Molecular and Crystal Structure of a Lanthanide Complex, DyDTPA–BMA Hydrate

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1,7-Bis-[(N-methylcarbamoyl)methyl]-1,4,7-triazaheptane-1,4,7-triacetic acid dysprosium(III) hydrate, DyDTPA–BMA hydrate, $C_{16}H_{40}DyN_5O_{15}$, $M_w = 705.0$ g mol^{-1}, crystallizes in a monoclinic cell, $P2_1/n$, $Z = 4$. The cell dimensions are $a = 9.358(2)$, $b = 25.187(4)$, $c = 12.009(2)$ Å, $\beta = 109.52(1)°$ and $V = 2667.6(8)$ Å^3. $T = 120$ K, $D_{calc} = 1.76$ Mg m^{-3}, $\lambda(MoK\alpha) = 0.71069$ Å, $F(000) = 1416$. $R = 0.024$ for 4543 unique reflections.

The compound crystallizes as discrete nonionic (8+1) coordinate dysprosium complexes. Eight of the ligands are three amine nitrogen atoms, three carboxyl oxygen atoms and two amide oxygen atoms. The ninth ligand is a water molecule. There is no particular strain in the complex: distances and angles in the ligand are of normal values. The Dy–O distances are shorter than the sum of the respective ionic radii, and the Dy–N distances are longer.

The resulting complex has one hydrophobic and one hydrophilic side. The ligating water molecule is bonded on the latter side, where the water molecules of crystallization also appear in highest concentration. The complex is hydrogen-bonded to water molecules and to other complexes, making a three-dimensional network. There are no intramolecular hydrogen bonds.

In the search for new contrast agents for magnetic resonance imaging (MRI), the title compound was found to be of interest. Contrast agents are paramagnetic substances that enhance water proton T_1 and T_2 relaxation rates.[1] The compound studied is non-ionic. This is important, as several side-effects have been observed using ionic contrast agents.

Experimental

Colourless single crystals were made by slow evaporation from a methanol solution at room temperature.

Intensities were measured on a Nicolet P3 automatic diffractometer at liquid-nitrogen temperature. Table 1 lists the crystallographic data and experimental conditions. 5252 intensities were measured, of which 4543 had $I > 3 \sigma(I)$ and were considered observed. Unit-cell dimensions were determined by a least-squares fit of 2θ values for 25 general reflections, accurately measured on the diffractometer. During data collection the intensities of three test reflections were monitored, and none of these showed significant fluctuations as a function of time.

The compound crystallizes in a monoclinic cell, space group $P2_1/n$ (No. 14), $Z = 4$. The intensity data were corrected for Lorentz and polarization effects, and absorption correction was performed by use of the program DI-FABS.[2] The structure was solved by Patterson and Fourier

syntheses.[3] Positional parameters for dysprosium, from a Patterson map, formed the basis of Fourier syntheses. The positions of all atoms, except water molecules and hydro-

Table 1. Crystal data and intensity collection.

Formula	$C_{16}H_{40}DyN_5O_{15}$
Formula weight/g mol^{-1}	705.03
Crystal dimensions/mm^3	0.4×0.35×0.3
Density calculated/g cm^{-3}	1.76
Linear absorption coefficient, μ/cm^{-1}	29.0
Space group	$P2_1/n$ (No. 14)
Z	4
a/Å	9.358(2)
b/Å	25.187(4)
c/Å	12.009(2)
β/°	109.52(1)
V/Å^3	2667.6(8)
Diffractometer	Nicolet P3
Radiation	$MoK\alpha$
Wavelength/Å	0.71069
Monochromator	Graphite
Temperature/K	120
Scan type	θ–2θ
Scan range/°	$\alpha_1 -1.0$–$\alpha_2 +1.0$
Scan speed/° min^{-1}	3
2θ range/°	3.0–50.0
Background/scan ratio	0.7
No. of unique data	5252
No. of observed data [$I > 3\sigma(I)$]	4543
$R = \Sigma\,(|F_o| - |F_c|)/\Sigma|F_o|$	0.024
$R_w = [\Sigma w\,(|F_o| - |F_c|)^2/\Sigma w|F_o|^2]^{1/2}$	0.034

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gen, were found from these first electron-density maps. The water molecules were located from a difference Fourier synthesis after some refinement. 36 out of 40 hydrogen atoms were also located from difference electron density maps. The remaining four were positioned according to the hybridization of atoms bound to hydrogen, and the expected hydrogen-bonding pattern.

Atomic parameters were refined by a full-matrix least-squares minimization of $\Sigma w(\Delta F)^2$, where $w = 1/\sigma^2$. Initially only atomic coordinates and the isotropic thermal parameter for dysprosium were included. Then the corresponding parameters for non-hydrogen atoms, except water molecules, were refined. Anisotropic vibration for dysprosium was included, and water molecules and most of the hydrogen atoms were localized. At this stage an attempt was made to introduce anisotropic thermal parameters for all the heavy atoms (carbon, nitrogen and oxygen). However, this appeared to be physically impossible (negative B val-

Fig. 1. A perspective drawing of the complex with thermal ellipsoids of vibration.

