The X-ray structure determination of the series of prepared M[Ln(Hdo3ap)(H₂O)_n] \cdot xH₂O complexes (M = Li, H; Ln = Nd, Er, Tb, Dy, Lu, Y; *n* = 0, 1; *x* = 5–11.5) shows that the (Hdo3aP)^{4−} anion is octadentate and is coordinated to a lanthanide(III) ion similarly to other H₄dota-like ligands, forming O₄ and N₄ planes that are parallel and have a mutual angle of less than 3°. The lanthanide(III) ions lie between these planes, closer to the O₄ than the N₄ plane. All of the structures present the lanthanide(III) complexes in their twisted-square-antiprismatic (TSA) configuration. Direct coordination of the water molecule to the central ion was found only in the neodymium(III) and terbium(III) complexes. The terbium(III) complex showing the longest Ln–O_w distance so far observed is a reasonable model for TSA isomers of gadolinium(III) complexes such as [Gd(dota)(H₂O)][−]. Organization of the water of hydration in the solid state points to a possible arrangement of the second hydration sphere for complexes with H₄dota-like ligands in solution. It shows that protonation of the pendant arms influences the formation of a hydrogen-bond network from the coordinated water and water of hydration above the O₄ plane, and this might change the water exchange rate in solution. Such an explanation has been used to interpret the difference in the water exchange rate between deprotonated and protonated gadolinium(III) H₅do3ap complexes.²⁵ The design of new MRI contrast agents should consider that the exclusive formation of the complexes with the TSA configuration might lead to a too-long Gd–O_w distance, thus decreasing the overall relaxivity, as was stated for europium(II) amino-carboxylate complexes.³¹ On the other hand, the second-sphere water arrangement in complexes with ligands capable of forming an extended hydrogen-bond network might significantly change the observed quantities relevant to MRI utilization.

A comparison of distances of the O₄ and N₄ planes with the twist angle of the pendants for a number of Ln(III) complexes with H₄dota-like ligands shows that the arrangement of the TSA isomers is flexible. On the other hand, the arrangement of the SA isomers is rigid, and the derived structural parameters are almost identical for different ligands and lanthanide(III) ions. Complexes of monophosphorus acid derivatives make just a borderline between complexes of ligands with acetate pendants (H₄dota and H₄dota-amides) and phosphorus acid pendants (H₈dotp, H₄dotp^R, and H₃do3p^{Ph}).

Experimental Section

Solutions of the complexes were prepared by mixing stoichiometric amounts of H₅do3ap²⁵ and the appropriate LnCl₃ hydrates in water. The pH was slowly adjusted to ~8 with a dilute solution of LiOH, and the solutions were briefly heated. After being allowed to stand overnight, the solutions were filtered, and the pH was

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Table 3. Experimental Data for the X-ray Diffraction Studies of Studied Ln Complexes^a