Table 2. Fractional atomic coordinates with estimated standard deviations and equivalent isotropic thermal parameters.

Atom	x	y	z	$B_{eq}/Å^2$ [a]
Dy	0.24769(2)	0.15413(1)	0.15814(1)	1.06
O1	0.0167(3)	0.1552(1)	−0.0038(2)	1.6
O2	0.3459(3)	0.1953(1)	0.0268(2)	1.7
O3	0.3849(3)	0.2116(1)	−0.1432(2)	2.3
O4	0.1871(3)	0.0650(1)	0.1787(2)	1.6
O5	0.2508(3)	−0.0138(1)	0.2653(2)	2.0
O6	0.3000(3)	0.3250(1)	0.1639(2)	1.7
O7	0.2197(3)	0.2442(1)	0.1888(2)	1.7
O8	0.3300(3)	0.1374(1)	0.3622(2)	1.6
O9	0.0286(3)	0.1605(1)	0.2275(2)	1.8
O10	0.5682(3)	0.2982(1)	0.9493(2)	2.2
O11	0.1836(3)	0.0253(1)	0.6758(3)	2.8
O12	0.2275(4)	−0.0337(1)	0.4937(2)	2.9
O13	0.3316(4)	0.2404(1)	0.6162(3)	3.0
O14	0.9864(3)	0.1176(1)	0.5772(3)	2.7
O15	0.8985(3)	0.0555(1)	0.1885(3)	3.0
N1	−0.1765(4)	0.1059(1)	−0.1199(3)	1.8
N2	0.2327(3)	0.0960(1)	−0.0395(3)	1.4
N3	0.4800(3)	0.0907(1)	0.2000(3)	1.4
N4	0.4995(3)	0.2033(1)	0.2750(3)	1.4
N5	0.5071(4)	0.1379(1)	0.5436(3)	1.7
C1	−0.2928(5)	0.1413(2)	−0.1066(4)	2.6
C2	−0.0310(4)	0.1150(2)	−0.0674(3)	1.4
C3	0.0796(4)	0.0737(2)	−0.0826(3)	1.5
C4	0.2589(4)	0.1314(2)	−0.1286(3)	1.6
C5	0.3369(4)	0.1836(1)	−0.0776(3)	1.4
C6	0.3529(4)	0.0550(2)	−0.0035(3)	1.8
C7	0.4968(4)	0.0760(2)	0.0854(3)	1.8
C8	0.4507(4)	0.0425(2)	0.2598(3)	1.6
C9	0.2838(4)	0.0300(1)	0.2318(3)	1.5
C10	0.6236(4)	0.1169(2)	0.2764(3)	1.6
C11	0.6276(4)	0.1753(2)	0.2528(3)	1.6
C12	0.4858(4)	0.2581(1)	0.2305(3)	1.6
C13	0.3211(4)	0.2774(1)	0.1917(3)	1.3
C14	0.5194(4)	0.2042(2)	0.4019(3)	1.5
C15	0.4458(4)	0.1567(1)	0.4361(3)	1.5
C16	0.4351(5)	0.0959(2)	0.5896(4)	2.6

[a] $B_{eq} = \frac{8}{3} \pi^2 \, \mathrm{Tr} \, \bar{U}$.

ues), and the isotropic parameters were reintroduced. We then corrected the data for absorption, after which it was possible to introduce anisotropy for the heavy atoms. During the last cycles of refinement the parameters of all atoms, including hydrogen, were refined. Atomic parameters are given in Table 2. Atomic scattering factors were taken from Ref. 4.