param	Li[Dy(HL)]·5H ₂ O	Li[Lu(HL)]·5H ₂ O	Li[Y(HL)]·5H ₂ O	Li[Tb(HL)(H ₂ O)]·0.5HCl·5H ₂ O	H[Er(HL)]·5H ₂ O	H[Lu(HL)]·6H ₂ O
<i>M_w</i>	695.88	708.35	622.29	746.56	698.74	722.45
cryst dimen/mm	0.25 × 0.30 × 0.35	0.13 × 0.25 × 0.38	0.12 × 0.25 × 0.25	0.05 × 0.18 × 0.20	0.20 × 0.25 × 0.30	0.08 × 0.15 × 0.40
shape	prism	prism	plate	plate	prism	prism
color	colorless	colorless	colorless	colorless	colorless	colorless
<i>a</i> /Å	12.7145(2)	12.6830(2)	12.7110(2)	33.9680(3)	8.6769(1)	8.7320(2)
<i>b</i> /Å	13.2805(2)	13.1770(2)	13.2590(2)	9.1920(6)	9.4160(2)	9.3130(2)
<i>c</i> /Å	14.9862(2)	14.9850(2)	15.0090(2)	16.9130(9)	16.8348(3)	16.8830(4)
α/deg	90	90	90	90	83.126(1)	82.742(1)
β/deg	93.355(9)	93.017(1)	93.298(1)	90	83.251(1)	83.364(1)
γ/deg	90	90	90	90	67.494(1)	68.355(1)
<i>Z</i>	4	4	4	8	2	2
space group	<i>P</i> 2(1)/ <i>c</i> (No. 14)	<i>P</i> 2(1)/ <i>c</i> (No. 14)	<i>P</i> 2(1)/ <i>c</i> (No. 14)	<i>P</i> 2(1)/ <i>c</i> (No. 14)	<i>P</i> 1̄ (No. 2)	<i>P</i> 1̄ (No. 2)
<i>U</i> /Å ⁻³	2526.32(6)	2500.88(6)	2525.35(7)	5280.8(4)	1257.68(4)	1262.36(5)
<i>D_s</i> /g cm ⁻³	1.830	1.881	1.637	1.878	1.834	1.895
<i>μ</i> /mm ⁻¹	3.094	4.085	2.446	2.870	3.473	4.051
<i>F</i> (000)	1396	1416	1288	3016	698	724
θ range of data collection/deg	2.55–27.48	2.57–27.50	3.12–27.50	3.60–25.04	3.67–7.45	2.56–27.51
index ranges						
<i>h</i>	0, 16	0, 16	0, 16	–39, 38	–11, 11	–11, 11
<i>k</i>	–17, 17	–17, 17	0, 17	–10, 10	–12, 12	–12, 12
<i>l</i>	–19, 19	–19, 19	–19, 19	–19, 20	–21, 21	–21, 20
reflns measd	36006	34027	11278	3300	10537	23023
<i>R_σ</i>	0.0361	0.0495	0.0402	0.0437	0.0337	0.0679
reflns obsd [<i>I</i> > 2σ(<i>I</i>)]	5430	5035	4613	2847	5420	5251
ind reflns	5774	5721	5789	3300	5690	5740
<i>R_{int}</i>	0.0718	0.1091	0.0289	0.0000	0.0214	0.1133
coeffs in weighting scheme ^b	0.0220	0.0436	0.0274	0.0074	0.0697	0.0734
data/constraints/params	5774/0/466	5721/0/466	5789/0/466	3300/0/354	5690/0/347	5740/0/370
GOF on <i>F</i> ²	1.107	1.083	1.022	1.080	1.095	1.023
final <i>R</i> , <i>R'</i> indices	0.0249,	0.0318,	0.0309,	0.0390,	0.0523,	0.0509,
[<i>I</i> ≥ 2σ(<i>I</i>)] ^c	0.0639	0.0838	0.0634	0.0738	0.1366	0.1289
max shift/esd	0.003	0.003	0.001	0.002	0.001	0.003
largest diff peak and hole/e Å ⁻³	0.786	2.077	0.417	0.788	2.200	3.008
	–1.026	–2.658	–0.379	–0.531	–1.736	–2.925

^a Data were obtained at 150(1) K, using CCD rotation scans ($\lambda = 0.71070 \text{ \AA}$). ^b $w = 1/[\sigma^2(F_o^2) + (AP)^2 + BP]$, where $P = (F_o^2 + 2F_c^2)/3$ (SHELXL97³⁴). ^c $R_1 = \sum|F_o - F_c|/\sum|F_c|$; $wR_2 = [\sum w(F_o^2 - F_c^2)^2/\sum w(F_o^2)^2]^{1/2}$ (SHELXL97³⁴).

lowered to ~4 (lithium salts) or ~2.5 (acids) with dilute HCl. Diffraction-quality crystals of the complexes were grown from aqueous solutions by the slow vapor diffusion of alcohols (EtOH, *i*PrOH) at room temperature over the course of several weeks. Selected crystals were quickly transferred into Fluorolub oil, mounted on glass fibers in random orientation and cooled to 150(1) K. Diffraction data were collected using a Nonius Kappa CCD diffractometer (Enraf-Nonius) at 150(1) K (Cryostream Cooler Oxford Cryosystem) with $\lambda = 0.71070 \text{ \AA}$ using CCD rotating scans. They were analyzed using the HKL program package.³² The structures were solved by direct methods and refined by full-matrix least-squares techniques (SIR92³³ and SHELXL97³⁴). The scattering factors for neutral atoms were included in the SHELXL97 program. Final geometric calculations were carried out with SHELXL97 and a recent version of the PLATON program.³⁵ Table 3 reports pertinent crystallographic data. All of the data for the reported structures have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC-250495

{Li[Dy(Hdo3ap)]·5H₂O}, CCDC-250497 {Li[Lu(Hdo3ap)]·5H₂O}, CCDC-250500 {Li[Y(Hdo3ap)]·5H₂O}, CCDC-250496 {H[Er(Hdo3ap)]·5H₂O}, CCDC-250498 {H[Lu(Hdo3ap)]·6H₂O}, and CCDC-259499 {Li[Tb(Hdo3ap)(H₂O)]·0.5HCl·5H₂O}. Copies of the data can be obtained free of charge by application to the CCDC, e-mail deposit@ccdc.cam.ac.uk, or as Supporting Information to this paper.

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Supporting Information Available: Table S1 containing survey of selected structural parameters (twist and opening angles) for lanthanide(III) complexes of H₄dota-like ligands. Crystallographic data in CIF format. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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