Results and discussion

Coordination around dysprosium. The nonionic complex, DyDTPA–BMA hydrate, is nine-coordinated. It is shown in an ORTEP[2] drawing (Fig. 1), together with a stereoscopic picture made by the use of the program PLUTO[5] (Fig. 2). Three amine nitrogens (N2, N3 and N4), three carboxylate oxygens (O2, O4 and O7) and two amide oxygens (O1 and O8) in the ligand are bound to the central atom (Table 3). This rather unusual bonding, with two amide oxygens coordinating to the central atom, is also found in other lanthanide complexes.[6,7] The coordination to dysprosium is such that the complex shows one hydrophilic and one hydrophobic side. The compound crystallizes with seven water molecules. One of the seven (O9) is directly coordinated to dysprosium, the other six being waters of crystallization. The distances from dysprosium to the oxygen atoms in the ligand vary from 2.318(2) to 2.376(3) Å. This is 0.06–0.12 Å shorter than the sum of their ionic radii, 2.433 Å.[8] The Dy–N distances are between 2.609(3) and 2.751(3) Å, which is 0.07–0.21 Å longer than the sum of the ionic radii (2.543 Å). There is a good
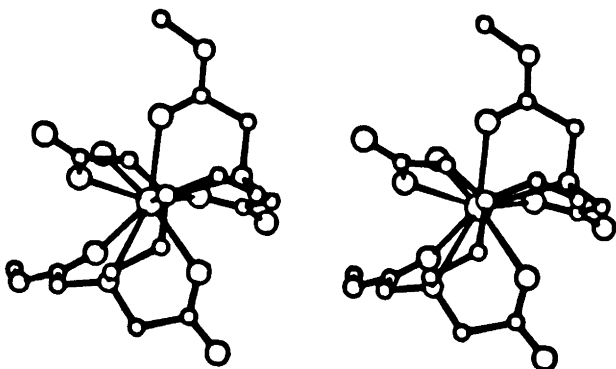
Fig. 2. Stereoscopic view of the complex.

Table 3. Coordination around dysprosium (in Å), with standard deviations in parenthesis.

Dy–O$_{carboxylate}$		Dy–O$_{water}$	
Dy–O2	2.318(2)		
Dy–O4	2.350(3)		
Dy–O7	2.326(3)	Dy–O9	2.463(3)
Average	2.331(3)		
Dy–O$_{amide}$		Dy–N	
		Dy–N2	2.751(3)
Dy–O1	2.376(3)	Dy–N3	2.609(3)
Dy–O8	2.348(2)	Dy–N4	2.616(3)

correlation between these results and the results found for the structure of a GdDTPA–BEA [gadolinium diethyl-enetriaminepentaacetic acid bis(ethylamide)] complex,[6] taking into account the increased ionic radii of the central atom. Short metal–oxygen and long metal–nitrogen bonds have also been found in other lanthanide–polyaminopoly-carboxylate complexes. This relates, for example, to EDTA (ethylenediaminetetraacetate) complexes of praseodymium, samarium, gadolinium and dysprosium[9] and ytterbium.[10] In all these compounds there is a correlation between bond lengths and size of the central atom. Other studies concerning correlations among different structural parameters of complexed nonpeptide polyamino acids have also been carried out.[11]

The distance from dysprosium to the oxygen (O9) of the water molecule which is a ligand is significantly longer than other Dy–O bonds. In solution, water molecules surrounding the complex are able to exchange site with the coordinated water molecule. This exchange increases the contrast effect of the complex, since atoms directly coordinated to the central atom have the greatest relaxation effect.[12,13] There is also a contribution to the water proton relaxation from hydrogen-bonded water molecules in the second coordination sphere.[1] A stereoview of the coordinating body surrounding dysprosium is shown in Fig. 3.

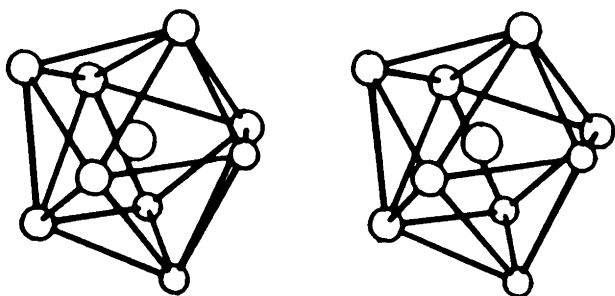The stability of complexes involving lanthanide ions

should be high for their use as MRI agents, as these ions in free form are highly toxic to man. Stability studies of polyaminopolycarboxylates and their lanthanide ion complexes have recently been carried out[14,15] using molecular-mechanics calculations and molecular-dynamics simulations. For the DTPA–BMA complex, the resulting lowest-energy conformation varies, depending on the starting conformation. However, the energy difference is small, only 2.5 kcal mol^{-1}. The coordination polyhedron found for DyDTPA–BMA is trigonal tricapped prismatic, and is similar to that determined from X-ray analysis for GdDTPA–BEA. This is not the energetically most favourable according to the calculations, but the difference is, as mentioned, small.

The ligand DTPA–BMA. The interatomic distances and angles within the ligand are of normal values, there being no signs of strain in the coordination sphere. Within experimental error the lengths of the C=O bonds in the three carboxylic acid groups are equal. There is a considerable amount of double-bond character in all of them. Distances involving the three oxygen atoms coordinated to dysprosium are somewhat longer than the others. Bond lengths in the ligand are listed in Table 4. It is worth noting that the two bonds between sp^3 carbon atoms are short. The average carbon–hydrogen distance is 0.95 Å; the corresponding distance for nitrogen atoms is 0.90 Å. This agrees with values found in X-ray experiments.[16] Angles in the ligand are given in Fig. 4. On the basis of standard deviations in the observations and vibrations out of the plane, the two amide groups in the ligand may be considered planar.

Hydrogen bonding. There are four intermolecular hydrogen bonds from each complex to surrounding complexes. The donors of these bonds are the nitrogen atoms in both amide groups (N1 and N5) and the acceptors are oxygen atoms (O5 and O6) from two carboxylic acid groups. The donor–acceptor distances are 2.798 and 2.845 Å, respectively. In the literature[17] a normal nitrogen–oxygen distance in a hydrogen bond is on average 2.88 Å [2.73–3.22 (10) Å].

In addition to these bonds there are many hydrogen

Fig. 3. Stereoscopic view of the trigonal tricapped prismatic coordination body.

Table 4. Bond lengths in the ligand DTPA–BMA (in Å), with standard deviations in parenthesis.

$C=O_{amide}$			1.253(5)
O1–C2	1.257(4)	O8–C15	1.248(5)
$C=O_{carboxylate}$			1.255(4)
O2–C5	1.263(4)	O3–C5	1.246(4)
O4–C9	1.270(4)	O5–C9	1.250(4)
O6–C13	1.243(4)	O7–C13	1.257(4)
$N_{amine}–C_{sp3}$			1.480(4)
N2–C3	1.462(4)	N2–C4	1.475(5)
N2–C6	1.482(4)	N3–C7	1.483(4)
N3–C8	1.482(5)	N3–C10	1.503(5)
N4–C11	1.488(5)	N4–C12	1.469(4)
N4–C14	1.473(4)		
$N_{amide}–C_{amide}$			1.314(5)
N1–C2	1.315(5)	N5–C15	1.313(5)
$N_{amide}–C_{sp3}$			1.458(5)
N1–C1	1.456(5)	N5–C16	1.459(5)
$C_{sp3}–C_{sp2}$			1.521(5)
C2–C3	1.520(5)	C4–C5	1.529(5)
C8–C9	1.516(5)	C12–C13	1.533(5)
C14–C15	1.505(5)		
$C_{sp3}–C_{sp3}$			1.505(5)
C6–C7	1.507(5)	C10–C11	1.502(5)

bonds due to the seven water molecules. They make up a three-dimensional network in which different complexes are connected by hydrogen bonds. Four oxygen atoms (O3, O4, O5 and O6) of the carboxylic acid groups are hydrogen-bond acceptors. The average donor–acceptor bond is 2.826 Å, and of normal value.[17] Most of the water molecules are bound both to ligand oxygens and to other water molecules. Although the water molecules are distributed between the complexes, they appear in highest concentration close to the hydrophilic side of the complexes.
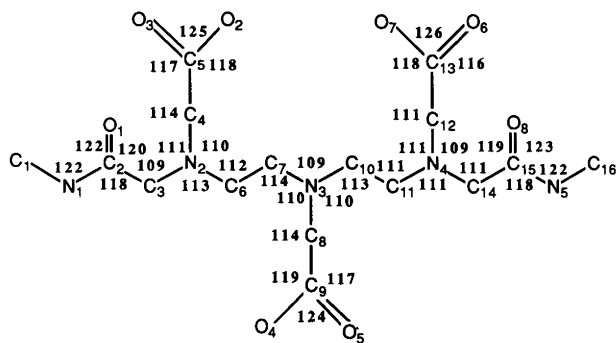
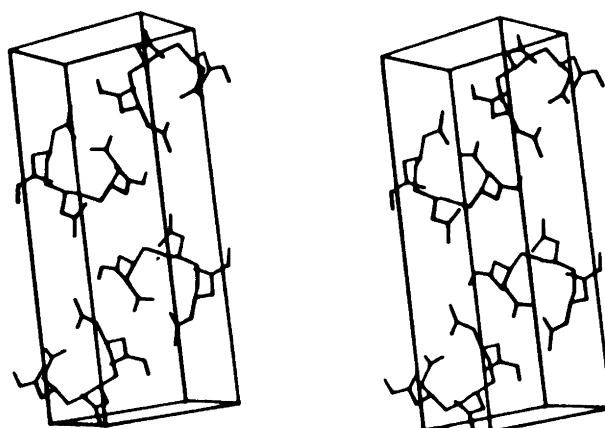*Fig. 4.* Angles (in °) in the ligand.

Fig. 5. Stereoscopic view showing the packing pattern of the complex seen along the *c*-axis.

Packing patterns. The hydrophilic part of the complex is mainly composed of oxygen atoms, and the coordinated water molecule is also located here. This side is more open, which leads to a diminished shielding of dysprosium. The consequence of these factors is that it will be easier for the water molecules of crystallization to reach the central atom. This exchange of water molecules affects the ability of the investigated compound to act as a contrast agent for magnetic resonance imaging.

The orientation of the four complexes in each unit cell is shown in Fig. 5.

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